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Review

Engineering multifunctional dynamic hydrogel for biomedical and tissue regenerative applications

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ABSTRACT

Hydrogels have emerged in various biomedical applications, including tissue engineering and medical devices, due to their ability to imitate the natural extracellular matrix (ECM) of tissues. However, conventional static hydrogels lack the ability to dynamically respond to changes in their surroundings to withstand the robust changes of the biophysical microenvironment and to trigger on-demand functionality such as drug release and mechanical change. In contrast, multifunctional dynamic hydrogels can adapt and respond to external stimuli and have drawn great attention in recent studies. It is realized that the integration of nanomaterials into dynamic hydrogels provides numerous functionalities for a great variety of biomedical applications that cannot be achieved by conventional hydrogels. This review article provides a comprehensive overview of recent advances in designing and fabricating dynamic hydrogels for biomedical applications. We describe different types of dynamic hydrogels based on breakable and reversible covalent bonds as well as noncovalent interactions. These mechanisms are described in detail as a useful reference for designing crosslinking strategies that strongly influence the mechanical properties of the hydrogels. We also discuss the use of dynamic hydrogels and their potential benefits. This review further explores different biomedical applications of dynamic nanocomposite hydrogels, including their use in drug delivery, tissue engineering, bioadhesives, wound healing, cancer treatment, and mechanistic study, as well as multiple-scale biomedical applications. Finally, we discuss the challenges and future perspectives of dynamic hydrogels in the field of biomedical engineering, including the integration of diverse technologies.

1. Introduction

Hydrogels are polymer networks with high water content and have been extensively utilized in biomedical applications in various fields, including scaffolds in biological tissue engineering and components of medical devices, because of their ability to emulate the natural extracellular matrix (ECM) of tissues [1-6]. Hydrogels were primarily investigated for their swelling behavior and water absorption capacity in the

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1960-70s [7]. Synthetic hydrogels are typically created by chemically crosslinking polymer chains through covalent bonds, resulting in the formation of static networks that may lack the ability to dynamically respond to changes in their surroundings [8]. Typically, the covalent crosslinking can be mediated by Michael addition reactions, Schiff-based reactions, and enzymatic reactions. These hydrogels can serve as precisely defined two-dimensional (2D) substrates or three-dimensional (3D) networks for investigating the effects of physico-chemical and biological stimuli on cells presented by the hydrogel [9-12], as well as an interface of biodevices to human skin/tissue [13]. Dynamic hydrogels, on the other hand, possess the ability to adapt and respond to external stimuli that undergo reversible and controllable changes according to their physical and chemical properties [14-17]. Therefore, the application of hydrogels strongly depends on their mechanical properties, including toughness, stiffness, viscoelasticity, porosity, shape memory, and self-healing. It is imperative to also amplify the importance of other attributes, *e.g.*, hydrogel morphology and surface energy, on cell interactions and affinities in specific applications such as tissue engineering. However, the overarching objective of this review is on the mechanics of dynamic hydrogels; the interested readers are referred to the available body of work on cell-hydrogel interactions for more details, for example [18]. Unlike conventional static hydrogels, which have fixed chemical crosslinks that determine their mechanical properties, dynamic hydrogels contain reversible covalent bonds or supramolecular interactions that can be broken by external stimuli such as changes in temperature, pH, light, mechanical strength, or the presence of specific molecules [19,20] and subsequently re-form or remodel. In the 1970s-80s, researchers began experimenting with synthetic polymers and investigating their stimuli-responsive properties. Temperature responsiveness emerged as a significant area of interest during this time. Studies on hydrogels like poly(N-isopropylacrylamide) (PNIPAAm) demonstrated a reversible volume phase transition near the lower critical solution temperature (LCST) [21]. In the 1990s, advancements in polymer chemistry and materials science led to the discovery and development of hydrogels with pH-responsive behaviors [22]. Researchers explored polymers like poly(acrylic acid) (PAA) and its derivatives, which exhibited swelling or shrinking in response to changes in pH levels. This opened up possibilities for targeted drug delivery and controlled release systems. In the late 1990s-2000s, light-responsive hydrogels gained attention during this period. Scientists began incorporating photoactive molecules or photoresponsive crosslinkers into hydrogel networks [23]. These materials could undergo reversible changes in their properties upon exposure to specific wavelengths of light, allowing precise spatiotemporal control over hydrogel behavior. In the 2000s-10s, enzyme-responsive hydrogels emerged as an area of focus. Researchers introduced enzymatically cleavable linkers within hydrogel networks, enabling controlled degradation and drug release in response to specific enzymes [24]. Enzyme-responsive hydrogels have found applications in targeted drug delivery, tissue engineering, and diagnostics. From the 2010s to the present, self-healing and multi-responsive hydrogels gained prominence during this period. Therefore, dynamic hydrogels have drawn great attention in recent studies in the fields of drug delivery, skin patches, tissue engineering, cancer treatment, mechanistic studies, and wound healing [25-27].

There are several types of dynamic hydrogels, each with its own unique properties and applications. One example is based on breakable and reversible covalent bonds, such as dynamic disulfide bonds, dynamic imine bonds, or dynamic boronate ester bonds [28-30]. The other type is based on noncovalent interactions, such as host-guest interactions, π–π stacking, hydrophobic interactions, and hydrogen bonding, to construct supramolecular architecture since these bonds are selective and directional [31]. These processes help hydrogel materials dissipate energy, thereby providing injectable and self-healing properties that are critical for clinical applications [32]. On the other hand, irreversible dynamic hydrogels are often hydrolytically or proteolytically degradable to influence structural dynamics for purposes such as creating spaces/mechanical feedback to facilitate cell spreading, proliferation, and migration in a 3D environment and drug/cell delivery for biomedical studies [33-35]. These hydrogels can be degraded in response to biological signals, such as enzymes and pH, which can be controlled with temporal and spatial precision [33,36]. Nevertheless, physically crosslinked hydrogels usually show weak mechanical properties and are combined with chemically crosslinked hydrogels as an interpenetrating network (IPN) to reinforce their mechanical properties with enhanced functionalities [37].

Apart from the widely combined hydrogel precursors/prepolymers of modified natural polymers, including proteins (e.g., collagen, gelatin, fibroin, fibrin), glycosaminoglycans (e.g., hyaluronic acid) and polysaccharides (*e.g.*, chitosan, alginate, starch, and cellulose),[38] functional and injectable nanocomposite hydrogels have merged through implementing nanosized or nanostructure materials (matrix fillers) to gain extra/enhanced properties from the constituents. For instance, nanomaterials possess a high surface-to-volume ratio as nano-crosslinkers to reinforce the skeleton and endow them with improved mechanical properties, such as shear-thinning properties and injectability [39]. Also, hydrogels alone cannot effectively sustain the release of hydrophobic drugs and lack the loading capacity to store drugs compared to nanoparticles (NP)s, which can be modified to load a tremendous number of water-insoluble drugs. Moreover, NPs can grant hydrogels with several stimuli-responsive functionalities, such as magnetism, electric field, and light, to empower the on-demand remote control triggered events. These characteristics offer the benefits of both hydrogels and nanomaterials.

Numerous reviews summarized the fabrication and design of polymer-based dynamic hydrogel for cell and tissue regenerative medicines, particularly cell response to the physicochemical properties of the hydrogel [16,35,40,41]. Yet, few reports discuss the possibility of integrating multiple functions into a single dynamic hydrogel system, which has been an active area of research recently. Moreover, the applications of dynamic hydrogels are not limited to wound dressings, tissue engineering and regenerative medicine, but multi-scale biomedical applications for cell adhesions/migration, skin/tissue patches, immunotherapy, and vaccination. These applications can be potentially achieved by nanocomposite hydrogels with multi-responsiveness for drug release, improved mechanical properties and tailored-made bioactivity. Thus, hydrogels integrated with diverse technologies to enable the development of complex and advanced biomedical devices and systems should be further explored. Our review aims to address these gaps in knowledge that are critical to the development of safe and effective dynamic hydrogels for clinical use. Furthermore, there is up to now only one report mentioning and categorizing nanocomposite hydrogels with multiple release of payloads (cited in the review)[42]. The application was curing of breast cancer. In section 3 of our review, we discuss different strategies to combine multi-release systems (responsive or non-responsive release of multi-drugs) with dynamic nanocomposite hydrogels. Our review also discusses more applications such as wound dressing, tissue engineering, drug delivery systems, and immunotherapy.

2. Dynamic hydrogels vs. conventional static hydrogels

Dynamic hydrogels can be derived from conventional static hydrogels with unique properties and applications (Figure 1a). In this section, we introduce the advantages of multifunctional dynamic hydrogels, discuss the crosslinking types, and explore how these crosslinking influence mechanical properties [43-45].

2.1. Advantages of dynamic hydrogels for biomedical engineering

The development of dynamic hydrogels has opened up new possibilities for the use of hydrogels in biomedical applications [46-50]. These hydrogels can be used for drug delivery, tissue engineering, and

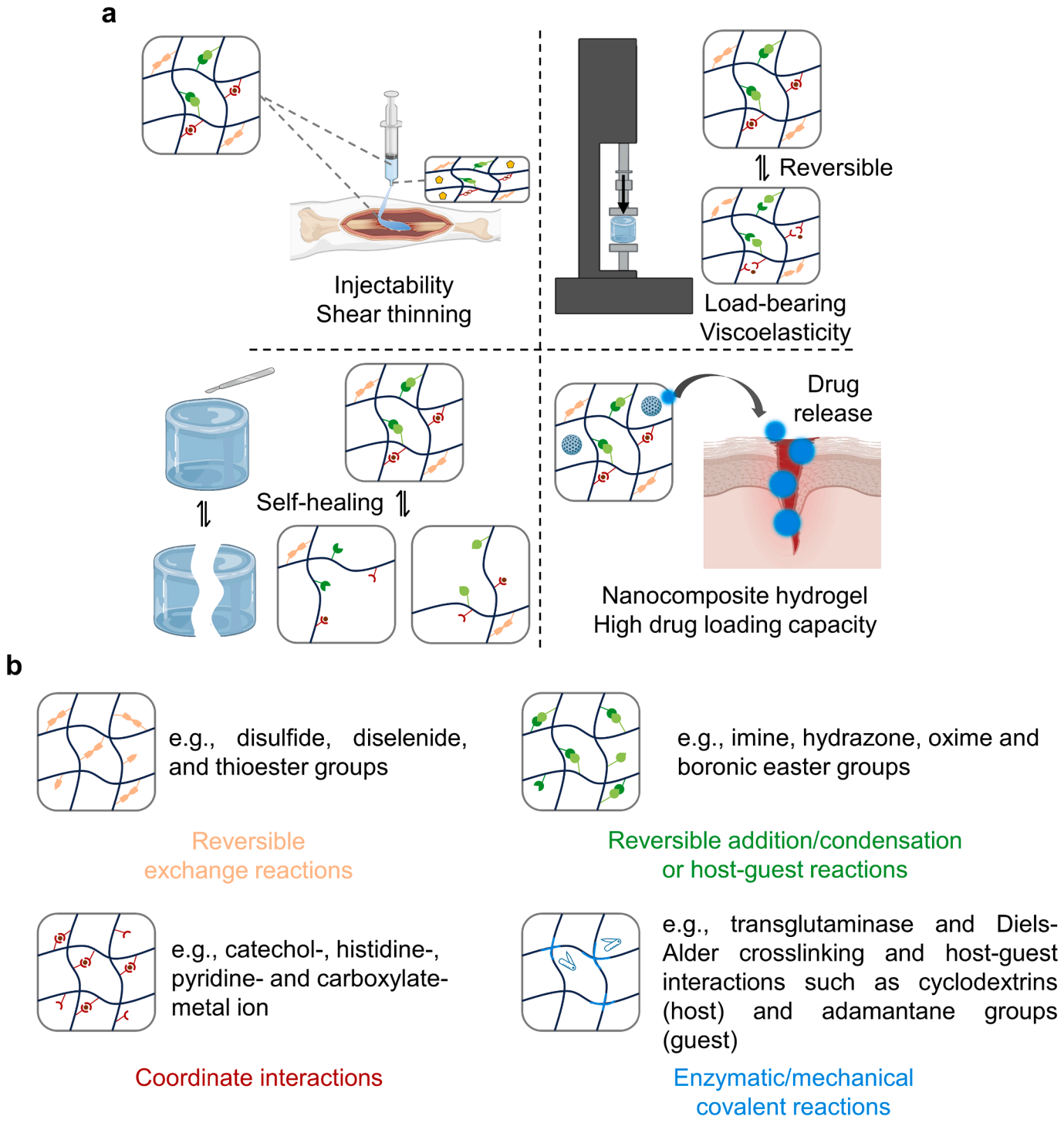

Figure 1. Overview of dynamic hydrogels. (a) The general properties of dynamic hydrogels. (b) Common types of crosslinking for dynamic hydrogels. Parts of the figure are created by Biorender.com.

regenerative medicine. They can be designed to release drugs in response to biological signals, provide structural support to encapsulated cells, or promote tissue regeneration. For example, ECM-based dynamic hydrogels can be the components of artificial tissues, such as cartilage or bone, by providing the necessary structural support and promoting the growth and differentiation of encapsulated cells [51-53]. Dynamic hydrogels that can respond to localized mechanical forces and biological signals with temporal and spatial precision have been an active area of research. These hydrogels have the potential to revolutionize biomedical applications.

Dynamic hydrogels can be made from biocompatible materials such as natural polymers, synthetic polymers, or a combination of both. ECM-based biocompatible hydrogels can be further integrated with stimuli-responsive functionality that can change their properties in response to specific stimuli such as temperature, pH, light, or specific biomolecules to facilitate biomedical therapy [54]. For example, temperature-responsive hydrogels can undergo a reversible phase transition in response to changes in temperature, allowing them to release drugs or growth factors on demand. pH-responsive hydrogels can also control the release of drugs or other bioactive molecules in response

to changes in pH, such as those that occur in diseased or inflamed tissues [55-57]. Degradable dynamic hydrogels are useful when the material needs to be in the body for a specific amount of time but then must be cleared from the body to avoid complications [58-64].

Dynamic hydrogels display tunable mechanical properties due to reversible bondings, allowing them to conform to the shape of biological tissues and organs to support the growth and development of new tissue [65-69]. Self-healing is an attractive property for repairing hydrogels post-damage, which is particularly useful for implants or drug delivery vehicles that are constantly subjected to mechanical stress or wear. These hydrogels can re-form crosslinking points and regain their original shape and properties after stress loading, which increases their durability and lifespan [70-76]. Conventional hydrogels have relatively low mechanical strength, which limits their use in load-bearing applications. Researchers are working on developing hydrogels with improved elasticity and toughness to make them more suitable for these applications [77,78].

Another active area of research is enhancing the biocompatibility of dynamic hydrogels. Recent research has been investigating hydrogels that are more compatible with living tissues and cells, allowing for long-term implantation without causing adverse reactions. Furthermore, the biofunctionalization of hydrogels, such as presenting cell-adhesion ligands, growth factors, and ECM-based bioactive moieties, can enable the creation of more biomimetic and functional hydrogel matrices for tissue engineering and regenerative medicine applications [79].

One of the main challenges is predicting and rationally designing hydrogels with specific mechanical properties. Kinetics of the dynamic covalent bonds that make up the hydrogel network play a crucial role in determining its mechanical properties. However, obtaining this information at the single molecule level is difficult, and new methods of measurement are needed [80]. Single-molecule force spectroscopy is a promising technique, but further development is necessary to improve its accuracy and reliability. Another challenge is designing hydrogels with spatial inhomogeneities in mechanical properties, which is essential for creating hydrogels that mimic the mechanical properties of natural tissues [81]. However, measuring the local mechanics of the hydrogel and studying how cells respond to local biophysical cues is also challenging. Advances in imaging and cell culture techniques are necessary to overcome these challenges and enable the creation of hydrogels with spatially varying mechanical properties [82]. Reconciling microscopic dynamics and macroscopic stability is a major challenge for dynamic hydrogels in biomedical applications. The dynamic properties of hydrogels need to be carefully balanced with their macroscopic stability and mechanical properties for safe and effective applications [16]. Achieving these design requirements involves a combination of experimental and theoretical approaches to optimize hydrogel composition, cross-linking strategies, and structural dynamics.

2.2. Type of crosslinking

Dynamic hydrogels contain reversible dynamic bonds in addition to conventional crosslinking bonds in static hydrogels (Figure 1b). Reversible dynamic bonds allow the hydrogel to respond to changes in stimuli, undergo reversible changes in properties such as swelling and recover from mechanical damage. Conventional static hydrogels, on the other hand, contain only conventional crosslinking bonds that form a stable and fixed network structure. Once these bonds are broken, they are unable to re-bond spontaneously. The dynamic covalent chemistry for hydrogels can be categorized as (1) reversible exchange reactions that include disulfide, diselenide, and thioester groups; (2) reversible addition/condensation reactions, including imine, hydrazone, oxime and boronic easter groups; (3) coordination bonds, such as catechol-, histidine-, pyridine- and carboxylate-metal ion coordination bonds; (4) enzymatic/mechanical covalent reactions, such as transglutaminase and Diels-Alder crosslinking [83]; and host-guest interactions such as cyclodextrins (host) and adamantane groups (guest).

2.2.1. Reversible exchange reactions

Reversible exchange reactions are a class of chemical reactions that involve the exchange of covalent bonds between polymer chains, allowing for the creation of dynamic hydrogels with reversible crosslinking [84]. Disulfide exchange reactions involve the exchange of disulfide bonds between polymer chains, which can be triggered by changes in pH, heating or redox potential [85,86]. Diselenide exchange reactions are similar to disulfide exchange reactions but involve the exchange of diselenide bonds. For example, poly(ethylene glycol) diacrylate (PEGDA) can be modified with disulfide-containing groups to form crosslinked hydrogels [87,88]. Poly(N-isopropylacrylamide) (PNIPAM) can be functionalized with disulfide groups, making it suitable for the fabrication of thermoresponsive hydrogels [89,90]. Diselenide bonds are more reversible than disulfide bonds, allowing for a more dynamic network [91]. Poly(selenocysteine) polymer containing selenocysteine residues, which forms diselenide bonds[92]. Poly(selenide disulfide) is a copolymer that combines both disulfide and diselenide functionalities, offering a high level of reversibility and control in hydrogel formation. Thioester exchange reactions involve the exchange of thioester bonds between polymer chains, which can be triggered by changes in pH or temperature [93]. Thioester bonds are less stable than disulfide and diselenide bonds but can be more dynamic, allowing for faster exchange and reformation of the network. under acidic and basic conditions [94]. Poly(acrylic acid) can be modified to include thioester groups [95]. Poly(β-thioester ester) polymer contains thioester linkages and is responsive to changes in pH and temperature. It can form hydrogels that are more dynamic than those based on disulfide or diselenide bonds [96].

2.2.2. Reversible addition/condensation reactions

Reversible addition/condensation reactions are a class of chemical reactions that involve the formation and breaking of covalent bonds between polymer chains, allowing for the creation of dynamic hydrogels with reversible crosslinking [97,98]. Four common examples of reversible addition/condensation reactions used for dynamic hydrogel crosslinking are imine, hydrazone, oxime, and boronic ester reactions. Imine reactions involve the formation and breaking of imine bonds between polymer chains, which can be triggered by changes in pH or the presence of certain chemical groups [99]. Hydrazone reactions are similar to imine reactions but involve the formation and breaking of hydrazone bonds between polymer chains [100]. Hydrogels made from polymers containing hydrazone bonds can be crosslinked under acidic conditions, and the bonds can be broken under basic conditions. Oxime reactions involve the formation and breaking of oxime bonds between polymer chains, which can be triggered by changes in pH or the presence of certain chemical groups [101]. Oxime bonds are less stable than imine and hydrazone bonds but can be more dynamic, allowing for faster exchange and reformation of the network under varying pH conditions [101].

2.2.3. Coordination bonds

Coordination bonds are a class of chemical bonds that involve the interaction between a metal ion and a ligand, allowing for the creation of dynamic hydrogels with reversible crosslinking [102]. The use of coordination bonds can reduce the toxicity associated with traditional crosslinking methods, such as *N,N'*, methylenebisacrylamide [103]. Catechol groups can be found in natural materials such as mussel adhesive proteins and can form reversible bonds with metal ions, creating hydrogels with reversible crosslinking. Histidine residues can be found in natural materials such as proteins and can form reversible bonds with metal ions, allowing for the creation of hydrogels with reversible crosslinking [102]. Carboxylate groups can be found in natural materials such as proteins and can form reversible bonds with metal ions, creating hydrogels with reversible crosslinking [104]. Adding metal ions can crosslink all these hydrogels made from coordination bonds and can be broken by removing metal ions.

2.2.4. Enzymatic/mechanical covalent reactions

Enzymatic and mechanical covalent reactions involve the formation of covalent bonds between polymer chains, allowing for the creation of dynamic hydrogels with reversible crosslinking [34,105]. Two common examples of enzymatic and mechanical covalent reactions used for dynamic hydrogel crosslinking are transglutaminase and Diels-Alder crosslinking. Transglutaminase crosslinking involves the use of the enzyme transglutaminase to catalyze the formation of covalent bonds between polymer chains [106]. Transglutaminase is an enzyme that can catalyze the formation of covalent bonds between amino acid residues, lysine, and glutamine. Hydrogels made from polymers containing lysine and glutamine residues can be crosslinked using transglutaminase, and the addition of reducing agents breaks the bond. Transglutaminases are effective for in situ integrating hydrogels with native host tissues by forming an amide linkage between the γ-carboxamide group that might be available in the surrounding proteins [106-108]. Furthermore, transglutaminases can successfully induce crosslinking in poly(ethyne glocal), elastin, and gelatin [106,108-110]. Diels-Alder crosslinking involves a chemical reaction between a diene and a dienophile to form a cyclohexene ring [111]. Hydrogels made from polymers containing diene and dienophile groups can be crosslinked using Diels-Alder chemistry, and the bonds can be broken by increasing the temperature or using chemical agents. Using enzymes or mechanical force as catalysts allows for the creation of hydrogels under mild conditions, reducing the potential for damage to biological molecules.

2.2.5. Host-guest interactions

Host-guest interactions involve non-covalent bonds between two molecules, where one molecule, the host, has a cavity that can accommodate the other molecule, the guest. One example of a host-guest interaction is the use of cyclodextrins (CDs) and adamantane derivatives as crosslinking agents to form hydrogels [112]. CDs have a hydrophobic cavity that can accommodate hydrophobic guest molecules, such as adamantane derivatives. When CDs and adamantane derivatives are mixed, they form inclusion complexes due to the host-guest interactions [113]. Another example is the interaction between cucurbiturils (CBs) and paraquat derivatives [114]. CBs have two identical cavities that can accommodate guest molecules and paraquat derivatives are positively charged molecules that can be encapsulated by CBs due to the electrostatic interactions between their charges. The advantages of host-guest interactions include their reversibility, which allows for dynamic control over the properties of the system. They are also versatile, as they can form a wide range of structures and materials. However, the specificity of the interaction can limit the range of guest molecules that can be used, and the strength of the interaction may be weaker than covalent bonds, affecting the stability of the system [115]. The synthesis of host and guest molecules can be challenging, limiting their use in applications.

However, there are some limitations associated with the use of reversible bonding for dynamic hydrogel crosslinking. One major limitation is that the bonds formed by these reactions may not be as strong as other covalent bonds, which can affect the mechanical properties of the hydrogels. Additionally, the reversibility of the crosslinking can lead to a loss of mechanical stability over time, which may limit the long-term applications of these hydrogels. Hence, these hydrogels can be mechanically supported by integrating them with conventional static hydrogels.

2.3. Crosslinking effect on mechanical properties

The interrelationship between the mechanical properties and type of crosslinking in hydrogels is symbiotic, as arguably is the case for the general class of polymers [116-118]. The mechanical properties broadly encompass time-independent attributes, *e.g.*, stiffness, stretchability, and strength, and time-dependent behaviors, such as relaxation, self-healing, and long-term resiliency [118-121]. From a performance perspective, shear modulus, swelling, molecular porosity, degradation, and toughness are crucial metrics to assess the response of novel or existing hydrogels based on specific application requirements [3,116,122,123]. On the molecular level, the approach to modulate or tune the altering nature of crosslinking entails hybridization (with NPs, fibers, or chemical species) or different crosslinking types [118,124]. In other words, hydrogels plagued with insufficient strain energy, affecting stiffness, strength, and toughness, are undergoing transformational progress by amending their molecular structures using novel approaches such as hydrophobic association [125,126], ionic crosslinking [127,128], double networking [129,130], hydrogen bonding or dipole-dipole enhancing [131,132], super-molecules, and hybridization with nanocomposites and reinforcements [124,133-135] (Figure 2). In general, there has been a keen interest in developing tough and antifatigue hydrogels, given the arduous operating conditions necessitated by the ever-expanding application domains [117-120,136,137].

Natural gums such as guar gum, gum arabic, tragacanth gum, gum karaya, gum ghatti, gellan gum, kondagogu gum, locust bean gum, gum tamarind, and xanthan gum have been applied to form hydrogels [138-140]. The chemical crosslinking hinges on forming covalent bonds between the hydrogel chains, creating permanently strong hydrogels [4,141-143]. Chemical crosslinking involves free radical polymerization, enzymes and 'click' chemistry [116,141]. Similarly, physical crosslinking encompasses many formation strategies based on reversible intermolecular interactions, including entangled chains, ionic and electrostatic interactions, hydrogen bonding, thermally induced interactions, and acoustically-activated interactions [4,141]. While chemically crosslinked hydrogels outperform their physically crosslinked counterparts in stability and mechanical properties, the latter excels in stimulus responsiveness (*e.g.*, temperature and pH) and self-healing [4,116,141]. Other crosslinking approaches, including those listed above, can be fundamentally classified as chemical, physical, or hybrid, which may result in single, double, or multiple network hydrogels [144,145].

As stated above, physical crosslinking approaches can be used to tune the mechanical response of hydrogels, such as high stretchability, toughness, and fracture energy [4,142,143,146,147]. For example, the mechanical properties of alginate hydrogels, polysaccharide derivatives from brown algae [4], have been improved by ionically crosslinking using univalent (*e.g.*, sodium Na^{+}), divalent (*e.g.*, calcium Ca^{2+}, strontium Sr^{2+}, barium Ba^{2+}, and magnesium Mg^{2+}) and trivalent (*e.g.*, iron Fe^{3+} and aluminum Al^{3+}) cations, interpenetrating networks of polyacrylamide (PAAm), and glass fibers [4,124,148,149]. Yang *et al.* reported a tremendous increase in the elastic modulus for trivalent crosslinked hydrogels, increasing from ~3.8kPa (for Na-alginate/PAAm) to >250kPa for Fe-alginate/PAAm [148]. Zhang *et al.* demonstrated the self-recovery, notch-insensitivity, and fatigue resistance properties of double-network, physically crosslinked hydrophobic polyacrylamide (with alginate through a divalent agent (*i.e.*, calcium, Ca^{2+}), where they associated the improved properties to the PAAm associations and ionic crosslinking [149]. Martin *et al.* elucidated the dynamic properties (*i.e.*, storage and loss moduli) of divalent and trivalent crosslinked alginate/PAAm hydrogels and glass-fiber reinforced versions of the same formulations, showing a further substantial increase in the mechanical properties, as expected, due to the addition of the stiff, short fibers at 2 *wt.* and 3 *wt.*% [124]. Martin *et al.* also postulated that crosslinking with multivalent agents effectively improved the stiffness and dampening attributes of alginate/PAAm hydrogels, specifically when crosslinked with higher molecular weight elements, irrespective of valency [124]. Suo *et al.* reported on the recovery behavior of alginate/PAAm interpenetrating network hydrogels, stating a 74% recovery after first loading with penalized tensile strength [150,151]. Chen *et al.* studied agar/PAAm double network hydrogels with 1.0 MPa tensile stress and 65% toughness recovery at specific conditions (time and temperature) [152,153]. Similar improvements in the mechanical behavior of physically crosslinked hydrogels have been reported via the

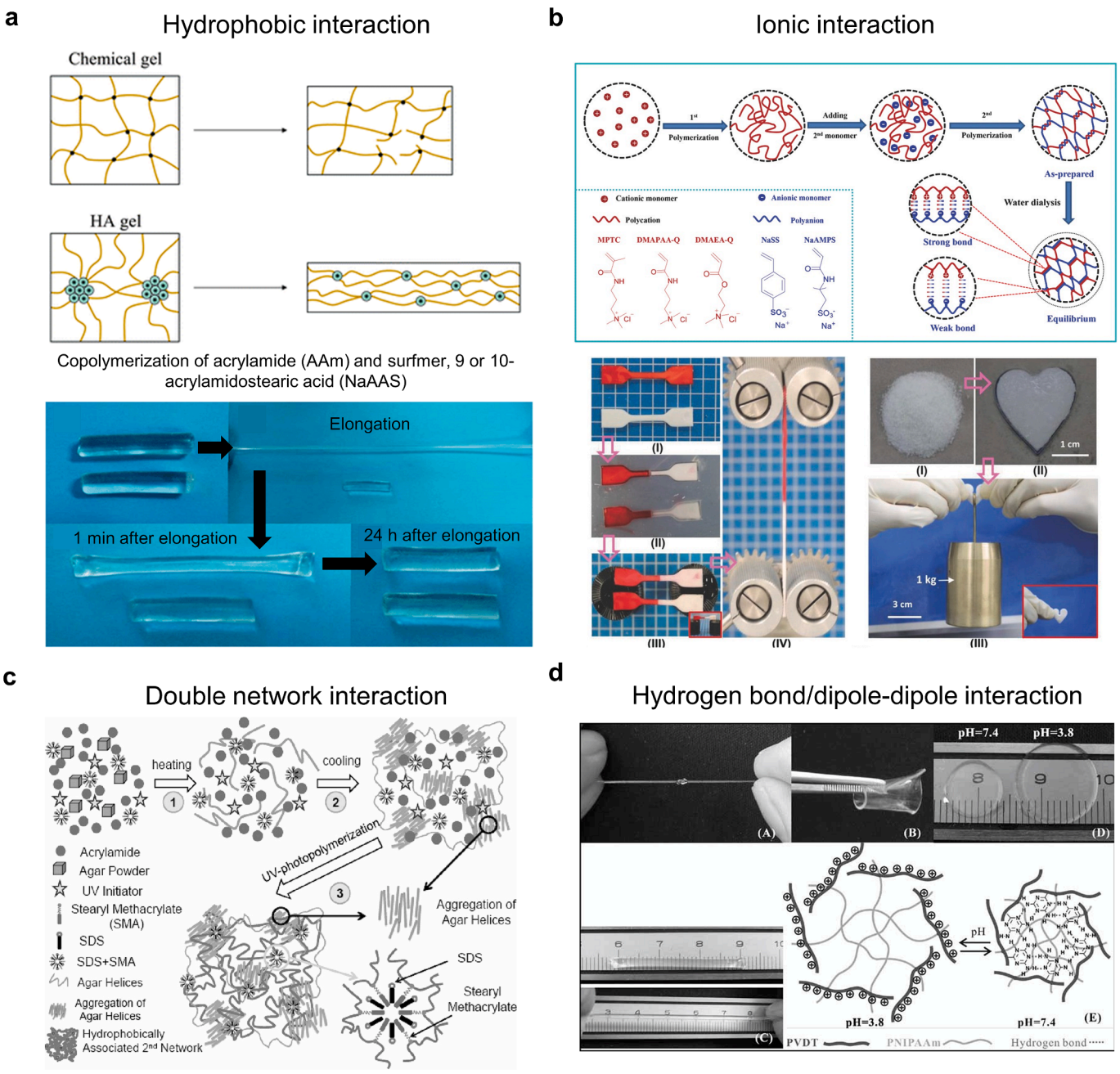

Figure 2. Diverse reversible interactions for dynamic hydrogel crosslinking. (a) Hydrophobic interaction based on physically cross-linked HA hydrogel by micellar copolymerization of acrylamide and NaAAS without adscititious surfactant or chemical cross-linkers. Adapted from [126] Copyright (2012) Royal Society of Chemistry. (b) Ionic interaction based on two oppositely charged polymers, 3-(methacryloylamino)propyl-trimethylammonium chloride and sodium p-styrenesulfonate. Adapted from [128] Copyright (2015) Wiley-VCH. (c) Double network interaction formed by physically crosslinking of (1) a hydrogen bond-associated agar gel and (2) a hydrophobically associated polyacrylamide gel. Adapted from [129] Copyright (2015) Wiley-VCH. (d) Hydrogen bond/dipole dipole interaction based on crosslinking copolymerization of N-isopropylacrylamide, 2-vinyl-4,6-diamino-1,3,5-triazine, and the crosslinker poly(ethylene glycol) diacrylate (Mn = 575). Adapted from [132] Copyright (2010) Wiley-VCH.

addition of various NPs, also resulting in multifunctionality due to the unique attributes of the nanoparticle additives [41,57,154,155]. The premise of hybridization of hydrogels using nanomaterials (*e.g.*, organic and inorganic particles) is motivated by the high surface-to-volume and the broad range of aspect ratios of these enhancement agents [57,154]. The nanocomposite hydrogel networks were associated with novel mechanical properties based on hybridizing the neat hydrogel with carbon-based nanostructures (*e.g.*, carbon nanotubes, graphene, and fullerene), organic NPs (such as dendrimers), inorganic NPs (ceramics: hydroxyapatite, silica, and clay; metals: gold, silver, titanium-oxide, and iron-oxide) [41,57,154,156]. For example, adding silicate nanoplatelets enhanced the mechanical response of poly(ethylene oxide) by increasing elongation at low silicate concentrations and improving the stiffness at higher percentages (*ca.* > 40%) [157,158].

Recently, there has been a notable development in further improvement of the mechanical behavior, coined as 'super tough' hydrogels [159-161]. The interest stems from structure-property interrelationships, where the mechanical properties of homopolymer hydrogels are often compromised (*i.e.*, well-below those required for a specific application domain). Furthermore, the pursuit of hydrogels with

super toughness stems from the dichotomy between the intrinsic properties of most artificial materials and their natural counterparts, *e.g.*, cartilage exhibits super mechanical properties, including high toughness and shock absorption [161]. The development of super tough hydrogels was motivated by hybridizing several networks, such as interpenetrating network hydrogels consisting of multi-polymers, which have gained keen interest. Double network hydrogels were developed with high stiffness in the range of 0.1 – 1 MPa, average failure tensile strength in the order of 5 MPa, and an exceptional range of tearing toughness (0.1-4.4 kJ/m^2) [161]. These properties are reported to be several folds higher than the individual polymers used in synthesizing the double network hydrogels [162,163]. For example, the failure strength of double network cellulose and gelatin was measured to be *ca.* 3.75 MPa at strain to failure of ~ 40%, exceeding the strength of the individual gelatin and cellulose (< 1 MPa)[152,164,165]. Gonzales *et al.* reported strong, tough, and stretchable hydrogels consisting of covalently crosslinked proteins with and without divalent agents (*e.g.*, zinc, Zn^{2+}), noting comparable fracture toughness (<30 J/m^2) without Zn^{2+} but reported drastic changes to the modulus and toughness as the Zn^{2+} concentrations increased, exceeding 1200 J/m^2 of fracture toughness values for metal crosslinked proteins [146,166]. Song *et al.* recently reported an alternative hydrogel that they characterized as super tough and stretchable with additional functionality (*e.g.*, responsiveness) [167]. This hydrogel consists of crosslinked supramolecular formed by self-assembling amphiphilic block copolymers with guest groups at the end and vinyl functionalized cyclodextrin [167], resulting in a tensile strength of 0.475 MPa with uniaxial stretch > 2100%, and modulus of the toughness of 2.68±0.69 MJ/m^3) [167]. Comparably, Wang *et al.* reported physically crosslinked alginate/gelatin hydrogel that showed reversible behavior with similar mechanical strength and strain to failure to that of the hydrogel reported by Song *et al.* [167,168].

As mentioned above, the type of crosslinking (physical vs. chemical) plays a role in the physical and mechanical properties of hydrogels, providing a pathway for tunability and customization for specific applications. Physically crosslinked hydrogel can be externally stimulated to provide desirable responses under given operating conditions, making them a viable bioactive platform for encapsulations, *e.g.*, drug delivery [141]. For example, Chung *et al.* demonstrated that thermo-sensitive biodegradable hydrogels comprising multi-block Pluronic copolymers linked by D-lactide and L-lactide oligomers for sustained release of human growth hormone [169]. Along the same line, alginate hydrogels physically crosslinking by ionic and electrostatic interactions have been demonstrated in several other applications due to its inherent self-healing attributes[141], including wound healing[170,171] and tissue engineering [172,173]. On the other hand, chemically crosslinked hydrogels, owing to strong and permanent covalent bonds, generally exhibit improved and potentially tunable mechanical and physiological stability, positioning them for biomedical applications, irrespective of the crosslinking strategy[141,174]. For example, photopolymerized hydrogels were recently utilized in cytokines encapsulations [175,176]. Edwards *et al.* recently reported composite, photocurable hydrogel consisting of gelatin/gelatin methacryloyl microgel, showing rapid spread and proliferation of human dermal fibroblasts and mesenchymal within the microstructure this composite microgel [175]. Notably, the biomedical applications of physically and chemically crosslinked hydrogels have attracted assiduous and burgeoning research, which can be further explored in an independent review.

3. Design of nanocomposite hydrogels for releasing multiple drugs

The incorporation of nanocarriers in hydrogels is a potent tool to use for overcoming some limitations and challenges involved in the applications of hydrogels for drug delivery systems. These limitations include low mechanical properties in the swollen state, especially for single-network superhydrophilic hydrogels, and difficulty loading hydrophobic agents. Nanoparticles can be embedded into hydrogels through physical interactions between nanoparticles and hydrogels, chemical reactions between nanoparticles and hydrogels, or chemical reactions between nanoparticles to reinforce the mechanical properties of hydrogels (Figure 3) [177]. Moreover, nanocomposite hydrogels are promising for designing delivery systems for multidrug therapy with rational combinations of drugs at desired concentrations [178], which is increasingly prevalent in treatments such as antibiotic-resistant infections [179], cancers [180], and cardiovascular diseases [181]. Suitable nanocarriers include metal/metal-oxide/metalloid nanoparticles and polymeric nanoparticles. Additionally, the strategy to control the release of several drugs from nanocomposite hydrogels was also applied successfully to tissue engineering applications. For example, a dual delivery of the adenosine ligand from nanocomposite hydrogel and Mg^{+2} ion through dissolution of Mg nanoparticles promoted osteogenic differentiation of stem cells through the synergistic activation of the adenosine A2b receptor.[182] The nanocomposite hydrogels induced rapid formation of fully integrated neo-bone tissue by activating the A2b receptor, leading to the healing of rat tibial bone defects. In another report, the co-release of gentamicin sulfate from pH-sensitive alginate hydrogel and phenamil from silica nanoparticles exhibited antibacterial activity and synergistically increased osteogenic differentiation ability. [183] The pH-responsive hydrogel-incorporating silica nanoparticles significantly enhanced new bone formation in a critical-sized mouse cranial bone defect model. The challenges in this field remain the improvement of physical properties of nanocomposite hydrogel such as self-healing, stimuli-shape memory, adhesiveness, and ultra-durability. This would broaden the usage of nanocomposite hydrogel for tissue engineering, biological adhesives, and advanced medical devices. Herein, we discuss the development of advanced hydrogels for loading and releasing several drugs.

3.1. Non-responsive nanocomposite hydrogels

Depending on their hydrophobicity, various payloads can either be encapsulated in nanoparticles or in a hydrogel matrix. The release of drugs is regulated by molecular diffusions, hydrophobicity of payloads, porosity and size of the nanocarrier, and hydrogel properties, such as swellability and degradability. The compositions and methods of formation of the nanocomposite hydrogels are presented in Table 1.

3.1.1. Nanocomposite hydrogels formed through chemical networks

Nanocomposite hydrogels can be produced by the reactions between functional groups of polymers and crosslinking in the matrix of the hydrogels via thiol-Michael addition reaction, amine-epoxy addition, or/and amine-carboxylic acid condensation.

To achieve efficient combinatorial therapy through only one intervention, a sequence of two release kinetics from nanocarriers embedded in hydrogels can be programmed using nanocarriers of different sizes and/or different compositions. A hydrogel was formed by a Michael addition reaction between hyaluronic acid modified with double bonds and poly(ethylene glycol) terminated with thiol groups [187]. Vascular endothelial growth factor (VEGF) was loaded in poly(lactic-*co*-glycolic acid) (PLGA) porous microspheres for continuous angiogenesis induction, while 6-bromoindirubin-3′-oxime (BIO), a glycogen synthase kinase 3 beta inhibitor, was loaded in Pluronic 127 (PF127) nanoparticles for inhibiting the inflammatory response and decrease cell apoptosis. Due to the small size and water solubility of the PF127 nanoparticles, BIO was quickly released (80% in 3 days), whereas 50% of VEGF was released from the microspheres after 15 days through the degradation of PLGA, enabling the promotion of angiogenesis in the later stage of ischemic stroke.

Mesoporous silica nanoparticles and silver nanoparticles were incorporated into networks formed by the reaction between poly (ethylene glycol) diglycidyl ether and a poly(amidoamine) G3 dendrimer (amine-epoxy reaction) [188]. The hydrophilic isoniazid was

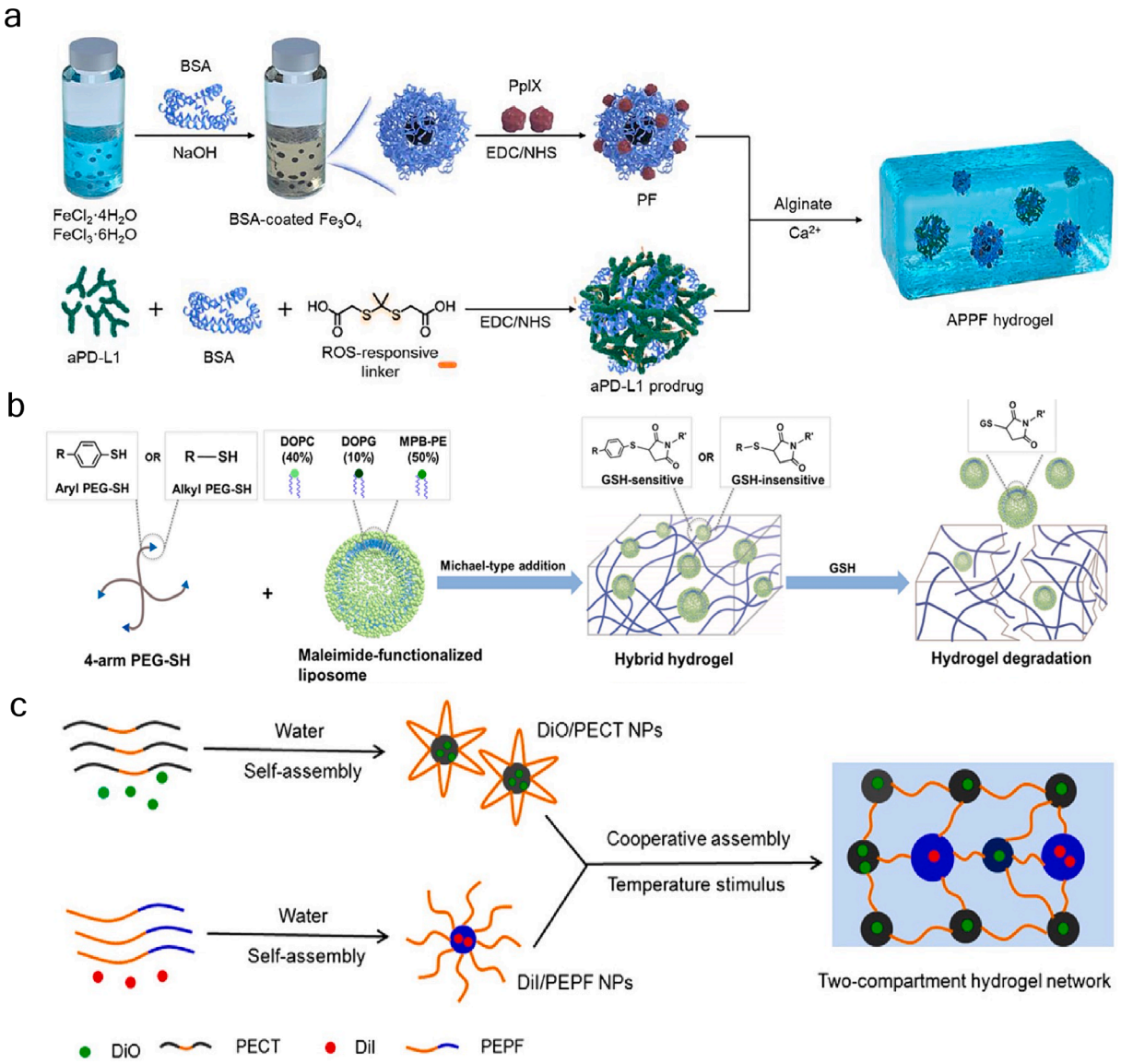

Figure 3. Representative systems for incorporating nanoparticles into hydrogels through a) physical interactions between nanoparticles and hydrogels. Adapted with permission from [184] Copyright (2022) Elsevier. b) chemical reactions between nanoparticles and hydrogels. Reproduced with permission from [185] Copyright (2016) American Chemical Society, and c) chemical reactions between nanoparticles. Adapted with permission from [186] Copyright (2023) Elsevier.

loaded into the PEG network, whereas the hydrophobic rifampicin was encapsulated in the silica particles. The nanocomposite hydrogel provided a burst release of isoniazid (up to 50% after 4 h of release assay), related to the swelling kinetics of the hydrogel and diffusion of isoniazid. The prolonged release of rifampicin (68% after 9 days) was due to double barriers created by the silica nanoparticles and the dendritic networks of the hydrogel.

Gelatin hydrogels can simply be formed by a temperature-induced gelation process or by the covalent crosslinking of gelatin chains with the transglutaminase enzyme [189]. Highly porous and interconnected structures were observed by electron microscopy after introducing poly (3-hydroxybutyrate) polymeric nanoparticles into the gelatin hydrogels. The water could be absorbed or expelled from porous structures by convection, which is a faster process than diffusion. Therefore, 90% of naproxen sodium was released from the gelatin matrix in 3 days, while 40% of curcumin was released from the nanoparticles inside the gel.

The combination of three complementary factors in one injection is expected to treat diseases more effectively than single-agent therapies. Tissue inhibitor of metalloproteinases-3 (TIMP-3) was loaded in a fibrin gel for signaling in the initial phase of the treatment, while basic fibroblast growth factor (FGF-2) and stromal cell-derived factor 1-alpha (SDF-1a) were encapsulated in heparin-based coacervates [190]. Then, the coacervates were distributed within the fibrin gel to provide a treatment of myocardial infarction over a long period. 90% of TIMP-3 was released within 1 week, while a longer sustained release for FGF-2 and SDF-1a was observed over 6 weeks (55% and 48% total release, respectively). The contractility of rat hearts treated with nanocomposite hydrogels was stabilized after the first week. Furthermore, the hearts of treated rats displayed reduced ventricular dilation, inflammation, and extracellular matrix degradation compared to rat hearts treated with free protein or buffer saline solutions.

3.1.2. Nanocomposite hydrogels formed through physical networks

The nanocomposite hydrogels are formed by physical networks of polymeric chains through protein interactions, such as the interaction between amino acids of microfibril networks for silk hydrogels [193], or supramolecular complexations, such as the interaction between α-cyclodextrin units and linear poly(ethylene glycol) chains [191,192]. Another approach is the crosslinking network between two types of polymer chains on the surface of NPs (particle-particle crosslinking)

Table 1
Composition and reaction of formation of non-responsive nanocomposite hydrogels.

Method	Hydrogel matrix			Nanocarriers		[Ref]
	Reaction	Materials	Payloads	Materials	Payloads	
Chemical crosslinking	Michael addition	Hyaluronic acid modified with methacrylate groups/poly(ethylene glycol) modified with thiol groups	-	Poly(lactic-*co*-glycolic acid) microspheres/Pluronic NPs	Vascular endothelial growth factor/bromoindirubin-3'-oxime	[187]
	Amine-epoxy	Poly(ethylene glycol) diglycidyl ether/poly(amido)amine dendrimer	Isoniazid	Silica NPs/Silver NPs	Rifampicin	[188]
	Protein crosslinking	Gelatin/trans-glutaminase	Naproxen sodium	Poly(3-R-hydroxybutyrate) NPs	Curcumin	[189]
		Fibrinogen/thrombin	Tissue inhibitor	Heparin coacervates	Fibroblast growth factor/ stromal cell-derived factor	[190]
Physical crosslinking	Host-guest interaction	α-cyclodextrin/poly(ethylene glycol)	-	Adjuvant CpG NPs	Doxorubicin/adjuvant CpG	[191]
			CD47 antibody	Bovine serum albumin NPs	Apatinib/adjuvant CpG	[192]
	Hydrophobic interaction	PEGylated fluorocarbon NPs/ PEGylated hydrocarbon NPs	-	PEGylated fluorocarbon NPs/PEGylated hydrocarbon NPs	Fluorescence donor and receptor	[186]
Chemical & physical crosslinking	Supramolecular assembly &radical polymerization	Aromatic of gelatin/acrylate-β cyclodextrin/acrylate phosphonate	-	MgFe nanolayer	Mg^{2+}Adenosine	[182]

through hydrophobic interaction [186]. The NPs with incompatible cores cooperatively self-assembled and transformed into a semi-solid multicompartment hydrogel. Fluorocarbon chains with strong hydrophobicity on the nanoparticle surface facilitated hydrophobic interaction and bridging between nanoparticles, leading to the aggregation of microstructure for gelation. Drugs encapsulated in nanoparticles display release kinetics showed more sustained release compared to those in the hydrogel matrix due to the low water solubility of drugs and the specific affinity formed by the NPs.

3.1.3. *Nanocomposite hydrogels formed through a combination of chemical and physical networks*

Gelatin hydrogel was synthesized through host-guest complexation between the aromatic residues of gelatin (tyrosine, tryptophan, and phenylalanine units) and acrylate-β-cyclodextrin to form a physical network, followed by and the polymerization of the acrylate derivative for building a chemical network [182]. Adenosine was loaded between the layers of MgFe hydroxide nanohybrid by electrostatic interaction. A low release of adenosine (< 20%) was observed after 28 days due to the strong interactions between adenosine and the MgFe layer. Mg^{2+} and Fe^{3+} ions were released from the MgFe nanohybrid, reaching a concentration of 1-3 mM. The complementary release of adenosine and Mg^{2+} ions induced high adenosine A2b receptor expression, promoting osteogenic differentiation of the treated human mesenchymal stem cells. Then, the nanohybrids and stem cells were embedded in the gelatin hydrogel to promote the healing of rat bones. Dual sequential delivery of adenosine and Mg^{2+} ions and stem cells from the hydrogel facilitated the formation of newly formed bone tissue, which displayed calcification, mature tissue morphology, and vascularization similar to native bone.

Nanocarrier dispersion embedded in hydrogels is either lyophobic (hydrophobic) or lyophilic (hydrophilic). In the latter case, the nanocarriers are readily dispersable in the hydrogel matrix. For the dispersion of hydrophobic colloids in hydrogels, the colloids typically need to be stabilized with amphiphilic molecules. Recently, a method was developed for dispersing nanocarriers in hydrogels. Emulsions, nanoparticles, and nanocapsules were electrospun to fabricate composite nanofibers [194-196]. The fibers can also be spun directly in hydrogel's precursors and were dissolved rapidly, releasing nanocarriers well dispersed in the formed hydrogel [197].

3.2. *Single-responsive nanocomposite hydrogels*

The release of drugs from responsive hydrogels is controlled by changing the structure of the hydrogel in response to changes in the surrounding environment, such as changes in pH, ionic strength, temperature, or light irradiation [54]. The stimulus-responsive property can be imparted to the hydrogel matrix, nanocarriers, or both, leading to the release of multiple drugs on-demand (Figure 4). The functions and formation methods of single-responsive nanocomposite hydrogels are listed in Table 2.

3.2.1. *pH-responsive nanocomposite hydrogels*

Acid-responsive nanocomposite hydrogels can be achieved by forming acid-cleavable bonds. Oxidized polysaccharides containing carbonyl groups were reacted with the amine groups of chitosan [198] or gelatin methacryloyl [183] to form imine bonds, which can be cleaved under acidic conditions. The formation of double-crosslinking for these nanocomposite hydrogels was achieved by catechol-catechol adducts formed between oxidized dopamine and polymerized gelatin methacrylate, respectively, leading to hydrogels with excellent mechanical properties. The drugs embedded in the nanocomposite hydrogels displayed an acid-responsive release even though they were loaded in different positions in the nanoparticles or the hydrogels matrix.

The complexation of a drug with cations is another strategy to achieve an acid-responsive release from nanocomposite hydrogels. Tetracycline, a hydrophilic antibiotic, was complexed with Ca^{2+}, used as a counterion, and an oleate anion, used as a co-negative charge molecule, to form a hydrophobic complex that was then encapsulated in silica nanocapsules [199]. A pH of ~5 facilitated the dissociation of complexes, leading to the release of tetracycline in the inflammation stage of wound healing. Moreover, another hydrophilic antibiotic was loaded in the shell of silica nanocapsules, providing an initial burst release driven by diffusion at the initial stage of wound healing. The pH-responsive nanocapsules loading dual drugs were embedded in a hydrogel so that the nanocomposite hydrogel displayed a pH-responsive property and could be used to efficiently eliminate bacteria in wounds. In another study, pH-responsive networks were generated in a nanocomposite hydrogel via a Schiff base reaction between aldehyde polysaccharide and poly(L-lysine) grafted human-like collagen [200]. Then, coordination polymer nanoparticles formed by self-assembly of curcumin and Fe^{3+} were incorporated in a hydrogel. The complex nanoparticles were pH-responsive and displayed abundant dynamic crosslinking sites of coordinatively unsaturated Fe(III) on their surfaces, which rapidly interacted with carboxylic acid groups in the polysaccharide, forming the hydrogel network. Thus, a self-healing property was achieved by the fast crosslinking of the unsaturated Fe^{3+} on particles and carboxylic acids in the hydrogel matrix after mechanical damage.

Nanocomposite hydrogels were fabricated by the Michael addition of

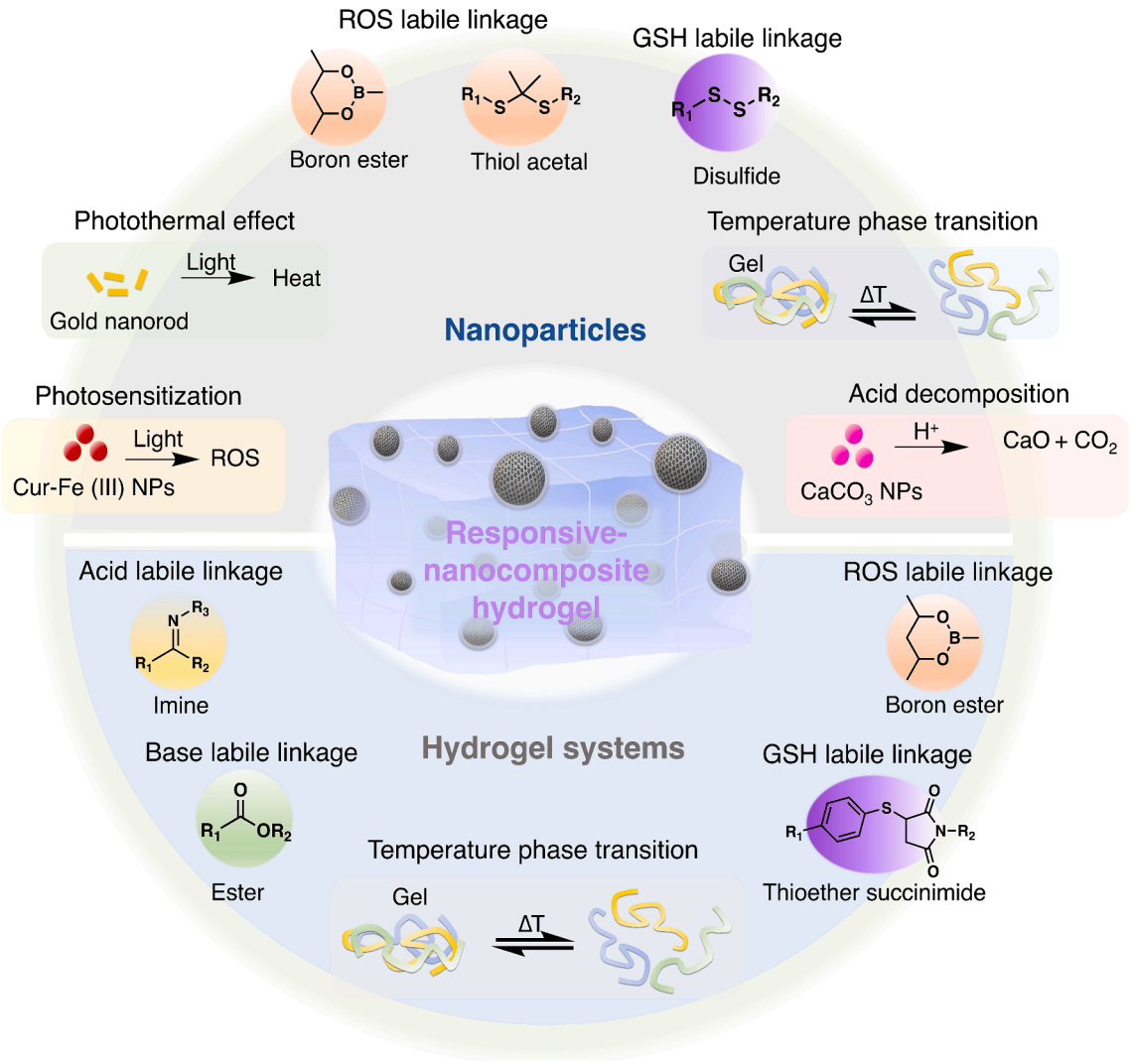

Figure 4. Structure of functional linkages cleaved by acids, bases, glutathione (GSH), reactive oxygen species (ROS), light, or temperature in nanocomposite hydrogels.

Table 2
Function, composition, and reaction of formation of single-responsive nanocomposite hydrogels.

Stimuli	Hydrogel matrix			Nanocarriers			[Ref]
	Sensitive bond	Materials	Payloads	Responsive part	Materials	Payloads	
Acid	Imine	Dextran modified with aldehyde/chitosan modified with dopamine	Deferoxamine	-	Silver NPs	Ag^{+}	[198]
		Alginate modified with aldehyde/gelatin methacryloyl	Gentamicin	-	Silica NPs	Phenamil	[183]
		Hyaluronic acid modified with aldehyde/poly-lysine-	-	Coordination polymer NPs	Iron NPs	$CurcuminFe^{3+}$	[200]
	-	Poly(acrylamide)	-	Hydrophobic ion pairing	Silica nanocapsules	Tetracycline/amoxicillin	[199]
Base	Ester bond	Poly(ethylene glycol) modified with thiol/pullulan nanogel	-	-	Pullulan nanogel/liposomes	Polysaccharide/lipid	[201]
GSH	Thioether succini-mide	Poly(ethylene glycol) modified with arylthiol/unsaturated lipids	Cytochrome c	-	Liposomes	Doxorubicin	[185]

acryloyl groups present in pullulan nanogels functionalized with acryloyl groups and cholesterol with thiol groups in pentaerythritol tetra (mercaptoethyl) poly(oxyethylene), used as crosslinker [201]. The nanogels contained ester bonds, which could be degraded under certain conditions. The nanogels were adhered to the surface of liposomes by hydrophobic interaction. Then, the nanogel and nanogel-coated liposomes were mixed with the thiol-functionalized polymer to form a nanocomposite hydrogel. The release rate of liposomes at pH 8.0 was larger than that at pH 7.4 due to the hydrolysis of the ester bond under basic conditions. Moreover, the nanogels were released first, followed by the release of nanogel-coated liposomes due to the smaller number of crosslinking sites in the nanogels compared to liposome complexes.

3.2.2. Glutathione (GSH)-responsive nanocomposite hydrogels

The tumor microenvironment displays a higher concentration of GSH (2-10 mM) compared to the extracellular environment of normal tissue such as blood plasma, interstitial fluid, and lymph (2 to 20 μM) [202]. Indeed, GSH is encountered at high concentrations in the intracellular compartment (0.5-15 mM) [203] and cancer cells [202,204,205], whereas it is present only at low concentrations in the extracellular environment of normal tissue (1-10 μM).

The release of payloads from the hydrogels in the presence of GSH can be achieved by cleaving labile bonds in the polymeric network of the hydrogel by GSH via thiol-exchange reactions. GSH-sensitive networks were formed by the reaction of arylthiol groups in functionalized poly (ethylene glycol) and maleimide groups present in lipids on liposomes via Michael addition [185]. The degradation of arylthioether succinimide was achieved via a thiol-exchange reaction in the presence of GSH. In the presence of GSH, the release of drugs loaded in liposomes was dominated by the erosion-mediated release of liposomes from the hydrogel surface. However, the release of hydrophilic drug dispersed in the hydrogel matrix followed a Fickian diffusion, with almost 100% release within 6 days related to the degradation duration of the hydrogel.

3.2.3. Light-responsive nanocomposite hydrogel

Photosensitive and photothermal nanomaterials such as gold nanoparticles, metal-organic framework nanoparticles, and carbon nanomaterials have been widely applied for light-stimulated photothermal therapy (PTT) and photodynamic therapy (PDT) to generate reactive oxygen species (ROS) or high temperatures upon near-infrared (NIR) light [206-209]. Light-stimulated treatments for combatting cancer or bacterial infections are non-invasive and allow deep-tissue penetration [210,211]. High therapeutic effects against bacterial infection or cancer were demonstrated through the combination of nanoparticles and hydrogels.

Supraparticles of liquid metal nanoparticles and zeolitic-imidazolate frameworks were incorporated in an alginate hydrogel [212]. The metal-organic frameworks allowed a sustainable release of zinc ions and methylimidazole for killing bacteria, while the metal droplets generated heat upon NIR irradiation. Thus, the composite hydrogel showed excellent therapeutic efficacy in tumor and skin infections.

Photothermal-sensitive sodium nitroprusside, platinum, and gold nanoparticles were loaded in porphyrin-organic frameworks embedded in gelatin hydrogel to form a multifunctional injectable hydrogel [213]. The porphyrin-organic frameworks generated ROS upon light irradiation, directly killing bacteria by disrupting their DNA and cell membranes [214]. The Pt-modified nanoplatform promoted the continuous decomposition of endogenous H_2O_2 into O_2, thus enhancing the PDT effect under hypoxia, while Au NPs induced hyperthermia by photothermal effects. Therefore, the hydrogel-produced heat under NIR irradiation also generated reactive oxygen species, triggering NO release from sodium nitroprusside, contributing to a 99.9% reduction in the bacterial burden on wounds.

3.3. Dual-responsive nanocomposite hydrogels

Specific applications such as swelling or degradation are inefficient in releasing payloads and achieving effective treatments. Therefore, nanocomposite hydrogels have been programmed to release payloads in response to several stimuli, providing faster responsive systems (Table 3). Moreover, the multi-responsive hydrogels enhance their potential for treating cancer, gliomas, and diabetic wounds via the smart controlled release.

3.3.1. Intrinsic dual-responsive nanocomposite hydrogels

Intrinsically responsive hydrogels are formed by introducing stimuli-labile bonds in the polymer matrix of the hydrogel. This causes degradation or changes in the hydrogel's structure after activation by stimuli, leading to the release of payloads entrapped in the hydrogels. Gelatin modified with 3-carboxy-phenylboronic acid was crosslinked with poly (vinyl alcohol) to a nanocomposite hydrogel [215]. The modified gelatin contains boronic moieties, which could interact with hydroxyl groups in poly(vinyl alcohol), producing a boronic ester bond. The tumor microenvironment has a high content of reactive oxygen species (ROS) compared to normal tissue. Dissociation of the boronic ester bond in the presence of ROS and acidic conditions induced the release of payloads in the tumor microenvironment by the degradation of the nanocomposite hydrogel. Indeed, silver nanoclusters conjugated with vancomycin and pH-sensitive micelles loaded with nimesulide were released from the hydrogel after its degradation in the presence of acid and ROS [215]. This led to the inhibition of bacterial infection and reduced the inflammatory response of an infected diabetic wound.

Another study also used boronic ester as a pH and ROS-responsive bond to form a hydrogel by crosslinking poly(vinyl alcohol) with molecules containing boronic acid groups. A hydrophilic anticancer drug and pH-sensitive calcium carbonate nanoparticles loaded with antibodies were simultaneously introduced in the pH- and ROS-responsive hydrogel [216]. The calcium nanoparticles were degraded in acidic environments, generating carbon dioxide and the sustained release of the antibodies. Combination therapy enabled by the nanocomposite hydrogel induced the inhibition of tumor growth and increased survival time of melanoma-bearing mice.

3.3.2. Extrinsic dual-responsive nanocomposite hydrogels

Two types of NPs containing responsive bonds are dispersed in a hydrogel to form an extrinsic dual-responsive nanocomposite hydrogel.

Table 3
Function, composition, and reaction of formation of the dual-responsive nanocomposite.

Stimuli	Hydrogel matrix			Nanocarriers			[Ref]
	Sensitive bond	Materials	Payloads	Responsivity	Materials	Payloads	
Acid and ROS	Boronic ester(acid and ROS)	Gelatin modified with phenylboronic acid/poly (vinyl alcohol)	-	-	Silver NPs/ micelles	Ag^+Vancomycin/ Nimesulide	[215]
		Crosslinker containing phenylboronic acid/poly (vinyl alcohol)	Zebularine	Acid decomposition (acid)	$CaCO_3$ NPs	Anti-PD 1	[216]
ROS and light	-	AlginateCa^{2+}	-	Photosensitization (light) reduction of thioacetal bond (ROS)	Fe_3O_4 NPs/ antibody NPs	Porphyrin IX/programmed death ligand 1 antibody	[184]
Temperature and light	Temperature phase transition	Poly (*N*-isopropyl acrylamide)	Curcumin	Gelation phase transition (temperature)/photothermal effect (light)	NIPAM NPs/ Au nanorod	Doxorubicin	[217]
Temperature and ROS		Gelatin/chitosanβ-glycerophosphate	-	Hydrolysis of phenylboronic ester (ROS)	PLGA NPs	Bis(2-chloroethyl) nitrosourea/Temozolomide	[218]

ROS-responsive nanoparticles were formed by the reaction of amine groups in bovine serum albumin (BSA) and carboxylic acid groups of 2,2'-[propane-2,2-diylbis(thio)]diacetic acid, which was used as a ROS-responsive crosslinker [184]. The programmed death ligand 1 antibody (PDL1, antitumor drug) was loaded in the NPs, and the ROS-responsive release of the drug was achieved by the degradation of the thioacetal groups in the crosslinker. In addition, light-responsive protoporphyrin IX, a photosensitizer, was conjugated to iron oxide nanoparticles modified with BSA via condensation of amine groups of BSA and carboxylic acid groups in protoporphyrin IX to generate ROS upon exposure to light.

Then, the ROS-responsive NPs and light-responsive iron oxide nanoparticles were embedded in an alginate hydrogel to kill cancer cells. The combination of antitumor drugs, released from ROS-responsive nanoparticles, and a large amount of ROS produced from the light-responsive protoporphyrin led to the inhibition of the growth of primary and distant tumors and the effective prevention of lung and liver metastases.

3.3.3. Combination of intrinsic and extrinsic dual-responsive nanocomposite hydrogels

Temperature-responsive hydrogels were fabricated using poly(*N*-isopropyl acrylamide) (PNIPAM), gelatin, poly(*N*-acryloyl glycinamide), or poly(lactic acid-*co*-glycolic acid)-*block*-poly(ethylene glycol)-*block*-poly(lactic acid-*co*-glycolic acid) (PLGA-PEG-PLGA). Changes in the network structure of the polymer upon a specific temperature regulated the gelation phase transition, inducing the release of the payload under desired circumstances. The excess vinyl moieties in PNIPAM nanogels introduced by the crosslinker were used further as crosslinker during the polymerization of NIPAM in water so that hydrogels containing nanogels were formed [217]. To control the phase transition of the PNIPAM hydrogel, gold nanorods were introduced in the nanocomposite hydrogel as heat generators triggered by near-infrared (NIR) light via a photothermal effect. The release of drugs encapsulated in nanogels and the polymer matrix was increased by increasing temperature and upon NIR light irradiation.

A combination of chitosan, gelatin, and β-glycerophosphate was used to tune the phase transition temperature of temperature-responsive hydrogels [218]. Besides the temperature-induced formation of triple-helices in gelatin, crosslinking provided by electrostatic interactions between β-glycerophosphate (anionic) and chitosan (cationic) also facilitated a sol-gel transition at physiological pH and temperature. Therefore, the gelation phase transition temperature could be tuned from 15 °C to 40 °C by changing the composition of the hydrogel. Moreover, ROS-sensitive nanoparticles containing nitrosourea and temozolomide were synthesized by covalently linking phenyl-boronic acid groups of diammonium molecules with hydroxyl groups in PLGA. The nanoparticles were subsequently embedded in the temperature-responsive hydrogel containing chitosan, gelatin, and β-glycerophosphate. The nanocomposite hydrogel displayed a synergistic effect of drugs, revealed by measured high apoptosis of cancer cells.

3.3.4. Multi-responsive nanocomposite hydrogels

Triple-responsive nanocomposite hydrogels were formed by incorporating several types of responsive nanoparticles. Thus, pH-responsive calcium carbonate nanoparticles ($CaCO_3$) and redox-responsive mesoporous silica nanoparticles were incorporated into a temperature-responsive PLGA-PEG-PLGA hydrogel [219]. $CaCO_3$ nanoparticles loaded with the immunoadjuvant imiquimod were degraded in acidic conditions, while silica nanoparticles loaded with paclitaxel were modified with peptide-based proteolysis-targeting chimeras for cancer therapy via a disulfide bond, which was cleaved in an environment abundant with GSH, leading to the release of the peptide and paclitaxel. The combination of immunoadjuvant, paclitaxel, and peptide with specific triggers of temperature, GSH concentration, and pH suppressed both the growth and metastasis of mouse squamous cell carcinoma.

Another interesting approach for fabricating a triple-responsive nanocomposite hydrogel is to create a labile bond between nanoparticles and hydrogels. Boronic ester groups, which are pH- and ROS-responsive, were formed by the reaction between phenylboronic acid moieties on the shell of polymeric nanoparticles and aromatic diols of a copolymer forming the hydrogel matrix, leading to a dual-responsive release of payloads and NPs [220]. Moreover, bis(2-methacryloyl) oxyethyl disulfide was applied as a crosslinker in the NPs for giving a GSH-responsive property due to the cleavage of disulfide bonds by GSH. Combretastatin-A4 phosphate and doxorubicin were loaded in the pH- and ROS-responsive hydrogel matrix and the GSH-responsive nanoparticles, respectively, for rapid and sustained release in acidic conditions and presence of GSH for antiangiogenesis and anticancer combination therapy.

4. Bioadhesive properties of dynamic hydrogels

Injectability is one of the rheological properties of dynamic hydrogels. It refers to the ability of the hydrogel to be delivered through a needle or catheter into a specific location in the body. This property is particularly important for biomedical applications, as it allows for minimally invasive procedures and targeted delivery of therapeutic agents. These applications involve prolonged contact with tissues and body fluids. Hence, the hydrogel must be held at the application site for a certain period to provide a therapeutic effect. Therefore, in addition to adequate rheological properties and biocompatibility, hydrogels must have appropriate bioadhesion, including mucosal adhesion and/or cell adhesion. Under physiological conditions, adhesion of the materials used to wet surfaces is required. However, achieving underwater adhesion is difficult due to the formation of hydration overlays that are present on surfaces under wet conditions or the effect of swelling stress [221,222]. The phenomenon of mucoadhesion is complex due to the complexity of tissue surfaces and differences between target tissues. Multiple theories have been developed to describe mucoadhesion, including diffusion theory [223], electronic theory [224], adsorption theory [225], wetting theory [226,227] and fracture theory [228,229]. The process of polymer-to-mucous adhesion is recognized to consist of three steps: 1. wetting and swelling of the polymer; 2. permeation of the chains and formation of entanglements between the polymer and mucin chains, which leads to physical anchoring of the two together; 3. formation of chemical interactions between the polymer and mucin chains [227], which include ionic bonds, van der Waals interactions, hydrogen bonds or/and covalent bonds. To attain proper adhesion to the mucus, we require a combination of proper flexibility/mobility of the polymer chains in the pH and ionic strength of the application site, along with the presence of active groups that can interact with the mucous components.

The mobility of polymer chains in hydrogels strongly depends on the cross-linking degree of the polymer matrix. In the case of dynamically cross-linked networks, the kinetics of cross-link exchange also affect the diffusivity of polymer chains in the matrix [230]. In consequence, the degree of cross-linking has a significant impact on the mechanical performance of polymer gels. In addition, the degree of swelling, which also influences mucoadhesion, is strictly correlated with a cross-linking degree. Finally, the rate of gel degradation is correlated with the number of cross-links. Therefore, the network parameters of a mucoadhesive hydrogel must be carefully adjusted for a given application. The formation of chemical interaction between polymer and mucin is related to the functional groups present in the polymer structure, including hydroxyl and carboxyl, groups that can form hydrogen bonds [231], ammonium, carboxylate, and sulfonate groups that can interact ionically[232], as well as thiol [233], acrylate [234] and catechol moieties can form covalent bonds with mucosal glycoproteins (Figure 5).

4.1. Design of bioadhesive dynamic hydrogels

Incorporation of catechol moieties into the hydrogel network is a

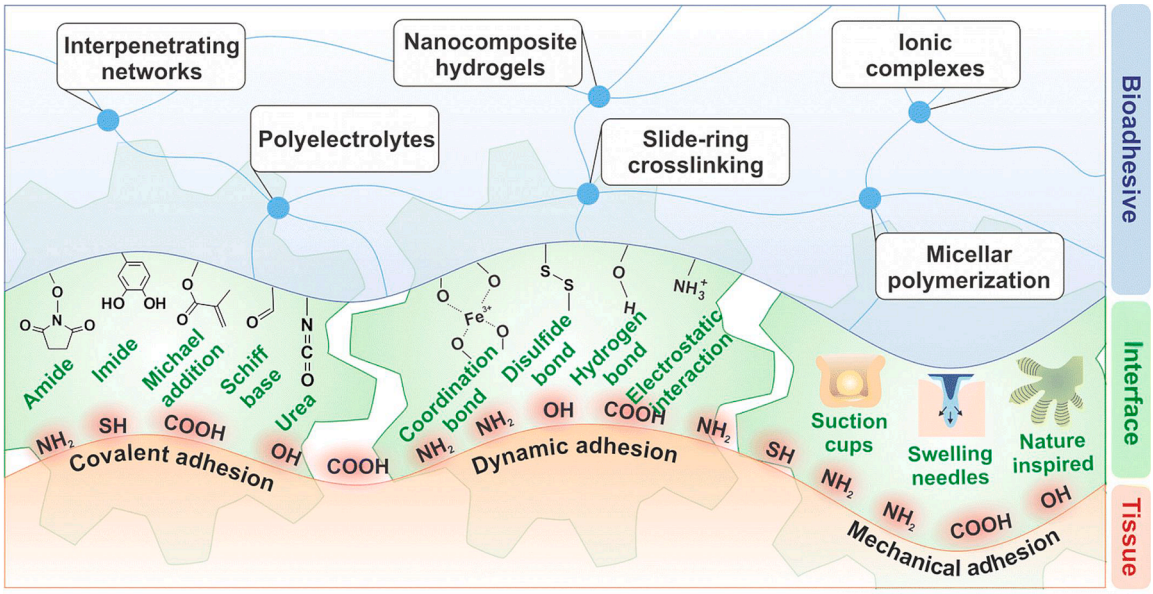

Figure 5. An overview of the material design roadmap for tough bioadhesives. Development of bioadhesive materials involves the design for cohesion, where a combination of the polymer backbone and crosslinking strategy is selected to ensure mechanical durability in a tough hydrogel, and design for bioadhesion, where a mixture of covalent and dynamic interactions, as well as mechanical interlocks, are incorporated into the material design. Reproduced from Ref. [235] with permission from Royal Society of Chemistry 2022.

common strategy for endowing them the adhesion properties at wet conditions. It originates from proteins secreted by marine mussels displaying underwater adhesive properties on different surfaces such as rocks, reefs, and boats. These mussel foot proteins typically contain a high percentage of a post-translationally modified amino acid, L-3,4-dihydroxyphenylalanine (DOPA) [236], which is responsible for interfacial binding and intermolecular cross-linking mechanisms.

Polysaccharides possess numerous functional groups that can be modified with catechol groups to form dynamic bioadhesive hydrogels via the covalent immobilization of dopamine. Guo *et al.* obtained hydrogel with enhanced adhesion by replacing guar gum with catechol-modified oxidized hyaluronic acid (OHAdop) in the network composed of glycol chitosan (GC)/borax [237]. The presence of OHAdop in the hydrogel structure assured the formation of interactions between

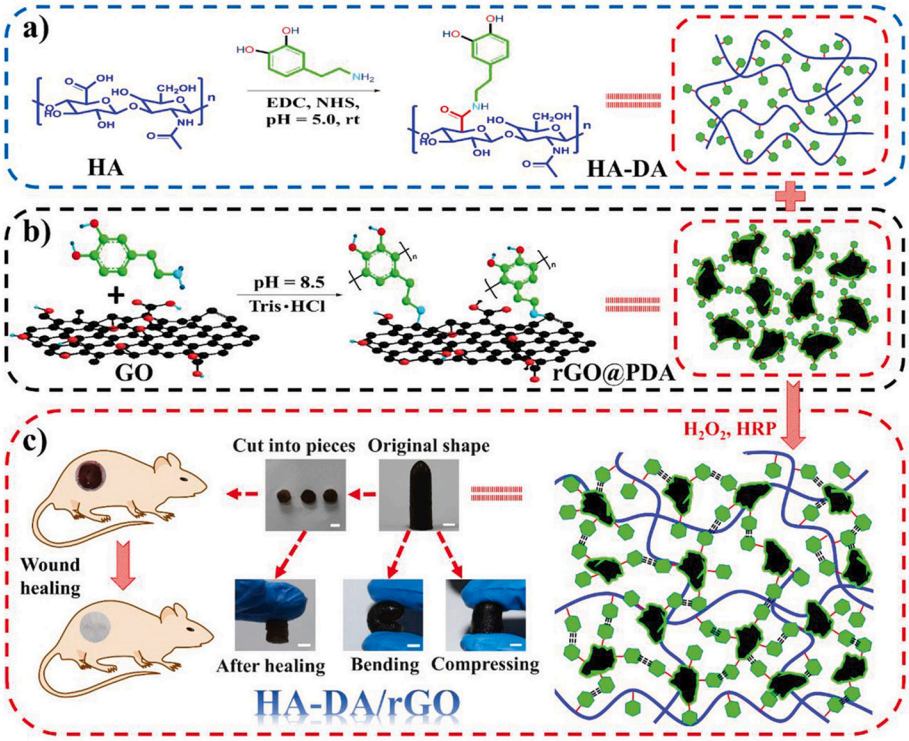

Figure 6. Diagrammatic sketch of HA-DA/rGO hydrogel preparation. (a) Preparation scheme of HA-DA polymer and (b) rGO@PDA, (c) scheme of HA-DA/rGO hydrogel and the original, bending, compressing, self-healing, and the application in wound healing. Scale bar: 5 mm. The figure is reprinted from Ref. [242] with permission from Wiley-VCH 2019.

catechol groups and the amine, imidazole, and thiol groups present on pig skin [238]. The addition of $NaIO_4$ caused catechol moieties oxidation into quinone groups, which were prone to intermolecular cross-linking, promoting the adhesion of the hydrogel to pig skin. The usage of both OHAdop and GG for the network construction resulted in the formation of hydrogel displaying better adhesive properties, as the network construction was based beside dynamic covalent bonds such as imine bonds between OHAdop and GC, and borate/didiol bonds between GG and borax, and also non-specific interactions such as hydrogen bonding between catechol moieties of OHAdop and hydroxyl groups of guar gum. In addition, the formation of composite hydrogel via network enrichment with polydopamine, PDA nanoparticles equipped with quinone groups prone to the formation of additional cross-links via Schiff base reactions with primary amines in glycol chitosan caused further improvement of adhesive properties. Such obtained hydrogel displayed adhesive properties to the finger skin surface and pig skin underwater, and was adapted to the movement under bent and twisted states.

Hyaluronic acid (HA), a polysaccharide, which is naturally produced in the wound during its repair process [239-241], is a natural candidate as a polymer for building wound dressing hydrogels. However, HA shows poor adhesion to the wound site. To overcome this shortcoming, Liang et al. prepared composite hyaluronic acid/graphene oxide (HA/GO) hydrogel (Figure 6) [242]. Firstly, to increase mucoadhesion, HA was modified with dopamine, which endowed hydrogel with antioxidant ability besides promoting bioadhesion. The gel was filled with graphene oxide covered with polydopamine (pDA), facilitating GO water dispersity. Dopamine can be a reducing agent for GO leading to its improved conductivity. The network was obtained via cross-linking by an oxidative coupling using H_2O_2 and horseradish peroxidase. Prepared hydrogels were injectable and self-healable, probably due to physical bonds between pDA-covered GO and DA-modified HA, including hydrogen bonds and π–π stacking [243]. Proper rheological properties along with good mucoadhesion (up to 6.3 ± 1.2 kPa in the lap-shear test) allowed the hydrogel to be easily applied as a hemostatic agent to the wound. The hydrogel also showed good tensile strength (strain at break up to 200%, stress at break up to 65.1 kPa), which was on par with human skin [244]. The reported GO-reinforced hydrogel showed high levels of L929 cell proliferation and significantly higher wound healing rates compared to Tagederm. The authors demonstrated that GO addition increased granulation tissue thickness, collagen deposition and promoted regeneration of hair follicles and blood vessels.

Besides polysaccharides, other natural macromolecules can be modified with catechol groups. For example, ECM mimetic hydrogel was constructed of protein-based dopamine-decorated methacrylated gelatin (GelMA-DA), phenylboronic acid-tethered methacrylated chondroitin sulfate (CSMA-PBA) and 4-arm PEG thiol (PEG-4SH). The reported hydrogel was a dual network system. In addition to boronate ester cross-links formed in the reaction of phenylboronic acid with catechol, thioether bonds were formed via Michael's addition of PEG-4SH to methacrylate groups. The hydrogel was formed in vivo conditions after injection into the backs of a nude mouse [245]. The hydrogel tightly adhered to the surrounding tissues, which was ascribed to numerous interactions between abundant bioactive groups and complex microstructure on the tissue. The H&E staining experiment confirmed that the hydrogel does not induce changes in the morphology of related tissues.

Besides nature-derived polymers, functional synthetic polymers can also be modified with catechol groups. For example, catechol-modified ε-poly-L-lysine (PL-Cat) was applied for the construction of a dual network. Amine groups of lysine formed imine bonds with aldehyde oxidized dextran (ODex) moieties, while catechol groups were engaged in coordinated cross-links with Fe^{3+} ions. The obtained dynamic hydrogels displayed repeatable adhesion [246]. Generally, it is known that catechol and aldehyde groups present in applied copolymers improve the tissue adhesion capacity via multiple non-covalent and covalent bonds [247,248]. PL-Cat/Fe^{3+} solution and ODex solution were premixed and then subcutaneously injected into the backs of the rats using a 20G needle. In situ formed PL-Cat/Fe^{3+}/ODex hydrogel was able to efficiently adhere to the wet tissue. The wet tissue adhesion capacity was ascribed to the synergistic effect of catechol groups and cationic lysine residues [249]. The double cross-linked hydrogel showed no cytotoxicity against murine fibroblast cells (L 929) and mouse embryonic fibroblast (NIH 3T3). The hydrogel was designed to wound dressing for wound closure and healing, the effectiveness of which has been proven in *in vivo* tests. The hydrogel exhibited repeatability in adhesion, as it could be destroyed upon the application of external force, and its structure could be reconstructed by adding a drop of water and reassembling the gel components.

Underwater adhesive hydrogels based on 12 wt% aqueous solutions of catechol-modified poly(L-lysine), Cat-PLL (P80D20) or catechol- and glucose-modified poly(L-lysine), (R-Gel-2 and (R-Gel-3, respectively), Cat-PLL (R-Gel-1) differing the degree of grafted glucose moieties (P60G20D20, P40G40D20) cross-linked with Fe^{3+} via Fe^{3+}-catechol complexes also displayed wet tissue adhesion [250]. The adhesion was dictated by covalent bonds between thiol and amine groups of the tissue and catechol moieties as a result of Michael addition reaction and non-covalent interactions such as hydrogen bonding, π-π stacking, and π-cation interactions. The strength of adhesion determined based on a lap-shear method varied between 83.9 kPa and 70.9 kPa. The presence of numerous catechol moieties in the hydrogel assured the formation of both covalent and non-covalent bonds with the tissue. The oxidation of catechol moieties via horseradish oxidase resulted in diminished interfacial hydrogel adhesion, which was an effect of the formation of more stable networks and less mobile catechols. Hydrogels R-Gel-1-3 and oxidized hydrogel displayed better attachment of red blood cells and platelets than the fibrin glue. No effect of glycosylation was observed on the coagulation and the hemostasis. In the case of hydrogels R-Gels-1, 2 and 3, the complete hemostasis was achieved in 30-33 s with a lower blood loss of 9-11 %. Because of their higher adhesive strength and similar blood coagulation performance, these hydrogels are excellent candidates for wound healing and hemostatic effects. For comparison, fibrin glue took 64 s to achieve hemostasis with a severe blood loss of 40 %, which was an effect of both adhesion and blood coagulation properties.

Zhao *et al.* used poly(glycerol sebacate)-co-poly(ethylene glycol)-g-catechol, PEGSD2 with $FeCl_3$ and gelatin (GTU) modified with different weight fractions of ureidopyrimidinone (Upy) motifs varying from 2.5 to 7.5 wt% to the formation of dynamic doubly cross-linked hydrogels of adhesive properties. The network was constructed of catechol-Fe^{3+} coordination cross-links and hydrogen bonding of ureido-pyrimidinone (Upy) moieties [251]. It is noteworthy that with the increase of Upy content, the mechanical properties of synthesized hydrogels increased along with the enhanced cohesive strength, and the stiffness of the network was increased, which weakened the polymer chain flexibility and interactions between the hydrogel and the tissue interface. This behavior resulted in reduced interfacial adhesion capacity [252]. The hydrogel composed of PEGSD2 with gelatin containing 5.0 wt% of Upy content was optimal in the interface adhesion, balanced intrinsic strength, and polymer chain flexibility. Hydrogels based on PEGSD2/GTU5.0 and PEGSD2/GTU7.5 gave satisfying reduced blood clotting index values up to 65 and 56 %, respectively, compared to the blank group. Adhesive hydrogels can adhere to the wound site, sealing it and thus creating a physical barrier to stop bleeding. Using a rabbit ear artery bleeding model in vivo, hemostatic capacity was confirmed for PEGSD2/GTU5.0-based hydrogel, which was ascribed to hemostatic components of gelatin, catechol, and Upy moieties accelerating blood clotting, good skin adhesiveness sealing the bleeding site. Tissue adhesive and hemostatic properties of PEGSD2/GTU5.0 were crucial in skin wound repair and wound closure. This hydrogel displayed a faster wound contraction rate after a 5-day therapy than PEGSD2 and commercially available Tegaderm film. In addition, H&E and toluidine blue staining revealed only very mild inflammatory responses after

hydrogel was implanted over 7 days.

Four-armed poly(ethylene glycol), PEG-D4 ended with dopamine motifs was applied to form injectable composite hydrogels [253]. It was observed that the incorporation of Laponite, a synthetic nanosilicate, into the network caused the increase of cross-linking density of PEG-D4-based hydrogel, along with the increase in the loss modulus as an effect of elevated viscous dissipation properties as a result of reversible catechol-Laponite interactions. The strength of the network increased along with the weight fraction of Laponite. A comparable dependence was observed for adhesion strength. For hydrogels equipped with 1 and 2 wt% of Laponite, the adhesion strength was approximately 6.1 and 7.9 kPa, respectively. Moreover, subcutaneous implantation of hydrogels with and without laponite showed that laponite facilitates cellular infiltration and reduces the foreign-body reaction to the hydrogel.

Another composite dynamic hydrogel displaying conductive and repeatable adhesion to porcine skin (adhesion strength equal to 5.2 kPa) mimicking human skin tissue was constructed of poly(vinyl alcohol), PVA, single-wall carbon nanotube, FSWCNT, and polydopamine, PDA and tetrafunctional borate (borax) were designed in view of wearable human-motion sensors [254]. The network was based on reversible interactions such as hydrogen bonding, π-π stacking, and reversible covalent ester bonds formed between 1,3-diol groups of PVA and borax ions. The adhesion/peel-off test for the hydrogel was performed for three cycles, revealing no obvious loss in adhesion strength. The incorporation of FSWCNT particles, however, did not affect the adhesive ability. Numerous catechol groups present in the hydrogel network were responsible for repeated adhesive properties.

Several hemostatic chitosan-based dressings have been developed and are commercially available, for example, Hemcon, Chitoflex, Celox-A and Syvek Excel. Chitosan, known for its good mucoadhesion, binds to the wound, physically sealing the bleeding wound by forming a plug [255]. The crosslinking strategy is mainly based on electrostatic interactions between the positive charge of protonated amine groups of chitosan and the negative charge of erythrocyte cell membranes. To enhance chitosan performance as a hemostatic agent performance, Pillai *et al.* designed a composite chitosan hydrogel with whitlockite ($Ca_{18}Mg_2(HPO_4)_2(PO_4)_{12}$) nanoparticles [256].

Ca^{2+} ions play a major role in activating coagulation factors [257], Mg^{2+} ions are involved in the blood coagulation cascade [258], while PO_4^{3-} is involved in platelet activation and aggregation [259]. The hydrogel consisting of 2% chitosan and 4% whitlockite nanoparticles, without any additional cross-linking agent, was shown to have better hemostatic properties than commercial Floseal agents. An in vivo study on liver injury showed an over 2-fold decrease in hemostasis time and an approximately 2-fold reduction in blood loss compared to sham control. Authors indicate that developed composite hydrogel might have the ability to control bleeding during critical emergencies.

4.2. Reversible covalent bonds promoting bioadhesion of dynamic hydrogels

Besides the adhesion mechanisms based on catechol interactions, boronate esters formation was also applied. The bioadhesive properties of hydrogel based on alginate enriched with boronic acid moieties were demonstrated [260]. The presence of sialic acid in the mucosa causes the formation of boronate esters between the hydrogel and the tissue generating interfacial tissue-hydrogel interactions. The adhesive strength of the hydrogel was approximately 15 kPa. On the other hand, upon pH increase, the strength attained 22 kPa as an effect of more favorable conditions for boronate ester formation.

Another hydrogel's adhesion mechanism was based on the formation of imine bonds between aldehyde and amine groups is applied to obtain interfacial hydrogel-tissue interactions. Aldehyde-functionalized chondroitin sulfate (CS), gelatin (Gel), and borax were applied to the construction of the hydrogels based on dynamic Schiff base bonds, hydrogen bonding, and boronate-diol ester cross-links [261]. The synthesized hydrogels displayed adhesive properties to porcine skin tissue. Hydrogels tightly adhered to the tissue underwater without any detachment upon stretching, twisting, or water immersion for 24 h. The hydrogels were prepared using sulfate chondroitin oxidized at different degrees, i.e., medium and high degrees of oxidation. The hydrogel adhesion to the porcine tissue was governed by the Schiff base reaction between the free aldehyde groups of oxidized CS and primary amines in the tissue proteins [262,263]. It was observed that the adhesive strength of Gel/CS hydrogels with a medium degree of CS oxidation increased from 8.7 to 21.2 and 24.2 kPa with increasing Gel concentration at a fixed 10% (w/v) CS content. The highest adhesive strength, approximately 31 kPa, was found in the case of hydrogel constructed of 30% (w/v) Gel and CS of a high degree of oxidation. For comparison, the hydrogel composed of a medium degree of oxidation gave the adhesive strength equal to 10.40 kPa. Similarly, the increase of CS aldehyde and borax enhanced the adhesive properties of the resulting hydrogels. For example, the adhesion strength of Gel-CS hydrogels increased from 15.3 to 38.1 kPa upon increasing CS aldehyde concentration from 5 to 15 %. In addition, the presence of numerous functional groups in the polymer components building the hydrogel network, such as -OH, -CONH, and $-NH_2$ with the corresponding components of the tissue surface (-OH and $-NH_2$ functional groups), reinforce the interfacial bonding between the hydrogel and tissue. These hydrogel formulations were promising candidates as surgical sealants adhering tissues with defects that withstand the bursting pressure exerted by body fluids or blood without inducing any side effect in the treated tissue, as revealed in the histological study.

4.3. Stimuli-responsive and bioadhesive dynamic hydrogels

In medical practice, painless and reversible detachment is required when the function of the hydrogel adhesive is fulfilled or when the adhesives inadvertently enter unwanted spaces or require immediate correction for appropriate surgical treatment. Hence, removing hydrogel adhesive on demand is desirable without causing any secondary damage. For example, reversible adhesion is crucial in temporary organ sealing or drug delivery therapies in localized cancer chemotherapies. In the case of the Gel/CS hydrogels, thermally reversible adhesion and local temperature change triggered adhesion, or the hydrogel detachment was observed [261]. At 37 ^oC, the Gel/CS hydrogels adhered tightly to the surface of the finger skin, resulting in the hydrogel chain spreading across and diffusing deeper into the tissue, which increases the interfacial contact area due to low modulus and high polymer mobility. Upon cooling to 20 ^oC, the hydrogel adhesive detached as the effect of the gel hardening resulted from the further formation of interchain Schiff base bonds and hydrogen bonds. Then, the contact between the hydrogel and the tissue surface is weakened.

The removal of the bioadhesive hydrogel triggered by temperature was also demonstrated for hydrogel based on thiol-aldehyde cross-linking using a hyperbranched polymer with thiol groups and benzaldehyde-terminated poly(ethylene glycol), PEG-CHO [264]. The solid-fluid transition was observed at 50 ^oC and was completely reversible by cooling the hydrogel. The adhesive strength of the hydrogel to porcine skin was strictly dependent on PEG-CHO content that ranged from 20 to 50 kPa. Notably, the initial gradual increase of PEG-CHO content increased the adhesion, but an excessive molar fraction of aldehyde groups led to the decrease of both the cohesion and adhesion of the hydrogel. Moreover, an increase in PEG-CHO content in the hydrogels led to an increase in cytotoxicity against L929 cells, which was attributed to the leakage of aldehyde-terminated PEG.

The detachment of dynamic hydrogel triggered with temperature was also shown for lignosulfonate (LS)/polyvinylpyrrolidone (PVP) complex hydrogel obtained via first dissolution of LS at pH 10, and then mixing it with PVP solution and decrease of pH to neutral [265]. The obtained series of hydrogel differing LS content in the range from 3 to 10 wt% at constant PVP concentration (12 wt%) displayed adhesion at body temperature. However, the decrease in temperature to 10 ^oC

resulted in diminished adhesion to a finger and could be easily separated from the skin. The adhesion/removal behavior after 10 adhere/peel off cycles, the adhesion strength of the hydrogel attached to porcine skin remained approximately 90% of the initial value. The hydrogel composed of 7 wt% LS displayed a maximum adhesion strength of 58.1 kPa, attributing to the improved cohesion strength. The adhesion was testified on various organs like the spleen, kidney, and lung of the rat. Histological study of tissues with subcutaneously implanted complex hydrogel revealed inflammation after 3 days and its gradual disappearance in 14 days.

The thermosensitive hydrogels with tunable adhesive properties were demonstrated for the network based on polyacrylic acid and N-isopropylacrylamide-dopamine methacrylamide, NIPAM-DMA copolymer. The network was based on hydrogen bonding and hydrophobic association [266]. However, the adhesion strength was tuned with the concentration of NIPAM-DMA-based copolymer. The adhesion strength of the hydrogel at 15 ^{o}C increased from 340 kPa to 543 kPa upon increasing the copolymer concentration from 1.2 to 2.2 wt%. Moreover, upon heating, the phase transition of copolymer caused hydrogen bonding between carboxyl groups of PAA, phenolic hydroxyl groups of DMA, and amide groups of both DMA and NIPAM constitutional units below the phase transition temperature that caused the dominant hydrophobic association. Stronger hydrophobic interactions resulted in higher adhesion strength.

Chemical agent-based methods can also trigger the detachment of the hydrogel besides the temperature. Kang *et al.* constructed a hydrogel by crosslinking gelatin and tannic acid quinone using boronic ester cross-links and Schiff base bonds [267]. The dynamic character of crosslinks endowed not only self-healable properties but also on-demand removability upon acidification due to pH-responsive boronate ester bonds and Schiff-base bonds. The adhesive strength of the hydrogel decreased notably from 65 to 5 kPa after treatment with acid. The adhesion strength of gelatin/tannic acid quinone increased with tannic acid quinone content, strengthening the network's cohesion and interfacial adhesion.

The appropriate adhesive strength makes the hydrogel suitable as a wound sealant. Sealed skin injury may be reopened as an effect of the frequent motion of the human body and thus, repeated closure is needed to avoid infection or a delayed healing process. In wound healing, applied hydrogel should display skin adhesive properties and self-healable properties to regenerate the hydrogel material to form a continuous layer to protect the injury. Liang *et al.* applied dual mechanisms of dynamic network formation based on catechol-Fe^{3+} and Schiff base using protocatechualdehyde (PA), $FeCl_3$, and quaternized chitosan to obtain hydrogel of adhesive and self-healable properties along with its controlled removal [268]. The reversible character of interactions applied for the network construction, their reversible breakage and reformation is assured, which endow the obtained hydrogels with both injectable and self-healable properties. These systems were dedicated to both wound closure and enabling post-wound-closure care. The adhesive strength of hydrogels was tuneable with the weight fraction of PA@Fe content by the change of the molar ratio of amine to aldehyde groups. Upon its gradual decrease, the adhesive strength of hydrogels was increased and was ranging from 3 to 40 kPa. These data input that the adhesive strength was strictly dependent on the cohesion and interfacial adhesion of the hydrogel. The increased cross-linking density improved the cohesion of the hydrogel and the increased content of aldehyde and catechol groups, which strengthened the interfacial adhesion. The adhesive properties of hydrogels were diminished on demand using a competing chelating agent, including deferoxamine mesylate, which resulted in at first reduction of the adhesive strength from 10.4 kPa to 1.30 kPa, and then the controlled removal of the hydrogel dressing without secondary injury of the wound. The in vivo evaluation in a rat skin incision model and full-thickness skin wound model revealed the high wound closure effectiveness and post-wound closure care of the hydrogels. The authors also took advantage of the ability of PA@Fe particles to convert NIR light to heat. Masson's trichrome staining test showed the highest levels of collagen deposition in wounds treated with NIR-assisted hydrogel compared to NIR-untreated hydrogel and the commercial sealant Tegaderm. In addition, the highest level of CD31 transmembrane protein expression and the lowest level of CD68 lysosomal glycoprotein expressed by macrophages were observed in the NIR-assisted hydrogel-treated wounds.

Benzaldehyde functionalized poly(ethylene glycol)-co-poly(glycerol sebacic acid) decorated with phenylboronic acid was applied to the formation of the dynamic hydrogel of adhesive properties with dihydrocaffeic acid and L-arginine-grafted chitosan (CDL) for the therapy of athletic ulcer foot [269]. In the case of athletic foot wounds, good tissue adhesion is of great importance to ensure complete bonding to the wound, thus reducing the potential harm of the external environment to the wound. The designed network was based on Schiff base bonds and boronate esters generated between boronic acid, and both dihydrocaffeic acid and L-arginine moieties. The concentration of applied CDL also modulated the adhesive properties. Moreover, incorporating graphene oxide sheets coated with polydopamine slightly increased the adhesion strength from 16.2 to 17.5 kPa. Due to the acid-sensitive cross-links, the addition of acid resulted in the transition of the hydrogel into a mobile liquid.

Chen *et al.* designed an interpenetrating polymer network composed of poly(vinyl alcohol), PVA, and poly(acrylic acid), PAA grafted with cleavable N-hydroxysuccinimide (NHS) ester in the dry state displaying instant bioadhesion on wet tissue, i.e., within 5 s, and can be benignly detached from the adhered tissues on demand (5 minutes) [270]. Then, NHS ester reacted with primary amine groups on the tissue surface, ensuring long-term adhesion stability. Adding an aqueous solution containing sodium bicarbonate and glutathione (GSH) triggered the detachment of the hydrogel by cleaving both physical and covalent linkages with the tissue.

4.4. Janus-type bioadhesive dynamic hydrogel

In certain biomedical therapies such as repair of myocardial infarction (MI), the usage of Janus reversible hydrogel is perspective, as it can exhibit asymmetric adhesive properties, and thus one side of the hydrogel can adhere strongly to the tissue, assuring efficient repair, whereas the second one can display anti-adhesion preventing tissue synechia and inflammatory intrusion after surgery [13]. In this application, the hydrogel system should not only exhibit adhesive properties but also proper elasticity and conductive properties are required. He *et al.* designed a Janus double-layer reversible hydrogel for non-invasive cardiac repair (Figure 7) [271]. A bottom hydrogel was responsible for adhesion onto wet cardiac tissue and was constructed of a mussel-inspired adhesive ionic interpenetrating network poly(acrylic acid)/polyethyleneimine/aldehyde cellulose PAA/PEI/CNC-CHO/CA based both on covalent cross-linking and noncovalent interactions using acrylic acid, polyethyleneimine, aldehyde cellulose with N, N-bis (acryloyl)cystamine, BAC as dynamic cross-linker responsive to ROS enriched in the infarcted myocardial region, 3-sulfonic acid propyl methyl acrylic acid potassium (MASEP) and caffeic acid with catechol groups for enhanced interfacial interactions including hydrogen bonding, electrostatic interactions and cation-π interaction between tissue and hydrogel patch. A top hydrogel layer preventing tissue synechia was constructed of acrylic acid, carboxylated cellulose, and polyethylene glycol diacrylate of anti-cell adhesive and anti-fouling properties as a cross-linking agent. Live-dead staining and the CCK-8 test showed that all the hydrogels used had good biocompatibility. However, a higher density and activity of cardiomyocytes was observed on the hydrogel used as the lower adhesion layer than on the hydrogel-forming the upper antifouling layer. Well-adhered hydrogel to the wet surface can be easily detached thanks to redox-responsive disulfide cross-links present in the adhesive layer, and thus the process of on-demand detachment was easy to operate. The adhesive layer of the

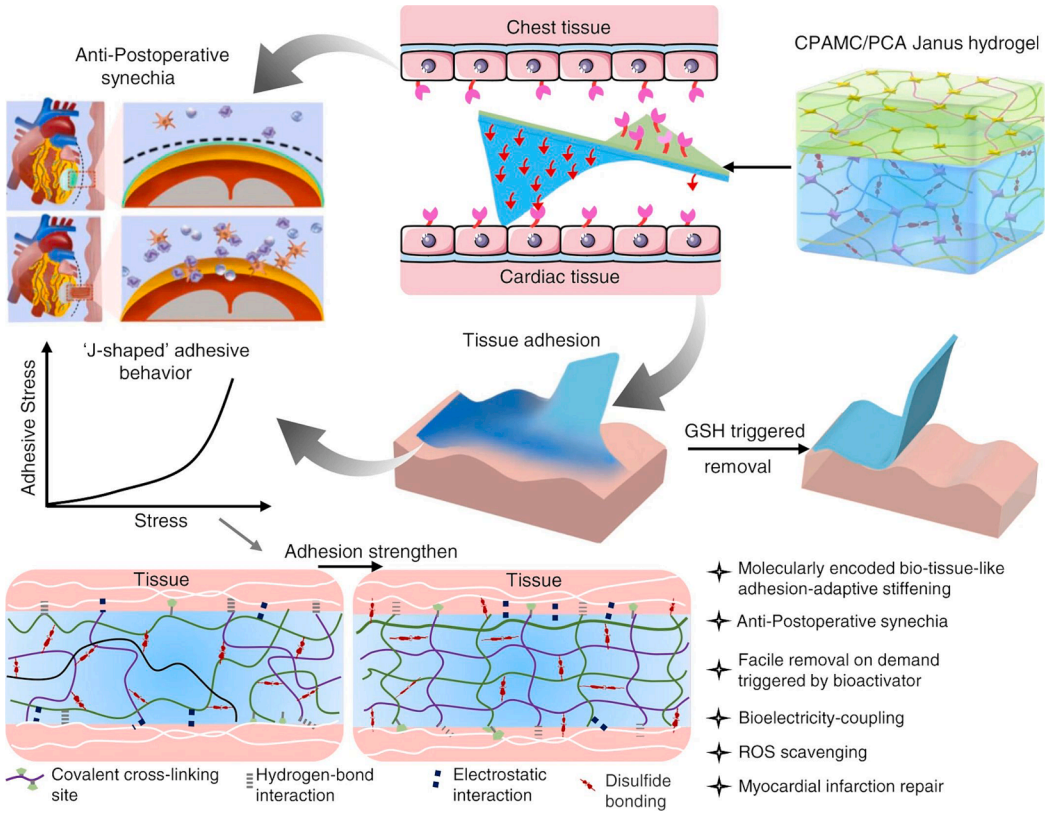

Figure 7. Schematic illustration of the smart Janus adhesive and on-demand removable hydrogel as a multifunctional engineered cardiac tissue patch (ECP) to repair rat's myocardial infarction (MI). The image is reprinted from [271] (Springer Nature).

Janus hydrogel can be fixed to the target tissue for a long time, avoiding the disadvantages of easy shedding of the common anti-adhesion barrier and preventing the occurrence of tissue adhesion after most surgeries. However, it was observed that the adhesion strength increased with the adhesion time along with the improvement of the mechanical properties. The strength of the hydrogel increased from 25.35 to 207.60 kPa, whereas the adhesive strength increased from 251.14 to 16101.15 kPa.

4.5. Polymer-induced bioadhesion of dynamic hydrogels

The bioadhesive character of polymers can be applied to endow the hydrogels with the desired adhesive properties. Thanks to good mucoadhesive properties and biocompatibility, predestine chitosan is used for biomedical applications, including wound dressing. In addition, chitosan degradation product N-acetyloglucosoamine mimics the extracellular matrix composition and therefore enhances tissue regeneration[272]. The chitosan mucoadhesion was based on interactions with negatively charged groups, such as carboxylate (COO^-) and sulfonate (SO_3^-) moieties present in mucine [273], hydrogen bonding, and hydrophobic effects [274]. The presence of chitosan in hydrogel systems increases mucoadhesion behavior. Nimal *et al.* reported dynamic composite hydrogel showing anti-staphylococcal activity for infectious wound healing [275]. Chitosan injectable gel, based only on chitosan intermolecular interactions, was loaded with platelet-rich plasma to promote fibroblast proliferation and migration and to promote a granulation phase during wound healing, as confirmed by the Alamar blue assay. Moreover, an antibiotic called tigecycline was encapsulated to prevent bacterial growth on the wound. Tygeciline was first encapsulated in chitosan nanoparticles that were obtained by adding tripolyphosphate to the chitosan tigecycline solution. Nanoparticles were then blended with hydrogel. Their in vitro studies showed prolonged antibacterial activity of the construct for up to 14 days.

Xing *et al.* developed the attractive biomedical properties of collagen by designing a hybrid hydrogel based on collagen crosslinked within situ-formed gold nanoparticles (GNP) [276]. Non-covalent interaction was formed between collagen and GNP via coordination interaction and/or electrostatic interaction, providing injectability and self-healing properties to the hydrogel. In addition, it was found that $AuCl_4^-$ ions, the GNP precursor, can also trigger the rapid self-assembly of collagen nanofibers. The mechanical properties of the collagen/GNP composite hydrogel can be tuned with the initial $HAuCl_4$ concentration that influences the size distribution of formed GNP in the hydrogel. It has been shown that such a construct is suitable for localized antitumor therapy, in which the drug-loaded hydrogel is injected into the diseased area. The prepared collagen-based hydrogel was shown to provide local retention and sustained release of a model drug tetra(4-*N*-methylpyridyl)porphine (TMPyP). Moreover, GNP-embedded hydrogel can convert visible light to heat, enabling combinatorial photothermal therapy.

4.6. Bioadhesive hydrophobized dynamic hydrogels

In the case of dynamic hydrogels, in which structure hydrophobic domains can be distinguished [277], the adhesion to wet surfaces is limited. Reduced adhesive properties of the hydrophobized hydrogels are an effect of the formation of large hydrophobic domains of limited dynamics. Hydrophobic polymer chains contract in contact with water molecules and thus, their diffusion to the adherent matrix is limited. In recent years, numerous research has been performed to improve the adhesion of the hydrogel in wet conditions, in which hydrophobic association can be crucial in the construction of hydrogels with underwater adhesive properties. For this goal, the size of hydrophobic domains in the hydrogel is reduced to assure the dynamic nature of hydrophobic crosslinks and thus strengthen the hydrogel adhesion. Han *et al.* prepared a dynamic hydrophobic hydrogel that displayed outstanding, repeatable, long-term stable underwater adhesion to various substrates, including wet biological tissues, as an effect of self-

hydrophobization induced *via* Fe^{3+} ions (Figure 8) [278]. The hydrogel was synthesized via a micellar copolymerization of hydrophilic acrylamide and hydrophobic stearyl methacrylate (C_{18}) accompanied with sodium dodecyl sulfate, SDS in the presence of a small fraction of N,N'-methylenebisacrylamide, MBAA units delivered covalent linkages between macromolecules in the network, whereas hydrophobic C_{18} alkyl chains were stabilized in SDS micelles generating hydrophobic dynamic associations. Fe^{3+} ions assured the reorganization of C_{18}-loaded SDS micelles into larger aggregates, which is typical for SDS solutions at high ionic strength. Therefore, Fe^{3+} ions triggered the self-hydrophobization process of hydrogel, which repelled water molecules from the interface between the hydrogel surface and the covered surface generating the molecular bridges. This mechanism endowed the hydrogel the outstanding underwater hydrogel-substrate adhesion, which the strength increased along with the contact time as an effect of further water molecules repelling. This system adhered to biological tissues in the presence of sweat, blood, and body fluids, even at dynamic movement typical for *in vivo*, which was demonstrated for a porcine beating heart. The adhesion properties of such hydrogel to a substrate were strong enough to resist water blasting for 10 s. Such hydrogel is highly promising in repairing tissues and attaching devices *in vivo*. The pictures showing Fe^{3+} ions induced adhesion of the hydrogel to porcine muscle,

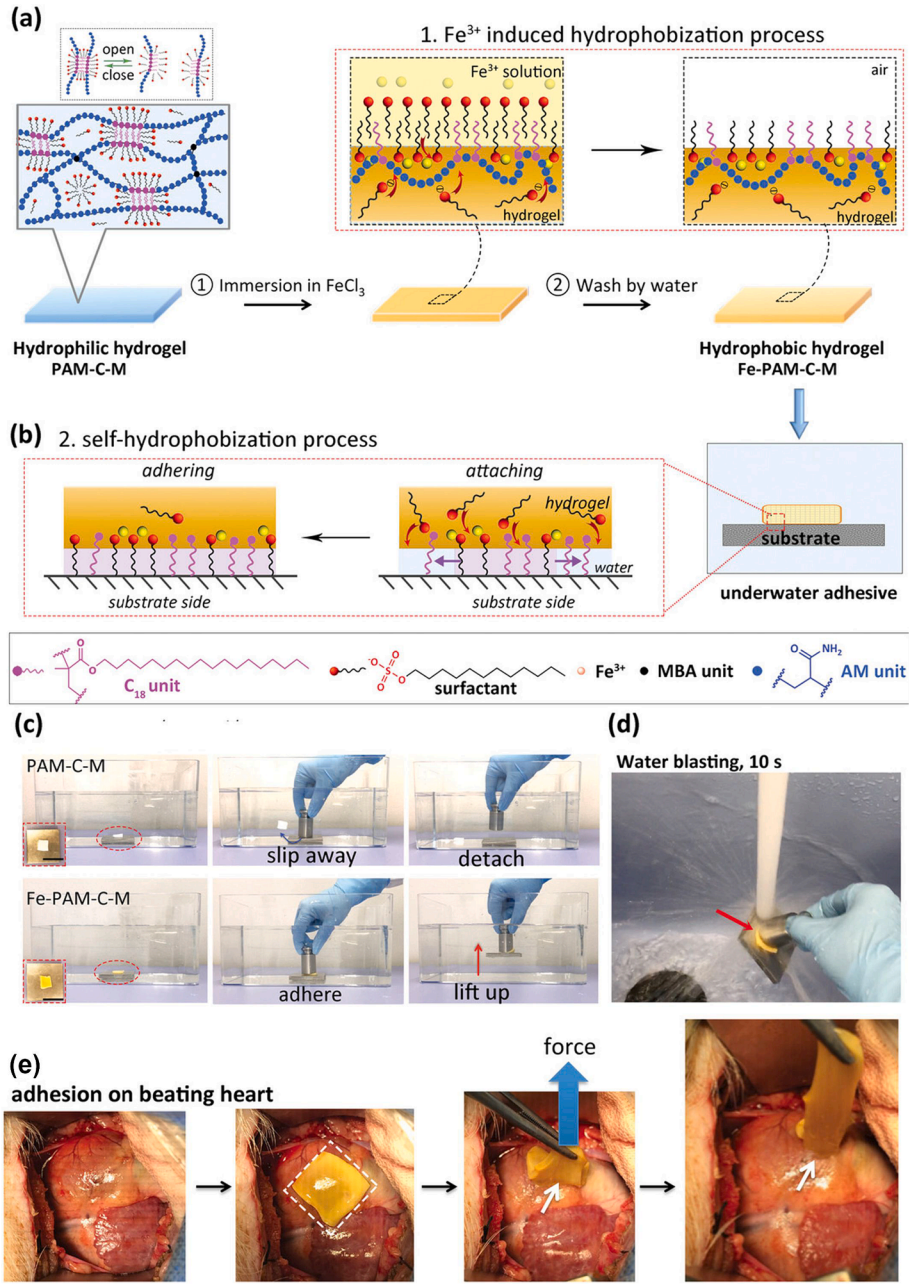

Figure 8. Fabrication and performance of underwater adhesion hydrogels: (a) Schematic representation of the fabrication process of the Fe^{3+} induced hydrophobization process. Hydrophilic PAM-C-M made from poly(acrylamide-co-C_{18}) was immersed in an aqueous Fe^{3+} solution, followed by a water-rinsing to obtain a hydrogel (Fe-PAM-C-M) with a hydrophobic surface. (b). Schematic illustration of the self-hydrophobization process for the formation of firm underwater adhesion between the hydrogel and substrate. The compression between hydrogel and substrate creates hydrophobic interactions which repels water away from the interface. (c) Practical demonstration (with photographs) of underwater adhesion. PAM-C-M hydrogel was detached from the metal surface, while Fe-PAM-C-M was firmly attached to the metal block surface. (d) Demonstration of adhesion between hydrogel and substrate by water blasting for 10s. (e) In vivo adhesion tests of hydrogels on the porcine heart with blood exposure. Adapted from [278] Copyright (2019) WILEY-VCH.

wet bone tissue, fresh porcine skin, and *in vivo* adhesion test to a beating porcine heart with blood exposure (Figure 8).

To summarize, the adhesion strength of a hydrogel intended for biomedical applications, such as surgical sealants or drug delivery systems, should be tailored to the application. The hydrogel should easily adhere to *in vivo* substrates under wet conditions and remain in place after administration. When designing a hydrogel for *in vivo* applications, we need to consider not only the contact of the biomaterial with body fluids (e.g., blood, sweat, and urine) but also factors that may adversely affect the adhesion of the material to the surface, such as mechanical forces caused by bleeding, organ dynamics, such as heart beating and muscle bending.

It should be noted that there are no general guidelines for hydrogel adhesion strength for a specific application. The adhesion strength of hydrogels designed for biomedical applications is mainly in the range of 10^1 to 10^2 kPa, with a few systems exceeding this range. Surgical sealants, whose adhesion force reaches 80 kPa along with resistance to burst pressures exceeding 1000 mmHg, can be taken as a reference [279].

4.7. Facilitating cell adhesion by dynamic hydrogels

Cell adhesion is crucial to the proliferation, migration, and differentiation of cells upon their contact with a substrate. Interaction between materials and cells can influence cytoskeletal tension, cellular morphology, signal transduction, and gene expression [280]. Therefore, cell adhesion is critical to the function of implanted materials and devices. Yet, the extent of desired cell adhesion depends on implant function and varies from high in the case of scaffolds for tissue regeneration to lack of adhesion in the case of devices that interact with blood to avoid thrombosis and embolism [281].

When the interaction between polymer substrate and cell is considered, the cell behavior on similar materials varies based on cell type. For example, fibroblasts were observed to spread and migrate on more rigid substrates, while more compliant substrates have been shown to support longer neurite outgrowth [282]. In addition, the presence and density of specific ligands in the polymer matrix are essential for cell spreading, migration, and outgrowth [283]. To enhance interactions between cells and polymer matrix, cell membrane receptors are commonly targeted. It is achieved using peptide/protein ligands such as ECM proteins, including laminin or fibrinogen [284-286]. The peptide ligands are derived from such proteins as fibronectin (e.g., RGD, KQAGDV, REDV and PHSRN), laminin (e.g., IKLLI, LRE, LRGDN, PDGSR, IKVAV, LGTIPG, and YIGSR), collagen (e.g., DGEA, GFOGER) and elastin (e.g., VAPG), of which the most widely used is the arginine–glycine–aspartate (RGD) sequence [287], a ubiquitous receptor adhesion motif found in most ECM proteins [284,288]. RGD functionalized hydrogel has already been commercialized under the tradename VitroGel®. Moreover, such proteins as sericin [289], fibrin [290], collagen and its derivatives [291,292] are applied as cell adhesion enhancers. In addition, aptamers, the short sequence of nucleic acids that bind a specific target molecule or family of target molecules, were utilized to promote cell adhesion [293,294].

Enriching the hydrogel formulation with easily available proteins offers a low-cost way to ensure adhesion to cells. For example, Deepthi *et al.* synthesized a composite hydrogel consisting of chitosan, alginate, and fibrin [290]. Subsequently, alginate was ionically crosslinked with chitosan, fibrin and thrombin with pH adjustment. Thrombin was used to promote fibrin clot formation. The polymer components were chosen due to their biological activity. Chitosan, an analog of glycosaminoglycan, played a role in sustaining chondrocyte morphology function and differentiation. The alginate promoted cell proliferation and long culture duration. The fibrin possessed RGD sequences and promoted cell attachment. In addition, the hydrogel was loaded with the osteoporotic drug strontium ranelate. To achieve a sustained drug release, strontium ranelate was first encapsulated within chitosan nanoparticles that were then blended into the hydrogel. Such a composite hydrogel showed both injectability with a yield stress of 435 Pa and self-healing properties, which allows hydrogel application to the defect area. DNA quantification and cell attachment experiment revealed that cells were viable in the hydrogel with normal cell proliferation and homogenous distribution in the matrix. Moreover, nanocomposite hydrogel was found to be a proper environment for chondrogenic differentiation, making it a potential candidate for cartilage regeneration.

Fibrin was also applied to enhance cell adhesion of composite chitin/$CaSO_4$ crystals hydrogel designed as a bone regeneration platform for small and non-loading defects. Fibrin, in the form of microparticles prepared in an emulsion process, was mixed in chitin injectable hydrogel prepared by solvent regeneration technique [295]. The cell attachment test revealed that upon the addition of fibrin, the cells showed a well-attached and spread morphology instead of a rounded morphology in the case of hydrogel without fibrin. In addition, fibrin influenced the formation of $CuSO_4$ x$2H_2O$ crystals that grew as hexagonal rather than needle-like crystals. The role of $CuSO_4$ crystals was to improve chitin hydrogel's mechanical stability and promote osteogenic differentiation of cells, which was confirmed by alkaline phosphatase (ALP) level measurement.

Alginate has been extensively used for the synthesis of biomaterials. Its cell adhesion is, however, poor unless incorporated with other components that promote cell binding [296]. To overcome the lack of cell adhesion of alginate, Wang *et al.* constructed a composite dynamic hydrogel from the mixture of alginate and gelatin that were crosslinked both covalently, using EDC/NHS chemistry, ionically with Zn^{2+} cation [292]. To provide proper mechanical properties to hydrogel, it was filled with cellulose nanocrystals (CNC) that provided guidance to oriented cell growth on the surface or within hydrogels making it potentially viable for bone regeneration. Damouny *et al.* also employed the combination of gelatin and CNC [297]. In this case, authors prepared ionically cross-linked hydrogel from HA, gelatin, and cationically modified CNC. It is noteworthy that in both cases, the authors indicated that the addition of CNC slowed down the degradation of hydrogels. Thus, the addition of CNC improves the mechanical properties of hydrogels and prevents their rapid degradation under physiological conditions, to which dynamically crosslinked gels are particularly susceptible.

Introducing specific ligands that target cell membrane receptors is a common method of promoting the cell adhesive property of the hydrogel. Diba *et al.* showed the strategy toward artificial ECM by the incorporation of RGD ligands into the structure of hydrogel composed of PEG, which is known for its antifouling properties [298]. The authors reported dynamic supramolecular hydrogel made of a mixture of telechelic and one-side UPy-modified PEG. A mixture of PEGs modified in this manner self-assembled into nanofibers, which formed cell adhesive dynamic hydrogels at higher concentrations. The effect was not induced when RGD was not attached to the polymer but mixed in the formulation. The use of a synthetic PEG polymer that can be synthesized in a controlled manner, instead of using a polymer of natural origin, allows the properties of the hydrogel to be tailored precisely. For example, it was shown that the dynamics of macromolecules in the hydrogel, and thus its properties, could be tuned with the component ratio. It was indicated, however, that excessively high dynamics of macromolecules in hydrogel prevent cell adhesion by not allowing RGD ligands to drive mechanotransduction [299,300]. Table 4 presents examples of tissue and cell-adhesive dynamic hydrogels, including their composition and properties, specific to a given application.

5. Diverse Biomedical Applications

Biomedical applications of dynamic hydrogels involve the fundamental study of cell-matrix interactions in 3D, tissue engineering, drug delivery [*e.g.*, extracellular vesicles (EVs), nucleic acids, protein and hydrophobic drugs, tumor therapy and immunotherapy [301-304]. Hence, developing hydrogels that can recapitulate the dynamic attributes of the ECM offers next-generation insights and technology into the

Table 4
Summary of bioadhesive dynamic hydrogels.

Composition	Dynamic bonds	Characteristics	Application	Ref.
poly(acrylic acid)/polyethyleneimine/aldehyde cellulose with N,N-bis(acryloyl)cystamine/caffeic acid, PAA/PEI/CNC-CHO/CA	disulphide bonds	Janus double-layer hydrogel containing adhesive and anti-adhesive layers; conductive properties; detachment on demand thanks to redox-responsive disulfide cross-links building the network	repair of myocardial infarction	[271]
catechol-modified ε-poly-L-lysine (PL-Cat)/oxidized dextran (ODex)	Schiff's base bonds; catechol-Fe^{3+} coordinate	double network; repeatable adhesion	wound dressing	[246]
poly(glycerol sebacate)-co-poly(ethylene glycol)-g-catechol/ureido-pyrimidone (Upy)	catechol-Fe^{3+} coordinate; Upy-Upy hydrogen bonding	double network; mechanical and adhesive properties tunable with Upy content; hemostatic	wound healing	[251]
phenylboronic acid-tethered-methacrylated chondroitin sulfate/dopamine decorated methacrylated gelatin/4-arm thiol-ended poly (ethylene glycol)	boronate esters; S-S linkages	double network; the adhesive strength is higher at higher pH	N/A	[245]
a micellar copolymerization of hydrophilic acrylamide and hydrophobic stearyl methacrylate (C_{18})/ N,N'-methylenebisacrylamide, MBAA/ sodium dodecyl sulfate, SDS	hydrophobic association	repeatable adhesion at wet conditions in contact with sweat, blood, etc; long-term stable underwater adhesion; strong adhesion despite water blasting; adhesion to beating heart	wound sealing	[278]
alginate-BA (boronic acid)	boronate esters	the presence of sialic acid in the mucosa causes the formation of boronate esters between the hydrogel and the tissue generating interfacial tissue-hydrogel interactions.	N/A	[260]
PVA-FSWCNT-PDA/borax ions	hydrogen bonding, boronate ester, π-π stacking	composite hydrogel; conductive properties, repeatable adhesion	wearable human sensors	[254]
dopamine-modified 4-armed poly(ethylene glycol)/ Laponite	catechol/quinone interactions with Laponite	composite hydrogel;dissipative effect; the adhesion strength modulated with Laponite content	N/A	[253]
protocatechualdehyde (PA)/ $FeCl_3$/quaternized chitosan	catechol-Fe^{3+};Schiff base bonds	tunable adhesion with PA/$FeCl_3$ content via changing aldehyde/amine molar ratio	wound healing	[268]
benzaldehyde-poly(ethylene glycol)-co-poly(glycerol sebacic acid) with phenylboronic acid and dihydrocaffeic acid and L-arginine-grafted chitosan, CDL	Schiff base bonds,boronate ester	the adhesion strength modulated with CDL content	therapy of athletic ulcer foot	[269]
aldehyde-functionalized chondroitin sulfate, CS/ gelatin/borax	Schiff base bonds,boronate ester, hydrogen bonding	adhesive strength dependent on CS concentration	surgical sealants	[261]
hyperbranched polymer with thiol groups/ benzaldehyde-terminated poly(ethylene glycol), PEG-CHO	thiol-aldehyde cross-linking	the adhesive strength dependent on PEG-CHO content; the hydrogel detachment governed by the temperature change	N/A	[264]
poly(vinyl alcohol)/ poly(acrylic acid)-grafted with N-hydroxysuccinimide ester	hydrogen bonding	interpenetrating network, immediate adhesion, benign detachment upon sodium bicarbonate and glutathione	N/A	[270]
Gelatin/ tannic acid quinone/borax	boronate ester, Schiff base bonds	self-healable properties, the adhesive strength modulated with tannic acid, the hydrogel detachment upon the change of temperature	N/A	[267]
collagen-Au nanoparticles	coordination and electrostatic interactions	non-covalent interaction was formed between collagen and GNP via coordination interaction and/or electrostatic interaction, providing injectability and self-healing properties to the hydrogel.	localized anti-tumor therapy	[276]
chitosan	intermolecular interactions	hydrogel loaded with platelet-rich plasma and tigecycline-encapsulated in chitosan nanoparticles	N/A	[275]
chitosan	intermolecular interactions	hydrogel loaded with whitlockite nanoparticles	N/A	[256]
hyaluronic acid modified with dopamine, HA/DA graphene oxide covered with polydopamine	physical interactions between HA/DA and graphene oxide/polydopamine supported with covalent bonds between oxidized dopamine groups	mechanical performance on par with human skin	hemostatic agent	[242]
chitosan/alginate/fibrin	chitosan-alginate intermolecular interactions	equipped with strontium ranelate – an osteoporotic drug; fibrin for increased cell-adhesion	cartilage regeneration	[290]
chitin/fibrin/CuSO4	chitin intramolecular interactions	fibrin microparticles for cell adhesion; CuSO4 crystals to increase mechanical stability; promotion of osteogenic differentiation	bone regeneration	[295]
poly(ethylene glycol) modified with Upy moieties	Upy-Upy hydrogen bonding, self-assembly into fibers	RGD-modified poly(ethylene glycol) to increase cell adhesion	N/A	[298]
alginate/gelatin/cellulose nanocrystals	ionic COOH/Zn^{2+} supported with covalent amide bonds	N/A	bone regeneration	[292]
hyaluronic acid/gelatin/CNC-cationically modified	ionic interactions	N/A	bone regeneration	[297]

biomaterial designs for these translational applications. In this section, we highlight and discuss several representative examples of applying dynamic hydrogels for various research fields.

5.1. Dynamic hydrogels for studying cell-matrix interactions in 3D

Cells can respond and remodel the surrounding ECM that regulates diverse cellular behaviors, including growth, proliferation, migration, differentiation and apoptosis [305-307]. Percellular ECM is a highly

dynamic network that can be associated/dissociated and crosslinked, giving rise to a temporal hierarchy of ECM biophysical properties [308]. Therefore, fabricating an ECM-based network with tunable dynamic properties is of great importance in unraveling cell behaviors in response to different physical parameters of ECM [309]. Yang *et al.* reported two types of physically crosslinked supramolecular hydrogels: monoacryloyl cyclodextrin (ac-β-CD) complexing with hyaluronic acid (HA), which was modified with ~30% modification degree of (1) adamantane (HA–ADA) or (2) cholic acid (HA–CA) (Figure 9**a**) [310]. Therefore, ac-β-CD was complexed with either HA–ADA (CD–ADA) or HA–CA (CD–CA) as the prepolymer. An additional step of photopolymerization enabled gelation to formulate hydrogels of two similar host-guest equilibrium binding constants (K_{eq}) but different kinetic binding constants (k_{off}, k_{on}). Critically, CD–ADA showed >6 orders of magnitude larger kinetic binding constants than CD–CA and hence presented a short lifetime and stable conjugation of cell-adhesive ligands. The authors adopted human mesenchymal stem cells (hMSCs) as a model of mechanosensitive cells and the source of tissue engineering in this study. As a result, their findings indicated that the CD–ADA hydrogel promoted rapid stellate spreading and β_1-class dependent mechanosensing and osteogenic differentiation of hMSCs in such a 3D hydrogel network. The reason that the rapid spreading and organization of cells in the dynamic hydrogels were facilitated by the coordinated interplay between cell adhesion structures interaction with newly formed extracellular matrix (ECM) proteins (nascent protein), and intracellular actomyosin contractility [310]. This study underscores the significance of selecting dynamic crosslinks and precise biofunctionalization in the design of dynamic hydrogels that can adapt to cells, particularly for promoting

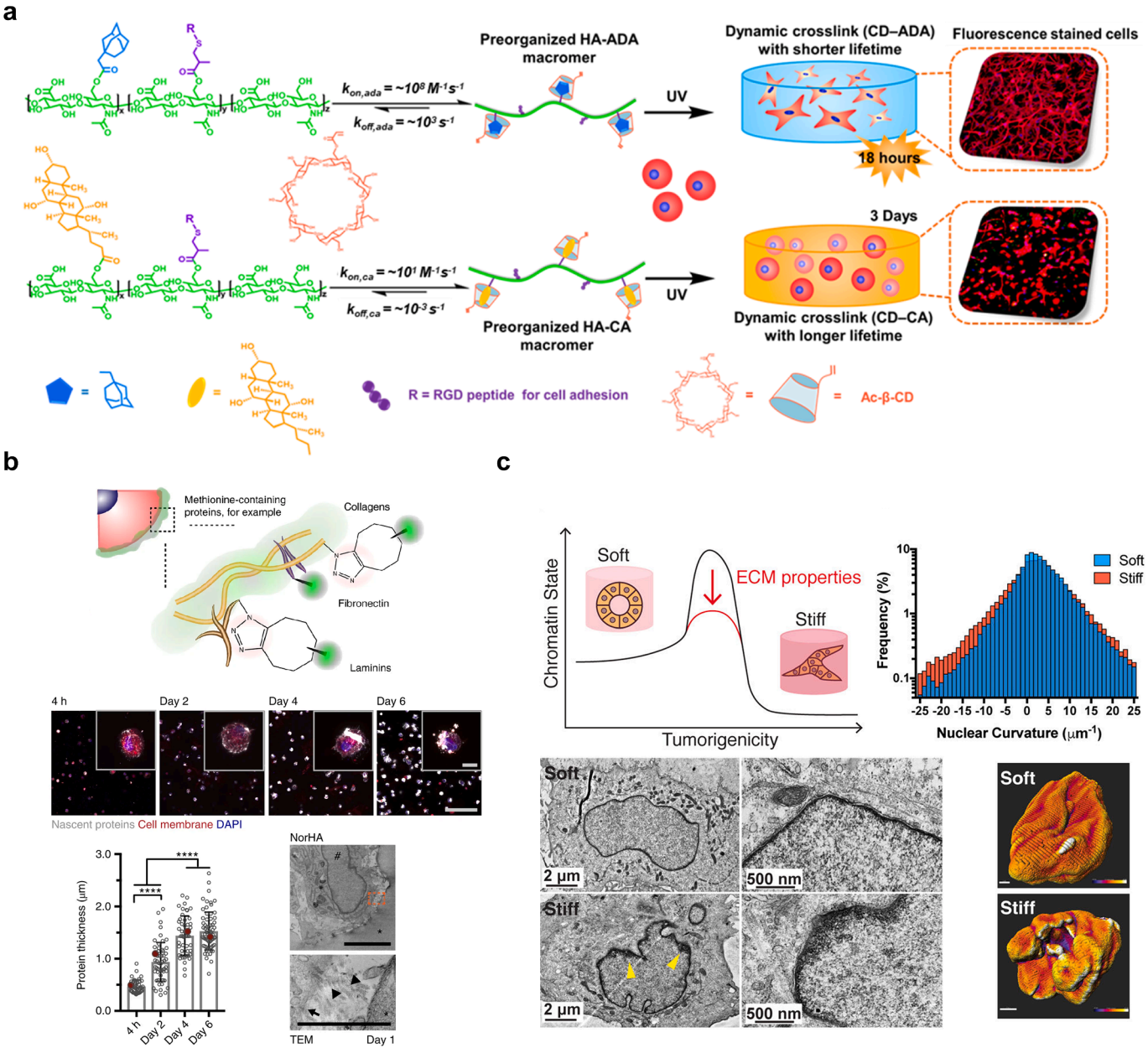

Figure 9. Highlighted examples of fundamental studies about cell-ECM interactions in the three-dimensional network. (a) Enhanced mechanosensing of stem cells in tunable ligand binding constant in host-guest crosslinked hyaluronic acid hydrogels. The figure is reprinted from Ref. [310] with permission from Springer Nature. (b) The deposition and remodeling of local nascent proteins by stem cells in the dynamic hydrogel network is highly relevant for later stage regulation of mechanosensing and differentiation. The figure is reprinted from Ref. [311] with permission from Springer Nature. (c) The regulation of chromatin state accessibility in cancers by hydrogel stiffnesses. The figure is reprinted from Ref. [312] with permission from Springer Nature.

fast cellular development in a 3D matrix.

The presentation and interaction of cells with microenvironmental cues are crucial for cell growth and tissue morphogenesis [313]. At the beginning stages of connective tissue development, cells interact with the ECM, which provides adhesion cues, mediates cell-cell interactions, and regulates growth factor presentation [314]. The ECM is continuously remodeled, degraded, and reassembled by cells to actively shape their surrounding matrix, making this bi-directional signaling crucial for a range of cell and tissue functions [315]. Cells embedded in hydrogels respond to both mechanical and chemical cues, but much of the initial cell-hydrogel interactions are lost during cell differentiation as cells secrete and assemble a pericellular matrix essential for tissue maturation [316,317]. To date, there have been no studies investigating the role of nascent matrix adhesion and remodeling in regulating cellular mechanics within complex hydrogel environments. Burdick *et al.* investigated this phenomenon by employing metabolic labeling [a fluorophore-conjugated cyclooctyne (DBCO-488)] to track the nascent proteins secreted and assembled by undifferentiated hMSCs within various hydrogels, including engineered proteolytically degradable and dynamic viscoelastic (HA) hydrogels, all with ~9 kPa elastic modulus (Figure 9**b**) [311]. These hydrogels facilitated cell spreading through both protease-dependent and protease-independent mechanisms with the early deposition and remodeling of local nascent protein to mediate a wide range of mechanosensing, such as YAP/TAZ signaling, leading to enhanced osteogenic differentiation.

The microenvironment of tumor ECM undergoes significant remodeling compared to normal tissue microenvironments, resulting in changes in the composition and density of the ECM network [318]. These alterations impact the mechanical properties of the microenvironment, such as an increase in matrix stiffness [319]. Research has shown that differences in ECM stiffness can induce changes in gene expression by affecting integrin binding and downstream signaling, cytoskeletal tension, activation of mechanosensing signaling complexes, and transcription factor activation and localization in cancer cells [320]. Even non-malignant mammary epithelial cells can exhibit malignant phenotypes when exposed to stiff matrices [321]. Despite the widely recognized role of the epigenome in gene regulation and its known misregulation in cancer, little is understood about how changes in the chromatin state regulate the effect of ECM mechanics [322]. Chaudhuri and colleagues recently adopted a 3D culture system based on interpenetrating networks (IPNs) of reconstituted basement membrane (rBM) matrix and alginate for studying the chromatin state of breast cancer (MCF10A) in various stiffnesses (Figure 9**c**) [312]. The matrix stiffness of IPNs can be modulated independent of ligand density, matrix pore size and matrix architecture. This study demonstrates that changes in the stiffness of the ECM can impact the chromatin state of cells, which in turn regulates phenotypic changes. Specifically, enhanced matrix stiffness promotes chromatin remodeling through HDAC3 and HDAC8 to drive the tumorigenic phenotype in mammary epithelium via Sp1-mediated pathways. The authors highlighted the role of chromatin in mechanotransduction and identified changes in chromatin organization in response to matrix stiffness on a genome-wide level. The findings suggest that mechanical signals can be transduced to the nucleus to alter chromatin through a complex of regulatory proteins that drive different phenotypic outcomes [312]. The study also highlights the importance of culture conditions in epigenomic studies, showing that soft matrices match the chromatin state of the mammary epithelium more closely than conventional 2D culture on rigid TCPS. The use of ATAC-seq allowed for the site-specific detection of changes in chromatin accessibility, which would have been masked by conventional bulk assays. The study underscores the need for chromatin profiling experiments in biomimetic culture systems, particularly in models that are known to be mechanically responsive, such as cancer progression and stem cell differentiation.

5.2. Dynamic hydrogels for drug delivery

Delivery of therapeutics to the heart can be achieved through various methods, including intravenous (IV), intramyocardial (IM), and intracoronary injection [323-325], as well as tissue engineering approaches such as laying a cardiac patch on the surface of the heart [326]. However, each method has its limitations. IV injection is safe and convenient but has poor cardiac retention of the therapeutics [327]. IM injection can deliver a sizable amount of drug to the heart but usually requires open chest surgery or sophisticated systems [328]. The intracoronary injection can be readily performed, but cardiac retention is not ideal [329]. Tissue engineering approaches by laying a cardiac patch on the surface of the heart generate the greatest cardiac retention but are challenging to perform the invasive surgery and unsuitable for patients with mild-to-moderate heart diseases [326]. To overcome these limitations, Cheng *et al.* developed a minimally invasive method that utilized the pericardial cavity as a natural “mold” for injectable hydrogels to form a uniform cardiac patch covering the entire heart to minimize invasiveness (Figure 10**a**) [330]. Their hydrogel was derived from decellularized ECM of porcine heart crosslinking with HA hydrogel and aimed to deliver induced pluripotent stem cell-derived cardiac progenitor (iPS-CPCs) and MSCs-derived exosomes with extra retention for repairing myocardial infarction (MI) in a rodent model. Exosomes show great potential for bioactive molecules for treating various diseases [304]. The injected hydrogels in the pericardial cavity formed a cardiac patch-like structure that reduced immune response and increased cardiac retention of therapeutics. This approach promoted cardiovascular repair and stimulated epicardium-derived cells, mitigating cardiac remodeling and improving cardiac function after myocardial infarction. This work establishes a safe and effective method to deliver therapeutic-bearing hydrogels for cardiac repair.

To mitigate the devastating health and economic impacts of the recent COVID-19 pandemic, the development of effective vaccines that can be rapidly manufactured and distributed worldwide is necessary [332,333]. It is known that the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein, which facilitates the virus’s entry into host cells, is an attractive antigen for subunit vaccines due to its efficiency in manufacturing, stability, and targetability by neutralizing antibodies [334,335]. However, RBD is poorly immunogenic, and adjuvants are usually added to subunit vaccines to enhance their immunogenicity [336]. Besides, clinically relevant adjuvants like Alum, AddaVax, and CpG/Alum have been found to be ineffective in eliciting neutralizing responses following prime-boost immunization [337]. To address these limitations, Appel *et al.* delivered RBD subunit vaccines with CpG/Alum adjuvant through an injectable polymer-nanoparticle (PNP) hydrogel elicited potent anti-RBD and anti-spike antibody titers, providing broader protection against SARS-CoV-2 variants of concern compared to bolus administration of the same vaccine and vaccines with other clinically-relevant adjuvant systems (Figure 10**b**) [338]. This PNP hydrogel is composed of dodecyl-modified hydroxypropylmethylcellulose (HPMC-C12) complexing with poly(ethylene glycol)-b-poly(lactic acid) (PEG-PLA) and vaccine cargo (RBD, CpG, and Alum). This PNP hydrogel was injected into subcutaneous space to deliver vaccines over weeks. Notably, hydrogel-based vaccines induced potent neutralizing responses in a SARS-CoV-2 spike-pseudotyped lentivirus neutralization assay, which could not be achieved by bolus vaccines [338]. These findings suggest that slow delivery of RBD subunit vaccines with PNP hydrogels can significantly enhance the immunogenicity of RBD and induce neutralizing humoral immunity.

As temperature-responsive hydrogels and drug delivery systems are important components of stimuli-responsive systems, research groups have considered overlapping thermo-responsive hydrogels with drug delivery systems to provide thermally triggered drug delivery systems [339,340]. Zhao *et al.* [341] reported a dramatic increase in the bioavailability of proteins with temperature-sensitive hydrogel delivery systems, thus making up for the limitations of traditional oral cancer

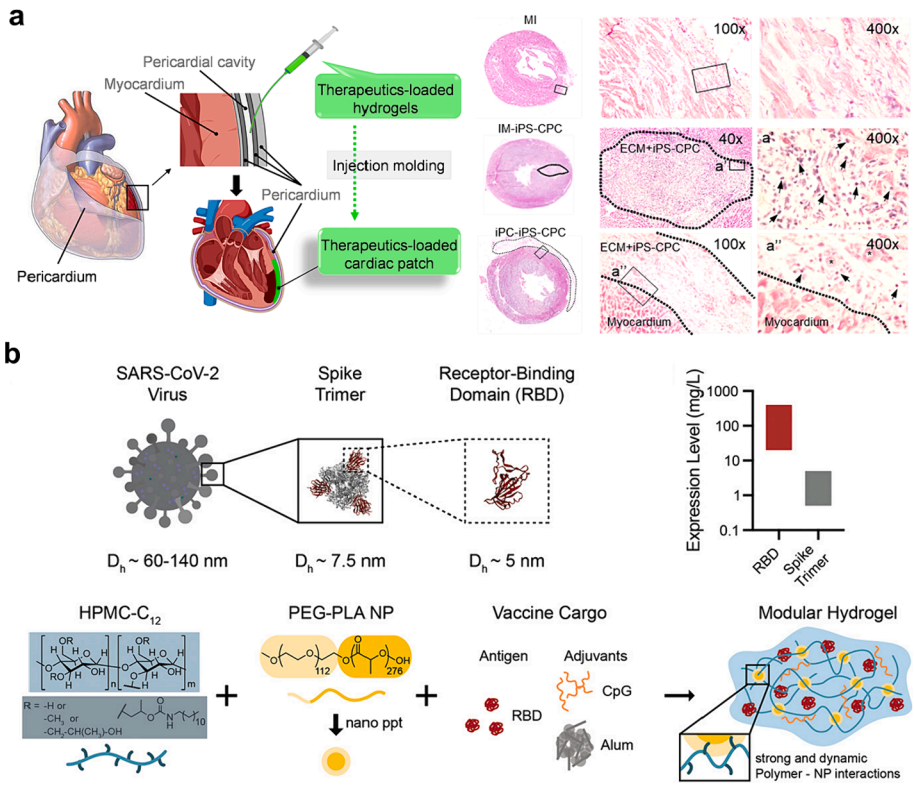

Figure 10. Controlled delivery of drugs for biomedical applications by injectable hydrogels. (a) A decellularized ECM from the porcine heart in HA-based hydrogel for the delivery of therapeutics, exosomes and induced pluripotent stem cells for treating myocardial infarction. The figure is reprinted from Ref. [330] with permission from Springer Nature. (b) An injectable nanocomposite hydrogel for slow release of receptor-binding domain subunit vaccine of SARS-CoV-2 to effectively elicit neutralizing antibody responses. The figure is reprinted from Ref. [331] with permission from Wiley-VCH.

treatment. The tissue responds to thermo-responsive hydrogels to release ocular drugs such as levocetirizine dihydrochloride (LD) [342] and adrenaline and chloramphenicol [343] has also been studied. Thermo-responsive polysaccharide hydrogels based on textile-based transdermal therapy were presented by Chatterjee *et al.* [344]. In addition to improving their suitability and sustainability as drug carriers for the non-invasive treatment of skin diseases, they modulated their temperature sensitivity to near-body temperatures by mixing thermo-sensitive biopolymers with natural polymers. In light of the distinct advantages of hydrogel Molecularly Imprinted Polymers (MIPs) for drug delivery, Lusina *et al.* [345] have competently described the benefits of developing stimuli-responsive MIPs and the perspective of single, dual and multi-responsive hydrogels for drug delivery. Due to their excellent properties, MIPs with non-stimuli and stimuli-responsive properties deserve more attention. Keyan Zhang and colleagues [346] presented the potential of thermosensitive drug-releasing nanofibrous hydrogels with phase-change materials for skin wound healing. Fibrous hydrogels containing fatty acids/aspirin (ASP) encapsulated polydopamine (PDA) provide excellent drug release and cell growth to accelerate wound healing. The design of functional dynamic hydrogels is also one of the main perspectives for achieving externally triggered drug delivery vehicles with improved performance. Hoare *et al.* [347] have developed a high-frequency AMF-induced magnetic drug release injection of a thermosensitive hydrogel-based vehicle without surgical implantation. Kim *et al.* [348] reported that SPION-loaded PNIPAM hydrogel beads intended for transdermal patches have been successfully heated with a light-induced stimulation strategy. Additionally, ultrasound triggering with the capability of highly effective penetration into soft tissues using novel materials designed to demonstrate that a switchable on-off release hydrogel could enhance the release of mitoxantrone under ultrasound in an *in vivo* cancer model [349], as well as provide ultrasound-mediated release with hydrogels based on double networks [350]. Tang and colleagues [351] constructed a magnetic double network hydrogel that meets the clinical requirements of tissue hyperthermia and drug release with their tunable magnetic induction heating. According to Sun *et al.* [352], injectable hydrogels show promising properties for sustained release and biodistribution. If the crosslinking reaction or procedure is reversible, external stimuli may positively influence the release rate. A review of the most widely reported smart peptide-based supramolecular hydrogels for drug delivery was presented by Oliveira *et al.* [353] They also discussed the application of magnetic nanoparticles [354] and enzyme-mediated release systems [355,356] as interesting perspectives in this field. A future focus in this field will be on multi-stimuli responsive systems, such as thermo-, redox-, and light-responsive supramolecular hydrogels that provide precisely targeted delivery for wound healing [357], cancer treatment [358-360], and neural disease control [361].

5.3. *Hydrogels as vaccine carriers for enhanced immunotherapy*

Tumor recurrence can be attributed to post-surgery inflammation, which can trigger tumor growth and metastasis [362,363]. Immunotherapy using immune-checkpoint blockade helps in reactivating T cells at the tumor site by blocking immune-checkpoint pathways and can potentially prevent tumor recurrence after surgery [364,365]. Systemic administration of checkpoint inhibitors has shown sustained clinical responses in less than 20% of patients with immunogenic tumors, and checkpoint blockade is ineffective in tumors with a low burden of somatic mutations that generate neoantigens and endogenous T-cell responses [366]. Furthermore, concerns about autoimmune diseases as side effects of checkpoint blockade persist [367]. A different approach to supplying tumor-specific T cells involves the adoptive transfer of engineered T cells (CAR T). However, the antitumor activity of chimeric antigen receptor T cells (CAR-T cells) is also reduced by the

immunosuppressive microenvironment of solid tumors by T cell exhaustion [368]. Therefore, the combination of CAR-T cells with immune checkpoint blockade may be crucial to enhance CAR-T cell activity in solid tumors [369]. Gu *et al.* have demonstrated that the implantation of a HA hydrogel can release CAR-T cells, polymer nanoparticles containing the cytokine interleukin-15, and platelets conjugated with the checkpoint inhibitor programmed death-ligand 1 (PDL1) into the tumor cavity of mice with a resected subcutaneous melanoma tumor (Figure 11**a**) [370]. The hydrogel functions as a reservoir, which facilitates the enhanced distribution of CAR-T cells within the surgical bed, and the inflammatory microenvironment triggers platelet activation, leading to the release of platelet-derived microparticles. Hence, this combination therapy inhibits both the local recurrence of the tumor and the growth of distant tumors through the abscopal effect. Their results suggested that the post-surgery local delivery of combination immunotherapy through a biocompatible hydrogel reservoir could serve as a translational route for preventing the recurrence of cancers with resectable tumors [370]. This approach has significant clinical implications as it provides a localized delivery of immunotherapy, which reduces the potential for systemic side effects and prevents the recurrence of various types of cancer.

There is growing interest in developing biomaterial-based vaccination systems that can enhance dendritic cell (DC) numbers in situ, a physical space for DCs to interact with transplanted tumor cells, and an immunogenic context [371]. DCs play an important role in adaptive immunity, and the adoptive transfer of immunogenic DCs loaded with tumor antigens has also been used in many cancer vaccination trials [372]. Hence, Mooney and colleagues created injectable cryogel sponges to deliver irradiated B16-F10, GM-CSF, and CpG ODN as a vaccine for treating melanoma in syngeneic C57BL/6 mice (Figure 11**b**) [373]. The sponges allowed for DC infiltration and trafficking, improving cell viability and localization. Their cryogel sponge could release GM-CSF (DC enhancement factor) and CpG ODN (activation adjuvant), induce DC maturation and generate a strong T-effector response, including cytotoxic T lymphocytes. Significantly, their strategy confirmed the enhanced survival rate and delayed tumor growth after tumor challenge in the mice model [373]. These findings highlight the critical role of injectable hydrogel in adoptive T cell immunotherapy for cancers.

Messenger RNA (mRNA) vaccines are an innovative approach to advanced cancer immunotherapy [374]. However, mRNA is prone to degradation, and lipid nanoparticles (LNPs) are commonly used as non-viral vectors to protect and deliver the mRNA to targeted cells [375]. Unfortunately, the stability of mRNA-laden LNPs is a significant barrier

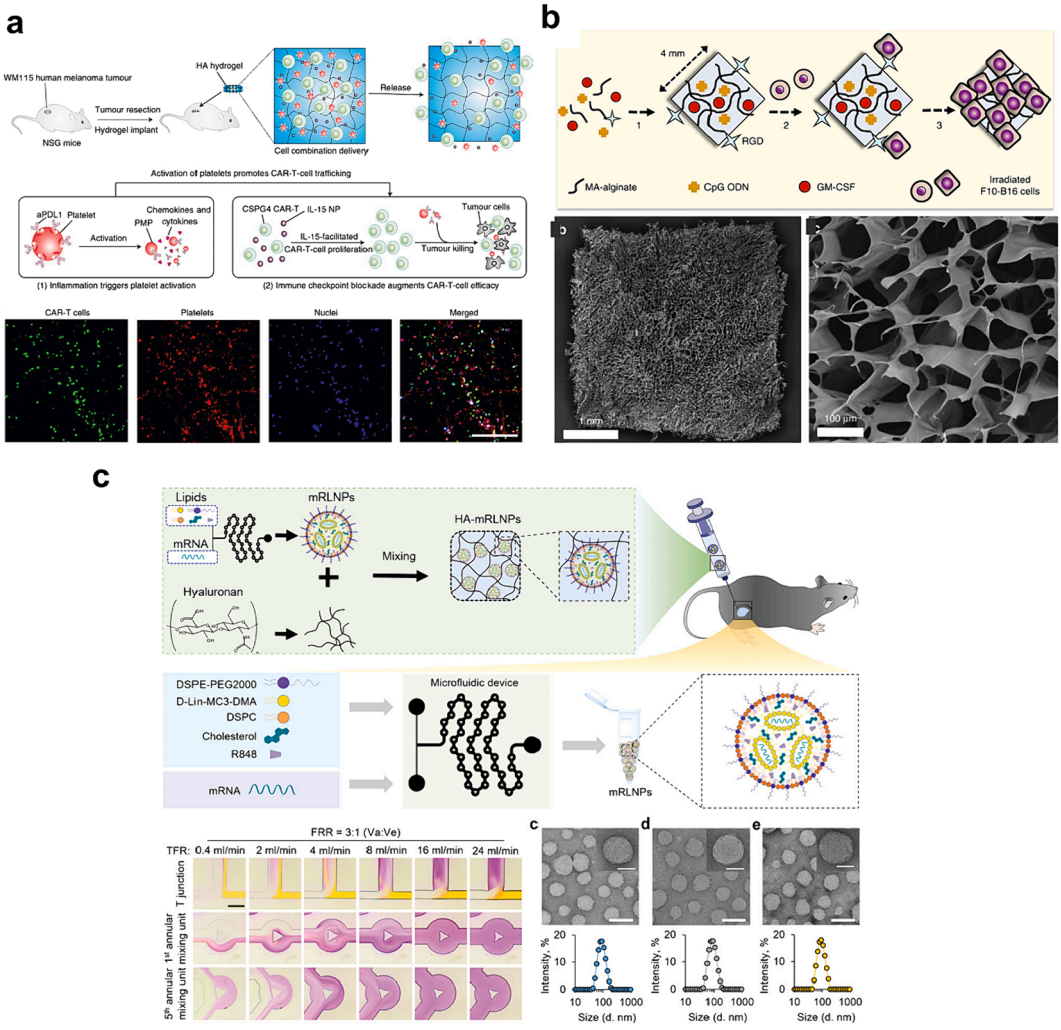

Figure 11. Recent advances in hydrogel-based vaccines to elicit immunotherapy for cancer. (a) Hyaluronic acid hydrogel for controlled release CAR T cells and anti-PDL1-conjugated platelets to suppress tumor recurrence post-surgery. The figure is reprinted from Ref. [370] with permission from Springer Nature. (b) Injectable alginate cryogel sponge for delivering irradiated B16-F10 cells and DC-activating factors for long-term immunomodulation. The figure is reprinted from Ref. [373] with permission from Springer Nature. (c) Dynamic HA hydrogel for stabilizing and controlled delivery of RNA nanovaccines for durable cancer immunotherapy. The figure is reprinted from Ref. [377] with permission from Springer Nature.

to their clinical application [376]. To address this issue, Wang *et al.* have developed a new type of thermostable and durable mRNA nanovaccines using a dynamic hyaluronan hydrogel (Figure 11**c**) [377]. They named this platform HA-mRLNPs containing mRNA encoding tumor antigens and the immunoadjuvant resiquimod (R848) in LNPs (mRLNPs), which were stabilized in the HA hydrogel. The hydrogel restricts the migration and fusion of LNPs, protecting them from degradation at room temperature for durable cancer immunotherapy. Additionally, the gel-like hyaluronan undergoes state transition, allowing for the controlled release of mRLNPs under physiological conditions. The HA-mRLNPs efficiently delivered mRNA to activate DCs, which presented the tumor antigens to induce antigen-specific CD8+ T cells for killing tumor cells. This LNPs-hydrogel system has demonstrated effectiveness as a potential cancer immunotherapy in the B16-F10-OVA tumor model [377].

6. Next-generation hydrogels for multiple-scale biomedical applications

By altering the chemistry or structure of the hydrogel network in real-time, dynamic hydrogels can be engineered as bioactive microenvironments. User-controlled mechanisms can control dynamic responses in hydrogel materials and cell-controlled mechanisms can respond to endogenous signals from cells and tissues [378]. Dynamic hydrogels provide fascinating systems for a wide range of applications despite manufacturing challenges. As a result of their progress, engineers designed more effective and complex platforms. Nevertheless, the advanced physicochemical characteristics of dynamic hydrogels are still being investigated. The fabrication of some emerging hydrogels with complicated properties will be a fascinating subject of future research in order to develop multiple-scale applications for them. In the following,

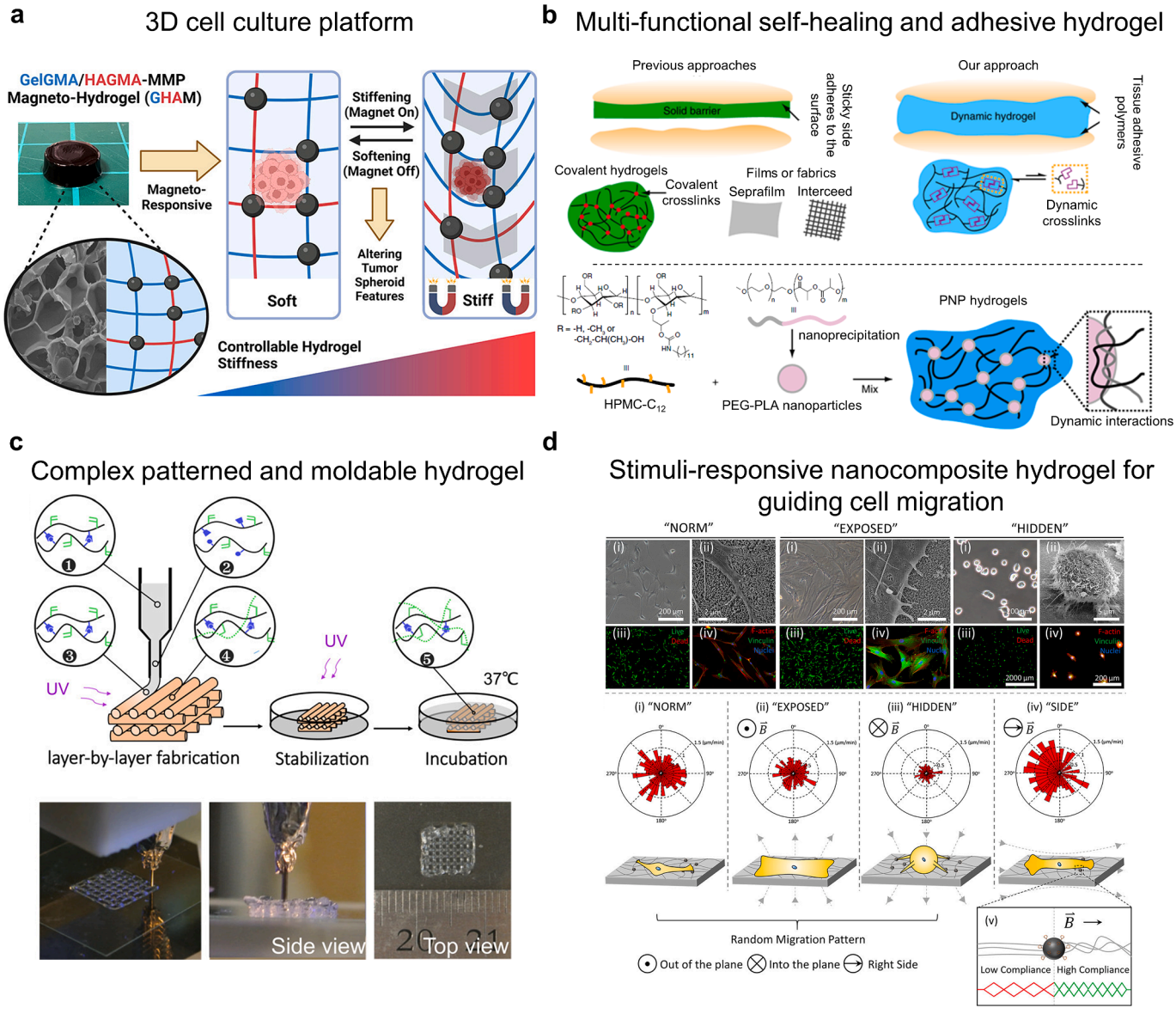

Figure 12. Next-generation Hydrogels for Multiple-scale Biomedical Applications. (a) 3D cell culture platform based on magnetic microparticles encapsulated methacrylate-crosslinked gelatin and hyaluronic acid hydrogel. Adapted from [384] Copyright (2023) American Chemical Society. (b) Multi-functional self-healing and adhesive hydrogel based on polymer–nanoparticle (PNP) interactions between hydrophobically modified cellulose derivatives (dodecyl (C12)-modified hydroxypropylmethylcellulose) and nanoparticles [poly(ethylene glycol)-b-poly(lactic acid) (PEG–PLA; b denotes the block copolymer)]. Adapted from [387] Copyright (2019) Springer Nature. (c) Complex patterned and moldable hydrogel based on adamantane (guest)-modified and β-cyclodextrin (host)-modified HA crosslinking hydrogel. Adapted from [388] Copyright (2016) American Chemical Society. (d) Stimuli-responsive nanocomposite hydrogel (Fe3O4 nanoparticles conjugated with covalently crosslinked HA hydrogel) for guiding cell migration. Adapted from [389] Copyright (2020) American Chemical Society.

we will discuss the latest hydrogels for multiple-scale biomedical applications under seven categories: cell culture platforms, multifunctional self-healing hydrogels, crosslink design strategies, complexly patterned hydrogels, self-folding hydrogels, dynamic hydrogels for guiding cell migration, and biochemically responsive dynamic hydrogels (Figure 12).

6.1. Cell culture platforms

3D cell culture has largely relied on hydrogels to mimic *in vivo* environments and with tailored properties to mimic the *in vivo* environment. Engineered hydrogels are presented for mimicking the natural cell environment and reproducing *in vivo* cell behavior. An increase in temperature triggers self-healing in a hydrogel developed by Zhang *et al.* [379] Following the incubation of mesenchymal stem cells in the precursor solution, they encapsulated them in the hydrogel network under physiological conditions. HeLa cells were also encapsulated using a biocompatible thermosensitive zwitterionic hydrogel by Nagao and colleagues [380], who reported that such a cell culture matrix has significant promise for cryopreservation. Chen *et al.* [381] reported chemically micromechanical self-healing hydrogels with 86% cell viability after 24 hours of culture, which could be used for controlling and regulating cell behaviors. A composite scaffold made from alginate hydrogels containing cells has been demonstrated to have excellent logical response and cell attachment by Noroozi *et al.* [382]. With the aid of photopolymerization and oxidation of methacryloyl gelatin (GelMA) and hyaluronic acid (HASH), Wang *et al.* [27] fabricated a dynamic hydrogel with an interpenetrating polymer network (IPN) with tunable viscoelasticity and adaptability to the extracellular matrix (ECM). Due to its ability to accelerate wound re-epithelialization, the presented scaffold makes an excellent candidate for full-thickness skin repair. An external magnet was used to modify the stiffness and softness of a dynamic 3D magnetic hydrogel developed by Shou *et al.* [383,384] (Figure 12**a**). The platform is suggested for a deeper understanding of the impact of matrix softening on cancer biology due to high extracellular matrix stiffness in malignant tumors. In addition, Goodrich *et al.* [385] developed a magneto-responsive hydrogel platform containing magnetic nanorods (MNRs) and a stress-responsive polymer matrix to dynamically regulate the physical niche for stem cells. A 3D dynamic hydrogel composed of magnetic particles embedded in a biocompatible gelatine scaffold was presented by Shou *et al.* [386]. The results described a dynamic hydrogel as an integrated solution from manufacturing to the clinical use of mesenchymal stem cells (MSCs). Additionally, adjusting the biodegradation level of the hydrogel in relation to cell proliferation and adherence as well as scaling it up to the level of single cells, is also crucial for future studies [340].

Researchers are exploring the introduction of natural nanofibers into hydrogels to develop complex matrices based on a high fibrillar extracellular matrix (ECM) for tissue engineering. Using a nanofibrillated cellulose (NFC) composite bioink, Nguyen *et al.* [390] bioprinted human-derived induced pluripotent stem cells (iPSCs) into cartilage-like tissues. They developed two bioinks, one using NFC with alginate (NFC/A) and the other using NFC with hyaluronic acid (NFC/HA) hydrogel. Their study demonstrates that the NFC/A bioink is suitable for bioprinting iPSCs in co-culture with irradiated chondrocytes, supporting cartilage production and potentially offering a treatment for cartilage lesions that can lead to secondary osteoarthritis. With the same strategy, Markstedt and their team [391] developed a bio-ink for tissue engineering, replicating the collagen ECM structure using cellulose nanofibers. They successfully bioprinted complex cartilage tissues like human ears and sheep meniscus disks, utilizing the bio-ink's shear-thinning properties. They showed that chondrocytes derived from humans, when bioprinted using the non-toxic nanocellulose-based bio-ink, demonstrated cell viability rates of 73% and 86% after 1 and 7 days of 3D culture, respectively.

Developing nanomaterials with electrical properties has opened up new possibilities for enhancing the multifunctional capabilities of hydrogels in tissue regenerative applications. Zhang and their team [392] demonstrated the potential of incorporating reduced graphene oxide (rGO) into hydrogels for skin regeneration. This not only improved antibacterial properties but also introduced electrical conductivity to the hydrogels. This electrical feature had a significant impact on cellular behaviors, including adhesion, proliferation, and migration, and it also caused damage to bacterial cell membranes. Furthermore, Dang and colleagues [393] explored the incorporation of carbon nanotubes (CNTs) and polypyrrole (PPY) into hydrogels. This approach enhanced hydrogels' ability to absorb near-infrared (NIR) light and convert it into heat. They observed that CNTs acted as physical crosslinking agents, while the flexible Poly(N-isopropyl acrylamide) chains formed an elastic network. These conductive hydrogels exhibit suitability for a wide range of applications, including smart electronics and biomedicine, such as pressure sensors and sensors for monitoring human motion.

6.2. Multifunctional self-healing hydrogels

In tissue-engineered skin, replacements have found widespread applications, and the implementation of hydrogel polymeric scaffold alternatives has been extensively extended in wound healing, particularly for deep burns and skin-related disorders [394]. Recent years have seen a great deal of interest in multi-functional self-healing hydrogels due to their high tunability and fast healing capabilities. Deng and colleagues [393] developed a cyclodextrin-based hydrogel that can be used as a biosensor and self-healing smart electronic device under near-infrared light. PH- and enzyme-responsive hydrogels were developed by Bilalis *et al.* for the treatment of pancreatic cancer [395]. Wang *et al.* developed a multifunctional wound-healing hydrogel that is both temperature-pH responsive and antimicrobial, a biomimetic self-healing strain-stiffening flexible hydrogel with antimicrobial properties, and an injectable self-healing hydrogel with anti-biofouling properties [396,397]. Furthermore, injectable hydrogels have successfully overcome the limitations of conventional hydrogel patches as postoperative anti-adhesion barriers for deep or narrow wounds and tissues with irregular shapes and folds. To further improve the postoperative anti-adhesion performance, supramolecular hydrogels [387] (Figure 12**b**), photo-crosslinked anti-adhesion hydrogels [398], and anti-biofouling hydrogels [399] were developed. In addition, a self-healing injectable anti-adhesive hydrogel that adapts to local biological environments (e.g., the gastric environment) is a significant challenge. Using dual-cross-linked network (DCN) hydrogels, Zhao *et al.* [400] demonstrated improved mechanical strength using dynamic imines and benzoxaboronic esters. DCN hydrogels exhibit excellent self-healing abilities after fractures and possess excellent potential as cell culture scaffolds due to their multiple responsiveness to pH, sugar, and hydrogen peroxide. By functionalizing poly[2-(dimethylamino)ethyl methacrylate] with light-activated 2-ureido-4-pyrimidone units, multi-responsive hydrogels with self-healing properties were developed. The response and the self-healing properties of these hydrogels are decoupled from each other and can be tuned independently in response to temperature, swelling and pH stimulation [401]. Under moisture, multivalent cations, and pH, Zhang *et al.* [402] developed a novel, highly stretchable hydrogel that was capable of self-healing, actuation, and shape memory. By providing multifunctionality and stretchability, hydrogels are suitable for electronic skin, actuators, and soft robotics applications. Cheng *et al.* [403] demonstrated that epsilon-PL/A-Pul/BPEI hydrogels with dynamic imine bonds crosslinking could serve as antitumor drug carriers *in vitro* and *in vivo*. With dynamic boronic ester bonds, Peng *et al.* [404] developed a bio-inspired self-healing hydrogel with multi-responsiveness, injectability, and tunable mechanical properties. Moreover, hydrogel scaffolds exhibit 3D cell encapsulation, which meets current biomedical demands [405]. In addition, a self-healing hydrogel was prepared by dynamic covalent bonds of borate esters in a photoinitiation polymerization process while displaying pH, temperature, glucose, and redox tetra-responsive derived

from the reversible dynamic covalent bonds. A multifunctional hydrogel has been recommended for use in sensors, actuators, and controlled drug delivery systems. Using boronate-catechol interactions between disulfide-containing, boronic acid-based crosslinkers and catechol-functionalized poly (N-isopropyl acrylamide), Chen *et al.* [406] developed a multifunctional hydrogel with a double dynamic network. In addition to temperature, pH, and glucose stimulus sensitivity, the hydrogel also demonstrated autonomic self-healing properties and biomimetic adhesion properties. Multi-responsive hydrogels can be achieved by using more than one dynamic cross-link within the network. The use of multiple cross-linking chemistries can, for instance, enable the fabrication of pH-sensitive hydrogel drug delivery systems [407].

6.3. Crosslink designing strategies

The management of polymeric cross-linking forms is another significant focus of ongoing research. In the design of dynamic polymer hydrogels, the cross-linking form is one of the most critical components [408]. In addition to the backbone chemistry of the polymer, the cross-linking density (the total number of physical or chemical cross-links in each volume) of the network plays a significant role in the physical and mechanical properties of hydrogels [408,409]. Besides solubility and swelling, cross-linking also affects the elasticity, viscosity, thermal stability, strength, and toughness of hydrogels and changes thermoplastics into thermosets depending on the degree of cross-linking [410]. Hydrogel can be applied in clinical applications by crosslinking in situ because of its negligible adverse effects on the body and easy formation in the desired shape for irregular injuries. Through a Schiff-base reaction, a novel type of in-situ crosslinked injectable hydrogel is fabricated using water-soluble oxidized chitosan (OC) and amidated pectin (AP). In addition to their in-situ crosslinking, AP-OC hydrogels have promising potential as wound dressings or skin substitutes [411]. The fabrication of a multifunctional self-healing hyaluronic acid-based hydrogel using an in-situ crosslinking strategy has recently been demonstrated with high mechanical strength, pH responsiveness, and cytocompatibility, making it ideal for cell culture, drug delivery, and 3D bioprinting [412]. Based on in-situ crosslinking (Schiff-based reaction) followed by UV irradiation, Fan *et al.* [413] constructed an injectable double-crosslinked hydrogel with excellent mechanical properties. García-Fernández *et al.* [414] synthesized injectable hydrogels loaded with anti-inflammatory drugs based on an in-situ crosslinking process. As a result of this research, C, H insertion crosslinking (CHic) has been recommended by Prucker *et al.* [415] for cartilage regeneration through surface-attached hydrogel coatings that were activated photochemically or thermally as a method of obtaining tailor-made bio-interfaces for implants and bioanalytical devices. Surface-attached gels prepared this way have unique swelling properties that prevent macromolecules from penetrating the layers, resulting in bioinert surfaces that are strongly protein- and cell-repellent. From biomolecules to living cells, this property can be used to control the interaction of surfaces with biological species. During simultaneous crosslinking and surface attachment, additional biomolecules present during the activation step, such as DNA or proteins, can also be incorporated into the formed network. Hydrogels with mild crosslinking reactions mediated by tyrosinase provide a dynamic scaffold that can be applied to a wide range of tissues, including tumor environments. As a potential structure for implantable bioelectronics, Choi *et al.* [416] suggested tyrosinase-mediated hydrogels as next-generation directions in enzyme-mediated systems. The one-way stiffness decreases or increases in crosslinking density at a constant temperature within the hydrogel polymer network was widely introduced by Ueki *et al.* [417] using a chemical or physical stimulus from the outside of the cell scaffold, the hydrogel can change its stiffness. Accordingly, the reversible stiffness changes property is suggested for some living tissues that are exposed to periodic stress changes, such as cardiomyocytes, are constantly exposed to heartbeats, and blood vessels undergo periodic stretching and compression synchronized with blood flow pulsations.

6.4. Complexly patterned hydrogels

Advances in 3D bioprinting techniques have enabled the precise fabrication of complex patterned hydrogel structures. Bioprinting allows the deposition of hydrogel materials layer-by-layer, creating intricate architectures that mimic native tissues [388]. Dynamic hydrogels offer several advantages in the context of 3D bioprinting. Firstly, their injectability and shear-thinning behavior enable the extrusion-based deposition of bioinks through fine nozzles, facilitating the fabrication of intricate tissue structures with high resolution [388]. The shear-thinning property allows the bioink to flow under shear stress during printing and regain its gel-like structure upon cessation of shear, ensuring the stability and integrity of printed construct [388] (Figure 12**c**). This property is particularly crucial for maintaining the structural fidelity of the printed tissues. Furthermore, the responsiveness of dynamic hydrogels to external stimuli can be harnessed to achieve spatial and temporal control over the deposition process. By incorporating stimuli-responsive elements into the bioink formulation, such as temperature-responsive or pH-responsive moieties, the gelation or crosslinking of the bioink can be triggered at specific locations or time points during the printing process [418]. This capability enables the precise patterning of multiple cell types or the sequential release of bioactive molecules within the printed construct, closely mimicking the complex architecture and functionality of native tissues.

Despite these advancements, challenges and limitations still need to be addressed in utilizing dynamic hydrogels for tissue fabrication. One challenge is achieving long-term stability and mechanical robustness of the printed constructs [419]. Dynamic hydrogels, by their nature, can undergo reversible changes and may exhibit weaker mechanical properties compared to static hydrogels. Strategies to enhance the mechanical strength and stability of printed dynamic hydrogel constructs, such as optimizing crosslinking mechanisms or incorporating reinforcing agents, need to be explored. Another consideration is the biocompatibility and biodegradability of dynamic hydrogels and their degradation byproducts [420]. To ensure the safety and functionality of the fabricated tissues, it is essential to carefully select and design the components of dynamic hydrogel systems. Biocompatible and biodegradable materials should be used to minimize any adverse effects on cells and surrounding tissues [421]. Furthermore, the kinetics and control of degradation should be precisely regulated to match the desired tissue regeneration timeline.

Dynamic hydrogels integrated with 3D bioprinting techniques have tremendous potential for advancing tissue fabrication and regenerative medicine. The ability of dynamic hydrogels to mimic the native ECM, respond to external stimuli, and provide a supportive microenvironment for cell growth and tissue development makes them highly versatile in creating functional tissue constructs. However, further research and development are needed to overcome mechanical stability, biocompatibility, and degradation control challenges. With continued innovation and interdisciplinary collaboration, dynamic hydrogels hold great promise for revolutionizing the field of tissue engineering and enabling the fabrication of complex and functional tissues for clinical applications.

Various strategies, such as extrusion-based, inkjet-based, and stereolithography-based bioprinting, have been employed to create patterned hydrogel constructs. Photolithography and other light-based patterning techniques have been utilized to create complex patterns within hydrogel matrices. Photocrosslinkable hydrogels, such as those based on methacrylated gelatin or polyethylene glycol (PEG), can be selectively crosslinked using light exposure through masks or advanced projection systems, allowing precise control over hydrogel structure and properties [422]. Microfluidics has emerged as a powerful tool for creating patterned hydrogels with high precision and control. Microfluidic devices are used to generate complex flow patterns and guide the

spatial distribution of hydrogel precursors, facilitating the formation of desired patterns [423]. This approach enables the creation of intricate structures, such as vascular networks or tissue-specific architectures, within hydrogel matrices. Self-assembly processes and molecular patterning techniques have been employed to create hierarchical structures within hydrogels. By incorporating specific molecular motifs or functional groups, hydrogel building blocks can self-assemble into complex patterns or structures [424]. Gradient hydrogel patterning techniques have been developed to create spatially varying properties or chemical cues within hydrogel matrices. Gradient formation methods, such as diffusion-based or microfluidic techniques, allow for the establishment of concentration gradients of bioactive molecules, growth factors, or mechanical properties within the hydrogel, enabling the study of cell behavior and tissue development [425]. These patterned hydrogels can be engineered to mimic the architecture and functionality of native tissues, such as blood vessels, cardiac tissue, or neural networks, facilitating tissue regeneration [426].

6.5. Self-folding hydrogels

Self-folding hydrogels have been explored as scaffolds for tissue engineering applications [427]. These hydrogels can be designed to fold into complex three-dimensional structures, mimicking the architecture of native tissues. By incorporating cells and bioactive cues, such as growth factors or extracellular matrix components, into the hydrogel, researchers can promote cell adhesion, migration, and tissue formation within the folded constructs. Self-folding hydrogels have been utilized for microgripping applications, enabling the manipulation of small objects or tissues at the microscale [428]. By incorporating stimuli-responsive hydrogels into micromechanical structures, researchers can achieve precise control over gripping and releasing forces. These self-folding hydrogel-based microgrippers have potential applications in minimally invasive surgeries, microassembly, and lab-on-a-chip systems. Self-folding hydrogels can be designed as shape-memory drug delivery systems. These hydrogels can undergo reversible shape changes in response to stimuli, such as temperature or pH, allowing them to encapsulate drugs or therapeutic agents in a compact form. Upon exposure to a specific stimulus, the hydrogel unfolds and releases the loaded payload, enabling controlled and targeted drug delivery [429]. Self-folding hydrogels can be integrated into surgical tools or medical devices to enable shape changes and enhance their functionality. For example, self-folding hydrogels can be used in the design of catheters or endoscopes that can navigate through complex anatomical structures more effectively [430]. The ability of these tools to self-fold allows for minimally invasive procedures and improved patient outcomes.

6.6. Dynamic hydrogels for guiding cell migration

Dynamic hydrogels offer the ability to precisely control and modulate the mechanical and biochemical properties of the microenvironment in real-time, allowing for a more accurate and dynamic representation of physiological conditions. Dynamic hydrogels with tuneable mechanical properties have been developed to investigate the influence of substrate stiffness, viscoelasticity, and stress relaxation on cell migration [389,431] (Figure 12**d**). Dynamic hydrogels have been engineered to provide spatiotemporal control over the presentation of biochemical cues for cell migration studies. These hydrogels can release or immobilize bioactive molecules, such as growth factors, chemokines, or cell adhesion ligands, in a controlled manner [432]. By modulating the timing and concentration of biochemical signals, researchers can investigate their effects on cell migration, including chemotaxis, haptotaxis, or contact guidance. Haptotactic gradient hydrogels have been developed to study cell migration in response to spatial gradients of adhesive ligands. These hydrogels can be designed to create gradients of cell adhesion ligands, such as ECM proteins, within the hydrogel matrix [433]. By culturing cells on these gradient hydrogels, researchers can investigate how cells sense and respond to different adhesive environments and how this impacts their migration and invasion capabilities. Hydrogels can also undergo cyclic or time-dependent changes in mechanical properties, such as strain, stiffness, or shear stress [389,434]. By subjecting cells to these dynamic mechanical cues, researchers can study how cells respond and adapt their migration behavior under physiological mechanical forces.

6.7. Biochemically responsive dynamic hydrogels

Recent advances in dynamic hydrogels with stimuli responsiveness to biochemical changes or DNA/RNA have shown great potential for various applications, including drug delivery, biosensing, and tissue engineering. Enzyme-responsive hydrogels have been designed to undergo changes in their properties or release cargo in response to specific enzymes [435]. These hydrogels can be engineered to incorporate enzyme-specific peptide substrates or cleavable linkers, allowing for controlled enzymatic degradation (*e.g.*, metalloproteinase, MMP) or triggered release of encapsulated molecules. This approach has been applied in various biomedical applications, including targeted drug delivery and enzyme-responsive biosensing. DNA/RNA-responsive hydrogels have emerged as versatile platforms for molecular recognition and controlled release. When the target DNA sequence is present, it triggers the dehybridization of the DNA crosslinkers, leading to the disassembly or degradation of the hydrogel and subsequent release of the encapsulated drugs [436]. The hydrogel can be designed to incorporate aptamers that specifically bind to a target analyte, such as a protein or a small molecule. When the target analyte is present, it binds to the aptamers, causing changes in the hydrogel properties, such as swelling or color change, which can be detected and quantified for biosensing purposes [437]. These recent advances in dynamic hydrogels with stimuli responsiveness to biochemical changes or DNA/RNA demonstrate their potential for a wide range of applications.

7. Conclusions and Future Prospects

In this comprehensive review, we have explored the design, fabrication, and biomedical applications of dynamic hydrogels, laying the foundation for groundbreaking advancements in the field. These remarkable materials, with their ability to dynamically respond to external stimuli, possess the potential to revolutionize various domains of biomedical engineering, thereby transforming healthcare and improving patient outcomes. Dynamic hydrogels have emerged as superior alternatives to conventional static hydrogels due to their unique capabilities. By incorporating reversible covalent bonds or supramolecular interactions, these hydrogels can undergo controlled changes in their properties in response to specific triggers. This inherent adaptability enables them to withstand the robust and ever-changing biophysical microenvironment, making them ideal candidates for on-demand functionality, such as triggered drug release, mechanical modulation, and controlled degradation. The integration of nanomaterials into dynamic hydrogels has unlocked a plethora of functionalities that were previously unattainable with conventional hydrogels. By judiciously designing nanocomposite hydrogels with diverse responsive mechanisms, such as chemical networks, physical networks, or hybrid combinations, we can achieve single-responsive, dual-responsive, or even multi-responsive behavior. This remarkable versatility opens up exciting avenues for applications in drug delivery, tissue engineering, bioadhesives, wound healing, cancer treatment, and mechanistic studies.

Looking towards the future, the potential of dynamic hydrogels in biomedical engineering is boundless. Next-generation hydrogels hold the promise of transforming multiple-scale biomedical applications. The design and engineering of advanced cell culture platforms using dynamic hydrogels will enable the creation of highly sophisticated three-dimensional environments to study cell-matrix interactions, fostering

breakthroughs in regenerative medicine, drug screening, and personalized therapies. The development of multifunctional self-healing hydrogels with exceptional mechanical properties will revolutionize the field of biomedical devices, leading to the creation of durable and long-lasting implants and prosthetics. Another exciting avenue is the development of dynamic hydrogels with stimuli-responsiveness to biochemical changes. By incorporating sensing elements and actuation systems, dynamic hydrogels can serve as intelligent biosensors and diagnostics, capable of detecting and responding to specific biomarkers or disease-associated signals. This has the potential to revolutionize disease diagnosis, monitoring, and personalized medicine, enabling timely interventions and precise therapeutic strategies.

However, to fully realize the world-changing potential of dynamic hydrogels, several challenges must be overcome. The integration of diverse technologies, such as advanced sensing platforms and actuators, necessitates interdisciplinary collaborations and innovative approaches. Scalability and reproducibility in fabrication methods must be improved to facilitate large-scale manufacturing of dynamic hydrogels, ensuring their widespread accessibility and affordability. Additionally, extensive evaluations of long-term stability, biocompatibility, and regulatory compliance are imperative to ensure the safety and efficacy of dynamic hydrogels in clinical settings.

Alongside these prospects, it is important to address the current drawbacks of dynamic hydrogel systems. Achieving long-term mechanical stability, improving biodegradability control, and minimizing potential toxicity or immunogenicity issues are key challenges that must be overcome. Innovative crosslinking strategies, integration of bioactive agents, and thorough biocompatibility assessments are essential steps toward mitigating these limitations. Hydrogel systems are typically created and synthesized at a small pilot-plant scale during the preclinical stages. Therefore, current good manufacturing practices (cGMP) are necessary for the clinical application and integration of biomaterial-based hydrogels in large-scale systems, as well as ensuring their compatibility. When these processes are carried out on a large scale, robustness, consistency between batches, safety profiles, reproducibility, and efficiency can be anticipated. Furthermore, the high water content of hydrogels adds complexity to the synthesis, fabrication, storage, sustainability, sterilization, and all related optimization processes. As previously discussed, gaining regulatory approval and FDA clearance can be lengthy, often taking years from lab synthesis to market introduction and monitoring. The variety of injectable hydrogel scaffolds and the range of crosslinking polymers and biomaterials used make their regulatory classification and approval complex [438].

In conclusion, dynamic hydrogels represent a paradigm shift in the field of biomedical engineering, holding immense potential to transform healthcare and improve patient outcomes. With their remarkable adaptability, responsiveness, and multifunctionality, dynamic hydrogels can revolutionize drug delivery, tissue engineering, biosensing, and diagnostics. By addressing the challenges ahead and fostering collaborations between scientists, engineers, clinicians, and regulatory bodies, we can unlock the full potential of dynamic hydrogels and propel them into the forefront of biomedical innovation, ultimately shaping the future of healthcare.

CRediT authorship contribution statement

Bohan Yin: Writing – original draft. **Monika Gosecka:** Writing – original draft, Formal analysis. **Mahdi Bodaghi:** Writing – original draft, Investigation. **Daniel Crespy:** Writing – original draft, Supervision, Methodology. **George Youssef:** Writing – original draft, Investigation. **Jagan Mohan Dodda:** Writing – original draft, Conceptualization, Writing – review & editing. **Siu Hong Dexter Wong:** Writing – original draft, Conceptualization, Writing – review & editing. **Abu Bin Imran:** Writing – original draft. **Mateusz Gosecki:** Writing – original draft. **Arjaree Jobdeedamrong:** Writing – original draft. **Moqaddaseh Afzali Naniz:** Writing – original draft. **Ali Zolfagharian:** Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data described in the article are openly available at https://doi.org/10.5281/zenodo.10000066. We would appreciate if other researchers could benefit from our literature and results. This will foster discussions and collaboration among scientists worldwide.

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References

[1] A.B. Imran, T. Seki, Y. Takeoka, Recent advances in hydrogels in terms of fast stimuli responsiveness and superior mechanical performance, Polym. J. 42 (11) (2010) 839–851.
[2] A. Imran, Design, development, characterization and application of smart polymeric hydrogel, Manufacturing Systems: Recent Progress Future Directions, Mellal MA , Nova Science Publishers, Inc 400 (2020) 11788-3619.
[3] N.A. Peppas, A.S. Hoffman. Hydrogels, Biomaterials science, Elsevier, 2020, pp. 153–166.
[4] Y.S. Zhang, A. Khademhosseini, Advances in engineering hydrogels, Sci. Cult. 356 (6337) (2017) eaaf3627.
[5] A. Richter, G. Paschew, S. Klatt, J. Lienig, K.-F. Arndt, H.-J.-P. Adler, Review on hydrogel-based pH sensors and microsensors, Sensors Actuators B: Chem. 8 (1) (2008) 561–581.
[6] Y. Wang, Programmable hydrogels, Biomater. Sci. 178 (2018) 663–680.
[7] B.D. Ratner, A.S. Hoffman, Synthetic hydrogels for biomedical applications, ACS Publications, 1976.
[8] Y. Huang, B. Yin, S.H.D. Wong, Multicomponent Hydrogels in Clinical and Pharmaceutical Applications, Multicomponent Hydrogels: Smart Materials for Biomedical Applications, The Royal Society of Chemistry, 2023, pp. 449–501.
[9] N. Annabi, A. Tamayol, J.A. Uquillas, M. Akbari, L.E. Bertassoni, C. Cha, G. Camci-Unal, M.R. Dokmeci, N.A. Peppas, A. Khademhosseini, 25th anniversary article: Rational design and applications of hydrogels in regenerative medicine, J. Adv. Mater. 26 (1) (2014) 85–124.
[10] J. Thiele, Y. Ma, S.M. Bruekers, S. Ma, W.T. Huck, 25th anniversary article: designer hydrogels for cell cultures: a materials selection guide, Adv. Mater. Processes 26 (1) (2014) 125–148.
[11] J. Liu, Y. Tan, H. Zhang, Y. Zhang, P. Xu, J. Chen, Y.C. Poh, K. Tang, N. Wang, B. Huang, Soft fibrin gels promote selection and growth of tumorigenic cells, Nat Mater 11 (8) (2012) 734–741, https://doi.org/10.1038/nmat3361.
[12] S.H.D. Wong, B. Yin, Z. Li, W. Yuan, Q. Zhang, X. Xie, Y. Tan, N. Wong, K. Zhang, L. Bian, Mechanical manipulation of cancer cell tumorigenicity via heat shock protein signaling, Sci. Adv. 9 (27) (2023) eadg9593, https://doi.org/10.1126/sciadv.adg9593.
[13] S.H.D. Wong, G.R. Deen, J.S. Bates, C. Maiti, C.Y.K. Lam, A. Pachauri, R. AlAnsari, P. Belsky, J. Yoon, J.M. Dodda, Smart Skin-Adhesive Patches: From Design to Biomedical Applications, Adv. Funct. Mater. 33 (14) (2023), https://doi.org/10.1002/adfm.202213560.
[14] W. Zou, J. Dong, Y. Luo, Q. Zhao, T. Xie, Dynamic covalent polymer networks: from old chemistry to modern day innovations, Adv. Mater. Processes 29 (14) (2017) 1606100.
[15] T. Maeda, H. Otsuka, A. Takahara, Dynamic covalent polymers: Reorganizable polymers with dynamic covalent bonds, Prog. Polym. Sci. 34 (7) (2009) 581–604.
[16] K. Zhang, Q. Feng, Z. Fang, L. Gu, L. Bian, Structurally dynamic hydrogels for biomedical applications: pursuing a fine balance between macroscopic stability and microscopic dynamics, Chem. Rev. 121 (18) (2021) 11149–11193.
[17] P. Chakma, D. Konkolewicz, Dynamic covalent bonds in polymeric materials, Angew. Chem. Int. Ed. 58 (29) (2019) 9682–9695.

[18] F.J. Vernerey, S.L. Sridhar, A. Muralidharan, S.J. Bryant, Mechanics of 3D Cell-Hydrogel Interactions: Experiments, Models, and Mechanisms, Chem. Rev. 121 (18) (2021) 11085–11148, https://doi.org/10.1021/acs.chemrev.1c00046.

[19] L. Hammer, N.J. Van Zee, R. Nicolaÿ, Dually crosslinked polymer networks incorporating dynamic covalent bonds, Polymers 13 (3) (2021) 396.

[20] F. Picchioni, H. Muljana, Hydrogels based on dynamic covalent and non covalent bonds: a chemistry perspective, Gels 4 (1) (2018) 21.

[21] H.G. Schild, Poly (N-isopropylacrylamide): experiment, theory and application, Prog. Polym. Sci. 17 (2) (1992) 163–249.

[22] L.F. Gudeman, N.A. Peppas, Preparation and characterization of pH-sensitive, interpenetrating networks of poly (vinyl alcohol) and poly (acrylic acid), J. Appl. Polym. Sci. 55 (6) (1995) 919–928.

[23] Y. Qiu, K. Park, Environment-sensitive hydrogels for drug delivery, Adv. Drug Deliv. Rev. 53 (3) (2001) 321–339, https://doi.org/10.1016/S0169-409x(01)00203-4.

[24] R.V. Ulijn, N. Bibi, V. Jayawarna, P.D. Thornton, S.J. Todd, R.J. Mart, A. M. Smith, J.E. Gough, Bioresponsive hydrogels, Mater. Today 10 (4) (2007) 40–48.

[25] L. Tan, M.H. Li, H. Chen, Y.C. Zhang, Y. Liu, M.H. Chen, Z. Luo, K.Y. Cai, Y. Hu, Dynamic hydrogel with environment-adaptive autonomous wound-compressing ability enables rapid hemostasis and inflammation amelioration for hemorrhagic wound healing, Nano Today 52 (2023) 101962, https://doi.org/10.1016/j.nantod.2023.101962.

[26] Y.Q. Zeng, C. Zhang, D. Du, Y. Li, L. Sun, Y.Y. Han, X.X. He, J.W. Dai, L.Y. Shi, Metal-organic framework-based hydrogel with structurally dynamic properties as a stimuli-responsive localized drug delivery system for cancer therapy, Acta Biomater 145 (2022) 43–51, https://doi.org/10.1016/j.actbio.2022.04.003.

[27] W.B. Wang, J.J. Dai, Y.F. Huang, X.M. Li, J.M. Yang, Y.Q. Zheng, X.A. Shi, Extracellular matrix mimicking dynamic interpenetrating network hydrogel for skin tissue engineering, Chem. Eng. J. 457 (2023) 141362. https://doi.org/10.1016/j.cej.2023.141362.

[28] H. Yuk, B. Lu, X. Zhao, Hydrogel bioelectronics, Chem. Soc. Rev. 48 (6) (2019) 1642–1667.

[29] R. Dong, Y. Pang, Y. Su, X. Zhu, Supramolecular hydrogels: synthesis, properties and their biomedical applications, Biomater. Sci. 3 (7) (2015) 937–954.

[30] S. Bashir, M. Hina, J. Iqbal, A. Rajpar, M. Mujtaba, N. Alghamdi, S. Wageh, K. Ramesh, S. Ramesh, Fundamental concepts of hydrogels: Synthesis, properties, and their applications, Polymers 12 (11) (2020) 2702.

[31] S.-L. Li, T. Xiao, C. Lin, L. Wang, Advanced supramolecular polymers constructed by orthogonal self-assembly, Chem. Soc. Rev. 41 (18) (2012) 5950–5968.

[32] R. Yang, X. Liu, Y. Ren, W. Xue, S. Liu, P. Wang, M. Zhao, H. Xu, B. Chi, Injectable adaptive self-healing hyaluronic acid/poly (γ-glutamic acid) hydrogel for cutaneous wound healing, Acta. Biomater. 127 (2021) 102–115.

[33] J.A. Burdick, W.L. Murphy, Moving from static to dynamic complexity in hydrogel design, Nat. Commun. 3 (1) (2012) 1269.

[34] H. Wang, S.C. Heilshorn, Adaptable hydrogel networks with reversible linkages for tissue engineering, Adv. Mater. Processes 27 (25) (2015) 3717–3736.

[35] A.M. Rosales, K.S. Anseth, The design of reversible hydrogels to capture extracellular matrix dynamics, Nat. Rev. Mater. 1 (2) (2016) 1–15.

[36] H. Cao, L. Duan, Y. Zhang, J. Cao, K. Zhang, Current hydrogel advances in physicochemical and biological response-driven biomedical application diversity, Signal Transduct Tar. 6 (1) (2021) 426.

[37] A.P. Dhand, J.H. Galarraga, J.A. Burdick, Enhancing biopolymer hydrogel functionality through interpenetrating networks, Trends Biotechnol. 39 (5) (2021) 519–538.

[38] K. Phogat, S.B. Ghosh, S. Bandyopadhyay-Ghosh, Recent advances on injectable nanocomposite hydrogels towards bone tissue rehabilitation, J. Appl. Polym. Sci. 140 (4) (2023) e53362.

[39] A. Mellati, E. Hasanzadeh, M. Gholipourmalekabadi, S.E. Enderami, Injectable nanocomposite hydrogels as an emerging platform for biomedical applications: A review, Mater. Sci. Eng. C 131 (2021) 112489.

[40] S. Mantha, S. Pillai, P. Khayambashi, A. Upadhyay, Y. Zhang, O. Tao, H.M. Pham, S.D. Tran, Smart hydrogels in tissue engineering and regenerative medicine, Materials 12 (20) (2019) 3323.

[41] A.K. Gaharwar, N.A. Peppas, A. Khademhosseini, Nanocomposite hydrogels for biomedical applications, Biotechnol. Bioeng. 111 (3) (2014) 441–453.

[42] R.Z. Tang, Z.Z. Liu, S.S. Gu, X.Q. Liu, Multiple local therapeutics based on nano-hydrogel composites in breast cancer treatment, J. Mater. Chem. B 9 (6) (2021) 1521–1535, https://doi.org/10.1039/d0tb02737e.

[43] A. Bin Imran, K. Esaki, H. Gotoh, T. Seki, K. Ito, Y. Sakai, Y.J.N.c., Takeoka, Extremely stretchable thermosensitive hydrogels by introducing slide-ring polyrotaxane cross-linkers and ionic groups into the polymer network, Nat. Commun. 5 (1) (2014) 5124.

[44] A.B. Ihsan, A.B. Imran, M.A.B.H. Susan, Advanced Functional Polymers: Properties and Supramolecular Phenomena in Hydrogels and Polyrotaxane-based Materials, Chemistry Africa 6 (1) (2023) 79–94.

[45] A.B. Imran, T. Seki, K. Ito, Y. Takeoka, Poly (N-isopropylacrylamide) gel prepared using a hydrophilic polyrotaxane-based movable cross-linker, Macromolecules 43 (4) (2010) 1975–1980.

[46] S. Khetan, M. Guvendiren, W.R. Legant, D.M. Cohen, C.S. Chen, J.A.J.N.m. Burdick, Degradation-mediated cellular traction directs stem cell fate in covalently crosslinked three-dimensional hydrogels, Nat. Mater 12 (5) (2013) 458–465.

[47] Y. Peng, Q.-J. Liu, T. He, K. Ye, X. Yao, J.J.B. Ding, Degradation rate affords a dynamic cue to regulate stem cells beyond varied matrix stiffness, Biomaterials 178 (2018) 467–480.

[48] N. Gjorevski, N. Sachs, A. Manfrin, S. Giger, M.E. Bragina, P. Ordóñez-Morán, H. Clevers, M.P.J.N. Lutolf, Designer matrices for intestinal stem cell and organoid culture, Nature 539 (7630) (2016) 560–564.

[49] R.J. Wojtecki, M.A. Meador, S.J.J.N.M. Rowan, Using the dynamic bond to access macroscopically responsive structurally dynamic polymers, Nat. Mater 10 (1) (2011) 14–27.

[50] T. Matsuda, R. Kawakami, R. Namba, T. Nakajima, J.P.J.S. Gong, Mechanoresponsive self-growing hydrogels inspired by muscle training, Science 363 (6426) (2019) 504–508.

[51] C.B. Rodell, J.E. Mealy, J.A. Burdick, Supramolecular guest–host interactions for the preparation of biomedical materials, Bioconjug. Chem. 26 (12) (2015) 2279–2289.

[52] S. Tang, B.M. Richardson, K.S. Anseth, Dynamic covalent hydrogels as biomaterials to mimic the viscoelasticity of soft tissues, Prog. Mater. Sci. 120 (2021) 100738.

[53] X. Ding, Y. Wang, Weak bond-based injectable and stimuli responsive hydrogels for biomedical applications, J. Mater. Chem. B 5 (5) (2017) 887–906.

[54] F. Seidi, R. Jenjob, D. Crespy, Designing Smart Polymer Conjugates for Controlled Release of Payloads, Chem. Rev. 118 (7) (2018) 3965–4036, https://doi.org/10.1021/acs.chemrev.8b00006.

[55] E.N. Zare, P. Makvandi, Stimuli-Responsive Materials for Biomedical Applications, ACS Publications (2023).

[56] Y. Wang, C.K. Adokoh, R. Narain, Recent development and biomedical applications of self-healing hydrogels, Expert Opin. Drug Deliv. 15 (1) (2018) 77–91.

[57] S. Huang, X. Hong, M. Zhao, N. Liu, H. Liu, J. Zhao, L. Shao, W. Xue, H. Zhang, P. Zhu, Nanocomposite hydrogels for biomedical applications, Bioeng. Transl. Med. 7 (3) (2022) e10315.

[58] L. Shi, Y. Zhao, Q. Xie, C. Fan, J. Hilborn, J. Dai, D.A. Ossipov, Moldable hyaluronan hydrogel enabled by dynamic metal–bisphosphonate coordination chemistry for wound healing, Adv. Healthc. Mater. 7 (5) (2018) 1700973.

[59] Y. Osada, Gels Handbook, Four-Volume Set, Elsevier2000.

[60] Q. Feng, K. Wei, S. Lin, Z. Xu, Y. Sun, P. Shi, G. Li, L. Bian, Mechanically resilient, injectable, and bioadhesive supramolecular gelatin hydrogels crosslinked by weak host-guest interactions assist cell infiltration and in situ tissue regeneration, Biomater. Sci. 101 (2016) 217–228.

[61] I. Levental, P.C. Georges, P.A. Janmey, Soft biological materials and their impact on cell function, Soft Matter 3 (3) (2007) 299–306.

[62] O. Chaudhuri, Viscoelastic hydrogels for 3D cell culture, Biomater. Sci. 5 (8) (2017) 1480–1490.

[63] M. Darnell, S. Young, L. Gu, N. Shah, E. Lippens, J. Weaver, G. Duda, D. Mooney, Substrate stress-relaxation regulates scaffold remodeling and bone formation in vivo, Adv. Healthc. Mater. 6 (1) (2017) 1601185.

[64] Y.J. Chuah, Y. Peck, J.E.J. Lau, H.T. Hee, D.-A. Wang, Hydrogel based cartilaginous tissue regeneration: recent insights and technologies, Biomater. Sci. 5 (4) (2017) 613–631.

[65] T. Distler, A.R. Boccaccini, 3D printing of electrically conductive hydrogels for tissue engineering and biosensors–A review, Acta Biomater. 101 (2020) 1–13.

[66] C. Xu, G. Dai, Y. Hong, Recent advances in high-strength and elastic hydrogels for 3D printing in biomedical applications, Acta Biomater. 95 (2019) 50–59.

[67] P. Rastogi, B. Kandasubramanian, Review of alginate-based hydrogel bioprinting for application in tissue engineering, Biofabrication 11 (4) (2019) 042001.

[68] B. Peña, M. Laughter, S. Jett, T.J. Rowland, M.R. Taylor, L. Mestroni, D. Park, Injectable hydrogels for cardiac tissue engineering, Macromol. Biosci. 18 (6) (2018) 1800079.

[69] L.L. Wang, J.A. Burdick, Engineered Hydrogels for Local and Sustained Delivery of RNA-Interference Therapies, Adv. Healthc. Mater. 6 (1) (2017) 1601041.

[70] R.C. Cooper, H. Yang, Hydrogel-based ocular drug delivery systems: Emerging fabrication strategies, applications, and bench-to-bedside manufacturing considerations, J. Controlled Release 306 (2019) 29–39.

[71] J. Ostrowska-Czubenko, M. Gierszewska-Drużyńska, Effect of ionic crosslinking on the water state in hydrogel chitosan membranes, Carbohydr. Polym. 77 (3) (2009) 590–598.

[72] L.T. Saldin, M.C. Cramer, S.S. Velankar, L.J. White, S.F. Badylak, Extracellular matrix hydrogels from decellularized tissues: Structure and function, Acta Biomater. 49 (2017) 1–15.

[73] S.P. Zustiak, R. Durbal, J.B. Leach, Influence of cell-adhesive peptide ligands on poly (ethylene glycol) hydrogel physical, mechanical and transport properties, Acta Biomater. 6 (9) (2010) 3404–3414.

[74] Y. Wei, W. Tian, X. Yu, F. Cui, S. Hou, Q. Xu, I.-S. Lee, Hyaluronic acid hydrogels with IKVAV peptides for tissue repair and axonal regeneration in an injured rat brain, Biomed. Mater. 2 (3) (2007) S142.

[75] C. Mao, Y. Xiang, X. Liu, Z. Cui, X. Yang, K.W.K. Yeung, H. Pan, X. Wang, P. K. Chu, S. Wu, Photo-inspired antibacterial activity and wound healing acceleration by hydrogel embedded with Ag/Ag@ AgCl/ZnO nanostructures, ACS Nano 11 (9) (2017) 9010–9021.

[76] K. Zhang, S. Lin, Q. Feng, C. Dong, Y. Yang, G. Li, L. Bian, Nanocomposite hydrogels stabilized by self-assembled multivalent bisphosphonate-magnesium nanoparticles mediate sustained release of magnesium ion and promote in-situ bone regeneration, Acta Biomater. 64 (2017) 389–400.

[77] V.S. Madamsetty, M. Vazifehdoost, S.H. Alhashemi, H. Davoudi, A. Zarrabi, A. Dehshahri, H.S. Fekri, R. Mohammadinejad, V.K. Thakur, Next-Generation Hydrogels as Biomaterials for Biomedical Applications: Exploring the Role of Curcumin, ACS omega (2023).

[78] A. Kumar, A. Datta, A. Kumar, A. Kumar, Recent advancements and future trends in next-generation materials for biomedical applications, CRC Press, Advanced Materials for Biomedical Applications, 2022, pp. 1–19.
[79] S.H.D. Wong, X. Xu, X. Chen, Y. Xin, L. Xu, C.H.N. Lai, J. Oh, W.K.R. Wong, X. Wang, S. Han, W. You, X. Shuai, N. Wong, Y. Tan, L. Duan, L. Bian, Manipulation of the Nanoscale Presentation of Integrin Ligand Produces Cancer Cells with Enhanced Stemness and Robust Tumorigenicity, Nano Lett 21 (7) (2021) 3225–3236, https://doi.org/10.1021/acs.nanolett.1c00501.
[80] Y. Han, Y. Cao, H. Lei, Dynamic Covalent Hydrogels: Strong yet Dynamic, Gels 8 (9) (2022), https://doi.org/10.3390/gels8090577.
[81] A.M.S. Costa, J.F. Mano, Extremely strong and tough hydrogels as prospective candidates for tissue repair - A review, Eur. Polym. J. 72 (2015) 344–364, https://doi.org/10.1016/j.eurpolymj.2015.07.053.
[82] A.M. Kloxin, C.J. Kloxin, C.N. Bowman, K.S. Anseth, Mechanical Properties of Cellularly Responsive Hydrogels and Their Experimental Determination, Adv. Mater. 22 (31) (2010) 3484–3494, https://doi.org/10.1002/adma.200904179.
[83] Y. Han, Y. Cao, H. Lei, Dynamic Covalent Hydrogels: Strong yet Dynamic, Gels 8 (9) (2022) 577.
[84] J. Dahlke, S. Zechel, M.D. Hager, U.S. Schubert, How to design a self-healing polymer: general concepts of dynamic covalent bonds and their application for intrinsic healable materials, Adv. Mater. Interfaces 5 (17) (2018) 1800051.
[85] T. Yimyai, R. Thiramanas, T. Phakkeeree, S. Iamsaard, D. Crespy, Adaptive Coatings with Anticorrosion and Antibiofouling Properties, Adv. Funct. Mater. 31 (37) (2021) 2102568. https://doi.org/10.1002/adfm.202102568.
[86] S.Y. Lee, H. Lee, I. In, S.Y. Park, pH/redox/photo responsive polymeric micelle via boronate ester and disulfide bonds with spiropyran-based photochromic polymer for cell imaging and anticancer drug delivery, Eur. Polym. J. 57 (2014) 1–10, https://doi.org/10.1016/j.eurpolymj.2014.04.020.
[87] Z. Stillman, B.M. Jarai, N. Raman, P. Patel, C.A. Fromen, Degradation profiles of poly(ethylene glycol)diacrylate (PEGDA)-based hydrogel nanoparticles, Polym Chem-Uk 11 (2) (2020) 568–580, https://doi.org/10.1039/c9py01206k.
[88] O. Yom-Tov, D. Seliktar, H. Bianco-Peled, PEG-Thiol based hydrogels with controllable properties, Eur. Polym. J. 74 (2016) 1–12, https://doi.org/10.1016/j.eurpolymj.2015.11.002.
[89] J.Q. Gan, X.X. Guan, J. Zheng, H.L. Guo, K. Wu, L.Y. Liang, M.G. Lu, Biodegradable, thermoresponsive PNIPAM-based hydrogel scaffolds for the sustained release of levofloxacin, Rsc Adv. 6 (39) (2016) 32967–32978, https://doi.org/10.1039/c6ra03045a.
[90] X.M. Xu, Y. Liu, W.B. Fu, M.Y. Yao, Z. Ding, J.M. Xuan, D.X. Li, S.J. Wang, Y.Q. Xia, M.W. Cao, Poly(N-isopropylacrylamide)-Based Thermoresponsive Composite Hydrogels for Biomedical Applications, Polymers-Basel 12(3) (2020). https://doi.org/ARTN 58010.3390/polym12030580.
[91] S. Ji, W. Cao, Y. Yu, H. Xu, Dynamic diselenide bonds: exchange reaction induced by visible light without catalysis, Angew. Chem. Int. Ed. 53 (26) (2014) 6781–6785.
[92] S. Muller, H. Senn, B. Gsell, W. Vetter, C. Baron, A. Bock, The Formation of Diselenide Bridges in Proteins by Incorporation of Selenocysteine Residues - Biosynthesis and Characterization of (Se)(2)-Thioredoxin, Biochemistry-Us 33 (11) (1994) 3404-3412. https://doi.org/DOI 10.1021/bi00177a034.
[93] M.Y. Folikumah, M. Behl, A. Lendlein, Thiol-Thioester Exchange Reactions in Precursors Enable pH-Triggered Hydrogel Formation, Biomacromolecules 22 (5) (2021) 1875–1884.
[94] M.M. Perera, N. Ayres, Dynamic covalent bonds in self-healing, shape memory, and controllable stiffness hydrogels, Polym. Chem. 11 (8) (2020) 1410–1423.
[95] R.A. Smith, G.Y. Fu, O. McAteer, M.Z. Xu, W.R. Gutekunst, Radical Approach to Thioester-Containing Polymers, J. Am. Chem. Soc. 141 (4) (2019) 1446–1451, https://doi.org/10.1021/jacs.8b12154.
[96] H. Sun, D.J. Dobbins, Y.Q. Dai, C.P. Kabb, S.J. Wu, J.A. Alfurhood, C. Rinaldi, B. S. Sumerlin, Radical Departure: Thermally-Triggered Degradation of Azo-Containing Poly(β-thioester)s, Acs Macro Lett. 5 (6) (2016) 688–693, https://doi.org/10.1021/acsmacrolett.6b00327.
[97] C.L. Lewis, E.M. Dell, A review of shape memory polymers bearing reversible binding groups, J. Polym. Sci. B 54 (14) (2016) 1340–1364.
[98] C.J. Kloxin, C.N. Bowman, Covalent adaptable networks: smart, reconfigurable and responsive network systems, Chem. Soc. Rev. 42 (17) (2013) 7161–7173.
[99] A.W. Jackson, D.A. Fulton, Making polymeric nanoparticles stimuli-responsive with dynamic covalent bonds, Polym. Chem. 4 (1) (2013) 31–45.
[100] R.J. Wojtecki, M.A. Meador, S.J. Rowan, Using the dynamic bond to access macroscopically responsive structurally dynamic polymers, Nat. Mater. 10 (1) (2011) 14–27.
[101] S. Mukherjee, M.R. Hill, B.S. Sumerlin, Self-healing hydrogels containing reversible oxime crosslinks, Soft Matter 11 (30) (2015) 6152–6161.
[102] E. Khare, N. Holten-Andersen, M.J. Buehler, Transition-metal coordinate bonds for bioinspired macromolecules with tunable mechanical properties, Nat. Rev. Mater. 6 (5) (2021) 421–436.
[103] R. Parhi, Cross-linked hydrogel for pharmaceutical applications: A review, Advanced pharmaceutical bulletin 7 (4) (2017) 515–530.
[104] A.Y. Mehandzhiyski, E. Riccardi, T.S. van Erp, T.T. Trinh, B.A. Grimes, Ab Initio Molecular Dynamics Study on the Interactions between Carboxylate Ions and Metal Ions in Water, J. Phys. Chem. B 119 (33) (2015) 10710–10719, https://doi.org/10.1021/acs.jpcb.5b05616.
[105] F. García, M.M. Smulders, Dynamic covalent polymers, J. Polym. Sci. A Polym. Chem. 54 (22) (2016) 3551–3577.
[106] L.S.M. Teixeira, J. Feijen, C.A. van Blitterswijk, P.J. Dijkstra, M. Karperien, Enzyme-catalyzed crosslinkable hydrogels: Emerging strategies for tissue engineering, Biomaterials 33 (5) (2012) 1281–1290, https://doi.org/10.1016/j.biomaterials.2011.10.067.
[107] D. Aeschlimann, M. Paulsson, Transglutaminases - Protein Cross-Linking Enzymes in Tissues and Body-Fluids, Thromb Haemostasis 71 (4) (1994) 402–415.
[108] J.J. Sperinde, L.G. Griffith, Synthesis and characterization of enzymatically-cross-linked poly(ethylene glycol) hydrogels, Macromolecules 30(18) (1997) 5255-5264. https://doi.org/DOI 10.1021/ma970345a.
[109] B.H. Hu, P.B. Messersmith, Enzymatically cross-linked hydrogels and their adhesive strength to biosurfaces, Orthod. Craniofac. Res. 8 (3) (2005) 145–149, https://doi.org/10.1111/j.1601-6343.2005.00330.x.
[110] C.W. Yung, W.E. Bentley, T.A. Barbari, Diffusion of interleukin-2 from cells overlaid with cytocompatible enzyme-crosslinked gelatin hydrogels, J. Biomed. Mater. Res. A 95a(1) (2010) 25–32, https://doi.org/10.1002/jbm.a.32740.
[111] C.R. Ratwani, A. Abdelkader, Self-healing by Diels-Alder cycloaddition in advanced functional polymers: A review, Prog. Mater Sci. 101001 (2022).
[112] J. Jin, L. Cai, Y.-G. Jia, S. Liu, Y. Chen, L. Ren, Progress in self-healing hydrogels assembled by host–guest interactions: preparation and biomedical applications, J. Mater. Chem. B 7 (10) (2019) 1637–1651.
[113] G. Liu, Q. Yuan, G. Hollett, W. Zhao, Y. Kang, J. Wu, Cyclodextrin-based host–guest supramolecular hydrogel and its application in biomedical fields, Polym. Chem. 9 (25) (2018) 3436–3449.
[114] X. Ji, M. Ahmed, L. Long, N.M. Khashab, F. Huang, J.L. Sessler, Adhesive supramolecular polymeric materials constructed from macrocycle-based host–guest interactions, Chem. Soc. Rev. 48 (10) (2019) 2682–2697.
[115] S.M. Mantooth, B.G. Munoz-Robles, M.J. Webber, Dynamic Hydrogels from Host-Guest Supramolecular Interactions, Macromol. Biosci. 19 (1) (2019) e1800281.
[116] G. Youssef, Applied mechanics of polymers: properties, processing, and behavior, Elsevier, 2021.
[117] H. Somaweera, A. Ibraguimov, D. Pappas, A review of chemical gradient systems for cell analysis, Anal. Chim. Acta 907 (2016) 7–17.
[118] J. Maitra, V.K. Shukla, Cross-linking in hydrogels-a review, Am. J. Polym. Sci 4 (2) (2014) 25–31.
[119] B.S. Kaith, A. Singh, A.K. Sharma, D. Sud, Hydrogels: Synthesis, classification, properties and potential applications—a brief review, J. Polym. Environ. 29 (12) (2021) 3827–3841.
[120] Y. Oladosu, M.Y. Rafii, F. Arolu, S.C. Chukwu, M.A. Salisu, I.K. Fagbohun, T. K. Muftaudeen, S. Swaray, B.S. Haliru, Superabsorbent polymer hydrogels for sustainable agriculture: A review, Horticulturae 8 (7) (2022) 605.
[121] H. Khalesi, W. Lu, K. Nishinari, Y. Fang, New insights into food hydrogels with reinforced mechanical properties: A review on innovative strategies, Adv. Colloid Interface Sci. 285 (2020) 102278.
[122] A.S. Hoffman, Hydrogels for biomedical applications, Ann. N. Y. Acad. Sci. 944 (1) (2001) 62–73.
[123] C.J. Flaim, D. Teng, S. Chien, S.N. Bhatia, Combinatorial signaling microenvironments for studying stem cell fate, Stem Cells Dev. 17 (1) (2008) 29–40.
[124] N. Martin, G. Youssef, Dynamic properties of hydrogels and fiber-reinforced hydrogels, J. Mech. Behav. Biomed. Mater. 85 (2018) 194–200.
[125] S. Abdurrahmanoglu, V. Can, O. Okay, Design of high-toughness polyacrylamide hydrogels by hydrophobic modification, Polymer 50 (23) (2009) 5449–5455.
[126] W. Li, H. An, Y. Tan, C. Lu, C. Liu, P. Li, K. Xu, P. Wang, Hydrophobically associated hydrogels based on acrylamide and anionic surface active monomer with high mechanical strength, Soft Matter 8 (18) (2012) 5078–5086.
[127] J. You, S. Xie, J. Cao, H. Ge, M. Xu, L. Zhang, J. Zhou, Quaternized chitosan/poly (acrylic acid) polyelectrolyte complex hydrogels with tough, self-recovery, and tunable mechanical properties, Macromolecules 49 (3) (2016) 1049–1059.
[128] F. Luo, T.L. Sun, T. Nakajima, T. Kurokawa, Y. Zhao, K. Sato, A.B. Ihsan, X. Li, H. Guo, J.P. Gong, Oppositely charged polyelectrolytes form tough, self-healing, and rebuildable hydrogels, Adv. Mater. 27 (17) (2015) 2722–2727.
[129] Q. Chen, L. Zhu, H. Chen, H. Yan, L. Huang, J. Yang, J. Zheng, A novel design strategy for fully physically linked double network hydrogels with tough, fatigue resistant, and self-healing properties, Adv. Funct. Mater. 25 (10) (2015) 1598–1607.
[130] J.P. Gong, Why are double network hydrogels so tough? Soft Matter 6 (12) (2010) 2583–2590.
[131] T. Bai, P. Zhang, Y. Han, Y. Liu, W. Liu, X. Zhao, W. Lu, Construction of an ultrahigh strength hydrogel with excellent fatigue resistance based on strong dipole–dipole interaction, Soft Matter 7 (6) (2011) 2825–2831.
[132] L. Tang, W. Liu, G. Liu, High-Strength Hydrogels with Integrated Functions of H-bonding and Thermoresponsive Surface-Mediated Reverse Transfection and Cell Detachment, Adv. Mater. 22 (24) (2010) 2652–2656.
[133] Y. Yue, X. Wang, Q. Wu, J. Han, J. Jiang, Highly recyclable and super-tough hydrogel mediated by dual-functional TiO2 nanoparticles toward efficient photodegradation of organic water pollutants, J. Colloid Interface Sci. 564 (2020) 99–112.
[134] G. Gao, G. Du, Y. Sun, J. Fu, Self-healable, tough, and ultrastretchable nanocomposite hydrogels based on reversible polyacrylamide/montmorillonite adsorption, ACS Appl. Mater. Interfaces 7 (8) (2015) 5029–5037.
[135] X. Ren, C. Huang, L. Duan, B. Liu, L. Bu, S. Guan, J. Hou, H. Zhang, G. Gao, Super-tough, ultra-stretchable and strongly compressive hydrogels with core–shell latex particles inducing efficient aggregation of hydrophobic chains, Soft Matter 13 (18) (2017) 3352–3358.
[136] M. Ramchandani, G. Rath, A. Goyal, Advances in hydrogel-based controlled drug-delivery systems, Smart Polymeric Nano-Constructs in Drug Delivery, Elsevier (2023) 329–350.

[137] M.H. Shahriari, A. Hadjizadeh, M. Abdouss, Advances in self-healing hydrogels to repair tissue defects, Polym. Bull. 80 (2) (2023) 1155–1177.
[138] S. Ahmad, M. Ahmad, K. Manzoor, R. Purwar, S. Ikram, A review on latest innovations in natural gums based hydrogels: Preparations & applications, Int. J. Biol. Macromol. 136 (2019) 870–890, https://doi.org/10.1016/j.ijbiomac.2019.06.113.
[139] R. Mohammadinejad, A. Kumar, M. Ranjbar-Mohammadi, M. Ashrafizadeh, S.S. Han, G. Khang, Z. Roveimiab, Recent Advances in Natural Gum-Based Biomaterials for Tissue Engineering and Regenerative Medicine: A Review, Polymers-Basel 12(1) (2020). https://doi.org/ARTN 17610.3390/polym12010176.
[140] K.M. Zia, S. Tabasum, M.F. Khan, N. Akram, N. Akhter, A. Noreen, M. Zuber, Recent trends on gellan gum blends with natural and synthetic polymers: A review, Int. J. Biol. Macromol. 109 (2018) 1068–1087, https://doi.org/10.1016/j.ijbiomac.2017.11.099.
[141] W. Hu, Z. Wang, Y. Xiao, S. Zhang, J. Wang, Advances in crosslinking strategies of biomedical hydrogels, Biomater. Sci. 7 (3) (2019) 843–855.
[142] J.-Y. Sun, X. Zhao, W.R. Illeperuma, O. Chaudhuri, K.H. Oh, D.J. Mooney, J. J. Vlassak, Z. Suo, Highly stretchable and tough hydrogels, Nature 489 (7414) (2012) 133–136.
[143] J.P. Gong, Y. Katsuyama, T. Kurokawa, Y. Osada, Double-network hydrogels with extremely high mechanical strength, Adv. Mater. 15 (14) (2003) 1155–1158.
[144] M.M. El Sayed, Production of Polymer Hydrogel Composites and Their Applications, J. Polym. Environ. (2023) 1–25.
[145] G.R. Bharskar, A review on hydrogel, World, J. Pharm. Pharm. Sci 9 (2020) 1288–1298.
[146] M.A. Gonzalez, J.R. Simon, A. Ghoorchian, Z. Scholl, S. Lin, M. Rubinstein, P. Marszalek, A. Chilkoti, G.P. López, X. Zhao, Strong, tough, stretchable, and self-adhesive hydrogels from intrinsically unstructured proteins, Adv. Mater. 29 (10) (2017) 1604743.
[147] T.L. Sun, T. Kurokawa, S. Kuroda, A.B. Ihsan, T. Akasaki, K. Sato, M.A. Haque, T. Nakajima, J.P. Gong, Physical hydrogels composed of polyampholytes demonstrate high toughness and viscoelasticity, Nat. Mater. 12 (10) (2013) 932–937.
[148] C.H. Yang, M.X. Wang, H. Haider, J.H. Yang, J.-Y. Sun, Y.M. Chen, J. Zhou, Z. Suo, Strengthening alginate/polyacrylamide hydrogels using various multivalent cations, ACS Appl. Mater. Interfaces 5 (21) (2013) 10418–10422.
[149] B. Zhang, Z. Gao, G. Gao, W. Zhao, J. Li, X. Ren, Highly Mechanical and Fatigue-Resistant Double Network Hydrogels by Dual Physically Hydrophobic Association and Ionic Crosslinking, Macromol. Mater. Eng. 303 (7) (2018) 1800072.
[150] M.C. Darnell, J.-Y. Sun, M. Mehta, C. Johnson, P.R. Arany, Z. Suo, D.J. Mooney, Performance and biocompatibility of extremely tough alginate/polyacrylamide hydrogels, Biomaterials 34 (33) (2013) 8042–8048.
[151] J. Li, Z. Suo, J.J. Vlassak, Stiff, strong, and tough hydrogels with good chemical stability, J. Mater. Chem. B 2 (39) (2014) 6708–6713.
[152] X. Yan, Q. Chen, L. Zhu, H. Chen, D. Wei, F. Chen, Z. Tang, J. Yang, J. Zheng, High strength and self-healable gelatin/polyacrylamide double network hydrogels, J. Mater. Chem. B 5 (37) (2017) 7683–7691.
[153] Q. Chen, D. Wei, H. Chen, L. Zhu, C. Jiao, G. Liu, L. Huang, J. Yang, L. Wang, J. Zheng, Simultaneous enhancement of stiffness and toughness in hybrid double-network hydrogels via the first, physically linked network, Macromolecules 48 (21) (2015) 8003–8010.
[154] S. Rafieian, H. Mirzadeh, H. Mahdavi, M.E. Masoumi, A review on nanocomposite hydrogels and their biomedical applications, Sci. Eng. Compos. Mater. 26 (1) (2019) 154–174.
[155] K. Haraguchi, T. Takehisa, Nanocomposite hydrogels: A unique organic–inorganic network structure with extraordinary mechanical, optical, and swelling/de-swelling properties, Adv. Mater. 14 (16) (2002) 1120–1124.
[156] C. Cha, S.R. Shin, N. Annabi, M.R. Dokmeci, A. Khademhosseini, Carbon-based nanomaterials: multifunctional materials for biomedical engineering, ACS Nano 7 (4) (2013) 2891–2897.
[157] A.K. Gaharwar, V. Kishore, C. Rivera, W. Bullock, C.J. Wu, O. Akkus, G. Schmidt, Physically crosslinked nanocomposites from silicate-crosslinked PEO: mechanical properties and osteogenic differentiation of human mesenchymal stem cells, Macromol. Biosci. 12 (6) (2012) 779–793.
[158] A.K. Gaharwar, S.M. Mihaila, A. Swami, A. Patel, S. Sant, R.L. Reis, A.P. Marques, M.E. Gomes, A. Khademhosseini, Bioactive silicate nanoplatelets for osteogenic differentiation of human mesenchymal stem cells, Adv. Mater. 25 (24) (2013) 3329–3336.
[159] S. Fuchs, K. Shariati, M. Ma, Specialty tough hydrogels and their biomedical applications, Adv. Healthc. Mater. 9 (2) (2020) 1901396.
[160] X. Zhang, J. Xiang, Y. Hong, L. Shen, Recent Advances in Design Strategies of Tough Hydrogels, Macromol. Rapid Commun. 43 (15) (2022) 2200075.
[161] M.A. Haque, T. Kurokawa, J.P. Gong, Super tough double network hydrogels and their application as biomaterials, Polymer 53 (9) (2012) 1805–1822.
[162] H. Tsukeshiba, M. Huang, Y.-H. Na, T. Kurokawa, R. Kuwabara, Y. Tanaka, H. Furukawa, Y. Osada, J.P. Gong, Effect of polymer entanglement on the toughening of double network hydrogels, J. Phys. Chem. B 109 (34) (2005) 16304–16309.
[163] T. Nakajima, H. Furukawa, Y. Tanaka, T. Kurokawa, Y. Osada, J.P. Gong, True chemical structure of double network hydrogels, Macromolecules 42 (6) (2009) 2184–2189.
[164] Q. Liu, J. Liu, S. Qin, Y. Pei, X. Zheng, K. Tang, High mechanical strength gelatin composite hydrogels reinforced by cellulose nanofibrils with unique beads-on-a-string morphology, Int. J. Biol. Macromol. 164 (2020) 1776–1784.
[165] T. Peng, J. Zhu, T. Huang, C. Jiang, F. Zhao, S. Ge, L. Xie, Facile preparation for gelatin/hydroxyethyl cellulose-SiO2 composite aerogel with good mechanical strength, heat insulation, and water resistance, J. Appl. Polym. Sci. 138 (23) (2021) 50539.
[166] X. Zhao, Multi-scale multi-mechanism design of tough hydrogels: building dissipation into stretchy networks, Soft Matter 10 (5) (2014) 672–687.
[167] M.-M. Song, Y.-M. Wang, B. Wang, X.-Y. Liang, Z.-Y. Chang, B.-J. Li, S. Zhang, Super tough, ultrastretchable hydrogel with multistimuli responsiveness, ACS Appl. Mater. Interfaces 10 (17) (2018) 15021–15029.
[168] L. Wang, H.J. Zhang, X. Liu, Y. Liu, X. Zhu, X. Liu, X. You, A physically cross-linked sodium alginate–gelatin hydrogel with high mechanical strength, ACS Appl. Polym. Mater. 3 (6) (2021) 3197–3205.
[169] H.J. Chung, Y.H. Lee, T.G. Park, Thermo-sensitive and biodegradable hydrogels based on stereocomplexed Pluronic multi-block copolymers for controlled protein delivery, J Control Release 127 (1) (2008) 22–30, https://doi.org/10.1016/j.jconrel.2007.12.008.
[170] C.M. Cleetus, F.A. Primo, G. Fregoso, N.L. Raveendran, J.C. Noveron, C. T. Spencer, C.V. Ramana, B. Joddar, Alginate Hydrogels with Embedded ZnO Nanoparticles for Wound Healing Therapy, Int. J. Nanomed. 15 (2020) 5097–5111, https://doi.org/10.2147/Ijn.S255937.
[171] M. Zhang, X. Zhao, Alginate hydrogel dressings for advanced wound management, Int. J. Biol. Macromol. 162 (2020) 1414–1428, https://doi.org/10.1016/j.ijbiomac.2020.07.311.
[172] S.J. Bidarra, C.C. Barrias, P.L. Granja, Injectable alginate hydrogels for cell delivery in tissue engineering, Acta Biomater. 10 (4) (2014) 1646–1662, https://doi.org/10.1016/j.actbio.2013.12.006.
[173] A.C. Hernández-González, L. Téllez-Jurado, L.M. Rodríguez-Lorenzo, Alginate hydrogels for bone tissue engineering, from injectables to bioprinting: A review, Carbohyd. Polym. 229 (2020) 115514. https://doi.org/10.1016/j.carbpol.2019.115514.
[174] K.T. Nguyen, J.L. West, Photopolymerizable hydrogels for tissue engineering applications, Biomaterials 23(22) (2002) 4307-4314. https://doi.org/Pii S0142-9612(02)00175-8 Doi 10.1016/S0142-9612(02)00175-8.
[175] S.D. Edwards, S.J. Hou, J.M. Brown, R.D. Boudreau, Y.H. Lee, Y.J. Kim, K. J. Jeong, Fast-Curing Injectable Microporous Hydrogel for Cell Encapsulation, ACS Appl. Bio. Mater. 5 (6) (2022) 2786–2794, https://doi.org/10.1021/acsabm.2c00214.
[176] J. Su, B.H. Hu, W.L. Lowe, D.B. Kaufman, P.B. Messersmith, Anti-inflammatory peptide-functionalized hydrogels for insulin-secreting cell encapsulation, Biomaterials 31 (2) (2010) 308–314, https://doi.org/10.1016/j.biomaterials.2009.09.045.
[177] Z. Liu, Y. Faraj, X.J. Ju, W. Wang, R. Xie, L.Y. Chu, Nanocomposite smart hydrogels with improved responsiveness and mechanical properties: A mini review, J. Polym. Sci. B 56 (19) (2018) 1306–1313.
[178] R. Jenjob, F. Seidi, D. Crespy, Encoding materials for programming a temporal sequence of actions, J. Mater. Chem. B 6 (10) (2018) 1433–1448.
[179] G.G. Perron, S. Kryazhimskiy, D.P. Rice, A. Buckling, Multidrug therapy and evolution of antibiotic resistance: when order matters, Appl. Environ. Microbiol. 78 (17) (2012) 6137–6142.
[180] H. Jin, L. Wang, R. Bernards, Rational combinations of targeted cancer therapies: background, advances and challenges, Nat. Rev. Drug Discov. 22 (3) (2023) 213–234.
[181] J.D. Duarte, L.H. Cavallari, Pharmacogenetics to guide cardiovascular drug therapy, Nat. Rev. Cardiol. 18 (9) (2021) 649–665.
[182] H. Kang, M. Kim, Q. Feng, S. Lin, K. Wei, R. Li, C.J. Choi, T.-H. Kim, G. Li, J.-M. Oh, Nanolayered hybrid mediates synergistic co-delivery of ligand and ligation activator for inducing stem cell differentiation and tissue healing, Biomaterials 149 (2017) 12–28.
[183] Q. Yao, Y. Liu, Y. Pan, Y. Li, L. Xu, Y. Zhong, W. Wang, J. Zuo, H. Yu, Z. Lv, Long-term induction of endogenous BMPs growth factor from antibacterial dual network hydrogels for fast large bone defect repair, J. Colloid Interface Sci. 607 (2022) 1500–1515.
[184] M. Ding, Y. Fan, Y. Lv, J. Liu, N. Yu, D. Kong, H. Sun, J. Li, A prodrug hydrogel with tumor microenvironment and near-infrared light dual-responsive action for synergistic cancer immunotherapy, Acta Biomater. 149 (2022) 334–346.
[185] Y. Liang, K.L. Kiick, Liposome-cross-linked hybrid hydrogels for glutathione-triggered delivery of multiple cargo molecules, Biomacromolecules 17 (2) (2016) 601–614.
[186] W. Wang, H. Song, J. Zhang, P. Li, C. Li, C. Wang, D. Kong, Q. Zhao, An injectable, thermosensitive and multicompartment hydrogel for simultaneous encapsulation and independent release of a drug cocktail as an effective combination therapy platform, J. Controlled Release 203 (2015) 57–66.
[187] Y. Liu, F. Zhang, L. Long, J. Li, Z. Liu, C. Hu, X. Chen, X. Zan, J. Xu, Y. Wang, Dual-function hydrogels with sequential release of GSK3β inhibitor and VEGF inhibit inflammation and promote angiogenesis after stroke, Chem. Eng. J. 433 (2022) 133671.
[188] J. Wang, B. Li, X. Pu, X. Wang, R.C. Cooper, Q. Gui, H. Yang, Injectable multicomponent biomimetic gel composed of inter-crosslinked dendrimeric and mesoporous silica nanoparticles exhibits highly tunable elasticity and dual drug release capacity, ACS Appl. Mater. Interfaces 12 (9) (2020) 10202–10210.
[189] R.A. Bini, M.F. Silva, L.C. Varanda, M.A. da Silva, C.A. Dreiss, Soft nanocomposites of gelatin and poly (3-hydroxybutyrate) nanoparticles for dual drug release, Colloids Surf. B Biointerfaces 157 (2017) 191–198.
[190] H. Awada, D. Long, Z. Wang, M. Hwang, K. Kim, Y. Wang, A single injection of protein-loaded coacervate-gel significantly improves cardiac function post infarction, Biomaterials 125 (2017) 65–80.

[191] X. Dong, A. Yang, Y. Bai, D. Kong, F. Lv, Dual fluorescence imaging-guided programmed delivery of doxorubicin and CpG nanoparticles to modulate tumor microenvironment for effective chemo-immunotherapy, Biomaterials 230 (2020) 119659.
[192] A. Yang, S. Sheng, Y. Bai, G. Xing, X. Yu, D. Zhu, L. Mei, X. Dong, F. Lv, Hydrogel/nanoparticles-mediated cooperative combination of antiangiogenesis and immunotherapy, Acta Biomater. 153 (2022) 124–138.
[193] K. Numata, S. Yamazaki, N. Naga, Biocompatible and biodegradable dual-drug release system based on silk hydrogel containing silk nanoparticles, Biomacromolecules 13 (5) (2012) 1383–1389.
[194] S. Jiang, L.-P. Lv, K. Landfester, D. Crespy, Nanocontainers in and onto nanofibers, Acc. Chem. Res. 49 (5) (2016) 816–823.
[195] K. Thongchaivetcharat, R. Jenjob, D. Crespy, Encapsulation and release of functional nanodroplets entrapped in nanofibers, Small 14 (20) (2018) 1704527.
[196] C. Srikamut, K. Thongchaivetcharat, T. Phakkeeree, D. Crespy, Encapsulation of emulsion droplets and nanoparticles in nanofibers as sustainable approach for their transport and storage, J. Colloid Interface Sci. 577 (2020) 199–206.
[197] S. Boon-In, M. Theerasilp, D. Crespy, Marrying the incompatible for better: Incorporation of hydrophobic payloads in superhydrophilic hydrogels, J. Colloid Interface Sci. 622 (2022) 75–86.
[198] C. Hu, L. Long, J. Cao, S. Zhang, Y. Wang, Dual-crosslinked mussel-inspired smart hydrogels with enhanced antibacterial and angiogenic properties for chronic infected diabetic wound treatment via pH-responsive quick cargo release, Chem. Eng. J. 411 (2021) 128564.
[199] A. Jobdeedamrong, M. Theerasilp, N. Wongsuwan, N. Nasongkla, D. Crespy, Inflammation-responsive nanocapsules for the dual-release of antibacterial drugs, Chem. Commun. 56 (84) (2020) 12725–12728.
[200] S. Shen, D. Fan, Y. Yuan, X. Ma, J. Zhao, J. Yang, An ultrasmall infinite coordination polymer nanomedicine-composited biomimetic hydrogel for programmed dressing-chemo-low level laser combination therapy of burn wounds, Chem. Eng. J. 426 (2021) 130610.
[201] Y. Sekine, Y. Moritani, T. Ikeda-Fukazawa, Y. Sasaki, K. Akiyoshi, A Hybrid Hydrogel Biomaterial by Nanogel Engineering: Bottom-Up Design with Nanogel and Liposome Building Blocks to Develop a Multidrug Delivery System, Adv. Healthc. Mater. 1 (6) (2012) 722–728.
[202] M.P. Gamcsik, M.S. Kasibhatla, S.D. Teeter, O.M. Colvin, Glutathione levels in human tumors, Biomarkers 17 (8) (2012) 671–691.
[203] M. Deponte, Glutathione catalysis and the reaction mechanisms of glutathione-dependent enzymes, Biochim. Biophys. Acta, Gen. Subj. 1830 (5) (2013) 3217–3266.
[204] A.D. Kim, R. Zhang, X. Han, K.A. Kang, M.J. Piao, Y.H. Maeng, W.Y. Chang, J. W. Hyun, Involvement of glutathione and glutathione metabolizing enzymes in human colorectal cancer cell lines and tissues, Mol. Med. Rep. 12 (3) (2015) 4314–4319.
[205] A. Bansal, M.C. Simon, Glutathione metabolism in cancer progression and treatment resistance, J. Cell Biol. 217 (7) (2018) 2291–2298.
[206] M. Lan, S. Zhao, W. Liu, C.S. Lee, W. Zhang, P. Wang, Photosensitizers for photodynamic therapy, Adv. Healthc. Mater. 8 (13) (2019) 1900132.
[207] V. Shanmugam, S. Selvakumar, C.-S. Yeh, Near-infrared light-responsive nanomaterials in cancer therapeutics, Chem. Soc. Rev. 43 (17) (2014) 6254–6287.
[208] D. Crespy, K. Landfester, U.S. Schubert, A. Schiller, Potential photoactivated metallopharmaceuticals: from active molecules to supported drugs, Chem. Commun. 46 (36) (2010) 6651–6662.
[209] B.H. Yin, Q. Zhang, X.Y. Xia, C.Q. Li, W.K.H. Ho, J.X. Yan, Y.Y. Huang, H.L. Wu, P. Wang, C.Q. Yi, J.H. Hao, J.F. Wang, H.L. Chen, S.H.D. Wong, M. Yang, A CRISPR-Cas12a integrated SERS nanoplatform with chimeric DNA/RNA hairpin guide for ultrasensitive nucleic acid detection, Theranostics 12 (13) (2022) 5914–5930, https://doi.org/10.7150/thno.75816.
[210] A.M. Alkilany, L.B. Thompson, S.P. Boulos, P.N. Sisco, C.J. Murphy, Gold nanorods: their potential for photothermal therapeutics and drug delivery, tempered by the complexity of their biological interactions, Adv. Drug Deliv. Rev. 64 (2) (2012) 190–199.
[211] B.H. Yin, W.K.H. Ho, X.Y. Xia, C.K.W. Chan, Q. Zhang, Y.M. Ng, C.Y.K. Lam, J.C. W. Cheung, J.F. Wang, M. Yang, S.H.D. Wong, A Multilayered Mesoporous Gold Nanoarchitecture for Ultraeffective Near-Infrared Light-Controlled Chemo/Photothermal Therapy for Cancer Guided by SERS Imaging, Small 19 (6) (2023), https://doi.org/10.1002/smll.202206762.
[212] J. Li, Z. Fu, Y. Liu, Encapsulation of liquid metal nanoparticles inside metal–organic frameworks for hydrogel-integrated dual functional biotherapy, Chem. Eng. J. 457 (2023) 141302.
[213] T. Du, Z. Xiao, G. Zhang, L. Wei, J. Cao, Z. Zhang, X. Li, Z. Song, W. Wang, J. Liu, An injectable multifunctional hydrogel for eradication of bacterial biofilms and wound healing, Acta Biomater. 161 (2023) 112–133.
[214] B.H. Yin, W.K. Wong, Y.M. Ng, M. Yang, F.K.C. Leung, D.S.H. Wong, Smart Design of Nanostructures for Boosting Tumor Immunogenicity in Cancer Immunotherapy, Pharmaceutics 15 (5) (2023) 1427, https://doi.org/10.3390/pharmaceutics15051427.
[215] Y. Wang, Y. Wu, L. Long, L. Yang, D. Fu, C. Hu, Q. Kong, Y. Wang, Inflammation-responsive drug-loaded hydrogels with sequential hemostasis, antibacterial, and anti-inflammatory behavior for chronically infected diabetic wound treatment, ACS Appl. Mater. Interfaces 13 (28) (2021) 33584–33599.
[216] H. Ruan, Q. Hu, D. Wen, Q. Chen, G. Chen, Y. Lu, J. Wang, H. Cheng, W. Lu, Z. Gu, A dual-bioresponsive drug-delivery depot for combination of epigenetic modulation and immune checkpoint blockade, Adv. Mater. 31 (17) (2019) 1806957.
[217] S. Jiang, K. Wang, Y. Dai, X. Zhang, F. Xia, Near-Infrared Light-Triggered Dual Drug Release Using Gold Nanorod-Embedded Thermosensitive Nanogel-Crosslinked Hydrogels, Macromol. Mater. Eng. 304 (7) (2019) 1900087.
[218] S. Chen, Q. Qiu, D. Wang, D. She, B. Yin, G. Gu, M. Chai, D.N. Heo, H. He, J. Wang, Dual-sensitive drug-loaded hydrogel system for local inhibition of post-surgical glioma recurrence, J. Controlled Release 349 (2022) 565–579.
[219] Y. Wu, X. Chang, G. Yang, L. Chen, Q. Wu, J. Gao, R. Tian, W. Mu, J.J. Gooding, X. Chen, A Physiologically Responsive Nanocomposite Hydrogel for Treatment of Head and Neck Squamous Cell Carcinoma via Proteolysis-targeting Chimeras Enhanced Immunotherapy, Adv. Mater. 35 (12) (2023) 2210787.
[220] W.J. Yang, P. Zhou, L. Liang, Y. Cao, J. Qiao, X. Li, Z. Teng, L. Wang, Nanogel-incorporated injectable hydrogel for synergistic therapy based on sequential local delivery of combretastatin-A4 phosphate (CA4P) and doxorubicin (DOX), ACS Appl. Mater. Interfaces 10 (22) (2018) 18560–18573.
[221] P. Rao, T.L. Sun, L. Chen, R. Takahashi, G. Shinohara, H. Guo, D.R. King, T. Kurokawa, J.P. Gong, Tough Hydrogels with Fast, Strong, and Reversible Underwater Adhesion Based on a Multiscale Design, Adv. Mater. 30 (32) (2018) 1801884. https://doi.org/10.1002/adma.201801884.
[222] J.W. Yang, R.B. Bai, Z.G. Suo, Topological Adhesion of Wet Materials, Adv. Mater. 30 (25) (2018) 1800671. https://doi.org/10.1002/adma.201800671.
[223] S.S.V.S.S. Voyutskii, Autohesion and adhesion of high polymers, Interscience Publishers, New York, 1963.
[224] B.V. Derjaguin, I.N. Aleinikova, Y.P. Toporov, On the Role of Electrostatic Forces in the Adhesion of Polymer Particles to Solid-Surfaces, Prog. Surf. Sci. 45 (1–4) (1994) 119–123, https://doi.org/10.1016/0079-6816(94)90042-6.
[225] A.J. Kinloch, The Science of Adhesion. 1. Surface and Interfacial Aspects, J. Mater. Sci. 15 (9) (1980) 2141–2166, https://doi.org/10.1007/Bf00552302.
[226] C.M. Lehr, J.A. Bouwstra, H.E. Bodde, H.E. Junginger, A Surface-Energy Analysis of Mucoadhesion - Contact-Angle Measurements on Polycarbophil and Pig Intestinal-Mucosa in Physiologically Relevant Fluids, Pharmaceut Res 9(1) (1992) 70-75. https://doi.org/Doi 10.1023/A:1018931811189.
[227] J.D. Smart, The basics and underlying mechanisms of mucoadhesion, Adv Drug Deliver Rev. 57 (11) (2005) 1556–1568, https://doi.org/10.1016/j.addr.2005.07.001.
[228] N. Hussain, Bioadhesive Drug Delivery Systems: Fundamentals, novel approaches and development, Int. J. Pharm. 205 (1–2) (2000) 201–202, https://doi.org/10.1016/S0378-5173(00)00502-0.
[229] N.A. Peppas, Edith Mathiowitz, Donald E. Chickering III, and Claus-Michael Lehr: eds., Bioadhesive Drug Delivery Systems. Fundamentals, Novel Applications and Development, M. Dekker, New York, NY, xv+670 pages, $195.00, Journal of Controlled Release 68(1) (2000) 135-135. https://doi.org/10.1016/S0168-3659(00)00217-0.
[230] N.F. Jiang, H.D. Zhang, P. Tang, Y.L. Yang, Linear Viscoelasticity of Associative Polymers: Sticky Rouse Model and the Role of Bridges, Macromolecules 53 (9) (2020) 3438–3451, https://doi.org/10.1021/acs.macromol.0c00312.
[231] L. Serra, J. Domenech, N.A. Peppas, Engineering design and molecular dynamics of mucoadhesive drug delivery systems as targeting agents, Eur. J. Pharm. Biopharm. 71 (3) (2009) 519–528, https://doi.org/10.1016/j.ejpb.2008.09.022.
[232] I.S. Bayer, Recent Advances in Mucoadhesive Interface Materials, Mucoadhesion Characterization, and Technologies, Adv. Mater. Interfaces 9 (18) (2022) 2200211. https://doi.org/10.1002/admi.202200211.
[233] A. Bernkop-Schnurch, Thiomers: a new generation of mucoadhesive polymers, Adv. Drug Deliv. Rev. 57 (11) (2005) 1569–1582, https://doi.org/10.1016/j.addr.2005.07.002.
[234] M. Davidovich-Pinhas, H. Bianco-Peled, Novel mucoadhesive system based on sulfhydryl-acrylate interactions, J. Mater. Sci. Mater. Med. 21 (7) (2010) 2027–2034, https://doi.org/10.1007/s10856-010-4069-6.
[235] H. Montazerian, E. Davoodi, A. Baidya, M. Badv, R. Haghniaz, A. Dalili, A. S. Milani, M. Hoorfar, N. Annabi, A. Khademhosseini, P.S. Weiss, Bio-macromolecular design roadmap towards tough bioadhesives, Chem. Soc. Rev. 51 (21) (2022) 9127–9173, https://doi.org/10.1039/d2cs00618a.
[236] H.G. Silverman, F.F. Roberto, Understanding marine mussel adhesion, Mar Biotechnol 9 (6) (2007) 661–681, https://doi.org/10.1007/s10126-007-9053-x.
[237] H. Guo, S. Huang, A. Xu, W. Xue, Injectable Adhesive Self-Healing Multiple-Dynamic-Bond Crosslinked Hydrogel with Photothermal Antibacterial Activity for Infected Wound Healing, Chem. Mater. 34 (6) (2022) 2655–2671, https://doi.org/10.1021/acs.chemmater.1c03944.
[238] H. Zhang, L.P. Bre, T.Y. Zhao, Y. Zheng, B. Newland, W.X. Wang, Mussel-inspired hyperbranched poly(amino ester) polymer as strong wet tissue adhesive, Biomaterials 35 (2) (2014) 711–719, https://doi.org/10.1016/j.biomaterials.2013.10.017.
[239] D. Jiang, J. Liang, P.W. Noble, Hyaluronan in tissue injury and repair, Annu. Rev. Cell Dev. Biol. 23 (2007) 435–461, https://doi.org/10.1146/annurev.cellbio.23.090506.123337.
[240] W.Y.J. Chen, G. Abatangelo, Functions of hyaluronan in wound repair, Wound Repair Regen 7(2) (1999) 79-89. https://doi.org/DOI 10.1046/j.1524-475X.1999.00079.x.
[241] M.G. Neuman, R.M. Nanau, L. Oruna-Sanchez, G. Coto, Hyaluronic Acid and Wound Healing, J. Pharm. Pharm. Sci. 18 (1) (2015) 53–60, https://doi.org/10.18433/J3k89d.
[242] Y.P. Liang, X. Zhao, T.L. Hu, B.J. Chen, Z.H. Yin, P.X. Ma, B.L. Guo, Adhesive Hemostatic Conducting Injectable Composite Hydrogels with Sustained Drug Release and Photothermal Antibacterial Activity to Promote Full-Thickness Skin Regeneration During Wound Healing, Small 15(12) (2019). https://doi.org/ARTN 190004610.1002/smll.201900046.

[243] X. Zhao, M.Y. Zhang, B.L. Guo, P.X. Ma, Mussel-inspired injectable supramolecular and covalent bond crosslinked hydrogels with rapid self-healing and recovery properties via a facile approach under metal-free conditions, J Mater Chem B 4 (41) (2016) 6644–6651, https://doi.org/10.1039/c6tb01776b.
[244] R. Gharibi, H. Yeganeh, A. Rezapour-Lactoee, Z.M. Hassan, Stimulation of Wound Healing by Electroactive, Antibacterial, and Antioxidant Polyurethane/Siloxane Dressing Membranes, In Vitro and in Vivo Evaluations, ACS Appl. Mater. Inter. 7 (43) (2015) 24296–24311, https://doi.org/10.1021/acsami.5b08376.
[245] H. Fu, C.G. Yu, X.D. Li, H.Y. Bao, B. Zhang, Z.J. Chen, Z.J. Zhang, Facile engineering of ECM-mimetic injectable dual crosslinking hydrogels with excellent mechanical resilience, tissue adhesion, and biocompatibility, J. Mater. Chem. B 9 (48) (2021) 10003–10014, https://doi.org/10.1039/d1tb01914g.
[246] S.D. Li, N. Chen, X.P. Li, Y. Li, Z.P. Xie, Z.Y. Ma, J. Zhao, X. Hou, X.B. Yuan, Bioinspired Double-Dynamic-Bond Crosslinked Bioadhesive Enables Post-Wound Closure Care, Adv. Funct. Mater. 30 (17) (2020) 2000130. https://doi.org/10.1002/adfm.202000130.
[247] D.D. Lu, H.S. Wang, T.E. Li, Y.F. Li, F.J. Dou, S.B. Sun, H.Y. Guo, S.Q. Liao, Z. W. Yang, Q.B. Wei, Z.Q. Lei, Mussel-Inspired Thermoresponsive Polypeptide-Pluronic Copolymers for Versatile Surgical Adhesives and Hemostasis, ACS Appl. Mater. Inter. 9 (20) (2017) 16757–16767, https://doi.org/10.1021/acsami.6b16575.
[248] C.K. Song, M.K. Kim, J. Lee, E. Davaa, R. Baskaran, S.G. Yang, Dopa-Empowered Schiff Base Forming Alginate Hydrogel Glue for Rapid Hemostatic Control, Macromol. Res. 27 (2) (2019) 119–125, https://doi.org/10.1007/s13233-019-7026-3.
[249] G.P. Maier, M.V. Rapp, J.H. Waite, J.N. Israelachvili, A. Butler, BIOLOGICAL ADHESIVES, Adaptive synergy between catechol and lysine promotes wet adhesion by surface salt displacement, Science 349 (6248) (2015) 628–632, https://doi.org/10.1126/science.aab0556.
[250] L. Teng, Z.W. Shao, Q. Bai, X.L. Zhang, Y.S. He, J.Y. Lu, D.R. Zou, C.L. Feng, C.M. Dong, Biomimetic Glycopolypeptide Hydrogels with Tunable Adhesion and Microporous Structure for Fast Hemostasis and Highly Efficient Wound Healing, Adv. Funct. Mater. 31 (43) (2021) 2105628. https://doi.org/10.1002/adfm.202105628.
[251] X. Zhao, Y.P. Liang, Y. Huang, J.H. He, Y. Han, B.L. Guo, Physical Double-Network Hydrogel Adhesives with Rapid Shape Adaptability, Fast Self-Healing, Antioxidant and NIR/pH Stimulus-Responsiveness for Multidrug-Resistant Bacterial Infection and Removable Wound Dressing, Adv. Funct. Mater. 30 (17) (2020) 1910748. https://doi.org/10.1002/adfm.201910748.
[252] S.D. Li, N. Chen, Y. Li, J. Zhao, X. Hou, X.B. Yuan, Environment-Dependent Adhesive Behaviors of Mussel-Inspired Coordinate-Crosslinked Bioahesives, Macromol. Mater. Eng. 305 (1) (2020) 1900620. https://doi.org/10.1002/mame.201900620.
[253] Y. Liu, H. Meng, S. Konst, R. Sarmiento, R. Rajachar, B.P. Lee, Injectable Dopamine-Modified Poly(ethylene glycol) Nanocomposite Hydrogel with Enhanced Adhesive Property and Bioactivity, ACS Appl. Mater. Inter. 6 (19) (2014) 16982–16992, https://doi.org/10.1021/am504566v.
[254] M.H. Liao, P.B. Wan, J.R. Wen, M. Gong, X.X. Wu, Y.G. Wang, R. Shi, L.Q. Zhang, Wearable, Healable, and Adhesive Epidermal Sensors Assembled from Mussel-Inspired Conductive Hybrid Hydrogel Framework, Adv. Funct. Mater. 27 (48) (2017) 1703852. https://doi.org/10.1002/adfm.201703852.
[255] H. Khoshmohabat, S. Paydar, H.M. Kazemi, B. Dalfardi, Overview of Agents Used for Emergency Hemostasis, Trauma Mon 21 (1) (2016) e26023, https://doi.org/10.5812/traumamon.26023.
[256] N.S.M. Pillai, K. Eswar, S. Amirthalingam, U. Mony, P.K. Varma, R. Jayakumar, Injectable Nano Whitlockite Incorporated Chitosan Hydrogel for Effective Hemostasis, ACS Appl. Bio. Mater. 2 (2) (2019) 865–873, https://doi.org/10.1021/acsabm.8b00710.
[257] S.A. Smith, R.J. Travers, J.H. Morrissey, How it all starts: Initiation of the clotting cascade, Crit. Rev. Biochem. Mol. 50 (4) (2015) 326–336, https://doi.org/10.3109/10409238.2015.1050550.
[258] F. Sekiya, M. Yoshida, T. Yamashita, T. Morita, Magnesium(II), is a crucial constituent of the blood coagulation cascade. Potentiation of coagulant activities of factor IX by Mg2+ ions, J. Biol. Chem. 271 (15) (1996) 8541–8544, https://doi.org/10.1074/jbc.271.15.8541.
[259] S.A. Smith, J.H. Morrissey, Polyphosphate as a general procoagulant agent, J. Thromb. Haemost. 6 (10) (2008) 1750, https://doi.org/10.1111/j.1538-7836.2008.03104.x.
[260] S.H. Hong, M. Shin, E. Park, J.H. Ryu, J.A. Burdick, H. Lee, Alginate-Boronic Acid: pH-Triggered Bioinspired Glue for Hydrogel Assembly, Adv Funct Mater 30(26) (2020). https://doi.org/ARTN 190849710.1002/adfm.201908497.
[261] L. Zhou, C. Dai, L. Fan, Y.H. Jiang, C. Liu, Z.N. Zhou, P.F. Guan, Y. Tian, J. Xing, X.J. Li, Y.A. Luo, P. Yu, C.Y. Ning, G.X. Tan, Injectable Self-Healing Natural Biopolymer-Based Hydrogel Adhesive with Thermoresponsive Reversible Adhesion for Minimally Invasive Surgery, Adv. Funct. Mater. 31 (14) (2021) 2007457. https://doi.org/10.1002/adfm.202007457.
[262] Y. Hong, F.F. Zhou, Y.J. Hua, X.Z. Zhang, C.Y. Ni, D.H. Pan, Y.Q. Zhang, D.M. Jiang, L. Yang, Q.N. Lin, Y.W. Zou, D.S. Yu, D.E. Arnot, X.H. Zou, L.Y. Zhu, S.F. Zhang, H.W. Ouyang, A strongly adhesive hemostatic hydrogel for the repair of arterial and heart bleeds, Nat. Commun. 10 (2019) 2060. https://doi.org/10.1038/s41467-019-10004-7.
[263] Y.L. Yang, J.Y. Zhang, Z.Z. Liu, Q.N. Lin, X.L. Liu, C.Y. Bao, Y. Wang, L.Y. Zhu, Tissue-Integratable and Biocompatible Photogelation by the Imine Crosslinking Reaction, Adv. Mater. 28 (14) (2016) 2724–2730, https://doi.org/10.1002/adma.201505336.
[264] Y.F. Zhang, X.J. Li, G.H. Bai, W. Wei, X.Y. Liu, Hyperbranched polymer with dynamic thiol-aldehyde crosslinking and its application as a self-healable bioadhesive, J. Mater. Chem. B 9 (29) (2021) 5818–5828, https://doi.org/10.1039/d1tb00929j.
[265] J.F. Cao, Y.N. Zhao, S.C. Jin, J.Z. Li, P. Wu, Z.Q. Luo, Flexible Lignin-based hydrogels with Self-healing and adhesive ability driven by noncovalent interactions, Chem. Eng. J. 429 (2022) 132252. https://doi.org/10.1016/j.cej.2021.132252.
[266] R. Zhang, H.Z. Ruan, Q.L. Fu, X.D. Zhu, Y. Yao, A high strain, adhesive, self-healable poly(acrylic acid) hydrogel with temperature sensitivity as an epidermal sensor, Mater. Adv. 1 (3) (2020) 329–333, https://doi.org/10.1039/d0ma00282h.
[267] X.C. Kang, P.F. Guan, C.R. Xiao, C. Liu, Y.J. Guan, Y.Y. Lin, Y. Tian, K.Y. Ren, Y. T. Huang, R.M. Fu, C.Y. Ning, L. Fan, G.X. Tan, L. Zhou, Injectable Intrinsic Photothermal Hydrogel Bioadhesive with On-Demand Removability for Wound Closure and MRSA-Infected Wound Healing, Adv. Healthc. Mater. (2023), https://doi.org/10.1002/adhm.202203306.
[268] Y.Q. Liang, Z.L. Li, Y. Huang, R. Yu, B.L. Guo, Dual-Dynamic-Bond Cross-Linked Antibacterial Adhesive Hydrogel Sealants with On-Demand Removability for Post-Wound-Closure and Infected Wound Healing, ACS Nano 15 (4) (2021) 7078–7093, https://doi.org/10.1021/acsnano.1c00204.
[269] Y.P. Liang, M. Li, Y.T. Yang, L.P. Qiao, H.R. Xu, B.L. Guo, pH/Glucose Dual Responsive Metformin Release Hydrogel Dressings with Adhesion and Self-Healing via Dual-Dynamic Bonding for Athletic Diabetic Foot Wound Healing, ACS Nano 16 (2) (2022) 3194–3207, https://doi.org/10.1021/acsnano.1c11040.
[270] X.Y. Chen, H. Yuk, J.J. Wu, C.S. Nabzdyk, X.H. Zhao, Instant tough bioadhesive with triggerable benign detachment, P Natl Acad Sci USA 117 (27) (2020) 15497–15503, https://doi.org/10.1073/pnas.2006389117.
[271] Y. He, Q. Li, P. Chen, Q. Duan, J. Zhan, X. Cai, L. Wang, H. Hou, X. Qiu, A smart adhesive Janus hydrogel for non-invasive cardiac repair and tissue adhesion prevention, Nat. Commun. 13 (1) (2022) 7666, https://doi.org/10.1038/s41467-022-35437-5.
[272] J.K.F. Suh, H.W.T. Matthew, Application of chitosan-based polysaccharide biomaterials in cartilage tissue engineering: a review, Biomaterials 21 (24) (2000) 2589–2598, https://doi.org/10.1016/s0142-9612(00)00126-5.
[273] L. Mazzarino, C. Travelet, S. Ortega-Murillo, I. Otsuka, I. Pignot-Paintrand, E. Lemos-Senna, R. Borsali, Elaboration of chitosan-coated nanoparticles loaded with curcumin for mucoadhesive applications, J. Colloid. Interf. Sci. 370 (2012) 58–66, https://doi.org/10.1016/j.jcis.2011.12.063.
[274] L.M. Ensign, B.C. Tang, Y.Y. Wang, T.A. Tse, T. Hoen, R. Cone, J. Hanes, Mucus-Penetrating Nanoparticles for Vaginal Drug Delivery Protect Against Herpes Simplex Virus, Sci Transl Med 4(138) (2012). https://doi.org/DOI 10.1126/scitranslmed.3003453.
[275] T.R. Nimal, G. Baranwal, M.C. Bavya, R. Biswas, R. Jayakumar, Anti-staphylococcal Activity of Injectable Nano Tigecycline/Chitosan-PRP Composite Hydrogel Using Drosophila melanogaster Model for Infectious Wounds, ACS Appl. Mater. Inter. 8 (34) (2016) 22074–22083, https://doi.org/10.1021/acsami.6b07463.
[276] R.T. Xing, K. Liu, T.F. Jiao, N. Zhang, K. Ma, R.Y. Zhang, Q.L. Zou, G.H. Ma, X. H. Yan, An Injectable Self-Assembling Collagen-Gold Hybrid Hydrogel for Combinatorial Antitumor Photothermal/Photodynamic Therapy, Adv. Mater. 28 (19) (2016) 3669–3676, https://doi.org/10.1002/adma.201600284.
[277] M. Gosecka, M. Gosecki, D. Jaworska-Krych, Hydrophobized Hydrogels: Construction Strategies, Properties, and Biomedical Applications, Adv. Funct. Mater. (2023), https://doi.org/10.1002/adfm.202212302.
[278] L. Han, M.H. Wang, L.O. Prieto-Lopez, X. Deng, J.X. Cui, Self-Hydrophobization in a Dynamic Hydrogel for Creating Nonspecific Repeatable Underwater Adhesion, Adv. Funct. Mater. 30 (7) (2020) 1907064. https://doi.org/10.1002/adfm.201907064.
[279] L. Szymanski, K. Golaszewska, J. Malkowska, M. Golebiewska, J. Kaczynska, B. Gromadka, D. Matak, Safety and performance of surgical adhesives, PLoS One 17 (8) (2022) e0271531. https://doi.org/10.1371/journal.pone.0271531.
[280] Y.J. Zheng, A. Farrukh, A. del Campo, Optoregulated Biointerfaces to Trigger Cellular Responses, Langmuir 34 (48) (2018) 14459–14471, https://doi.org/10.1021/acs.langmuir.8b02634.
[281] A.A. Khalili, M.R. Ahmad, A Review of Cell Adhesion Studies for Biomedical and Biological Applications, Int. J. Mol. Sci. 16 (8) (2015) 18149–18184, https://doi.org/10.3390/ijms160818149.
[282] T. Yeung, P.C. Georges, L.A. Flanagan, B. Marg, M. Ortiz, M. Funaki, N. Zahir, W. Y. Ming, V. Weaver, P.A. Janmey, Effects of substrate stiffness on cell morphology, cytoskeletal structure, and adhesion, Cell Motil Cytoskel 60 (1) (2005) 24–34, https://doi.org/10.1002/cm.20041.
[283] S.E. Stabenfeldt, M.C. LaPlaca, Variations in rigidity and ligand density influence neuronal response in methylcellulose-laminin hydrogels, Acta Biomater. 7 (12) (2011) 4102–4108, https://doi.org/10.1016/j.actbio.2011.07.026.
[284] M.B. Rahmany, M. Van Dyke, Biomimetic approaches to modulate cellular adhesion in biomaterials: A review, Acta Biomater. 9 (3) (2013) 5431–5437, https://doi.org/10.1016/j.actbio.2012.11.019.
[285] A. Rezania, K.E. Healy, Biomimetic peptide surfaces that regulate adhesion, spreading, cytoskeletal organization, and mineralization of the matrix deposited by osteoblast-like cells, Biotechnol Progr 15 (1) (1999) 19–32, https://doi.org/10.1021/bp980083b.
[286] K. Lewandowska, E. Pergament, C.N. Sukenik, L.A. Culp, Cell-Type-Specific Adhesion Mechanisms Mediated by Fibronectin Adsorbed to Chemically Derivatized Substrata, J. Biomed. Mater. Res. 26 (10) (1992) 1343–1363, https://doi.org/10.1002/jbm.820261007.

[287] S.S. Lee, L. Laganenka, X.Y. Du, W.D. Hardt, S.J. Ferguson, Silicon Nitride, a Bioceramic for Bone Tissue Engineering: A Reinforced Cryogel System With Antibiofilm and Osteogenic Effects, Front Bioeng Biotech 9 (2021). https://doi.org/ARTN 794586 10.3389/fbioe.2021.794586.
[288] S.H.D. Wong, B.H. Yin, B.G. Yang, S.E. Lin, R. Li, Q. Feng, H.R. Yang, L. Zhang, Z. M. Yang, G. Li, C.H.J. Choi, L.M. Bian, Anisotropic Nanoscale Presentation of Cell Adhesion Ligand Enhances the Recruitment of Diverse Integrins in Adhesion Structures and Mechanosensing-Dependent Differentiation of Stem Cells, Adv. Funct. Mater. 29 (8) (2019) 1806822. https://doi.org/10.1002/adfm.201806822.
[289] Y. Zhang, J. Liu, L. Huang, Z. Wang, L. Wang, Design and performance of a sericin-alginate interpenetrating network hydrogel for cell and drug delivery, Sci. Rep. 5 (2015) 12374, https://doi.org/10.1038/srep12374.
[290] S. Deepthi, A.A.A. Gafoor, A. Sivashanmugam, S.V. Nair, R. Jayakumar, Nanostrontium ranelate incorporated injectable hydrogel enhanced matrix production supporting chondrogenesis in vitro, J. Mater. Chem. B 4 (23) (2016) 4092–4103, https://doi.org/10.1039/c6tb00684a.
[291] Y.N. Liu, D.D. Fan, Novel hyaluronic acid-tyrosine/collagen-based injectable hydrogels as soft filler for tissue engineering, Int. J. Biol. Macromol. 141 (2019) 700–712, https://doi.org/10.1016/j.ijbiomac.2019.08.233.
[292] K. Wang, K.C. Nune, R.D.K. Misra, The functional response of alginate-gelatin-nanocrystalline cellulose injectable hydrogels toward delivery of cells and bioactive molecules, Acta Biomater. 36 (2016) 143–151, https://doi.org/10.1016/j.actbio.2016.03.016.
[293] J. Li, L. Mo, C.H. Lu, T. Fu, H.H. Yang, W. Tan, Functional nucleic acid-based hydrogels for bioanalytical and biomedical applications, Chem. Soc. Rev. 45 (5) (2016) 1410–1431, https://doi.org/10.1039/c5cs00586h.
[294] D.S.H. Wong, J.N. Li, X.H. Yan, B. Wang, R. Li, L. Zhang, L.M. Bian, Magnetically Tuning Tether Mobility of Integrin Ligand Regulates Adhesion, Spreading, and Differentiation of Stem Cells, Nano Lett. 17 (3) (2017) 1685–1695, https://doi.org/10.1021/acs.nanolett.6b04958.
[295] A. Kumar, A. Sivashanmugam, S. Deepthi, J.D. Bumgardner, S.V. Nair, R. Jayakumar, Nano-fibrin stabilized CaSO4 crystals incorporated injectable chitin composite hydrogel for enhanced angiogenesis & osteogenesis, Carbohyd. Polym. 140 (2016) 144–153, https://doi.org/10.1016/j.carbpol.2015.11.074.
[296] K.Y. Lee, D.J. Mooney, Alginate: Properties and biomedical applications, Prog. Polym. Sci. 37 (1) (2012) 106–126, https://doi.org/10.1016/j.progpolymsci.2011.06.003.
[297] C.W. Damouny, P. Martin, G. Vasilyev, R. Vilensky, R. Fadul, I. Redenski, S. Srouji, E. Zussman, Injectable Hydrogels Based on Inter-Polyelectrolyte Interactions between Hyaluronic Acid, Gelatin, and Cationic Cellulose Nanocrystals, Biomacromolecules 23 (8) (2022) 3222–3234, https://doi.org/10.1021/acs.biomac.2c00316.
[298] M. Diba, S. Spaans, S.I.S. Hendrikse, M.M.C. Bastings, M.J.G. Schotman, J.F. van Sprang, D.J. Wu, F.J.M. Hoeben, H.M. Janssen, P.Y.W. Dankers, Engineering the Dynamics of Cell Adhesion Cues in Supramolecular Hydrogels for Facile Control over Cell Encapsulation and Behavior, Adv. Mater. 33 (37) (2021), https://doi.org/10.1002/adma.202008111.
[299] J.S. Zhang, S.H.D. Wong, X. Wu, H. Lei, M. Qin, P. Shi, W. Wang, L.M. Bian, Y. Cao, Engineering Photoresponsive Ligand Tethers for Mechanical Regulation of Stem Cells, Adv. Mater. 33 (48) (2021), https://doi.org/10.1002/adma.202105765.
[300] X.Y. Chen, N.C.H. Lai, K.C. Wei, R. Li, M. Cui, B.G. Yang, S.H.D. Wong, Y.R. Deng, J.S. Li, X.T. Shuai, L.M. Bian, Biomimetic Presentation of Cryptic Ligands Single-Chain Nanogels for Synergistic Regulation of Stem Cells, ACS Nano 14 (4) (2020) 4027–4035, https://doi.org/10.1021/acsnano.9b08564.
[301] H.-Y. Wu, L. Yang, J.-S. Tu, J. Wang, J.-G. Li, H.-Y. Lv, X.-N. Yang, Hydrogels with dynamically controllable mechanics and biochemistry for 3D cell culture platforms, Chin. J. Polym. Sci. 40 (2022) 38–46.
[302] J.A. Burdick, W.L. Murphy, Moving from static to dynamic complexity in hydrogel design, Nat. Commun. 3 (2012), https://doi.org/10.1038/ncomms2271.
[303] W.K. Wong, B. Yin, A. Rakhmatullina, J. Zhou, S.H.D. Wong, Engineering advanced dynamic biomaterials to optimize adoptive T-cell immunotherapy, Engineered Regeneration 2 (2021) 70–81.
[304] B.H. Yin, J.G. Ni, C.E. Witherel, M. Yang, J.A. Burdick, C.Y. Wen, S.H.D. Wong, Harnessing Tissue-derived Extracellular Vesicles for Osteoarthritis Theranostics, Theranostics 12 (1) (2022) 207–231, https://doi.org/10.7150/thno.62708.
[305] P.S. Briquez, L.E. Clegg, M.M. Martino, F.M. Gabhann, J.A. Hubbell, Design principles for therapeutic angiogenic materials, Nat. Rev. Mater. 1 (1) (2016) 1–15.
[306] L. Onfroy-Roy, D. Hamel, J. Foncy, L. Malaquin, A. Ferrand, Extracellular Matrix Mechanical Properties and Regulation of the Intestinal Stem Cells: When Mechanics Control Fate, Cells-Basel 9 (12) (2020), https://doi.org/10.3390/cells9122629.
[307] B.D. Hoffman, C. Grashoff, M.A. Schwartz, Dynamic molecular processes mediate cellular mechanotransduction, Nature 475 (7356) (2011) 316–323, https://doi.org/10.1038/nature10316.
[308] X. Yang, G. Liu, L. Peng, J. Guo, L. Tao, J. Yuan, C. Chang, Y. Wei, L. Zhang, Highly efficient self-healable and dual responsive cellulose-based hydrogels for controlled release and 3D cell culture, Adv. Funct. Mater. 27 (40) (2017) 1703174.
[309] L. Bian, Functional hydrogel bioink, a key challenge of 3D cellular bioprinting, AIP Publishing LLC, 2020, p. 030401.
[310] B. Yang, K. Wei, C. Loebel, K. Zhang, Q. Feng, R. Li, S.H.D. Wong, X. Xu, C. Lau, X. Chen, Enhanced mechanosensing of cells in synthetic 3D matrix with controlled biophysical dynamics, Nat. Commun. 12 (1) (2021) 3514.
[311] C. Loebel, R.L. Mauck, J.A. Burdick, Local nascent protein deposition and remodelling guide mesenchymal stromal cell mechanosensing and fate in three-dimensional hydrogels, Nat. Mater. 18 (8) (2019) 883–891.
[312] R.S. Stowers, A. Shcherbina, J. Israeli, J.J. Gruber, J. Chang, S. Nam, A. Rabiee, M.N. Teruel, M.P. Snyder, A. Kundaje, Matrix stiffness induces a tumorigenic phenotype in mammary epithelium through changes in chromatin accessibility, Nat. Biomed. Eng. 3 (12) (2019) 1009–1019.
[313] F. Gattazzo, A. Urciuolo, P. Bonaldo, Extracellular matrix: a dynamic microenvironment for stem cell niche, Biochimica et Biophysica Acta (BBA)-General Subjects 1840 (8) (2014) 2506–2519.
[314] K.E. Kadler, A. Hill, E.G. Canty-Laird, Collagen fibrillogenesis: fibronectin, integrins, and minor collagens as organizers and nucleators, Curr. Opin. Cell Biol. 20 (5) (2008) 495–501.
[315] N. Gjorevski, C.M. Nelson, Bidirectional extracellular matrix signaling during tissue morphogenesis, Cytokine Growth Factor Rev. 20 (5–6) (2009) 459–465.
[316] L.M. Bian, M. Guvendiren, R.L. Mauck, J.A. Burdick, Hydrogels that mimic developmentally relevant matrix and N-cadherin interactions enhance MSC chondrogenesis, P Natl Acad Sci USA 110 (25) (2013) 10117–10122, https://doi.org/10.1073/pnas.1214100110.
[317] N. Huebsch, E. Lippens, K. Lee, M. Mehta, S.T. Koshy, M.C. Darnell, R.M. Desai, C. M. Madl, M. Xu, X. Zhao, Matrix elasticity of void-forming hydrogels controls transplanted-stem-cell-mediated bone formation, Nat. Mater. 14 (12) (2015) 1269–1277.
[318] K.R. Levental, H.M. Yu, L. Kass, J.N. Lakins, M. Egeblad, J.T. Erler, S.F.T. Fong, K. Csiszar, A. Giaccia, W. Weninger, M. Yamauchi, D.L. Gasser, V.M. Weaver, Matrix Crosslinking Forces Tumor Progression by Enhancing Integrin Signaling, Cell 139 (5) (2009) 891–906, https://doi.org/10.1016/j.cell.2009.10.027.
[319] M. Aragona, T. Panciera, A. Manfrin, S. Giulitti, F. Michielin, N. Elvassore, S. Dupont, S. Piccolo, A mechanical checkpoint controls multicellular growth through YAP/TAZ regulation by actin-processing factors, Cell 154 (5) (2013) 1047–1059.
[320] M.J. Paszek, N. Zahir, K.R. Johnson, J.N. Lakins, G.I. Rozenberg, A. Gefen, C. A. Reinhart-King, S.S. Margulies, M. Dembo, D. Boettiger, D.A. Hammer, V. M. Weaver, Tensional homeostasis and the malignant phenotype, Cancer Cell 8 (3) (2005) 241–254, https://doi.org/10.1016/j.ccr.2005.08.010.
[321] O. Chaudhuri, S.T. Koshy, C. Branco da Cunha, J.W. Shin, C.S. Verbeke, K. H. Allison, D.J. Mooney, Extracellular matrix stiffness and composition jointly regulate the induction of malignant phenotypes in mammary epithelium, Nat Mater 13 (10) (2014) 970–978, https://doi.org/10.1038/nmat4009.
[322] C. Uhler, G.V. Shivashankar, Regulation of genome organization and gene expression by nuclear mechanotransduction, Nat. Rev. Mol. Cell Biol. 18 (12) (2017) 717–727, https://doi.org/10.1038/nrm.2017.101.
[323] A.J. Kanelidis, C. Premer, J. Lopez, W. Balkan, J.M. Hare, Route of delivery modulates the efficacy of mesenchymal stem cell therapy for myocardial infarction: a meta-analysis of preclinical studies and clinical trials, Circ. Res. 120 (7) (2017) 1139–1150.
[324] A. Aicher, W. Brenner, M. Zuhayra, C. Badorff, S. Massoudi, B. Assmus, T. Eckey, E. Henze, A.M. Zeiher, S. Dimmeler, Assessment of the tissue distribution of transplanted human endothelial progenitor cells by radioactive labeling, Circulation 107 (16) (2003) 2134–2139.
[325] S.B. Seif-Naraghi, J.M. Singelyn, M.A. Salvatore, K.G. Osborn, J.J. Wang, U. Sampat, O.L. Kwan, G.M. Strachan, J. Wong, P.J. Schup-Magoffin, Safety and efficacy of an injectable extracellular matrix hydrogel for treating myocardial infarction, Sci. Transl. Med. 5 (173) (2013) 173ra25.
[326] D. Zhang, I.Y. Shadrin, J. Lam, H.-Q. Xian, H.R. Snodgrass, N. Bursac, Tissue-engineered cardiac patch for advanced functional maturation of human ESC-derived cardiomyocytes, Biomaterials 34 (23) (2013) 5813–5820.
[327] C. Schlundt, C. Bietau, L. Klinghammer, R. Wiedemann, H. Rittger, J. Ludwig, S. Achenbach, Comparison of intracoronary versus intravenous administration of adenosine for measurement of coronary fractional flow reserve, Circ. Cardiovasc. Interv. 8 (5) (2015) e001781.
[328] K. Gabisonia, G. Prosdocimo, G.D. Aquaro, L. Carlucci, L. Zentilin, I. Secco, H. Ali, L. Braga, N. Gorgodze, F. Bernini, S. Burchielli, C. Collesi, L. Zandona, G. Sinagra, M. Piacenti, S. Zacchigna, R. Bussani, F.A. Recchia, M. Giacca, MicroRNA therapy stimulates uncontrolled cardiac repair after myocardial infarction in pigs, Nature 569 (7756) (2019) 418-+, https://doi.org/10.1038/s41586-019-1191-6.
[329] J.Y. Zhang, W.Q. Zhu, M. Radisic, G. Vunjak-Novakovic, Can We Engineer a Human Cardiac Patch for Therapy? Circ. Res. 123 (2) (2018) 244–265, https://doi.org/10.1161/Circresaha.118.311213.
[330] D. Zhu, Z. Li, K. Huang, T.G. Caranasos, J.S. Rossi, K. Cheng, Minimally invasive delivery of therapeutic agents by hydrogel injection into the pericardial cavity for cardiac repair, Nat. Commun. 12 (1) (2021) 1412.
[331] E.C. Gale, A.E. Powell, G.A. Roth, E.L. Meany, J. Yan, B.S. Ou, A.K. Grosskopf, J. Adamska, V.C.T.M. Picece, A.I. d'Aquino, B. Pulendran, P.S. Kim, E.A. Appel, Hydrogel-Based Slow Release of a Receptor-Binding Domain Subunit Vaccine Elicits Neutralizing Antibody Responses Against SARS-CoV-2, Adv. Mater. 33 (51) (2021), https://doi.org/10.1002/adma.202104362.
[332] N. Lurie, G.T. Keusch, V.J. Dzau, Urgent lessons from COVID 19: why the world needs a standing, coordinated system and sustainable financing for global research and development, Lancet 397 (10280) (2021) 1229–1236.
[333] S. Kashte, A. Gulbake, S.F. El-Amin III, A. Gupta, COVID-19 vaccines: rapid development, implications, challenges and future prospects, Hum. Cell 34 (3) (2021) 711–733.
[334] S.R. Bonam, N.G. Kotla, R.A. Bohara, Y. Rochev, T.J. Webster, J. Bayry, Potential immuno-nanomedicine strategies to fight COVID-19 like pulmonary infections, Nano Today 36 (2021) 101051.

[335] S.M. Pack, P.J. Peters, SARS-CoV-2–specific vaccine candidates; the contribution of structural vaccinology, Vaccines 10 (2) (2022) 236.
[336] H.-X. Tan, J.A. Juno, W.S. Lee, I. Barber-Axthelm, H.G. Kelly, K.M. Wragg, R. Esterbauer, T. Amarasena, F.L. Mordant, K. Subbarao, Immunogenicity of prime-boost protein subunit vaccine strategies against SARS-CoV-2 in mice and macaques, Nat. Commun. 12 (1) (2021) 1403.
[337] J. Yang, W. Wang, Z. Chen, S. Lu, F. Yang, Z. Bi, L. Bao, F. Mo, X. Li, Y. Huang, A vaccine targeting the RBD of the S protein of SARS-CoV-2 induces protective immunity, Nature 586 (7830) (2020) 572–577.
[338] G.A. Roth, E.C. Gale, M. Alcántara-Hernández, W. Luo, E. Axpe, R. Verma, Q. Yin, A.C. Yu, H. Lopez Hernandez, C.L. Maikawa, Injectable hydrogels for sustained codelivery of subunit vaccines enhance humoral immunity, ACS Central Sci. 6 (10) (2020) 1800–1812.
[339] C.A. Dreiss, Hydrogel design strategies for drug delivery, Curr. Opin. Colloid Interface Sci. 48 (2020) 1–17, https://doi.org/10.1016/j.cocis.2020.02.001.
[340] H.M. El-Husseiny, E.A. Mady, L. Hamabe, A. Abugomaa, K. Shimada, T. Yoshida, T. Tanaka, A. Yokoi, M. Elbadawy, R. Tanaka, Smart/stimuli-responsive hydrogels: Cutting-edge platforms for tissue engineering and other biomedical applications, Mater. Today Bio. 13 (2022), https://doi.org/10.1016/j.mtbio.2021.100186.
[341] Y.W. Zhao, B. Ran, X. Xie, W.R. Gu, X.W. Ye, J.F. Liao, Developments on the Smart Hydrogel-Based Drug Delivery System for Oral Tumor Therapy, Gels-Basel 8 (11) (2022), https://doi.org/10.3390/gels8110741.
[342] X.W. Chen, X.R. Li, Y.X. Zhou, X.N. Wang, Y.H. Zhang, Y.T. Fan, Y.Q. Huang, Y. Liu, Chitosan-based thermosensitive hydrogel as a promising ocular drug delivery system: Preparation, characterization, and in vivo evaluation, J. Biomater Appl. 27 (4) (2012) 391–402, https://doi.org/10.1177/0885328211406563.
[343] M. Hamcerencu, J. Desbrieres, M. Pop, G. Rxiess, Thermo-sensitive gellan maleate/N-isopropylacrylamide hydrogels: initial “in vitro” and “in vivo” evaluation as ocular inserts, Polym. Bull. 77 (2) (2020) 741–755, https://doi.org/10.1007/s00289-019-02772-5.
[344] S. Chatterjee, P.C.L. Hui, Review of Applications and Future Prospects of Stimuli-Responsive Hydrogel Based on Thermo-Responsive Biopolymers in Drug Delivery Systems, Polymers-Basel 13 (13) (2021) 2086, https://doi.org/10.3390/polym13132086.
[345] A. Lusina, M. Ceglowski, Molecularly Imprinted Polymers as State-of-the-Art Drug Carriers in Hydrogel Transdermal Drug Delivery Applications, Polymers-Basel 14 (3) (2022) 640, https://doi.org/10.3390/polym14030640.
[346] K.Y. Zhang, H.J. Lv, Y.Q. Zheng, Y.M. Yao, X.R. Li, J.Y. Yu, B. Ding, Nanofibrous hydrogels embedded with phase-change materials: Temperature-responsive dressings for accelerating skin wound healing, Compos. Commun. 25 (2021) 100752. https://doi.org/10.1016/j.coco.2021.100752.
[347] T. Hoare, B.P. Timko, J. Santamaria, G.F. Goya, S. Irusta, S. Lau, C.F. Stefanescu, D.B. Lin, R. Langer, D.S. Kohane, Magnetically Triggered Nanocomposite Membranes: A Versatile Platform for Triggered Drug Release, Nano Lett. 11 (3) (2011) 1395–1400, https://doi.org/10.1021/nl200494t.
[348] H. Kim, H. Lee, K.Y. Seong, E. Lee, S.Y. Yang, J. Yoon, Visible Light-Triggered On-Demand Drug Release from Hybrid Hydrogels and its Application in Transdermal Patches, Adv. Healthc. Mater. 4 (14) (2015) 2071–2077, https://doi.org/10.1002/adhm.201500323.
[349] N. Huebsch, C.J. Kearney, X.H. Zhao, J. Kim, C.A. Cezar, Z.G. Suo, D.J. Mooney, Ultrasound-triggered disruption and self-healing of reversibly cross-linked hydrogels for drug delivery and enhanced chemotherapy, P Natl Acad Sci USA 111 (27) (2014) 9762–9767, https://doi.org/10.1073/pnas.1405469111.
[350] W.X. Sun, H.T. Jiang, X. Wu, Z.Y. Xu, C. Yao, J. Wang, M. Qin, Q. Jiang, W. Wang, D.Q. Shi, Y. Cao, Strong dual-crosslinked hydrogels for ultrasound-triggered drug delivery, Nano. Res. 12 (1) (2019) 115–119, https://doi.org/10.1007/s12274-018-2188-4.
[351] J.D. Tang, Y.C. Qiao, Y.H. Chu, Z.F. Tong, Y.F. Zhou, W.L. Zhang, S.J. Xie, J. Hu, T.J. Wang, Magnetic double-network hydrogels for tissue hyperthermia and drug release, J. Mater. Chem. B 7 (8) (2019) 1311–1321, https://doi.org/10.1039/c8tb03301c.
[352] Y.N. Sun, D. Nan, H.Q. Jin, X.Z. Qu, Recent advances of injectable hydrogels for drug delivery and tissue engineering applications, Polym. Test 81 (2020) 106283. https://doi.org/10.1016/j.polymertesting.2019.106283.
[353] C.B.P. Oliveira, V. Gomes, P.M.T. Ferreira, J.A. Martins, P.J. Jervis, Peptide-Based Supramolecular Hydrogels as Drug Delivery Agents, Recent Advances, Gels-Basel 8 (11) (2022) 706, https://doi.org/10.3390/gels8110706.
[354] A. Carvalho, J. Gallo, D.M. Pereira, P. Valentao, P.B. Andrade, L. Hilliou, P.M. T. Ferreira, M. Banobre-Lopez, J.A. Martins, Magnetic Dehydrodipeptide-Based Self-Assembled Hydrogels for Theragnostic Applications, Nanomaterials-Basel 9 (4) (2019) 541, https://doi.org/10.3390/nano9040541.
[355] M.W. Cao, S. Lu, N.N. Wang, H. Xu, H. Cox, R.H. Li, T. Waigh, Y.C. Han, Y. L. Wang, J.R. Lu, Enzyme-Triggered Morphological Transition of Peptide Nanostructures for Tumor-Targeted Drug Delivery and Enhanced Cancer Therapy, ACS Appl. Mater. Inter. 11 (18) (2019) 16357–16366, https://doi.org/10.1021/acsami.9b03519.
[356] K. Kulkarni, R.L. Minehan, T. Gamot, H.A. Coleman, S. Bowles, Q.Q. Lin, D. Hopper, S.E. Northfield, R.A. Hughes, R.E. Widdop, M.I. Aguilar, H. C. Parkington, M.P. Del Borgo, Esterase-Mediated Sustained Release of Peptide-Based Therapeutics from a Self-Assembled Injectable Hydrogel, ACS Appl. Mater. Inter. 13 (49) (2021) 58279–58290, https://doi.org/10.1021/acsami.1c14150.
[357] G. Cirillo, M. Curcio, U.G. Spizzirri, O. Vittorio, P. Tucci, N. Picci, F. Iemma, S. Hampel, F.P. Nicoletta, Carbon nanotubes hybrid hydrogels for electrically tunable release of Curcumin, Eur. Polym. J. 90 (2017) 1–12, https://doi.org/10.1016/j.eurpolymj.2017.03.011.
[358] R. Jahanban-Esfahlan, K. Soleimani, H. Derakhshankhah, B. Haghshenas, A. Rezaei, B. Massoumi, A. Farnudiyan-Habibi, H. Samadian, M. Jaymand, Multi-stimuli-responsive magnetic hydrogel based on Tragacanth gum as a de novo nanosystem for targeted chemo/hyperthermia treatment of cancer, J. Mater. Res. 36 (4) (2021) 858–869, https://doi.org/10.1557/s43578-021-00137-1.
[359] K. Soleimani, H. Derakhshankhah, M. Jaymand, H. Samadian, Stimuli-responsive natural gums-based drug delivery systems for cancer treatment, Carbohyd. Polym. 254 (2021) 117422. https://doi.org/10.1016/j.carbpol.2020.117422.
[360] H. Derakhshankhah, R. Jahanban-Esfahlan, S. Vandghanooni, S. Akbari-Nakhjavani, B. Massoumi, B. Haghshenas, A. Rezaei, A. Farnudiyan-Habibi, H. Samadian, M. Jaymand, A bio-inspired gelatin-based pH- and thermal-sensitive magnetic hydrogel for in vitro chemo/hyperthermia treatment of breast cancer cells, J. Appl. Polym. Sci. 138 (24) (2021) e50578. https://doi.org/10.1002/app.50578.
[361] S. Kondaveeti, A.T.S. Semeano, D.R. Cornejo, H. Ulrich, D.F.S. Petri, Magnetic hydrogels for levodopa release and cell stimulation triggered by external magnetic field, Colloid Surface B 167 (2018) 415–424, https://doi.org/10.1016/j.colsurfb.2018.04.040.
[362] Z. Li, Y. Ding, J. Liu, J. Wang, F. Mo, Y. Wang, T.-J. Chen-Mayfield, P.M. Sondel, S. Hong, Q. Hu, Depletion of tumor associated macrophages enhances local and systemic platelet-mediated anti-PD-1 delivery for post-surgery tumor recurrence treatment, Nat. Commun. 13 (1) (2022) 1845.
[363] W.K. Wong, B.H. Yin, C.Y.K. Lam, Y.Y. Huang, J.X. Yan, Z.W. Tan, S.H.D. Wong, The Interplay Between Epigenetic Regulation and CD8 T Cell Differentiation/Exhaustion for T Cell Immunotherapy, Front Cell Dev Biol 9 (2022). https://doi.org/ARTN 78322710.3389/fcell.2021.783227.
[364] P. Darvin, S.M. Toor, V. Sasidharan Nair, E. Elkord, Immune checkpoint inhibitors: recent progress and potential biomarkers, Exp. Mol. Med. 50 (12) (2018) 1–11.
[365] J. Oh, X.Y. Xia, W.K.R. Wong, S.H.D. Wong, W.H. Yuan, H.X. Wang, C.H.N. Lai, Y. Tian, Y.P. Ho, H.L. Zhang, Y. Zhang, G. Li, Y. Lin, L.M. Bian, The Effect of the Nanoparticle Shape on T Cell Activation, Small 18(36) (2022). https://doi.org/ARTN 210737310.1002/smll.202107373.
[366] K. Ganesh, Z.K. Stadler, A. Cercek, R.B. Mendelsohn, J. Shia, N.H. Segal, L. A. Diaz Jr, Immunotherapy in colorectal cancer: rationale, challenges and potential, Nat Rev Gastro Hepat 16 (6) (2019) 361–375.
[367] H. Dietz, S.C. Weinmann, A.K. Salama, Checkpoint Inhibitors in Melanoma Patients with Underlying Autoimmune Disease, Cancer Manag. Res. (2021) 8199–8208.
[368] K. Newick, E. Moon, S.M. Albelda, Chimeric antigen receptor T-cell therapy for solid tumors, Mol Ther-Oncolytics 3 (2016) 16006.
[369] M. Martinez, E.K. Moon, CAR T cells for solid tumors: new strategies for finding, infiltrating, and surviving in the tumor microenvironment, Front Immunol 10 (2019) 128.
[370] Q. Hu, H. Li, E. Archibong, Q. Chen, H. Ruan, S. Ahn, E. Dukhovlinova, Y. Kang, D. Wen, G. Dotti, Inhibition of post-surgery tumour recurrence via a hydrogel releasing CAR-T cells and anti-PDL1-conjugated platelets, Nat. Biomed. Eng. 5 (9) (2021) 1038–1047.
[371] P.M. Kou, J.E. Babensee, Macrophage and dendritic cell phenotypic diversity in the context of biomaterials, J. Biomed. Mater. Res. A 96 (1) (2011) 239–260.
[372] R.L. Sabado, N. Bhardwaj, Directing dendritic cell immunotherapy towards successful cancer treatment, Immunotherapy 2 (1) (2010) 37–56, https://doi.org/10.2217/imt.09.43.
[373] S.A. Bencherif, R. Warren Sands, O.A. Ali, W.A. Li, S.A. Lewin, T.M. Braschler, T.-Y. Shih, C.S. Verbeke, D. Bhatta, G. Dranoff, Injectable cryogel-based whole-cell cancer vaccines, Nat. Commun. 6 (1) (2015) 7556.
[374] X. Zhang, K. Men, Y. Zhang, R. Zhang, L. Yang, X. Duan, Local and systemic delivery of mRNA encoding survivin-T34A by lipoplex for efficient colon cancer gene therapy, Int J Nanomedicine 14 (2019) 2733–2751, https://doi.org/10.2147/IJN.S198747.
[375] B.N. Aldosari, I.M. Alfagih, A.S. Almurshedi, Lipid nanoparticles as delivery systems for RNA-based vaccines, Pharmaceutics 13 (2) (2021) 206.
[376] L. Yang, L. Gong, P. Wang, X. Zhao, F. Zhao, Z. Zhang, Y. Li, W. Huang, Recent Advances in Lipid Nanoparticles for Delivery of mRNA, Pharmaceutics 14 (12) (2022), https://doi.org/10.3390/pharmaceutics14122682.
[377] F. Jia, W. Huang, Y. Yin, Y. Jiang, Q. Yang, H. Huang, G. Nie, H. Wang, Stabilizing RNA Nanovaccines with Transformable Hyaluronan Dynamic Hydrogel for Durable Cancer Immunotherapy, Adv. Funct. Mater. 33 (3) (2023) 2204636.
[378] C.M. Kirschner, K.S. Anseth, Hydrogels in healthcare: From static to dynamic material microenvironments, Acta Mater. 61 (3) (2013) 931–944, https://doi.org/10.1016/j.actamat.2012.10.037.
[379] G.Z. Zhang, Y.H. Chen, Y.H. Deng, T. Ngai, C.Y. Wang, Dynamic Supramolecular Hydrogels: Regulating Hydrogel Properties through Self-Complementary Quadruple Hydrogen Bonds and Thermo-Switch, ACS Macro Lett. 6 (7) (2017) 641–646, https://doi.org/10.1021/acsmacrolett.7b00275.
[380] M. Nagao, J. Sengupta, D. Diaz-Dussan, M. Adam, M. Wu, J. Acker, R. Ben, K. Ishihara, H.B. Zeng, Y. Miura, R. Narain, Synthesis of Highly Biocompatible and Temperature-Responsive Physical Gels for Cryopreservation and 3D Cell Culture, ACS Appl. Bio. Mater. 1 (2) (2018) 356–366, https://doi.org/10.1021/acsabm.8b00096.
[381] Y.J. Chen, D. Diaz-Dussan, D. Wu, W.D. Wang, Y.Y. Peng, A.B. Asha, D.G. Hall, K. Ishihara, R. Narain, Bioinspired Self-Healing Hydrogel Based on Benzoxaborole-Catechol Dynamic Covalent Chemistry for 3D Cell Encapsulation,

ACS Macro Lett. 7 (8) (2018) 904–908, https://doi.org/10.1021/acsmacrolett.8b00434.
[382] R. Noroozi, M.A. Shamekhi, R. Mahmoudi, A. Zolfagharian, F. Asgari, A. Mousavizadeh, M. Bodaghi, A. Hadi, N. Haghighipour, In vitro static and dynamic cell culture study of novel bone scaffolds based on 3D-printed PLA and cell-laden alginate hydrogel, Biomed. Mater. 17 (4) (2022) 045024, https://doi.org/10.1088/1748-605X/ac7308.
[383] Y.F. Shou, X.Y. Teo, X.L. Li, Z.C. Le, L. Liu, X.H. Sun, W. Jonhson, J. Ding, C. T. Lim, A. Tay, Dynamic Magneto-Softening of 3D Hydrogel Reverses Malignant Transformation of Cancer Cells and Enhances Drug Efficacy, ACS Nano 17 (3) (2023) 2851–2867, https://doi.org/10.1021/acsnano.2c11278.
[384] Y. Shou, X.Y. Teo, X. Li, L. Zhicheng, L. Liu, X. Sun, W. Jonhson, J. Ding, C.T. Lim, A. Tay, Dynamic Magneto-Softening of 3D Hydrogel Reverses Malignant Transformation of Cancer Cells and Enhances Drug Efficacy, ACS Nano 17 (3) (2023) 2851–2867, https://doi.org/10.1021/acsnano.2c11278.
[385] R. Goodrich, Y.Y. Tai, Z.Y. Ye, Y.D. Yin, J. Nam, A Magneto-Responsive Hydrogel System for the Dynamic Mechano-Modulation of Stem Cell Niche, Adv. Funct. Mater. 33 (12) (2023), https://doi.org/10.1002/adfm.202211288.
[386] Y.F. Shou, L. Liu, Q.M. Liu, Z.C. Le, K.L. Lee, H. Li, X.L. Li, D.Z. Koh, Y.W. Wang, T.M. Liu, Z. Yang, C.T. Lim, C. Cheung, A. Tay, Mechano-responsive hydrogel for direct stem cell manufacturing to therapy, Bioact. Mater. 24 (2023) 387–400, https://doi.org/10.1016/j.bioactmat.2022.12.019.
[387] L.M. Stapleton, A.N. Steele, H. Wang, H. Lopez Hernandez, A.C. Yu, M.J. Paulsen, A.A. Smith, G.A. Roth, A.D. Thakore, H.J. Lucian, Use of a supramolecular polymeric hydrogel as an effective post-operative pericardial adhesion barrier, Nat. Biomed. Eng. 3 (8) (2019) 611–620.
[388] L. Ouyang, C.B. Highley, C.B. Rodell, W. Sun, J.A. Burdick, 3D Printing of Shear-Thinning Hyaluronic Acid Hydrogels with Secondary Cross-Linking, ACS Biomater. Sci. Eng. 2 (10) (2016) 1743–1751, https://doi.org/10.1021/acsbiomaterials.6b00158.
[389] S.H.D. Wong, W.K.R. Wong, C.H.N. Lai, J. Oh, Z. Li, X. Chen, W. Yuan, L. Bian, Soft Polymeric Matrix as a Macroscopic Cage for Magnetically Modulating Reversible Nanoscale Ligand Presentation, Nano Lett 20 (5) (2020) 3207–3216, https://doi.org/10.1021/acs.nanolett.9b05315.
[390] D. Nguyen, D.A. Hägg, A. Forsman, J. Ekholm, P. Nimkingratana, C. Brantsing, T. Kalogeropoulos, S. Zaunz, S. Concaro, M. Brittberg, A. Lindahl, P. Gatenholm, A. Enejder, S. Simonsson, Cartilage Tissue Engineering by the 3D Bioprinting of iPS Cells in a Nanocellulose/Alginate Bioink, Sci Rep-Uk 7 (2017). https://doi.org/ARTN 65810.1038/s41598-017-00690-y.
[391] K. Markstedt, A. Mantas, I. Tournier, H.M. Avila, D. Hägg, P. Gatenholm, 3D Bioprinting Human Chondrocytes with Nanocellulose-Alginate Bioink for Cartilage Tissue Engineering Applications, Biomacromolecules 16 (5) (2015) 1489–1496, https://doi.org/10.1021/acs.biomac.5b00188.
[392] B.L. Zhang, J.H. He, M.T. Shi, Y.Q. Liang, B.L. Guo, Injectable self-healing supramolecular hydrogels with conductivity and photo-thermal antibacterial activity to enhance complete skin regeneration, Chem. Eng. J. 400 (2020) 125994. https://doi.org/10.1016/j.cej.2020.125994.
[393] Z.X. Deng, Y. Guo, X. Zhao, P.X. Ma, B.L. Guo, Multifunctional Stimuli-Responsive Hydrogels with Self-Healing, High Conductivity, and Rapid Recovery through Host-Guest Interactions, Chem. Mater. 30 (5) (2018) 1729–1742, https://doi.org/10.1021/acs.chemmater.8b00008.
[394] S.G. Priya, H. Jungvid, A. Kumar, Skin tissue engineering for tissue repair and regeneration, Tissue Eng Part B-Re 14 (1) (2008) 105–118, https://doi.org/10.1089/teb.2007.0318.
[395] P. Bilalis, D. Skoulas, A. Karatzas, J. Marakis, A. Stamogiannos, C. Tsimblouli, E. Sereti, E. Stratikos, K. Dimas, D. Vlassopoulos, H. Iatrou, Self-Healing pH- and Enzyme Stimuli-Responsive Hydrogels for Targeted Delivery of Gemcitabine To Treat Pancreatic Cancer, Biomacromolecules 19 (9) (2018) 3840–3852, https://doi.org/10.1021/acs.biomac.8b00959.
[396] W.D. Wang, L. Xiang, L. Gong, W.H. Hu, W.J. Huang, Y.J. Chen, A.B. Asha, S. Srinivas, L.Y. Chen, R. Narain, H.B. Zeng, Injectable, Self-Healing Hydrogel with Tunable Optical, Mechanical, and Antimicrobial Properties, Chem. Mater. 31 (7) (2019) 2366–2376, https://doi.org/10.1021/acs.chemmater.8b04803.
[397] W.D. Wang, Z.C. Zeng, L. Xiang, C. Liu, D. Diaz-Dussan, Z.G. Du, A.B. Asha, W. S. Yang, Y.Y. Peng, M.F. Pan, R. Narain, J.F. Liu, H.B. Zeng, Injectable Self-Healing Hydrogel via Biological Environment-Adaptive Supramolecular Assembly for Gastric Perforation Healing, ACS Nano 15 (6) (2021) 9913–9923, https://doi.org/10.1021/acsnano.1c01199.
[398] Y.L. Yang, X.L. Liu, Y. Li, Y. Wang, C.Y. Bao, Y.F. Chen, Q.N. Lin, L.Y. Zhu, A postoperative anti-adhesion barrier based on photoinduced imine-crosslinking hydrogel with tissue-adhesive ability, Acta Biomater. 62 (2017) 199–209, https://doi.org/10.1016/j.actbio.2017.08.047.
[399] Q. Guo, H. Sun, X.J. Wu, Z.W. Yan, C.J. Tang, Z.H. Qin, M.M. Yao, P.C. Che, F. L. Yao, J.J. Li, In Situ Clickable Purely Zwitterionic Hydrogel for Peritoneal Adhesion Prevention, Chem. Mater. 32 (15) (2020) 6347–6357, https://doi.org/10.1021/acs.chemmater.0c00889.
[400] J.Y. Zhao, D. Diaz-Dussan, M. Wu, Y.Y. Peng, J.Q. Wang, H.B. Zeng, W. Duan, L. X. Kong, X.J. Hao, R. Narain, Dual-Cross-Linked Network Hydrogels with Multiresponsive, Self-Healing, and Shear Strengthening Properties (vol 22, pg 800, 2021), Biomacromolecules 22 (4) (2021) 1756, https://doi.org/10.1021/acs.biomac.1c00376.
[401] J.X. Cui, D.P. Wang, K. Koynov, A. del Campo, 2-Ureido-4-Pyrimidone-Based Hydrogels with Multiple Responses, ChemPhysChem 14 (13) (2013) 2932–2938, https://doi.org/10.1002/cphc.201300367.
[402] F. Zhang, L.G. Xiong, Y.J. Ai, Z. Liang, Q.L. Liang, Stretchable Multiresponsive Hydrogel with Actuatable, Shape Memory, and Self-Healing Properties, Adv. Sci. 5 (8) (2018), https://doi.org/10.1002/advs.201800450.
[403] C. Cheng, X.L. Zhang, Y.B. Meng, Z.H. Zhang, J.D. Chen, Q.Q. Zhang, Multiresponsive and biocompatible self-healing hydrogel: its facile synthesis in water, characterization and properties, Soft Matter 13 (16) (2017) 3003–3012, https://doi.org/10.1039/c7sm00350a.
[404] Y.Y. Peng, Q.L. Cheng, W.D. Wang, M. Wu, D. Diaz-Dussan, P. Kumar, R. Narain, Multi-responsive, injectable, and self-healing hydrogels based on benzoxaborole-tannic acid complexation, Polym Chem-Uk 12 (39) (2021) 5623–5630, https://doi.org/10.1039/d1py00692d.
[405] X.Y. Pei, L.P. Fang, W.P. Chen, X. Wen, L.B. Bai, X.W. Ba, Facile Fabrication of Multiresponsive Self-Healing Hydrogels with Logic-Gate Responses, Macromol, Chem. Phys. 222 (2) (2021), https://doi.org/10.1002/macp.202000339, 2000339.
[406] J.K. Chen, Q. Su, R.W. Guo, J.W. Zhang, A.J. Dong, C.G. Lin, J.H. Zhang, A Multitasking Hydrogel Based on Double Dynamic Network with Quadruple-Stimuli Sensitiveness, Autonomic Self-Healing Property, and Biomimetic Adhesion Ability, Macromol, Chem. Phys. 218 (15) (2017), https://doi.org/10.1002/macp.201700166.
[407] M.C. Roberts, M.C. Hanson, A.P. Massey, E.A. Karren, P.F. Kiser, Dynamically restructuring hydrogel networks formed with reversible covalent crosslinks, Adv. Mater. 19 (18) (2007) 2503–+, https://doi.org/10.1002/adma.200602649.
[408] A.T. Metters, C.N. Bowman, K.S. Anseth, A statistical kinetic model for the bulk degradation of PLA-b-PEG-b-PLA hydrogel networks, J. Phys. Chem. B 104 (30) (2000) 7043–7049, https://doi.org/10.1021/jp000523t.
[409] Q. Bao, W. Nie, C.Q. Liu, H.H. Zhang, H.K. Wang, H. Jin, J.Y. Yan, Q. Liu, The preparation of a novel hydrogel based on crosslinked polymers for suppressing coal dusts, J. Clean. Prod. 249 (2020), https://doi.org/10.1016/j.jclepro.2019.119343.
[410] J.V.K.S.V.J. Maitra, Cross-linking in Hydrogels -, A Review 4 (2) (2014) 25–31, https://doi.org/10.5923/j.ajps.20140402.01.
[411] J. Amirian, Y. Zeng, M.I. Shekh, G. Sharma, F.J. Stadler, J. Song, B. Du, Y.X. Zhu, In-situ crosslinked hydrogel based on amidated pectin/oxidized chitosan as potential wound dressing for skin repairing, Carbohyd. Polym. 251 (2021), https://doi.org/10.1016/j.carbpol.2020.117005.
[412] M.F. Zhang, X. Chen, K.D. Yang, Q. Dong, H.J. Yang, S.J. Gu, W.L. Xu, Y.S. Zhou, Dual-crosslinked hyaluronic acid hydrogel with self-healing capacity and enhanced mechanical properties, Carbohyd. Polym. 301 (2023), https://doi.org/10.1016/j.carbpol.2022.120372.
[413] W. Fan, L. Yuan, J. Li, Z. Wang, J. Chen, C. Guo, X. Mo, Z. Yan, Injectable double-crosslinked hydrogels with kartogenin-conjugated polyurethane nano-particles and transforming growth factor beta3 for in-situ cartilage regeneration, Mater. Sci. Eng. C Mater. Biol. Appl. 110 (2020) 110705, https://doi.org/10.1016/j.msec.2020.110705.
[414] L. Garcia-Fernandez, M. Olmeda-Lozano, L. Benito-Garzon, A. Perez-Caballer, J. San Roman, B. Vazquez-Lasa, Injectable hydrogel-based drug delivery system for cartilage regeneration, Mat. Sci. Eng. C-Mater. 110 (2020), https://doi.org/10.1016/j.msec.2020.110702.
[415] O. Prucker, T. Brandstetter, J. Ruhe, Surface-attached hydrogel coatings via C, H-insertion crosslinking for biomedical and bioanalytical applications (Review), Biointerphases 13 (1) (2018), https://doi.org/10.1116/1.4999786.
[416] S. Choi, H. Ahn, S.H. Kim, Tyrosinase-mediated hydrogel crosslinking for tissue engineering, J. Appl. Polym. Sci. 139 (14) (2022), https://doi.org/10.1002/app.51887.
[417] J. Nakanishi, K. Uto, Dynamic Hydrogel, Materials-based Mechanobiology 1 (2020), https://doi.org/10.1039/9781839165375.
[418] D. Chimene, K.K. Lennox, R.R. Kaunas, A.K. Gaharwar, Advanced Bioinks for 3D Printing: A Materials Science Perspective, Ann. Biomed. Eng. 44 (6) (2016) 2090–2102, https://doi.org/10.1007/s10439-016-1638-y.
[419] X.N. Zhang, Q. Zheng, Z.L. Wu, Recent advances in 3D printing of tough hydrogels: A review, Compos. B Eng. 238 (2022) 109895.
[420] X. Ding, J. Gao, H. Awada, Y. Wang, Dual physical dynamic bond-based injectable and biodegradable hydrogel for tissue regeneration, J. Mater. Chem. B 4 (6) (2016) 1175–1185.
[421] Z. Sheikh, S. Najeeb, Z. Khurshid, V. Verma, H. Rashid, M. Glogauer, Biodegradable Materials for Bone Repair and Tissue Engineering Applications, Materials (Basel) 8 (9) (2015) 5744–5794, https://doi.org/10.3390/ma8095273.
[422] J.H. Li, C.T. Wu, P.K. Chu, M. Gelinsky, 3D printing of hydrogels: Rational design strategies and emerging biomedical applications, Mat. Sci. Eng. R 140 (2020), https://doi.org/10.1016/j.mser.2020.100543.
[423] Z.Y. Wei, S.Q. Wang, J. Hirvonen, H.A. Santos, W. Li, Microfluidics Fabrication of Micrometer-Sized Hydrogels with Precisely Controlled Geometries for Biomedical Applications, Adv. Healthc. Mater. 11 (16) (2022), https://doi.org/10.1002/adhm.202200846.
[424] S.J. Hu, X.X. Du, Y.H. Bi, P.P. He, Y.L. Mu, C. Liu, Q. Gao, M.Y. Yin, W.W. Guo, Smart Hydrogels Based on Self-Assembly of One Short Single-Stranded DNA for Functional Surface Patterning, ACS Appl. Polym. Mater. (2022), https://doi.org/10.1021/acsapm.2c00697.
[425] C.C. Li, L.L. Ouyang, J.P. Armstrong, M.M. Stevens, Advances in the Fabrication of Biomaterials for Gradient Tissue Engineering, Trends Biotechnol 39 (2) (2021) 150–164, https://doi.org/10.1016/j.tibtech.2020.06.005.
[426] A. Khademhosseini, R. Langer, J. Borenstein, J.P. Vacanti, Microscale technologies for tissue engineering and biology, P Natl Acad Sci USA 103 (8) (2006) 2480–2487, https://doi.org/10.1073/pnas.0507681102.

[427] D. Seliktar, Designing Cell-Compatible Hydrogels for Biomedical Applications, Science 336 (6085) (2012) 1124–1128, https://doi.org/10.1126/science.1214804.
[428] H. Yuk, T. Zhang, S.T. Lin, G.A. Parada, X.H. Zhao, Tough bonding of hydrogels to diverse non-porous surfaces, Nat. Mater. 15 (2) (2016) 190–+, https://doi.org/10.1038/Nmat4463.
[429] J. Yang, A.R. Webb, G.A. Ameer, Novel citric acid-based biodegradable elastomers for tissue engineering, Adv. Mater. 16 (6) (2004) 511–+, https://doi.org/10.1002/adma.200306264.
[430] H. Yuk, C.E. Varela, C.S. Nabzdyk, X.Y. Mao, R.F. Padera, E.T. Roche, X.H. Zhao, Dry double-sided tape for adhesion of wet tissues and devices, Nature 575 (7781) (2019) 169-+, https://doi.org/10.1038/s41586-019-1710-5.
[431] J.V. Accardo, J.A. Kalow, Reversibly tuning hydrogel stiffness through photocontrolled dynamic covalent crosslinks, Chem. Sci. 9 (27) (2018) 5987–5993, https://doi.org/10.1039/c8sc02093k.
[432] D.H.T. Nguyen, S.C. Stapleton, M.T. Yang, S.S. Cha, C.K. Choi, P.A. Galie, C. S. Chen, Biomimetic model to reconstitute angiogenic sprouting morphogenesis in vitro, P Natl Acad Sci USA 110 (17) (2013) 6712–6717, https://doi.org/10.1073/pnas.1221526110.
[433] S. Kim, H. Lee, M. Chunga, N.L. Jeon, Engineering of functional, perfusable 3D microvascular networks on a chip (vol 13, pg 1489, 2013), Lab Chip 13 (24) (2013) 4891.
[434] A.D. Doyle, N. Carvajal, A. Jin, K. Matsumoto, K.M. Yamada, Local 3D matrix microenvironment regulates cell migration through spatiotemporal dynamics of contractility-dependent adhesions, Nat. Commun. 6 (2015), https://doi.org/10.1038/ncomms9720.
[435] R. Chandrawati, Enzyme-responsive polymer hydrogels for therapeutic delivery, Exp. Biol. Med. 241 (9) (2016) 972–979, https://doi.org/10.1177/1535370216647186.
[436] Z.X. Wang, Y.F. Wang, W. Qi, R.X. Su, Z.M. He, Design, Self-Assembly and Application of DNA-Peptide Hybrid Molecules, Prog. Chem. 32 (6) (2020) 687–697, https://doi.org/10.7536/Pc191020.
[437] A. Roy, K. Manna, S. Pal, Recent advances in various stimuli-responsive hydrogels: from synthetic designs to emerging healthcare applications, Mater. Chem. Front 6 (17) (2022) 2338–2385, https://doi.org/10.1039/d2qm00469k.
[438] A. Mandal, J.R. Clegg, A.C. Anselmo, S. Mitragotri, Hydrogels in the clinic, Bioeng. Transl. Med. 5 (2) (2020) e10158.