Type 2 Diabetes – an Autoinflammatory Disease Driven by Metabolic Stress

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Type 2 diabetes has traditionally been viewed as a metabolic disorder characterised by chronic high glucose levels, insulin resistance, and declining insulin secretion from the pancreas. Modern lifestyle, with abundant nutrient supply and reduced physical activity, has resulted in dramatic increases in the rates of obesity-associated disease conditions, including diabetes. The associated excess of nutrients induces a state of systemic low-grade chronic inflammation that results from production and secretion of inflammatory mediators from the expanded pool of activated adipocytes. Here, we review the mechanisms by which obesity induces adipose tissue dysregulation, detailing the roles of adipose tissue secreted factors and their action upon other cells and tissues central to glucose homeostasis and type 2 diabetes. Furthermore, given the emerging importance of adipokines, cytokines and chemokines in disease progression, we suggest that type 2 diabetes should now be viewed as an autoinflammatory disease, albeit one that is driven by metabolic dysregulation.

Keywords:

Metabolic disease; obesity; adipokine; cytokine; chemokine

1. Introduction

Modern lifestyle, with abundant nutrient supply and reduced physical activity, has resulted in dramatic increases in the rates of obesity-associated disease conditions, including diabetes. Obesity is a worldwide pandemic that continues to grow at an alarming rate. Some of the detrimental consequences of obesity have been attributed to the induction of a low-grade chronic inflammatory state that results the production and secretion of inflammatory mediators from the expanded pool of activated adipocytes. This contributes to the pathogenesis of several diseases, including obesity-related insulin resistance (IR) and type 2 diabetes (T2D)[1]. This is typically manifest by an excess of nutrients which cause adipose tissue (AT) and pancreatic β-cells to secrete cytokines, thereby making them the source of inflammation[2]. In addition, T2D-associated complications in kidneys, arteries, and eyes are also characterised by inflammatory processes[3].

2. Obesity and dysregulation of adipose tissue

Obesity is a serious health problem that increases morbidity and mortality in a variety of acute and chronic diseases, most notably T2D and cardiovascular diseases[4]. AT, which comprises a wide variety of cell types (adipocytes, pre-adipocytes, tissue matrix, nerve tissue, stromal-vascular cells, macrophages, endothelial cells, fibroblasts)[5], was for long considered an inert tissue with the sole purpose of fat storage. However, in the past decade, AT endocrine activity has emerged[5],[6],[7], shedding light into more complex processes in which it is involved. AT, and in particular visceral AT, is known to store lipid-based hormones[8] and to express pro-inflammatory mediators with auto-/paracrine or endocrine properties which have been found to be increased in obese humans, and linked to IR[2].

As obesity develops and the adipose depot expands in size, a variety of AT cell populations begin to exhibit an inflamed or stressed state, thereby becoming activated[9]. This becomes apparent though various mechanisms (depicted in Figure 1). Rapid AT expansion causes a decrease in oxygen availability, exposing cells to hypoxia and resulting in activation of the transcription factor, hypoxia inducible factor 1α (HIF-1α). Among the genes under control of HIF-1α are a number involved in apoptosis[9]. Mitochondrial uncoupling from processing of excess nutrients and fatty acids (FA) in adipocytes results in increased production of reactive oxygen species (ROS)[10], which in turn triggers abnormal signalling pathways involving diverse mediators including transcription factors such as NF-κB, inflammatory cytokines and chemokines[11]. Moreover, activated adipocytes secrete a variety of biological peptides with cytokine-like properties, known as adipokines, as well as a number of cytokines themselves. These may have pro-inflammatory effects (Table 1-3), anti-inflammatory effects (Table 4-5) or tissue-dependent roles (Table 6-7).

2.1 Hypoxia

2.1.1 Adipose tissue

Hypoxia is the deprivation of oxygen from tissues. This is a common issue found in obese patients, particularly in AT, and is thought to be one of the mechanisms by which pro-inflammatory adipose signalling is initiated and maintained[12]. The association between hypoxia and obesity involves an hypertrophic process that increases the size of adipose cells to 140-180 μm, which is more than the 100 μm diffusion distance of oxygen, resulting in a reduced oxygen supply to this tissue[13]. Importantly, one of the

key indicators of obesity-related hypoxia in AT is the release of adipokines that cause widespread systemic inflammation[14].

Hypoxia causes alteration of many different cellular processes in AT. HIF is a heterodimeric transcription factor composed of two subunits, an oxygen sensitive HIF-α subunit and a constitutively expressed HIF-β subunit. HIF-1α is activated in response to cellular hypoxia and induces transcription of various genes, including erythropoietin, vascular endothelial growth factor (VEGF), glucose transporters (GLUT) and plasminogen activator inhibitor (PAI-1)[11]. H1F1 (histone cluster 1, H1a) is also part of the HIF family, and is a key controlling element in many hypoxic responses. In AT this includes build-up of the extracellular matrix (ECM), which brings inflammatory cells and overall dysregulation to AT[15]. The effect of the inhibition of HIF1 signalling on IR in AT of mice fed a high-fat diet (HFD) resulted in improvements in obesity and IR[16]. Furthermore, this improvement was associated with the induction of the anti-inflammatory adipokine, adiponectin, which is secreted by AT, and with the subsequent increase in insulin sensitivity[16].

2.1.2 Pancreas

Glucose-stimulated insulin secretion causes pancreatic β-cells to consume large amounts of oxygen in a short time period due to the high demand of mitochondrial respiration[17]. Pancreatic islets of diabetic mice, but not those of control mice, have been seen to be moderately hypoxic through expression of HIF-1α protein and target genes[18]. This suggests that hypoxia is a novel stressor of β-cells and that hypoxic stress may play a role in the deterioration of β-cell function.

In addition, hypoxia also inhibits the adaptive unfolded protein response (UPR) specifically in β-cells. This inhibition is associated with impaired ER-to-Golgi protein trafficking and has been implicated in increased apoptosis under hypoxic stress[19}. These effects are mediated by activation of c-Jun N-terminal kinase (JNK), and DNA-damage inducible transcript 3 (DDIT3), but are independent of HIF-1α[19]. Hypoxia can also activate the NLRP3 inflammasome (see section 4.5) and NF-êB signalling (see section 4.1) in LPS-primed mouse MIN6 cells. This occurs via reactive oxygen species (ROS) and thioredoxin-interacting protein (TXNIP) up-regulation[20].

2.2 Mitochondrial dysfunction

Mitochondrial dysfunction is one of the central events that contributes to IR in obese individuals[13][21]. It is the main reason for the decreased adipocyte release of adiponectin, contributing to IR and declined glucose utilization of other tissues[13],[22]. Hyperglycemia and hyperlipidemia can cause mitochondrial uncoupling in adipocytes, leading to increased production of ROS[10]. This increase in ROS production affects many cellular components and signalling pathways and can lead to several complications including renal injury, which eventually develops into chronic kidney disease[11].

T2D-assocated hyperglycemia and hyperlipidemia can induce ROS either by enzymatic pathways (including nicotinamide adenine dinucleotide phosphate oxidase -NADPH oxidase- and uncoupling of nitric oxide synthase -NOS-, amongst others), or by non-enzymatic pathways (including mitochondrial electron transport chain -mETC-deficiencies and advanced glycation end products -AGEs- formation, amongst others)[23],[24][25]. In a diabetic environment, certain factors such as excess reducing

equivalents NADH/$FADH_2$[26] induce mETC to produce ROS: An initial high glucose availability, together with the increased transcription of GLUT transporters caused by hypoxia results in an excess uptake of glucose into adipocytes[11]. This causes an impairment in intracellular glucose homeostasis, causing excessive production of pyruvate and NADH, which shuttle into the mitochondrial matrix, where pyruvate is oxidized to produce more NADH and $FADH_2$ resulting in excess oxidizing substrates, which increase electron donations to mETC, ultimately leading to increased ATP synthesis and ROS production[11].

Nuclear factor-kappa B (NF-κB) is a redox-sensitive transcription factor that can be activated by a wide variety of stimuli, including oxidative stress[27]. ROS-mediated activation of NF-κB can interfere with the transcription of a wide range of pro-inflammatory and pro-fibrotic genes coding for cytokines, adhesion molecules and growth factors causing vascular dysfunction, atherosclerosis, and inflammation. Therefore, pro-inflammatory cytokines (tumour necrosis factor TNF-α, interleukins IL-1β, IL-2, IL-6, IL-12), leukocyte adhesion molecules (E-selectin, vascular and intracellular cell adhesion molecules VCAM-1, and ICAM-1), growth factors (transforming growth factor TGF-β), and chemokines (monocyte chemoattractant protein MCP-1) are upregulated during persistent oxidative stress-induced NF-κB activation[28].

2.3 Inflammation

Inflammation occurs as a result of exposure of tissues to harmful stimuli such as microbial pathogens, irritants, or toxic cellular components. These will trigger an inflammatory response involving the major cells of the immune system (monocytes,

macrophages, neutrophils, basophils, dendritic cells, mast cells, T-cells and B-cells). These events are in turn controlled by a host of extracellular molecular regulators, including cytokines and chemokines that mediate both immune cell recruitment and complex intracellular signalling control mechanisms that characterise inflammation[29]. Adipose tissue, liver, muscle, brain and pancreas are themselves sites of the inflammation that is associated with obesity.

2.3.1 Adipose tissue

Accumulation of AT causes the release of inflammatory cytokines (referred to as adipokines), and results in low-grade inflammation throughout AT[30]. Adipokines take part in glucose and lipid metabolism as well as the body's immune response and are often the cause of obesity-related diseases[31], including T2D. Some of these adipocyte-secreted adipokines include leptin, which stimulates secretion of TNF-α from circulating monocytes[4], or resistin, which is associated with an increased production of pro-inflammatory cytokines and a decreased production of anti-inflammatory cytokines, with the former mediated through activation of NF-κB[4], the central pro-inflammatory transcription factor.

Activated adipocytes themselves also secrete pro-inflammatory cytokines, including TNF-α, IL-6, and C reactive protein (CRP), which is largely synthesized by the liver, with its production being in turn enhanced in response to TNF-α and IL-6, hence amplifying the pro-inflammatory effects of other adipokines[4]. Furthermore, the macrophage content of AT positively correlates with both adipocyte size and body mass[32], and there is an obvious obesity-induced phenotypic switch in AT from anti-inflammatory (M2) to pro-inflammatory (M1) macrophages[33], which express most of

the pro-inflammatory cytokines rather than adipocytes being the source of cytokine expression and secretion[32].

Free Fatty Acids (FFA), secreted from the AT, signal through toll-like receptor (TLR2/4) to activate c-Jun-N-terminal kinases (JNK) in muscle, liver, and adipose cells. This blocks the insulin signalling cascade, thereby promoting IR in these tissues[34]. It is likely that each of the above mechanisms (namely hypoxia, mitochondrial dysfunction and inflammation) contributes to the activation of pro-inflammatory cytokines such as IL-1β[9] and TNFα[35] in T2D. Furthermore, under stimulation of TNF-α, adipocytes are also able to secrete chemokines, which induce macrophage activation and infiltration.

Macrophages themselves, upon activation, also secrete numerous cytokines and chemokines, including TNF-α, IL-1, IL-6 and MCP-1[36], that can impair adipocyte insulin sensitivity and stimulate further activation and infiltration of peripheral monocytes and macrophages into fat. Peripheral monocytes of obese subjects have also shown an increased transcription of pro-inflammatory genes regulated by NF-κB[37], as well as an increased intranuclear expression of the major protein component of NF-κB (p65 or RelA), and diminished amounts of the inhibitor of NF-κB (IκB)[38]. All together, these amplifying signals increasingly impair adipocyte insulin signalling.

While the actions of a wide number of cytokines and adipokines are known to participate in obesity-induced inflammation that characterises the onset and progression of T2D, it is important to note however, that some adipokines (Table 6) and cytokines (Table 7) are less clear-cut in following the anti-inflammation vs pro-inflammation

paradigm, showing contradictory functions in different tissues or situations. This discordance may be due to the temporal and local regulation of inflammation, or to the possibility that several cytokines may be required to co-ordinately regulate the development of disease[39]. However, while some of the mechanisms still remain to be fully resolved, dysregulated production or secretion of adipokines caused by excess AT, together with AT dysfunction, clearly contributes to the development of obesity-related metabolic diseases[40].

2.3.2 Liver

Extensive epidemiological studies have shown a strong link between obesity and various types of cancers, with liver cancer showing the highest increase in risk[41]. This connection is particularly strong, with obesity also often resulting in other liver diseases such as non-alcoholic fatty liver disease (NAFLD) and the more severe non-alcoholic steatohepatitis (NASH). This disease is characterized by fatty liver inflammation and is thought to cause fibrosis and cirrhosis[42], a key liver cancer risk factor, resulting in elevated production of various cytokines and adipokines that have been implicated in hepatocarcinogenesis[43].

As outlined above, inflamed AT releases numerous adipokines and cytokines. These can increase activation and infiltration of Kupffer cells (resident liver macrophages), thereby increasing secretion of cytokines such as TNF, IL-6, IL-1β, IL-8, IL-10, IL-18 and IL-17, as well as adipokines such as leptin and adiponectin[44],[45],[46],[47]. Signalling through IL-6 receptors in hepatocytes also activates downstream signalling molecules including signal transducer and activator of transcription 3 (STAT3), which further contributes to liver inflammation and hepatocarcinogenesis[43].

2.3.3 Skeletal muscle

IL-6 levels are elevated in obesity due to increased secretion from AT, and this is associated with IR and T2D risk[48],[49]. The functional role and effect of IL-6 signalling in skeletal muscle is however highly complex. In normal conditions IL-6 functions as a myokine, with its expression and secretion level increasing in contracting skeletal muscle after exercise when insulin sensitivity is enhanced[50]. IL-6 induces skeletal muscle metabolism by increasing AMP-activated protein kinase (AMPK) α2 activity, FA oxidation, and glucose uptake[51]. However, obese and T2D subjects show abnormal IL-6 signalling. In particular, obese subjects have reduced skeletal muscle IL-6 receptor expression and abnormal STAT3/suppressor of cytokine signalling 3 (SOCS3) signalling, while T2D subjects show attenuated IL-6 induced AMPKα2 activation[52].

IL-10 has also been implicated in obesity and IR. In particular, the anti-inflammatory effects of IL-10 in skeletal muscle glucose homeostasis have been studied using a transgenic mouse model with muscle-specific overexpression of IL-10[52]. After HFD feeding, IL-10 over-expressing mice showed improved insulin sensitivity when compared to HFD-fed control mice. Additionally, HFD transgenic mice showed increased phosphorylation of insulin receptor substrate 1 (IRS-1) and reduced macrophage infiltration, with a corresponding reduction in IL-6 and TNF-α secretion in skeletal muscle[53].

2.3.4 Brain

It has previously been shown that obesity induces activation of inflammatory pathways in the hypothalamus, modulating the expression of TNF-α, IL-1β and IL-6 and resulting in induction of apoptosis of hypothalamic cells[54]. The hypothalamus is strongly implicated in neuronal circuits responsible for regulating food intake and energy expenditure and, in recent years, hypothalamic inflammation has emerged as an important driver of energy homeostasis dysfunction[55]. Inflammatory changes such as the upregulation of NF-κB signalling, an increase in ROS production or the release of pro-inflammatory cytokines (IL-1β and TNF-α), able to activate pro-apoptotic pathways, were observed in brain cortex and hypothalamus of HFD-fed rats[56],[57].

Interestingly, a recent study revealed a link between T2D and the development of multiple sclerosis (MS)[58]. MS is an immune-mediated disease of the central nervous system (CNS) with inflammatory and neurodegenerative characteristics that has also been linked to obesity[59], with vascular risk factors and typical vascular comorbidities (like obesity, T2D and dyslipidaemia) being involved in MS onset and progression[60]. The mechanistic link may involve lipid metabolism as obese people more frequently have an adverse lipid profile, and an increase in the levels of some aggressive and atherogenic molecules such as oxidized low-density lipoproteins (ox-LDL) have been reported in the serum of MS patients[61]. Importantly, caloric restriction, which contributes to low leptin levels, seems to reduce inflammation, demyelination and axon injury[62], suggesting that nutritional intervention is able to attenuate inflammatory responses in CNS pathology.

2.3.5 Pancreas

Reduced β-pancreatic cell mass and function are two hallmarks of T2D[63], which starts to develop when β-cells fail to secrete sufficient insulin to maintain normoglycemia in the face of IR[64]. Growing evidence from recent studies suggests that an important triggering factor for β-cell dysfunction and failure in T2D is chronic islet inflammation[65],[66],[67]. Interestingly, several reports have indicated that FAs potentiate inflammatory toxicity by directly activating inflammatory pathways in pancreatic islets[68], demonstrating that lipotoxicity may interact with inflammatory factors that initiate, sustain, and cause β-cell loss.

It is worth mentioning that different types of FA have different effects on the lipotoxicity of β-cells[69]. Saturated fatty acids (SFAs) have been associated with adverse health effects. Palmitic acid, the most common SFA found in the human body and one of the most abundant in the diet[70], has a major role in β-cell failure to respond to extracellular glucose, causing proinsulin build-up in the ER lumen and generating ER stress, reducing β-cell proliferation capacity and inducing apoptosis[71]. Palmitic acid has also been seen to induce chemokine (CXCL1 and CCL3) and cytokine (IL-6 and IL-8) expression within pancreatic islets *in vitro*[72][73].

By contrast, unsaturated fatty acids (UFAs), such as oleic acid, are generally associated with protective effects, including preventing β-cell apoptosis, regulating plasmatic glucose concentrations and enhancing insulin sensitivity[69]. Interestingly, treatment of monocytes with docosahexaenoic acid (DHA), a polyunsaturated fatty acid (PUFA), has been described to inhibit palmitic acid-induced secretion of proinflammatory cytokines such as IL-1β[74]. However, the effects of DHA on IL-1β release form β-cells remains to be determined.

An elevated number of islet-associated macrophages and an increased expression of IL-1β have been reported in pancreatic islets from T2D subjects[75],[76]. Moreover, enhanced macrophage infiltration results in an evident increase in inflammatory cytokine production, and this results in β-cell release of chemokines[77] that further drives recruitment of neutrophils, monocytes, and lymphocytes to the pancreas in obesity[78],[79]. Accordingly, depletion of resident islet macrophage in HFD-fed transgenic mice can reduce IL-1β expression and improve β-cell insulin secretion[67], while IL-1β signalling targeting improves β-cell function and glucose homeostasis in T2D[80].

Increased islet IL-1β levels have been reported following chronic exposure of human islets to elevated glucose, FA, or leptin [81],[82],[83]. Recent research suggests that this might in turn be triggered by upstream activation of the pro-inflammatory transcription factors NF-κB and STAT1 by a further cytokine, TNFR5/CD40[84]. An additional mechanism for β-cell failure and increased IL-1β production has also been reported, in which exposure of human and mouse islets to angiotensin II, produced by AT, induces an inflammatory state characterised by the increased expression of MCP-1 and IL-6, impaired mitochondrial function and insulin secretion, and increased β-cell apoptosis[85]. Interestingly, increased IL-1β expression has also been seen in islet-associated macrophages in HFD-fed mice[67], suggesting that macrophages might provide a further source of IL-1β to the toxic milieu found within the pancreas in T2D.

Recently, S100 calcium-binding protein A8 (S100A8), a member of the damage-associated molecular pattern molecules (DAMPs), has been implicated in â-cell

inflammation[86]. Co-culture of pancreatic islets and unstimulated peritoneal macrophages in the presence of palmitate and high glucose (to induce glucolipotoxicity) increased both the expression and release of islet-produced S100A8. S100A8 induced TLR4-mediated inflammatory cytokine production by migrating macrophages, macrophage infiltration of the islets and consequentially induced â-cell apoptosis. This effect was diminished after either inhibition of the TLR4 pathway in the macrophages or S100A8 neutralization in the pancreatic islets[86].

Finally, besides cell death, β-cell dedifferentiation has also recently been proposed as a mechanism underlying β-cell mass loss in T2D. In particular, it was recently observed that pro-inflammatory cytokines (IL-1β, IL-6 and TNFα) promoted β-cell dedifferentiation in cultured human and mouse islets, with IL-1β being the most potent of the cytokines. Furthermore, anti-IL-1β, anti-TNFα or NF-kB inhibiting sodium salicylate treatment was shown to improve insulin secretion of isolated islets. [87].

3. The role of cytokines in inflammation and T2D

Cytokines are a group of low molecular weight proteins that possess autocrine and paracrine effects[88] and are known products and effectors of the inflammatory and immune system. As outlined above, T2D involves cytokine release from AT and pancreatic β-cells, as well as from macrophages recruited into both AT and pancreas as a result of chemokine release from these cells. This causes inflammation and impaired function of both adipocytes[35] and β-cells[89].

As mentioned earlier, AT is an endocrine organ that secretes significant levels of cytokines called adipokines[9],[90]. These communicate with the brain and peripheral tissues to regulate energy homeostasis and metabolism[91]. Cytokine involvement also has a central role in another source of inflammatory state, namely when apoptotic cells induce an immune response when present in high enough numbers[92],[93]. One of the hallmarks of T2D is progressive β-cell failure, with increased apoptosis that leads to reduced β-cell mass[94]. Inflammatory mediators not only represent markers of metabolic abnormalities in T2D[95], but also contribute to β-cell death due to progressive decrease in β-cell function and mass[94].

It has been extensively demonstrated that exposure of pancreatic islets to elevated glucose levels results in increased production and release of IL-1β, followed by impaired β-cell function[81][96]. In addition, an intense activation of the acute-phase response has been associated with islet cell autoantibodies production in patients with T2D[97]. In some type 2 diabetics, when apoptosis is induced by high glucose or high FFA concentrations, mobilization of T-cells reactive to pancreatic β-cells results in autoimmune destruction of β-cells similar to that observed in type 1 diabetics[98]. In this way, a vicious cycle is created since pro-inflammatory cytokines, and in particular IL-1β, are important pathogenic effectors responsible for the induction of β-cell apoptosis in both types of diabetes. IL-1β (secreted by activated macrophages but also by β-cells under certain circumstances[81]), TNF-α (secreted by macrophages), and interferon-γ (IFN-γ, secreted by T-helper cells) act together following immune infiltration of the pancreas to induce β-cell damage and apoptosis. Indeed, while IL-1β appears the most cytotoxic cytokine in the inhibition of β-cell function, and may be

sufficient to promote an apoptotic response by itself[98], induction of apoptosis in β-cells usually involves a combination of IL-1β plus IFN-γ and/or TNF-α[81].

4. Inflammatory pathways and their metabolic regulating mechanisms

4.1 The IKK/NF-κB Pathway

NF-κB plays a critical role in regulating inflammation[99]. In the basal (resting) state, NF-κB is held in the cytoplasm in an inactive form, bound to the inhibitor of κB (IκB). When cells encounter pro-inflammatory stimuli, including growth factors, cytokines, and foreign pathogens, the IκB kinase (IKK) enzyme complex becomes activated, and IκB releases NF-κB following its phosphorylation. IκB is then polyubiquinated, prior to proteosomal degradation. This allows NF-κB to translocate to the nucleus, where it initiates the gene expression of various inflammatory mediators, including TNF-α, IL-6 and MCP-1[39]. NF-κB activity is increased in obese subjects, and it has been seen that its inhibition improves IR[100]. In non-obese individuals NF-κB signalling is mainly activated through TLR4, with its primary ligand being LPS. However, in obesity, the increased FFA also signal through TLR4[101], further activating NF-κB[102],[103]. Additionally, TNFα and IL-1β, both elevated in AT of obese and diabetic rodents, signal through TNF and IL-1 receptors respectively to activate NF-κB, stimulating the IKK signalling pathway to mediate proinflammatory signals[78] (Figure 2).

4.2 The c-Jun N-terminal kinase (JNK)–activator protein-1 (AP-1) pathway

The JNK/AP-1 pathway also exerts proinflammatory action. AP-1 is a transcription factor consisting of an heterodimer of the basic leucine zipper proteins c-Jun and c-Fos[104]. It regulates expression of genes involved in proliferation, differentiation,

apoptosis, cell migration and transformation[105],[106] in response to stimuli including cytokines, growth factors, stress, and bacterial and viral infections[107]. The activity of JNK is increased in insulin-responsive tissues (liver, muscle and AT), both in mice fed a HFD and in the leptin-deficient ob/ob mouse[78]. The JNK signalling pathway is also activated by ER stress, and can be induced by palmitate[108] (Figure 2).

4.3 The nuclear factor of activated T-cells (NFAT) pathway

Nuclear factor of activated T-cells (NFAT) proteins have crucial roles in the development and function of the immune system, and together with NF-κB they belong to the extended Rel family of transcription factors[109]. In T-cells, NFAT proteins not only regulate activation but also are involved in the control of thymocyte development, T-cell differentiation and self-tolerance[110]. However, as more NFAT members have been identified and characterised, it has become apparent that at least one NFAT family member is expressed not only by T-cells but also by almost every cell type that has been examined, including both immune system and non-immune cells[111],[112].

In resting cells, NFAT resides in the cytosol in a hyperphosphorylated form. A rise in intracellular calmodulin-bound Ca^{2+} levels activates calcineurin, which dephosphorylates multiple serine residues in NFAT, and results in the rapid translocation of the protein to the nucleus. Here it enhances local histone acetylation and promotes *de novo* gene transcription[113]. However, while Ca^{2+} and calcineurin are the main regulators of NFAT expression[114], cytokine signalling also plays an important role on NFAT activity regulation[110]. For example, IL-2 promotes the binding of NFAT2 to the CX3CR1 chemokine promoter, inducing its expression[115], while IL-6 signalling results in the preferential induction of NFAT1 transcripts in response to T-

cell stimulation, resulting in increased IL-4 production[116]. Given its role on T-cell activation, NFAT proteins have for long been targets for therapeutic approaches aimed at regulating immune responses by the use of inhibitors of calcineurin, such as cyclosporine A (CsA) and FK506, as immunosuppressive agents to treat autoimmune diseases[117],[118] (Figure 2).

4.4 The signal transducer and activator of transcription 1 (STAT1) and 3 (STAT3) pathways

JAKs (Janus activated kinases) and STATs are critical components of many cytokine receptor systems, regulating growth, survival, differentiation, and pathogen resistance. Signalling through cytokines such as IL-6, INF-α, -β and -γ[119], TLR agonists, or growth factors[120] induces receptor dimerization, which induces phosphorylation of the receptor-bound JAKs and subsequent phosphorylation of the receptor. These phosphorylated sites serve as docking sites for the SH2-containing STATs, such as STAT1 or STAT3, which then phosphorylate, dimerise and translocate to the nucleus to act as transcription factors[121]. Interferons can also potentiate TLR-induced macrophage activation via a STAT1-dependent pathway[122], thereby demonstrating a new paradigm of cross-talk between TLR and cytokine signalling pathways.

As well as cytokine signalling, increased metabolic stress also results in the activation of STAT1[123],[84], which, together with NF-κB, triggers the synthesis of a number of β-cell proteins, including IL-1β[81]. IL-1β is then released from the cell and amplifies both NF-κB activation and the subsequent cytokine response that is driven through activation of nucleotide-binding oligomerization domain (NOD) like receptor family

(NLR), pyrin domain containing 3 (NLRP3) inflammasomes[102] (detailed further in section 4.5).

STAT3 is a key mediator of intestinal inflammation and tumorigenesis[120]. It is a pleotropic transcription factor that mediates transcription of numerous proteins involved in fundamental biological activities, including the immune response and metabolism[124]. Interestingly, STAT3 can have anti-inflammatory or pro-inflammatory functions in different cell types but also within cell types. For instance, when dendritic cells (DCs) are stimulated by IL-6, the role of STAT3 is pro-inflammatory, but when stimulated by IL-10, STAT3 shows anti-inflammatory functions[125].

As well as inducing STAT3 phosphorylation, cytokines, and most notably IL-6, indirectly increase STAT3 expression through activation of NF-κB in a tumour microenvironment[126]. However, cytokine-induced phosphorylation is not the only posttranslational modification that modulates STAT3 activity. A previous study reported O-GlcNAcylated STAT3 in 3T3-L1 adipocytes after stimulation with insulin[127]. This same modification has also been observed in macrophages, where loss of O-GlcNAcylation in STAT3 leads to enhanced transcriptional activity, strongly suggesting that O-GlcNAcylation exerts an inhibitory effect on STAT3 phosphorylation[120] (Figure 2). These findings expand our understanding of metabolic regulation of immune signalling pathways and highlight an essential role of metabolism in regulating immunity, inflammation and inflammatory diseases.

4.5 Metabolic regulation of the NLRP3 inflammasome

Inflammasome biology is one of the most rapidly growing areas in immunology. Over the past decade, inflammasomes have been recognized for their roles in defence against invading pathogens and in the development of cancer, autoinflammatory, metabolic, and neurodegenerative diseases[128]. Inflammasomes are multiprotein scaffolding complexes, whose activation requires two signals in order to induce inflammation. Firstly, inflammatory cytokines activate the NF-κB signalling pathway to prime the NLRP3 inflammasome, which will then recruit and activate pro-caspase-1 to produce caspase-1. This then mediates proteolytic cleavage of pro-IL-1β and pro-IL-18 to mature IL-1β and IL-18, respectively[128],[129],[130]. Additionally, caspase-1 is also able to mediate cell death through a process termed pyroptosis, which both fragments DNA and leads to pore formation in the plasma membrane[131].

The second inflammasome-activating signal relies on cytosolic recognition of pathogen-associated molecular patterns (PAMPs) and endogenous damage-associated molecular patterns (DAMPs). These factors include palmitate and ceramide, which are increased in obesity. TLRs recognize exogenous PAMPs and endogenous DAMPs. In particular, TLR4 can distinguish between LPS and saturated FAs, with the latter being necessary for NF-κB signalling and induction of TNF, IL-6 and MCP-1 expression in AT[78]. The role of the inflammasome in metabolic disease is also supported by other studies, which demonstrate for example that mice deficient in various inflammasome components as well as IL-1β or its receptor IL-1R1 are protected from diet-induced IR[132]. The NLRP3 inflammasome therefore appears to be an important sensor of metabolic dysregulation, controlling obesity-associated IR and pancreatic β-cell dysfunction[133]. Recent studies indicate that caspase-8[134], caspase-11[135], IL-1R–associated kinases (IRAK)[136], and receptor-interacting protein (RIP) kinases[137] also contribute to

inflammasome functions. In addition, post-translational modifications, including ubiquitination, deubiquitination, phosphorylation and degradation control almost every aspect of inflammasome activities[128] (Figure 2).

5. Metaflammation and immunometabolism

As the connection between inflammation and chronic metabolic diseases such as obesity and diabetes has become clear, this new aspect of inflammation is now increasingly referred to as metaflammation[138],[139]. Altered homeostasis of nutritionally overloaded metabolic cells triggers the development of obesity-induced inflammation, characterised by elevated expression of the genes encoding for cytokines, chemokines and other inflammatory mediators through activation of transcription factors NF-κB, AP-1, NFAT and STAT3, together with activation of inflammasomes, resulting in an increase in pro-inflammatory cytokines released from the M1 macrophages of AT, and a decrease in anti-inflammatory cytokines released from M2 macrophages[139].

Metabolic organs (liver, brain, pancreas and AT) rely on inflammatory cell action for maintenance of tissue homeostasis and metabolic disease pathogenesis. Immune cells may sense and react to changes in nutrient availability, influencing the intrinsic metabolic action within adjacent cells critical for metabolic homeostasis, for instance by altering lipid metabolism or inhibiting glucose uptake. These tissues and the mediators that they produce trigger systemic inflammatory responses and disrupt metabolic homeostasis. As a result, immunometabolic diseases often appear, promoting ageing, disability and premature death[138].

6. Obesity and insulin resistance

In addition to inflammation, the most common symptom of obesity is insulin resistance (IR). This occurs when tissues do not respond appropriately to circulating insulin[140]. Moreover, it has long been recognized that obesity is associated with T2D, with the major basis for this link being the ability of obesity to induce IR in several tissues, mainly the AT, liver and muscle[39].

6.1 Adipose tissue

Normal insulin signalling in AT involves the binding of insulin to its receptor on adipocytes, triggering the phosphorylation and activation of insulin receptor substrate (IRS1) proteins. These can then activate two main signalling pathways: the Ras-mitogen-activated protein kinase (MAPK) pathway, which regulates cell growth (proliferation, differentiation, motility and survival), or the phosphatidylinositol 3-kinase (PI3K)-Akt/protein kinase B (PKB) pathway, which results in the translocation of glucose transporter 4 (GLUT4) to the plasma membrane, thus leading to an increase in adipocyte glucose uptake. This leads to increased glycogen synthesis and lipogenesis, and decreased gluconeogenesis and lipolysis[40]. These mechanisms thereby allow storage of triglycerides and differentiation of pre-adipocytes to adipocytes[141]. However, in the face of an excess of nutrient availability the release of FFA and adipokines from AT causes abnormal insulin signalling, by promoting protein kinases such as protein kinase C (PKC), MAPK, c-Jun *N*-terminal kinase (JNK), and the inhibitor of Nuclear Factor κB Kinase β (IκKβ)[142].

6.2 Liver

Many organisms store excess calories in the form of triglyceride droplets, which accumulate in diverse cells and tissue types, including the liver[143]. Ectopic lipid

accumulation in liver may lead to IR through the formation of metabolically toxic products. For instance, saturated FA have been shown to increase ceramide production, which appears to contribute to IR[144], and hepatic diacylglycerol content shows a strong correlation with systemic IR, especially in NAFLD patients[145]. However, IR in the liver is selective in that insulin fails to suppress gluconeogenesis, but continues to stimulate FA synthesis[146], which suggests that the point at which insulin signalling is disrupted in obesity is downstream of insulin receptor activation. This uncoupling of glucose and lipid metabolism in the hepatic insulin signalling pathway, which ultimately manifests as hyperglycemia and hyper-triglyceridemia, may involve the mammalian target of rapamycin complex (mTORC)[147].

6.3 Skeletal muscle

Skeletal muscle plays an important role in regulating whole-body homeostasis, being responsible for approximately 80% of the postprandial clearance of glucose[148] after stimulation with insulin[149], although glucose uptake can be insulin-dependent or independent[150]. Glycogen synthesis is the principal pathway for glucose disposal in both normal and T2D subjects[151], with defective glycogen synthesis being involved in IR and T2D development[152]. In insulin-stimulated normal skeletal muscle metabolism, similarly to normal insulin signalling in AT, insulin stimulates PI3K-mediated Akt phosphorylation. Activated Akt then phosphorylates Akt substrate 160 (AS160), allowing GLUT4 storage vesicles to translocate to the plasma membrane for glucose uptake[153].

Obesity-induced IR in skeletal muscle is a multifactorial process, but the specific mechanism(s) involved are largely unknown[154]. However, some potential

mechanisms have been proposed: 1. Increased intracellular fat content and lipid metabolites[155]; 2. Accumulation of intramyocellular lipid (IMCL) caused by an imbalance between fatty acid oxidation (FAO) and fatty acid synthesis[156]; 3. Accumulation of lipid intermediates (e.g., FA-CoA, DAG, and ceramide)[157],[158]; 4. Mitochondrial overload leading to excessive β-oxidation and generation of partially oxidized fatty acid (incomplete FAO) such as acylcarnitine[159],[160]; 5. Elevated mitochondrial oxidative stress (ROS production) resulting from overnutrition[161], constituting the primary factor for the development of IR in skeletal muscle[162]. However, although IR is correlated with mitochondrial respiratory chain deficiency, this may be a consequence, rather than a cause of insulin resistance[163].

6.4 Pancreas

As IR starts to develop, pancreatic β-cells respond by proliferating in a compensatory manner, initially increasing insulin secretion, which is critical to maintaining glucose homeostasis at the early stage of type 2 diabetes[164]. This overcomes IR for some time, but the compensatory hypersecretion eventually fails, leading to hyperglycemia and insulin dependence, which characterises the onset of T2D. Disruptions in insulin signalling, especially decreased insulin sensitivity, not only result in diabetes, but are also strongly associated with other comorbidities of metabolic syndrome[165].

Recently, the role of LDL receptor-related protein 1 (LRP1), a pleiotropic mediator of cholesterol, insulin, energy metabolism, and other cellular processes[166][167] on lipid metabolism in β-cells was reported[164]. It is known that high levels of glucose and lipids stimulate Erk, S6K1, and PPARγ2 signaling to enable the β-cells to manage the excess of energy and nutrients. The crucial function of LRP1 in pancreatic islets is to

prevent these signals from overactivation. Upon HFD exposure, it was observed that LRP1 ablation significantly impaired insulin secretion and proliferation of β-cells, highlighting its role as an essential regulator of intracellular lipid metabolism on β-cell function and viability in obesity and T2D[164].

7. The role of adaptive immunity in T2D

Inflammatory regulation has largely focused on innate immunity, especially with regards to macrophages. However, there is evidence for a critical role of the adaptive immune system in driving local and systemic inflammation in obesity and T2D, and in promoting IR. Indeed, there is increasing evidence to suggest that T-cells are crucial for the development of metabolic inflammation and IR[168].

AT contains most types of immune cells, with obesity increasing their numbers and activation levels. This is particularly the case for AT macrophages (ATMs), the major inflammatory cell type in the glucose-utilizing tissues, with their levels increasing from 5% in lean subjects to up to 50% of all AT cells in obese individuals[169]. However, there are other pro-inflammatory cells found in AT, including neutrophils, T-helper type 1 (Th1) CD4+ T-cells, CD8+ T-cells, B-cells, DCs, and mast cells[39], and it has been seen that, in addition to M1 macrophages levels increasing in AT of obese subjects, the number of total T-cells, and in particular pro-inflammatory T-cells[170], is also increased in obese humans and mice[171] in parallel with an increase in their proliferation and infiltration[172]. Moreover, it has been shown that one of the T-cell chemoattractant factors, regulated on activation normal T-cell expressed and secreted (RANTES), is induced in adipocytes after activation by IFN-γ and TNF-α[172]. Therefore, obesity-induced factors would contribute to changes in T-cell population

numbers and activity, leading to the accumulation of pro-inflammatory responses in obese AT.

AT also contains anti-inflammatory cells that are associated with insulin sensitivity[173], and these counter the pro-inflammatory immune cells that are responsible for the obesity-induced inflammation in this tissue. These anti-inflammatory cells include regulatory CD4+ T-cells (Tregs), Th2 CD4+ T-cells, and eosinophils[39]. It has been seen that induction or transfer of Treg cells improves glucose homeostasis in obese mice[174]. Notably, the beneficial effects of Treg cells require expression of peroxisome proliferator activated receptor gamma (PPARγ), an important metabolic mediator, and genetic deletion of PPARγ in Treg cells is sufficient to prevent anti-diabetic actions of PPARγ agonists[175], providing another layer of evidence into the immunometabolic nature of T2D.

B-cells also accumulate in the AT of obese mice[176], further adding to the presence of inflammatory cytokines[177]. Importantly, obesity also triggers abnormal B-cell function, characterised by the production of autoantibodies and pathological immunoglobulins[176]. While the relative contribution of the adaptive immune system activation to the pathologies of systemic glucose homeostasis in obesity remains incompletely understood, there are exciting potential opportunities in this area with translational possibilities.

8. Conclusions

Obesity is currently one the largest pandemics in the industrialized world. It is also a central driver of numerous chronic diseases that carry high economic impact to society,

including cardiovascular disease, hyperlipidemia, and T2D among others. As such, obesity should be studied as a causative condition rather than a consequential one deriving from other disease states. Over the last decade, important contributions have been made to the understanding of adipose as an endocrine organ. However, whilst our knowledge is increasing at a rapid pace, the interplay between the signalling cascades connecting the major outcomes of obesity, such as inflammation and IR, still remain to be fully elucidated. Adipose is however a highly functional endocrine organ, and, in obese individuals, one of the most prolific sources of pro-inflammatory signalling with organism-wide impact. Thus, the role of adipose tissue as an endocrine organ warrants further study, both from isolated and systemic chronic disease perspectives. Moreover, given the impact of central adiposity, plus the localized release of cytokines by pancreatic β-cells in T2D, we suggest that anti-inflammatory strategies incorporating either cytokine antagonists or anti-cytokine biologics should increasingly be viewed as potential T2D treatment options, albeit alongside existing therapies that target metabolic aspects of the disease.

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Abbreviations:

Acpr30, adipocyte complement-related protein 30kDa
ADSF, AT-specific secretory factor
Akt (PKB)
AMPK, adenosine monophosphate-activated protein kinase
ANGPTL, angiopoietin-like protein
AP-1, activator protein-1
ASP, acylation-stimulating protein
AT, adipose tissue
ATM, adipose tissue macrophage
ATP, adenosine triphosphate
BAFF, B-cell activation factor
BMI, body mass index
CART, cocaine and amphetamine–regulated transcript
CCL2/MCP-1, C-C motif chemokine ligand 2/macrophage chemoattractant protein-1
CMKLR1, chemokine-like receptor 1
CNS, central nervous system
COX-2, cyclooxygenase-2
CRP, C reactive protein
CsA, Cyclosporine A
DAG, diacylglycerol
DAMP, damage-associated molecular pattern
DC, dendritic cell
DDP-4, dypeptidyl-peptidase 4
ECM, extracellular matrix
ELAM-1, endothelial-leukocyte adhesion molecule 1
ER, endoplasmic reticum
FABP4, fatty acid binding protein 4
FAO, fatty acid oxidation
FFA, free fatty acids
FGF21, fibroblast growth factor 21
GLP-1, glucagon-like peptide 1
GLUT, glucose transporter
GSIS, glucose-stimulated insulin secretion
HDL, high density lipoproteins
HFD, high fat diet
HIF-1α, hypoxia Inducible Factor 1α
ICAM-1, intercellular adhesion molecule-1
IFN, interferon
IκB, inhibitor of κB
IKK, inhibitor of κB kinase
IL, interleukine
ILC, innate lymphoid cell
IMCL, intramyocellular lipid
IR, insulin resistance
IRAK, IL-1R–associated kinases
IRS, insulin receptor substrate
JAK, janus activated kinase
JNK, c-Jun-N-terminal kinase
LCN, lipocalin

LPS, lipopolysaccharide
MAPK, mitogen-activated protein kinase
MCP, monocyte chemoattractant protein
mETC, mitochondrial electron transport chain
MIF, macrophage migration inhibitory factor
MIP-1α, macrophage inflammatory protein 1α
MMP-2/9, matrix metalloproteinase 2/9
MS, multiple sclerosis
mTORC, mammalian target of rapamycin complex
NADP, nicotinamide adenine dinucleotide phosphate
NAFLD, non-alcoholic fatty liver disease
NAMPT, nicotinamide-monophosphate-transferase
NASH, non-alcoholic steatohepatitis
NFAT, nuclear factor of activated T-cells
NF-κB, nuclear factor κB
NLRP3, nucleotide-binding oligomerization domain-like receptor family pyrin containing 3
NOS, nitric oxide synthase
OA, osteoarthritis
Ox-LDL, oxidized low-density lipoproteins
PAI, plasminogen activator inhibitor
PAMP, pathogen-associated molecular patterns
PBMC, peripheral blood mononuclear cells
PGRN, progranulin
PI3K, phosphatidylinositol 3-kinase
PKB, protein kinase B
PKC, protein kinase C
PPARγ, peroxisome proliferator activated receptor gamma
RA, retinoic acid
RANTES, regulated on activation, normal T cell expressed and secreted
RBP-4, retinol-binding protein-4
RIP, receptor-interacting protein
ROS, reactive oxygen species
SAA, serum amyloid A
SAP, serum amyloid P
SFRP5, secreted frizzled-related protein 5
SOCS, suppressor of cytokine signalling
STAT, signal transducer and activator of transcription
T2D, type 2 diabetes
TGF-β, transforming growth factor-β
TLR, toll-like receptor
TNF-α, tumour necrosis factor-α
TNFR, tumour necrosis factor receptor
TSP1, thrombospondin-1
Vaspin, visceral adipose tissue-derived serine protease inhibitor
VCAM-1, vascular cell adhesion molecule-1
VEGF, vascular endothelial growth factor

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Table 1. Proinflammatory adipokines released from visceral adipose tissue

PEPTIDE	EFFECT ON INFLAMMATION AND T2D
TSP1	TSP1 is a matricellular protein firstly recognised as a proinflammatory adipokine in 2008 by Varma et al. in human AT[178]. It is an activator of TGF-β and its expression correlates with increased BMI and IR and with several macrophage-related inflammatory biomarkers. Its production by both adipocytes and macrophages in AT is upregulated in obesity and diabetes[179], suggesting a strong crosstalk between the pathways of macrophage-induced and adipose-induced inflammation[178].
Resistin/ ADSF	In rodents, it is primarily produced by adipocytes, while in humans it is mainly produced by monocytes and macrophages in response to LPS, IL-1β, IL-6, TNF-α and resistin itself[180]. In humans, elevated circulating levels of resistin are strongly related to increased risk of T2D through induction of hepatic IR and inflammation[181]: resistin inhibits the anti-inflammatory effects of adiponectin by promoting the expression of the pro-inflammatory VCAM-1, ICAM-1, MCP-1, TNF-α, IL-6, and IL-12 through NF-κB activation[4],[182].
Visfatin/ NAMPT	Abundantly expressed in the visceral AT with its expression being upregulated by other cytokines[183]. The increased serum levels of visfatin have been correlated with metabolic syndrome, inflammation, T2D and endothelial homeostasis[184],[185],[186]. It has a pro-inflammatory role, stimulating the production of interleukins and chemokines (IL-1β, IL-1Ra, TNF-α, IL-6, IL-8 and IL-10, CXCL12)[184],[187],[188], VEGF, and MMP-2/9[189]. Visfatin presents an insulin-like effect, regulating glucose homeostasis[190],[191],[192].
DDP-4	DPP4 is secreted by differentiated adipocytes, with its release strongly correlating with adipocyte size[193]. DPP-4 degrades GLP-1, which diminishes inflammation by reducing the levels of inflammatory mediators and macrophage proliferation[194], promoting an inflammatory state. By degrading GLP-1, DPP-4 also contributes to impaired glucose metabolism[195]. DPP-4 inhibitors such as linagliptin are being used to improve hyperglycemia in T2D patients with contraindications to the common drugs metformin, thiazolidinedione or sulfonylureas[196].
FABP4/ aP2	FABP4 is released from adipocytes and macrophages[197] under obesogenic conditions, such as hypoxia, to increase insulin secretion[198], and in turn, its release from adipocytes is inhibited by insulin, thus forming an endocrine loop that coordinates the β-cell response to obesity[198]. Serum FABP4 levels positively correlate with body fat percentage[199], and elevated FABP4 levels increase the risks of obesity-related metabolic disorders and hypertension[197].
PAI-1	PAI-1, a primary inhibitor of fibrinolysis, is also synthesized by adipocytes, pre-adipocytes, fibroblasts, vascular endothelial cells and a variety of immune cells in AT, in response to TNF-α, and its plasma levels correlate with cardiovascular dysfunction, obesity and IR[200],[201]. PAI-1 deficient mice fed a high-fat diet show reduced body weight gain, increased total energy expenditure, and improved IR[202]. PAI-1 also regulates expression of inflammatory factors (IL-8 and leukotriene B4) and monocyte migration[203].
ANGPTL2	ANGPTL2 is an adipocyte-derived inflammatory mediator that promotes inflammation and IR[204]. Expression of *ANGPTL2* in AT and circulating levels of ANGPTL2 are higher in diet-induced obese mice compared to control mice, and circulating levels of ANGPTL2 positively correlate with adiposity, IR and inflammation in mice and humans[205]. Loss of *ANGPTL2* decreases AT inflammation and IR whereas its overexpression promotes inflammation and IR in diet-induced obese mice[205]. Recently, Doi *et al.* reported that circulating ANGPTL2 levels positively correlate with T2D development in humans[206], although further studies are needed to characterise this association.
ASP	ASP is produced through a two-step process involving three proteins of the alternate complement system: C3, factor B and adipsin, all of which are synthesized and secreted by the AT[207]. Plasma ASP levels increase after meals and facilitates the synthesis and storage of triglycerides. Consistently, ASP deficiency increases postprandial FA levels and decreases weight gain and triglyceride synthesis[208]. In humans, ASP levels are increased in obesity, T2D, and cardiovascular disease, reversible with exercise or weight loss. Furthermore, similar to IR, a deleterious ASP-resistant state has been proposed to contribute to the abnormal AT metabolism and dyslipidemia common to diabetes and cardiovascular disease[209].
Angiotensin	Angiotensinogen and/or angiotensin peptides were firstly identified as secretory products of adipocytes early in the discovery of the dynamic role of AT[210]. Production of angiotensin II (Ang II) is linked to a variety of diseases, including hypertension, atherosclerosis, and kidney disease. An important aspect of adipose-derived angiotensin is its contribution to obesity-related hypertension. More recently, a role for angiotensin on differentiation of bone marrow-derived stem cells to adipocytes has also been described[211].
BAFF	It is mainly expressed in B-cell lineage cells and has a role in B-cell proliferation and differentiation[212],[213]. BAFF is also produced by adipocytes and functions as a pro-inflammatory adipokine[214], with its expression being increased during adipocyte differentiation and under TNF-α stimulation, and decreased when exposed to the anti-inflammatory drug rosiglitazone, suggesting a possible inflammatory role[212]. Kim et. al demonstrated that BAFF knockout in obese mice promotes lipogenesis in a depot-specific manner and reduces production of inflammatory molecules[214].

Table 2. Proinflammatory cytokines and chemokines released from visceral adipose tissue

PEPTIDE	TYPE	EFFECT ON INFLAMMATION AND T2D
TNF-α	Cytokine	TNF-α is primarily secreted from activated macrophages[81], although it may also be secreted by other cell types including monocytes, T-cells, mast cells, NK cells, keratinocytes, fibroblasts and neurons[215]. Its production is higher in the AT of obese individuals than of lean individuals[216]. It has a pro-inflammatory effect, impairing insulin signalling[190] and decreasing insulin sensitivity[195]. Treatment with TNF-α induces IR in AT[217], whereas deletion of *TNF-α* or its receptors or the use of a TNF-α antagonist improves insulin sensitivity in obese animals[218], although not in obese humans[219]. TNF-α is thought to affect IR through PI3K and the p80 TNF receptor, which is overexpressed in obesity[220]. TNF-α is a part of complex inflammation network and is capable of initiating cytokine cascades which control the synthesis and expression of other cytokines, hormones, and their receptors[221].
IL-1β	Cytokine	IL-1β expression is induced mainly in response to microbial molecules, although it can also stimulate its own expression[222]. It is mostly expressed in and secreted from AT and activated macrophages[223], however it can also be expressed by pancreatic β-cells under certain circumstances[81]. IL-1β is a pro-inflammatory cytokine which has been proposed to play a role in inflammatory pancreatic β-cell destruction leading to type 1 diabetes[224]. IL-1β activation depends on the cleavage of pro-IL-1β to mature IL-1β by caspase-1[225]. Bioactive IL-1β acts through the IL-1 receptor 1 (IL-1R1), inducing the production of inflammatory cytokines including IL-6[150] through NF-κB activation[226]. IL-1β expression is increased in visceral AT in obese subjects[227], with increased circulating IL-1β concentrations being associated with greater risk of developing T2D[48]. Recombinant IL-1 receptor antagonists such as Anakinra are being used as a treatment for diabetes[228], improving glycemia and β-cell function.
IL-8 (CXCL8)	Chemokine	Mainly produced by AT macrophages[229], IL-8 can be better classified as a chemokine, given its predominant chemoattractant properties[230]. Both mRNA levels and release of IL-8 are stimulated by the proinflammatory cytokine IL-1β[47]. Circulating IL-8 levels are increased in hyperinsulinemia and hyperglycemia[230], in obese compared with lean subjects[231], and in patients with both type 1 and type 2 diabetes compared with healthy subjects[232]. IL-8 is associated with IR, development of atherosclerosis[233], and cardiovascular disease[234].
CCL2/ MCP-1	Chemokine	CCL2/MCP-1 is one of the key chemokines that regulate migration and infiltration of monocytes/macrophages into AT[195],[35],[235], initiating adipose inflammation. CCL2/MCP-1 is expressed by adipocytes and circulating levels correlate with adiposity[40] and T2D[236].
MIF	Chemokine	MIF displays chemokine-like functions and acts as a major regulator of inflammatory cell recruitment and atherogenesis[237]. An association between MIF and obesity-induced IR has been suggested[37],[238] by which MIF promotes secretion of TNF-α, IL-6 and IL-1β, inhibits secretion of IL-10[239], and induces chemotaxis of macrophages and T-cells via CXCR2 and CXCR4 respectively[237]. Plasma MIF concentrations and PBMC MIF mRNA positively correlate with BMI, FFA concentration, impaired glucose tolerance and IR[240],[241]. Weight loss and treatment with metformin reduces plasma MIF concentrations as well as improving pancreatic β-cell function[242]. Loss of MIF in a mouse model resulted in less local WAT inflammation, reduced macrophage infiltration and enhanced systemic insulin sensitivity[243].
RANTES (CCL5)	Chemokine	RANTES is a chemotactic C-C motif cytokine originally detected as a T-cell-specific molecule[244]. Its secretion has been detected from mesenteric AT and from creeping fat[245] in patients with Crohn's disease (an inflammatory condition of the lining of the digestive system), as well as from perivascular AT, which plays a critical role in the pathogenesis of cardiovascular disease, including obesity and diabetes[246]. Together with other cytokines (IL-6, TNFα) and chemokines (MCP-1), and other pro-inflammatory mechanisms, RANTES takes part in the initiation of inflammatory cell infiltration[246]. It has also been implicated in the pathogenesis of atherosclerosis[247] and is present in AT of both humans and mice[248].

Table 3. Other proinflammatory factors released from visceral adipose tissue

PEPTIDE	TYPE	EFFECT ON INFLAMMATION AND T2D
TGF-β	Growth factor	TGF-β is a pleiotropic cytokine with potent regulatory and inflammatory activity[249]. It regulates cell proliferation, differentiation and apoptosis[195] and promotes the differentiation of induced Treg cells in combination with IL-2 and retinoic acid (RA)[250]. It is mostly secreted by M2 macrophages, which have immunosuppressive properties and high phagocytic capacity[251]. Adipocyte macrophage crosstalk results in increased expression of TSP-1, a multifunctional protein that promotes fibrosis by activating TGF-β signalling[179]. TGF-β has multiple effects on AT in addition to inducing fibrosis including inhibiting adipogenesis and complicated effects on angiogenesis. Marie J.C. et. al also demonstrated that TGF-β1 knockout mice develop severe multi-organ autoimmunity and die within a few weeks after birth[252].
CRP	Acute-phase protein	CRP is a member of the pentraxin family that attaches to the plasma membrane of damaged cells causing cell death through activation of the complement cascade[253]. It is mainly synthesized by the liver in response to TNF-α and IL-6[4]. Excess adipocyte lipid availability during obesity also induces CRP and SAP production both of which are mediators of the acute phase response that contributes to pro-inflammatory cytokine production[254]. A large volume of epidemiologic data connect CRP to coronary events, atherosclerotic disease, and progression to T2D[255],[256].
SAA	Acute-phase protein	Serum Amyloid A is an apolipoprotein found in the AT and in the liver in humans[257], and mainly in adipocytes in mice[258]. Expression of *SAA* in AT and circulating levels of SAA are higher in obese subjects than in lean subjects and are decreased by caloric restriction[257]. An inflammatory role has been proposed for SAA by which treatment with SAA increases expression of the pro-inflammatory cytokines IL-6 and TNF-α in pre-adipocytes and adipocytes *in vitro*[259]. Lewis *et al*. suggested that SAA might also have a potential role in the development of atherosclerosis by mediating retention of SAA-enriched HDL in vascular proteoglycans[260], which suggests that increased expression of SAA can promote dyslipidemia by affecting HDL structure and function as well as inflammation[40].
Haptoglobin (Hp)	Acute-phase protein	Hp is a plasma glycoprotein involved in the hepatic acute phase response to inflammation[261]. It is present in murine WAT[262], and its gene expression is dramatically increased in induced obese mice[263], as well as during inflammation, infection, and malignancy[264]. More recently, a strong positive correlation between circulating Hp and BMI has also been established[265]. Adipocyte Hp production is induced by several cytokines, the most important one being TNF-α[266].
Fetuin-A	Hepatokine	Circulating levels of fetuin-A correlate with high risk of T2D[267]. In NAFLD patients, Fetuin-A is secreted by the inflamed liver and acts as an adaptor protein between FFAs and TLR4 in the activation of chronic low-grade inflammation that leads to IR present in T2D[268],[269].
CART	Peptide	CART is a regulatory peptide expressed in the nervous system and in endocrine cells such as pancreatic islets[270]. CART is upregulated in islets of T2D rats and CART mRNA and protein were found to be expressed in both subcutaneous and visceral WAT from rat and human[270]. Banke et. al also saw that CART inhibited insulin-induced glucose uptake and lipogenesis by inhibition of PKB/Akt phosphorylation[270].

Table 4. Anti-inflammatory adipokines released from visceral adipose tissue

PEPTIDE	EFFECT ON INFLAMMATION AND T2D
Adiponectin/ Acpr30	Produced by adipocytes, placenta, the liver, epithelial cells, osteoblasts and myocytes in response to inflammatory, metabolic or oxidative stress[271]. Circulating adiponectin levels negatively correlate with BMI and are decreased in obese subjects, T2D and cardiovascular disease[272]. Acts through AdipoR1 and AdipoR2 receptors to inhibit gluconeogenesis, increase FA oxidation and inhibit oxidative stress and inflammation[190],[271]. It attenuates TNF-α, IL-6, MCP-1, VCAM-1, ICAM-1, and ELAM-1 expression, inflammation, oxidation, and fibrosis in AT through the inhibition of NF-κB activation[273], while it is able to boost the expression of anti-inflammatory signals such as IL-10 and IL-1RA to lower inflammation[30]. It has insulin sensitizing, anti-inflammatory and anti-apoptotic properties[195].
Adipsin	Primarily expressed by adipocytes in mice and by both adipocytes and monocytes-macrophages in humans[274]. It is one of the most abundant and specifically expressed adipose proteins[275]. Its expression is regulated by the differentiation of adipocytes, hormones such as insulin and adrenal glucocorticoid, and other factors such as retinoic acids and TNF-α[276]. Decreased adipsin activity has been observed in experimental models of obesity and diabetes[274],[277], and Lo, J. C. *et al.* have shown that T2D patients with β-cell failure are deficient in adipsin[275], proposing a beneficial role for adipsin in β-cell function.
Vaspin (SerpinA12)	High vaspin (Visceral AT-derived serpin) serum concentrations and mRNA expression in human AT are associated with obesity, IR, and T2D in humans[278]. It suppresses leptin, TNF-α, ICAM, and resistin synthesis and inhibits ROS production, decreasing NF-κB activation and relieving metabolic dysfunction and inflammatory responses in obesity[279]. Administration of vaspin to obese mice improves glucose tolerance and insulin sensitivity, and reduces food intake[278],[280], suggesting an anti-inflammatory role.
Omentin	Highly and selectively expressed in visceral stromal-vascular cells compared with subcutaneous AT[271]. Circulating levels are inversely correlated to obesity, BMI and leptin in healthy subjects[271]. As adiponectin, omentin may play a role in modulating insulin sensitivity: Herder, C. *et al.* suggest that omentin upregulates adiponectin secretion, affecting lipid metabolism and thereby indirectly enhancing insulin sensitivity[281]. Omentin inhibits Akt pathways, CRP production, TNF-α, TLR4, and NF-κB signalling pathways[190],[282], and enhances insulin-stimulated glucose uptake[283].
FGF21	FGF21 secretion is mostly induced by different kinds of stress[284]. Hepatic FGF21 acts on WAT to inhibit lipolysis and acts through the brain to increase systemic glucocorticoid levels in response to starvation[284], promoting weight loss[195]. Adipocytic FGF21 induces secretion of adiponectin from WAT[284]. Myocytic FGF21 protects against diet-induced obesity and IR, induces the browning of WAT and protects against cardiac hypertrophy[284].

Table 5. Anti-inflammatory cytokines and other anti-inflammatory factors released from visceral adipose tissue

PEPTIDE	TYPE	EFFECT ON INFLAMMATION AND T2D
IL-4	Cytokine	IL-4 is produced by resident AT cells (eosinophils, ILC2 cells, Tregs and Th2 cells[285], with the former being responsible for 90% of its production) and it stimulates M2 polarization[286] and Th2 cells differentiation[287]. M2 macrophages express arginase (promotes proliferation and growth) and anti-inflammatory cytokines such as IL-10[287]. IL-4 also acts directly on white AT to promote insulin sensitivity[285]. D. Wu et. al showed that eosinophil-deficient mice display increased fat mass and inflammatory responses, as well as glucose intolerance[288].
IL-10	Cytokine	IL-10 is produced by monocytes, M2 ATMs, DCs, T-cells, and B-cells[150]. It signals through the IL-10 receptor (IL-10R) exerting immuno-suppressive effects by blocking IκK activity[289] or by inducing phosphorylation of STAT3[290]. The IL-10/STAT3-mediated anti-inflammatory response works in opposition to the pro-inflammatory effect of IL-6 in AT, which also signals via STAT3[291]. IL-10 may play a protective role in obesity-induced metabolic dysregulation and IR[39]. IL-10 levels are decreased in obesity[40] and in T2D[292], while weight loss increases WAT expression of IL-10, accompanied by reduced pro-inflammatory gene expression[293]. Lumeng et al. showed that treatment of 3T3-L1-adiopcytes with IL-10 reduced MCP-1 secretion, blocked the effects of TNF-α and enhanced insulin-stimulated glucose transport[290]. IL-10 production by T_H cells inhibits production of MHC class II and co-stimulatory molecule expression in macrophages and DCs[294]. IL-10 can also inhibit the production of cytokines from $CD4^+$ T cells[295] and neutrophils[296].
IL-13	Cytokine	IL-13 is mainly produced by resident AT cells[285],[297]. However, adipocytes have also been identified as sources of IL-13[298]. Together with IL-4, IL-10 and other cytokines, it guarantees M2 polarization as well as differentiation of Th2 cells[287],[299], but also directly act on white AT to promote insulin sensitivity[285]. The IL-4/IL-13 effect is largely mediated via the phosphorylation and activation of STAT6[300], which interacts with PPARα repressing its transcription activity on target genes involved in FA oxidation, attenuating inflammation in AT[301].
C3	Compliment factor	C3a, a peptide generated by adipsin, has been identified as a potent insulin secretagogue and its receptor has been shown to be required for the beneficial effects of adipsin. C3a acts on islets by increasing ATP levels, respiration and cytosolic free Ca^{2+} ions[275]. C3a, downstream of adipsin catalytic action, strongly stimulates insulin secretion when coupled to hyperglycemic signals[275].

Table 6. Adipokines with dual role released from visceral adipose tissue

PEPTIDE	EFFECT ON INFLAMMATION AND T2D
Leptin	Mainly produced in WAT by mature adipocytes[271], with its expression being regulated by several inflammatory mediators such as LPS, TNF-α, IL-6, and IL-1β during acute inflammatory responses[302],[303]. Circulating levels[304] and mRNA expression in AT[305] are increased in obese subjects. Leptin has contrary functions depending on the tissue, as it improves insulin sensitivity in the liver and skeletal muscle and regulates pancreatic β-cell function[306], while it impairs insulin signalling in rat adipocytes[307]. Initially described as an appetite-regulating hormone[271], an innate immunity role has been described since, involving the activation of proliferation and phagocytosis of monocytes/macrophages, the chemotaxis of neutrophils, the release of oxygen radicals, the activation of NK cells and the induction of pro-inflammatory cytokines (TNF-α, IL-6, IL-12, IL-2 and IFN-γ)[4],[308],[309] and inhibition of anti-inflammatory cytokines (IL-4) by T-cells or mononuclear cells[310].
Apelin	High serum levels correlate with increased inflammation[190] and obesity[311]. Apelin was initially proposed as a novel beneficial adipokine[311], being able to improve glucose metabolism[195]. It acts through its receptor, APJ (a type of GPCR)[312]. The apelin/APJ system is associated with many complications, including IR[311], cardiovascular diseases and diabetes[312]. Apelin is able to regulate oxidative stress-related inflammatory diseases, presenting opposing roles depending on the disease[312]: Apelin activates ROS generation, inducing atherosclerosis through NF-κB activation[313], whilst it exerts anti-inflammatory properties in the pathogenesis of diabetic nephropathy, reversing diabetes-induced activation of NF-κB, elevation of monocyte and macrophage infiltration[314] and elevation of inflammatory factors MCP-1, ICAM-1 and iNOS in Akita mouse[315].
Nesfatin	Initially described as an anorexigenic modulator of food intake, nesfatin regulates appetite and body weight. Nesfatin-1 secretion from AT is negatively correlated with BMI, body weight, percentage body fat and fasting blood glucose and is increased by pro-inflammatory cytokines (IL-1β, TNF-α, and IL-6) as well as by insulin[316]. It has been linked to anti-apoptotic and anti-inflammatory properties, exerting neuroprotection in rats by inhibiting neutrophil infiltration and subsequent release of inflammatory mediators[190],[317]. Exerts both central and peripheral insulin-sensitizing effects[190] by enhancing GSIS[318]. However, Scotece, M. *et al.* showed that nesfatin-1 induces IL-6 and MIP-1α secretion in ATDC-5 cells treated with IL-1, inducing pro-inflammatory agents such as COX-2, IL-8, IL-6, and MIP-1α in human primary chondrocytes from OA patients[319].
SFRP5	SFRP5 is a new adipokine with insulin sensitizing and anti-inflammatory properties that exhibits beneficial effects on metabolic dysfunction[320], with its expression being higher in AT than in any other tissue[321]. A clinical study demonstrated that SFRP5 plasma levels were lower in humans with impaired glucose intolerance and T2D[322], and its levels have also been reported to decrease in obesity[40]. *SFRP5*-deficient mice showed impaired insulin sensitivity, increased risk of developing NAFLD and aggravated AT inflammation compared with control mice when fed a HFD[321]. Conversely, administration of SFRP5 improves metabolic function and reduces adipose inflammation in obese and diabetic mice[321]. However, Carstensen *et al.* reported a positive correlation between serum SFRP5 levels and parameters of IR in healthy and obese subjects[323].
RBP-4	Mainly synthesised in the liver, RBP-4 is involved in the transport of vitamin A (retinol)[324]. However, RBP4 has also been described to be secreted by adipocytes, with its expression being increased in AT in insulin-resistant mice[325]. RBP-4 affects visceral fat distribution[195], and in primary human adipocytes, it inhibits insulin-induced phosphorylation of IRS-1 and ERK1/2, impairing insulin signalling[326]. Circulating RBP4 levels have been associated with IR, impaired glucose tolerance and T2D in obese and non-obese subjects[327]. However, several clinical studies show no correlation between circulating RBP4 levels and obesity and IR[328],[329].
PGRN	PGRN has recently been described as a multifunctional regulatory protein with growth-promoting, neuroprotective and anti-inflammatory activities[330]. PGRN is able to significantly counteract the IL-1β-induced expression of NOS2, COX2, MMP13 and VCAM-1, mainly through TNFR1[331]. Although PGRN is one of the major anti-inflammatory molecules, it might also exert pro-inflammatory functions on different tissues. Anti-inflammatory roles of PGRN include inhibition of LPS-mediated IL-6, TNF-α, and MCP-1 cytokine release from macrophages[332], while it is also the major adipokine involved in HFD-induced IR by upregulating pro-inflammatory IL-6 expression in AT[333]. PGRN impairs insulin signalling and reduces insulin-induced glucose uptake both *in vitro* and *in vivo* contributing to IR and affecting glucose metabolism[330].
LCN2	LCN2 is abundantly expressed in WAT[334] and its expression is induced by inflammatory stimuli through activation of NF-κB. Circulating levels positively correlate with adiposity, hyperglycemia, IR, and CRP levels, as well as with other pro-inflammatory cytokines[271],[334]. Zhang, J. *et al.* showed that LCN2 administration to 3T3-L1 cells attenuated TNF-α effect on glucose uptake and decreased secretion of adiponectin and leptin. When added to macrophages, LCN2 suppresses LPS-induced cytokine production. This suggests that LCN2 acts as an anti-inflammatory molecule, downregulating secretion of adipokines[335]. Gomez-Chou, S. B. *et al* showed that LCN2 deficient animals had decreased numbers of leukocytes and macrophages, and presented weight gain and adiposity, suggesting a role for LCN2 in obesity prevention[336].

Table 7. Cytokines and chemokines with dual role released from visceral adipose tissue

PEPTIDE	TYPE	EFFECT ON INFLAMMATION AND T2D
IL-6	Cytokine	IL-6 is expressed by mononuclear phagocytes, T-cells, B-cells, fibroblasts, endothelial cells, keratinocytes, hepatocytes, and bone marrow cells[337], with AT contributing to 10–35% of circulating IL-6 levels in humans[338], with circulating levels positively correlating with AT hyperthrophy[339]. Its expression is supressed by insulin[190] and increased by hyperglycemia[340]. It decreases insulin sensitivity, contributing to IR[195]. However, Wallenius V. et al. showed that a lack of *IL-6* caused obesity and IR in mice[341]. The role of IL-6 appears to vary depending on the tissue: in adipocytes, IL-6 has a pro-inflammatory role, inducing IR[342] whereas in muscle, IL-6 has an anti-inflammatory effect; it enhances insulin-stimulated glucose disposal in humans *in vivo*, and increases glucose uptake and FA oxidation in cultured L6 myotubes[343].
IL-18	Cytokine	IL-18 is a pro-inflammatory cytokine produced by AT[344]. Circulating IL-18 levels are increased in obese subjects and decrease with weight loss[345]. Moreover, overexpression of *IL-18* worsened IR in rat[346]. However, IL-18 also appears to have opposing functions since Netea M.G. et al. showed that a lack of *IL-18* or its receptor in mice induces obesity and IR[347].
Chemerin	Chemokine	Physiological amounts of chemerin are secreted by adipocytes in early adipocyte differentiation, with its production increasing when they are mature[348]. It is an attractant for immune cells, contributing to macrophage infiltration into AT[190],[195]. High circulating levels also correlate with inflammatory (TNF-α, IL-6)[349],[350] and metabolic syndrome parameters[351],[352]. It exacerbates glucose intolerance, lowers serum insulin levels, and decreases tissue glucose uptake[353]. However, one *in vitro* study in 3T3-L1 adipocytes has demonstrated that chemerin promotes IR[350], whereas another study indicates the opposite[354]. Furthermore, some *in vitro* studies have reported anti-inflammatory functions of chemerin[355], which may be explained by the existence of different bioactive chemerin isoforms[356].

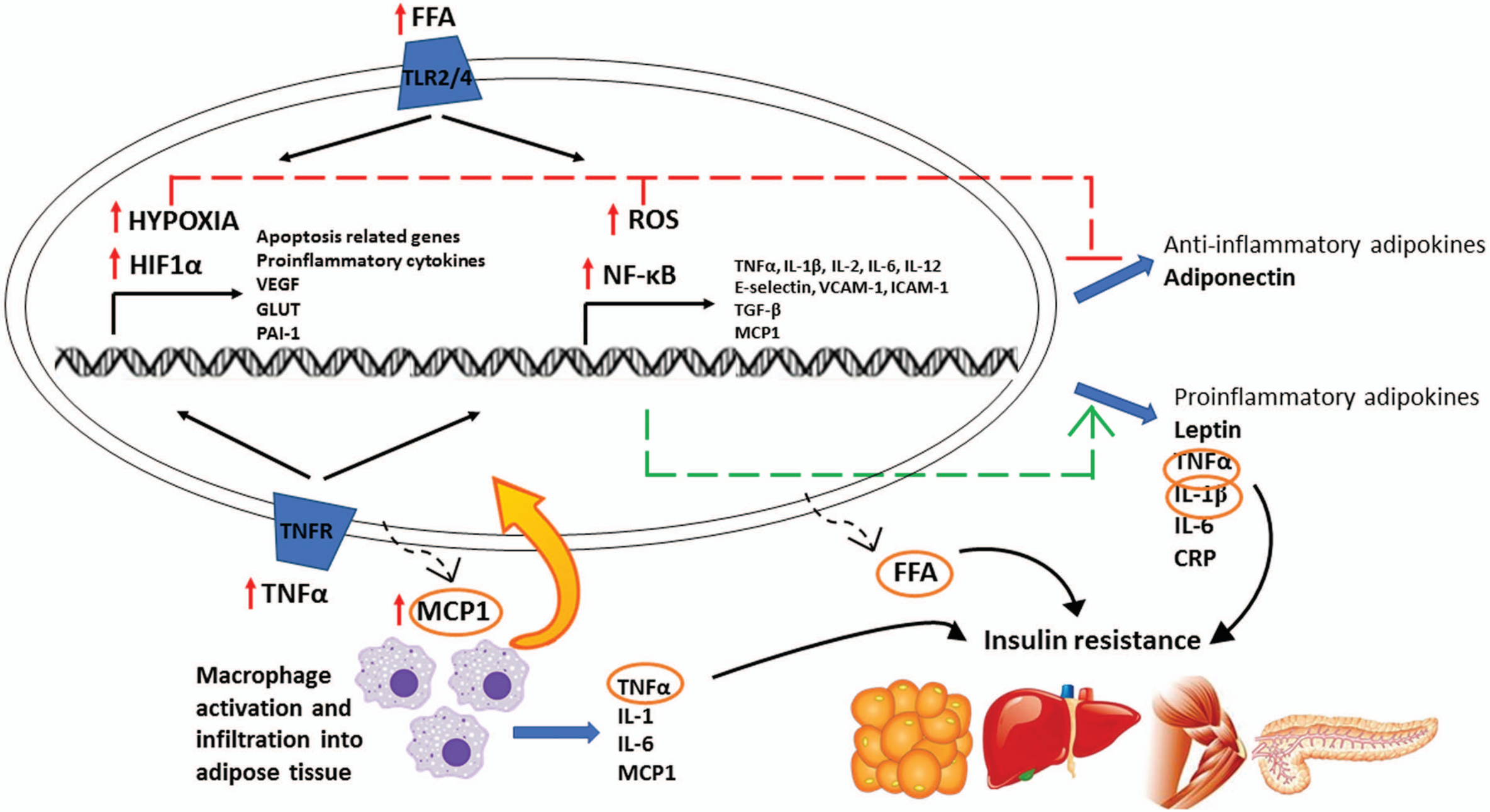
Figure Legends

Figure 1. Obesity causes adipose tissue dysregulation. Rapid AT expansion causes a decrease in oxygen availability, exposing cells to hypoxia, which will result in activation of HIF-1α, which activates transcription of apoptosis-related genes, VEGF, glucose transporters and PAI-1, and impedes adipocyte secretion of anti-inflammatory adipokines such as adiponectin. Mitochondrial uncoupling caused by the processing of excess nutrients and FA in adipocytes cause an enhanced production of ROS, which triggers abnormal signalling pathways involving NF-κB and its induction of inflammatory cytokines, chemokines, adhesion molecules and growth factors causing vascular dysfunction, atherosclerosis, and inflammation. Mitochondrial dysfunction is also the main cause of the decreased adipocyte release of adiponectin. Activated adipocytes secrete a wide number of adipokines and cytokines themselves, with either pro or anti-inflammatory effects. These mechanisms result in further activation of transcription of pro-inflammatory cytokines such as IL-1β and TNFα, that together with FFA secreted from the AT, signal through TLR2/4 in muscle, liver, and adipose cells promoting IR. Furthermore, under stimulation of TNF-α, adipocytes secrete MCP1, which induce macrophage activation and infiltration. Macrophages then secrete TNF-α, IL-1, IL-6 and MCP-1, also contributing to IR and to further activation and infiltration of macrophages into fat.

Figure 2. Inflammatory pathways and their metabolic regulating mechanisms. A. NFAT resides in the cytosol in a hyperphosphorylated form. A rise in intracellular calmodulin-bound Ca^{2+} levels activates calcineurin, which dephosphorylates NFAT, resulting in the translocation of the protein to the nucleus, where it enhances local chromatin acetylation and gene transcription. IL-2 promotes the binding of NFAT2 to

the CX3CR1 chemokine promoter, inducing its expression, while IL-6 signalling results in the induction of NFAT1 transcripts, resulting in increased IL-4 production. Inhibitors of calcineurin, such as CsA and FK506 are used as immunosuppressive agents to treat autoimmune diseases. B. NF-κB is held in the cytoplasm bound to IκB. When cells are stimulated with growth factors, cytokines or foreign pathogens or molecules, NF-κB translocates to the nucleus, activating expression of various inflammatory mediators, including TNF-α, IL-6, MCP-1 and IL-1β. FFA can signal through TLR4 to activate NF-κB. C. The AP-1 transcription factor, formed by c-Jun and c-Fos, regulates expression of genes involved in proliferation, differentiation, apoptosis, cell migration and transformation in response to cytokines, growth factors, stress, and bacterial and viral infections. The JNK signalling pathway is also activated by ER stress, which can be induced by palmitate. D. JAKs and STATs regulate growth, survival, differentiation, and pathogen resistance. Signalling through cytokines such as IL-6, INF-α, -β and -γ, TLR agonists, or growth factors induces receptor dimerization, phosphorylation of JAKs and phosphorylation of the receptor. Phosphorylated sites serve as docking sites for STATs, which then phosphorylate, dimerise and translocate to the nucleus to act as transcription factors. INF signalling and increased metabolic stress result in STAT1 activation, which, together with NF-κB induce IL-1β expression. IL-1β is then released from the cell and amplifies both NF-κB activation and NLRP3 inflammasome priming. IL-6 induces STAT3 and STAT5 activation. Insulin stimulation results in O-GlcNAcylation of STAT3 in macrophages and 3T3-L1 adipocytes, preventing phosphorylation, dimerization and nuclear translocation. E. IL-1β resulting from NF-κB activation primes the NLRP3 inflammasome, which recruits and activates pro-caspase-1 to produce caspase-1, which mediates proteolytic cleavage of pro-IL-1β and pro-IL-18 to mature IL-1β and IL-18, respectively. Caspase-1 is also able to

mediate cell death through pyroptosis, which fragments DNA and leads to pore formation in the plasma membrane.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HYPOXIA
HIF1α
Apoptosis related genes
Proinflammatory cytokines
VEGF
GLUT
PAI-1
ROS
NF-κB
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E-selectin, VCAM-1, ICAM-1
TGF-β
MCP1
Anti-inflammatory adipokines
Adiponectin
Proinflammatory adipokines
Leptin
TNFα
IL-1β
IL-6
CRP
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FFA
Insulin resistance
Macrophage activation and infiltration into adipose tissue
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IL-1
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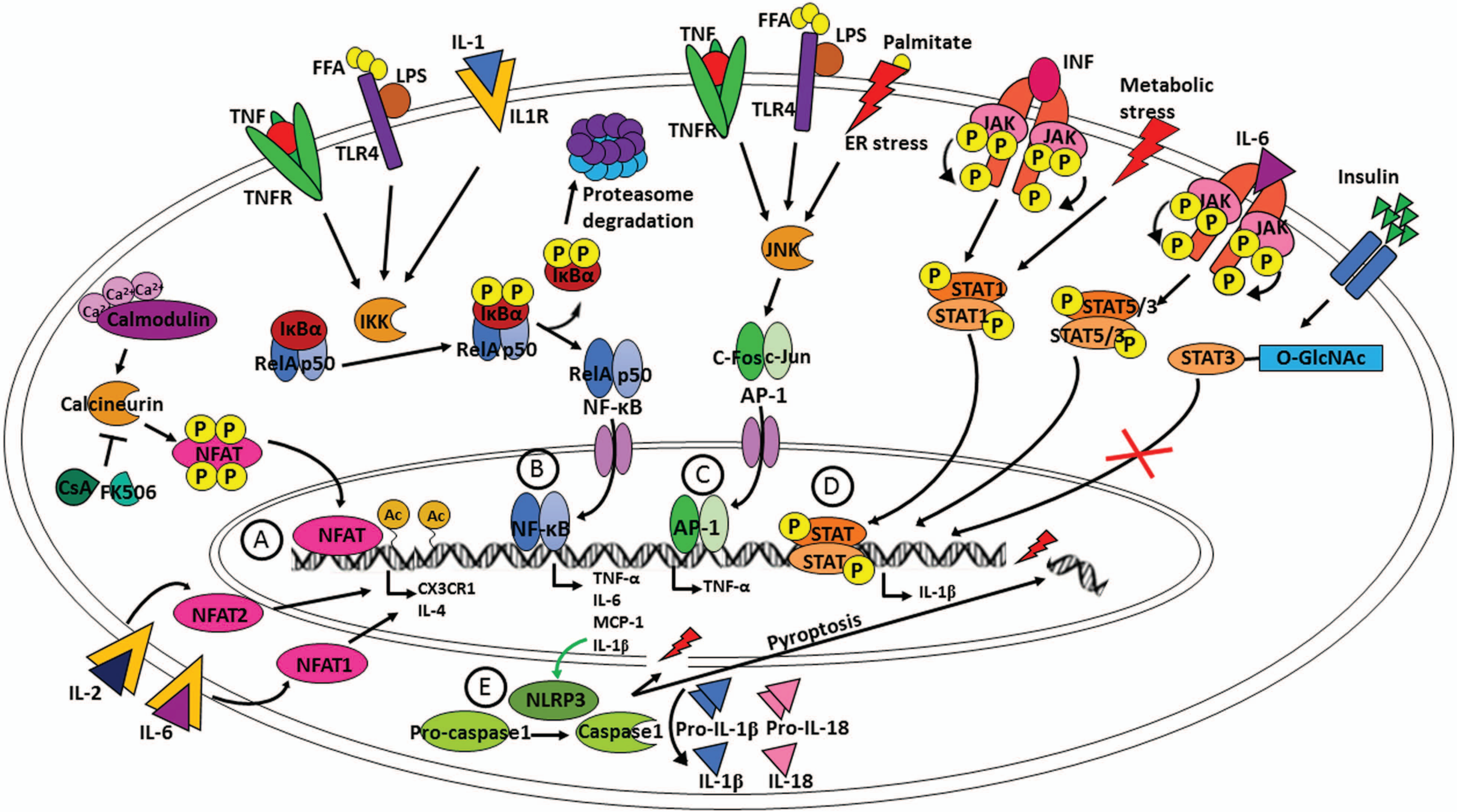
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RelA p50
IKK
NF-κB
JNK
C-Fos c-Jun
AP-1
Palmitate
ER stress
INF
JAK
P
Metabolic stress
IL-6
Insulin
STAT1
STAT5/3
STAT3
O-GlcNAc
Calmodulin
Ca2+
Calcineurin
NFAT
CsA
FK506
Ac
A
B
C
D
CX3CR1
IL-4
TNF-α
IL-6
MCP-1
IL-1β
NFAT2
NFAT1
IL-2
Pyroptosis
E
NLRP3
Pro-caspase1
Caspase1
Pro-IL-1β
Pro-IL-18
IL-18