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Inflammation in Obesity, Diabetes and related Disorders

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SUMMARY

Obesity leads to chronic, systemic inflammation and can lead to insulin resistance (IR), β-cell dysfunction and ultimately type 2 diabetes (T2D). This chronic inflammatory state contributes to long-term complications of diabetes, including non-alcoholic fatty liver disease (NAFLD), retinopathy, cardiovascular disease and nephropathy, and may underlie the association of type 2 diabetes with other conditions such as Alzheimer's disease, polycystic ovarian syndrome, gout, and rheumatoid arthritis. Here we review the current understanding of the mechanisms underlying inflammation in obesity, T2D and related disorders. We discuss how chronic tissue inflammation results in IR, impaired insulin secretion, glucose intolerance and T2D, and review the effect of inflammation on diabetic complications and on the relationship between T2D and other pathologies. In this context we discuss current therapeutic options for the treatment of metabolic disease, advances in the clinic and the potential of immune-modulatory approaches.

INTRODUCTION

Obesity along with genetic predisposition, as observed in some populations such as Pima Indians, Latinos, North Africans and Indians, is the most common cause of insulin resistance (IR). Additionally, IR is a key underlying etiology of type 2 diabetes (T2D). Before the onset of this disease, compensatory hyperinsulinemia is observed, which declines as a result of progressive β-cell dysfunction leading to deterioration of glucose homeostasis and eventually diabetes. In this way, the development of T2D is usually due to a combination of both, IR and β-cell dysfunction. Over time, T2D leads to a number of long-term

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DECLARATION OF INTERESTS

M.Y.D. is listed as the inventor on a patent filed in 2003 for the use of an IL-1 receptor antagonist for the treatment of or prophylaxis for type 2 diabetes.

complications, including microvascular disease (retinopathy, nephropathy, and neuropathy), macrovascular disease (stroke, myocardial infarction and peripheral arterial disease), heart failure and nonalcoholic fatty liver disease (NAFLD). Furthermore, it may contribute to the progression of Alzheimer's disease, polycystic ovarian syndrome, gout and rheumatoid arthritis among other diseases promoted by inflammation.

Although there is a significant palette of anti-diabetic drugs available, most subjects do not achieve optimal levels of glucose control. Additionally, glucose control per se is not always sufficient to prevent the long-term complications of diabetes. Indeed, only three classes of glucose-lowering drugs have shown prevention of complications; metformin, glucagon-like 1 (GLP-1) analogs and sodium-dependent glucose transporter 2 (SGLT-2) inhibitors. While GLP-1 analogs mitigate cardiovascular diseases and SGLT-2 inhibitors prevent heart failure and nephropathy, none of these drugs has demonstrated efficiency against other complications such as retinopathy, nonalcoholic fatty liver disease (NAFLD) and diabetes-associated inflammatory diseases. Most importantly, except for metformin, progression of diabetes is not delayed by the available drugs. This highlights the importance of improved understanding of the underlying mechanisms of IR and β-cell dysfunction.

In this regard, chronic tissue inflammation has emerged as a key feature of obesity and T2D and is observed in insulin target tissues, such as adipose tissue, liver, muscle and pancreatic islets. These observations have led to the term "immunometabolism", which incorporates the underlying interplay between immunologic processes and metabolic defects. The recruitment, accumulation and activation of pro-inflammatory macrophages in metabolic tissues is the ultimate driver of this chronic low-grade inflammation. While the macrophage is the major effector cell type, other types of immune cells participate in these inflammatory processes.

This review examines recent advances and underlying mechanisms of inflammation in obesity, T2D and related disorders. We describe how this chronic tissue inflammation includes multi-organ cross-talk causing IR, impaired insulin secretion, glucose intolerance and T2D. We also review the effect of inflammation on diabetic complications and how obesity and diabetes are connected to other inflammatory diseases. In particular, we span the spectrum from basic research to translational findings, including a review of current and potential immune-modulatory therapeutic options for metabolic disease aimed to treat disease progression and complications.

Inflammation in obesity and the pathogenesis of T2D

The potential contribution of chronic tissue inflammation to metabolic disease has been suggested for many years (Cook et al., 2000; Dandona et al., 2004; Donath and Shoelson, 2011). There are a number of key studies published over the past two decades which have provided foundational insights to the immunometabolism field. For example, Feingold et al. discovered that tumor necrosis factor (TNFα) leads to glucose intolerance in rodents (Feingold et al., 1989). The observation that adipose tissue in obesity expresses high levels of TNF-α and that its neutralization improves insulin sensitivity and glucose intolerance were key findings in establishing the association between immune cells and metabolic dysfunction (Hotamisligil et al., 1993; Yuan et al., 2001). Pro-inflammatory cytokines,

like TNF-α, can activate a number of intracellular signaling molecules, such as JNK and IKKβ that are critical components of the inflammatory signaling system, leading to impaired insulin action (Arkan et al., 2005; Hirosumi et al., 2002). Activation of IKKβ leads to nuclear translocation of NF-κB which drives increased expression of inflammatory mediators, including chemokines and cytokines (Chen et al., 2012b; Shoelson et al., 2006; Shoelson et al., 2003).

An additional key component of inflammatory activation is a multimeric protein complex termed “inflammasome”, which is activated by cell nutrients, such as glucose and free fatty acids, inducing IL-1β production (Boni-Schnetzler et al., 2009; Maedler et al., 2002). Intracellularly, the inflammasome regulates the activation of caspase-1. Activated caspase-1 cleaves precursor cytokines, such as pro-IL-1β, leading to increased tissue levels of active IL-1β (Thornberry et al., 1992). Accordingly, binding of lipopolysaccharide (LPS) or saturated fatty acids (SFAs) to Toll-Like receptor-4 (TLR-4), and glucose via oxidative stress stimulate NLRP3, mediating activation of caspase-1 (Okla et al., 2018; Paik et al., 2021; Zhou et al., 2010). Although some studies have indicated that IL-1β can blunt insulin action, the most prominent effects of IL-1β are in the islets, where it modulates β-cell mass and function, see below.

Another key finding was the simultaneous discovery by Weisberg et al. and Xu et al. that macrophages accumulate in both mouse and human adipose tissue during the course of obesity (Weisberg et al., 2003; Xu et al., 2003). The pro-inflammatory polarization state of these cells leads to the release of a number of inflammatory cytokines and other factors that contribute to decreased insulin signaling. Unlike the classification of *in vitro* polarized pro-inflammatory (M1) and anti-inflammatory, alternatively activated (M2) macrophages (Martinez and Gordon, 2014; Orecchioni et al., 2019), these terms do not strictly apply to the *in-vivo* situation. In recognition of phenotypic, transcriptomic, and polarization differences between *in-vitro* and *in-vivo* macrophages, the terms “M1-like” and “M2-like” will be used as general descriptors throughout the rest of this review, when appropriate.

Adipose tissue inflammation

Following the initial reports of increased numbers of adipose tissue macrophages (ATMs) in both mouse and human obesity (Weisberg et al., 2003; Xu et al., 2003), additional studies showed that these cells contribute to the insulin resistant state (Bigornia et al., 2012; Lackey and Olefsky, 2016; Xu et al., 2003). Indeed, prevention of ATM accumulation or pro-inflammatory macrophage signaling, protects obese mice from glucose intolerance and IR (Desai et al., 2017; Dror et al., 2017; Lee and Olefsky, 2021; Takikawa et al., 2016). In addition to macrophages, there are other immune cell types which participate in adipose tissue inflammation during obesity. However, while certain T and B cell subsets play important regulatory roles, it is generally thought that macrophages are the major effector cells leading to decreased insulin signaling (Chawla et al., 2011; McLaughlin et al., 2017). In lean mice and humans, ATMs make up 10% to 15% of the stromovascular cells and largely display an M2-like polarization state (Weisberg et al., 2003; Xu et al., 2003) (Figure 1, lean AT). In obesity, the number of ATMs increases and can comprise up to 40% of all adipose tissue cells (Lumeng et al., 2007). Most of these obesity-induced ATMs are

pro-inflammatory (M1-like) (Lumeng et al., 2007; Nguyen et al., 2007) (Figure 1, Obese AT) and similar findings have been shown in human ATMs (Fuchs et al., 2021; Wentworth et al., 2010). The phenotype of these macrophages is not fixed and can be modified by SFAs acting through a TLR-4 mechanism which stimulates the M1-like polarization state (Shi et al., 2006). Omega-3 fatty acids (fish oils) inhibit this inflammatory state by binding to the cell surface receptor GPR120 (Oh et al., 2010).

An interesting study by Wernstedt Asterholm et al. (Wernstedt Asterholm et al., 2014) points out the marked functional differences between acute and chronic inflammation specifically in adipocytes. This paper used genetic manipulations to express specific anti-inflammatory proteins within adipocytes and demonstrated that this affected only adipocytes and not ATMs. They went on to show that inhibiting acute inflammation within adipocytes during high-fat diet (HFD) led to a marked decrease in adipogenesis and angiogenesis. This principle finding supports their main conclusion, which is that “acute” inflammation promotes adipogenesis under the challenge of HFD. Interestingly, this also led to an increase in ATMs and crown-like structures with a deterioration of glucose tolerance and insulin sensitivity. The changes in glucose homeostasis might be explained by the fact that these mice developed a “leaky” gut. The authors found that the anti-inflammatory effects in adipocytes were most marked in mesenteric WAT which, in turn, could affect the gastro-intestinal epithelium leading to increased permeability. They suggest that LPS and perhaps other factors that leak into the circulation could be responsible for worsening glucose tolerance (Wernstedt Asterholm et al., 2014).

ATMs are the most abundant immune cells in adipose tissue and tend to accumulate in crown-like structures, which are observed surrounding enlarged and dying adipocytes (Murano et al., 2008; Strissel et al., 2007). In obesity, ATMs span a wide polarization spectrum (Hill et al., 2018; Jaitin et al., 2019). Single cell-RNA sequencing studies have shown that ATMs classified as “M1” or “M2” by using specific surface markers, are actually quite heterogeneous and comprise several different discrete clusters of cells within each category in mouse and human adipose tissue (Cox et al., 2021; Hildreth et al., 2021; Hill et al., 2018; Jaitin et al., 2019; Kratz et al., 2014; Shaul et al., 2010; Xu et al., 2013). ATMs within obese adipose tissue are generally pro-inflammatory and CD11c is a typical marker used to identify these M1-like ATMs (Wentworth et al., 2010). However, Hill et al. showed that CD9 expression can be used to further define M1-like ATMs (Hill et al., 2018). These $CD9^+$ ATMs exhibit unique locational and morphologic features, expressing high levels of pro-inflammatory cytokines and contain prominent intracellular lipid droplets. $CD9^+$ ATMs are found within crown-like structures and are CD11c positive or negative. There is also a cluster of ATMs in obesity which display the monocyte marker Ly6C (Hill et al., 2018). These cells are derived from recently recruited monocytes and are undergoing macrophage differentiation (Yang et al., 2014; Yona et al., 2013). Over a period of several days, these cells lose Ly6C expression and become mature macrophages found within and outside of the crown-like structures (Hill et al., 2018; Oh et al., 2012). The great majority of these $CD9^+$ or $Ly6C^+$ cells are bone marrow-derived and form distinct clusters depending on whether they express the lipid receptor TREM2. Double positive $TREM2^+CD9^+$ ATMs actively participate in lipid metabolism and have been termed lipid-associated macrophages (LAMs) (Jaitin et al., 2019). Interestingly, accumulation of LAMs is functionally dependent

on TREM2, since genetic deletion of TREM2 in obese mice promotes obesity, dyslipidemia, and glucose intolerance (Jaitin et al., 2019). These latter findings suggest that TREM2$^+$ LAMs can actually mitigate obesity and the associated metabolic abnormalities. Thus, depending on the relative expression of CD11c, CD9, and TREM2, ATM show distinct phenotypes and further studies of the functional properties of these subsets will be of great interest.

There are several other immune cell types which participate in the overall state of adipose tissue inflammation in obesity. For example, CD8$^+$ T cells are more abundant and can promote monocyte chemotaxis followed by differentiation into ATMs (Nishimura et al., 2009). Pro-inflammatory CD3$^+$CD4$^+$ T helper (Th1) cells are increased in obese adipose tissue and also contribute to the pro-inflammatory state via INF-y production (Winer et al., 2009). Of interest, several studies have examined the content and function of Tregs. These CD3$^+$CD4$^+$FOXP3$^+$ Tregs are the most abundant (40–80%) adipose CD4$^+$ T cell subset in normal adult mice (Bapat et al., 2015; Feuerer et al., 2009; Li et al., 2020). They can modulate the activity of other T cells and, importantly, inhibit monocyte immigration and drive them towards an anti-inflammatory polarization state (Romano et al., 2018). In obese fat, the number of Tregs decreases and this promotes increased ATM-mediated chronic inflammation (Feuerer et al., 2009). Interestingly, the transcriptomic profile of adipose Tregs is quite different from Tregs in other tissues. An important difference is the expression of peroxisome proliferator activated receptor γ (PPAR-γ), by adipose tissue Tregs (Cipolletta et al., 2012). Thiazolidinediones (TZDs) are insulin sensitizing PPAR-γ agonists and exert substantial anti-inflammatory effects via direct action on adipose Tregs. Interestingly, age appears to have independent effects on AT Tregs. Bapat et al. have found that Tregs in mouse visceral fat increase as a function of age, independent of obesity, and that Treg depletion in aged mice promotes insulin sensitivity (Bapat et al., 2015). Other immune cell types, such as mast cells, innate lymphoid cell type 1 (ILC1) cells, neutrophils, eosinophils, NK cells, invariant natural killer T (iNKT) cells, and B lymphocytes also participate in the overall inflammatory tone of adipose tissue largely by modifying ATM recruitment or phenotypes. Their role in the inflammatory process has been recently published and reviewed in detail elsewhere (Boulenouar et al., 2017; Kane and Lynch, 2019; Lee and Dixit, 2020; Lee et al., 2016; Lee and Olefsky, 2021; O'Sullivan et al., 2016; Wang et al., 2019; Wensveen et al., 2015; Zatterale et al., 2020).

Mechanism of adipose tissue macrophage accumulation

Increased monocyte chemotaxis into adipose tissue is the major mechanism leading to ATM accumulation (Kamei et al., 2006; Kanda et al., 2006; Nagareddy et al., 2014; Weisberg et al., 2006). As one example, injection of fluorescently labeled monocytes into obese mice, showed that enhanced monocyte uptake in obesity is induced via chemokines such as CCL2/MCP-1 and leukotriene B4 and galectin-3 (Amano et al., 2014; Li et al., 2016; Li et al., 2015). Another study shows that IL-6-mediated trans-signaling through the soluble form of the IL6 receptor (sIL-6R) interacting with glycoprotein 130 can also produce chemotactic effects for ATM accumulation (Kraakman et al., 2015). There are additional chemokines beyond these that can regulate macrophage recruitment and insulin resistance (Han and Levings, 2013; Xu et al., 2015). The majority of the literature show that genetic deletion

or pharmacological inhibition of chemokine receptors reduces monocyte influx into obese adipose tissue (Kanda et al., 2006; Li et al., 2015; Lumeng et al., 2007; Spite et al., 2011; Weisberg et al., 2006). After arriving in the adipose tissue, monocytes can efflux into surrounding lymph nodes or back into the circulation (Auffray et al., 2007; Palframan et al., 2001). In obesity, there is increased adipose tissue expression of Semaphorin 3E and Netrin-1 which inhibit this emigration process, causing macrophage retention and further increasing ATM content (Nakano et al., 2013; Ramkhelawon et al., 2014; Shimizu et al., 2013; Wanschel et al., 2013). Resident ATMs, as well as blood monocyte-derived ATMs, also undergo increased proliferation in the context of obesity, further contributing to the increase in ATMs (Amano et al., 2014; Haase et al., 2014; Zamarron et al., 2017; Zheng et al., 2016). It will be of interest to assess the functional properties and transcriptomic profiles of proliferated vs. non-proliferated macrophages in comparison to ATMs derived from chemotaxis.

Initiating mechanisms for chronic tissue inflammation

Several initiating mechanisms have been proposed to generate chronic tissue inflammation and these mechanisms are not mutually exclusive and could work in a complementary manner. Regardless of the specific mechanism, the ultimate inflammation triggers would have to initiate either proliferation of ATMs or monocyte chemotaxis into the tissue. Increased influx of nutrients is an obvious feature of obesity, and can participate in the production and release of reactive oxygen species (ROS), resulting in oxidative stress (Houstis et al., 2006). Nutrient overload can also promote endoplasmatic reticulum (ER) stress and an unfolded protein response, activating intracellular inflammatory pathways (Hotamisligil and Erbay, 2008). Glucose and free fatty acids activate inflammasomes and toll-like receptors (TLRs), specifically TLR-4, with stimulation of the downstream inflammatory pathways (Boni-Schnetzler et al., 2009; Maedler et al., 2002; Shi et al., 2006; Zhou et al., 2010).

Hypoxia is another activator of inflammation and, particularly in obesity, it is a very early event in the initiation of adipose tissue inflammation (Halberg et al., 2009; Hosogai et al., 2007; Lee et al., 2014). It has been well described in both mouse and human adipose tissue that oxygen (O_2) tension decreases in obesity (Halberg et al., 2009; Hosogai et al., 2007; Lawler et al., 2016; Pasarica et al., 2010; Pasarica et al., 2009; Seo et al., 2019; Smith et al., 2019). As adipocytes and adipose tissue expand, angiogenesis can lag behind with impaired capillary density leading to less interstitial perfusion of O_2. Importantly, interstitial and intracellular O_2 tension may not always go hand in hand, as the intracellular O_2 levels represent the balance between O_2 supply and demand. This is important since recent studies indicate that obesity leads to an increase in intracellular adipocyte O_2 consumption, accounting for about 40% of the decrease in the interstitial O_2 tension (Lee et al., 2014). The enhanced adipocyte O_2 consumption is secondary to activated uncoupled oxidative phosphorylation, which, in turn, is due to increased free fatty acid stimulation of a mitochondrial protein termed Adenine nucleotide translocase (ANT2) (Lee et al., 2014; Shabalina et al., 2006). ANT2 is highly activated by the abundant SFAs in obese adipocytes, leading to proton leakage from the intermembrane space and to uncoupled mitochondrial respiration and greater O_2 consumption. Therefore, stimulation

of ANT2 serves to uncouple O_2 utilization from ATP production in the mitochondria, lowering intracellular O_2 levels. The intra-adipocyte hypoxic state triggers induction of hypoxia inducible factor 1 alpha (HIF-1α), primarily by inhibiting degradation of HIF-1α (Schodel and Ratcliffe, 2019; Semenza, 2019; Seo et al., 2019). HIF-1α within adipocytes can then initiate an inflammatory response by inducing transcription of chemokines (Imtiyaz and Simon, 2010). These chemokines initiate monocyte recruitment, and differentiation into pro-inflammatory M1-like ATMs. Supporting this mechanism, deletion of adipocyte ANT2 prevents increased oxygen consumption, blocks HIF-1α induction and protects from adipose tissue inflammation, glucose intolerance, and IR (Seo et al., 2019). Likewise, adipocyte-specific deletion of HIF-1α prevents the development of adipose tissue inflammation in obese mice mitigating IR and glucose intolerance (Jiang et al., 2011; Sun et al., 2013).

How does inflammation cause IR

The underlying mechanisms by which ATMs cause IR have been widely studied. The general idea is that ATMs produce factors that work in a paracrine or systemic manner and interrupt insulin signaling in target cells. Since these M1-like macrophages produce a variety of chemokines and cytokines, significant attention has been focused on these molecules as causes of decreased insulin sensitivity. Chemokines stimulate chemotaxis of circulating monocytes and other immune cells by providing a concentration gradient between the blood and the interstitial space. While some of these chemokines can leak into the circulation in obesity, this would not generate a necessary concentration gradient to stimulate monocyte chemotaxis. Furthermore, the circulating concentrations of chemokines are much lower than the biologically relevant levels in the interstitial space of obese adipose tissue, so circulating chemokines are a marker of tissue inflammation but are quite unlikely to cause IR.

Therefore, the effects of cytokines to mediate tissue inflammation have been intensively studied. TNF-α, the most well-examined of these cytokines, reduces insulin sensitivity (Hotamisligil et al., 1994). TNF-α promotes inhibitory phosphorylation of insulin receptor substrate (IRS) proteins, and enhances ceramide synthesis, adipocyte lipolysis and inhibits PPARγ expression (Guilherme et al., 2008; Stephens et al., 1997). Normal levels of PPARγ are necessary to maintain insulin sensitivity and the effects of ceramides to inhibit AKT phosphorylation and insulin action are well-known. However, the circulating levels of TNF-α in obese states are below the concentrations which impair insulin signaling (Amar et al., 2007; McGillicuddy et al., 2011; Stephens et al., 1997). Because of this, it is unlikely that TNF-α-“leakage” out of obese adipose tissue into the circulation is responsible for the decreased muscle and liver insulin sensitivity. However, locally-produced high levels of TNF-α in the liver and muscle tissues could cause IR (Lang et al., 1992). Another cytokine released by M1-like ATMs is IL-6. Unlike other cytokines, blood IL-6 circulates at biologically active levels. However, the effects of IL-6 on insulin signaling are unclear, since some studies have reported IL-6-mediated IR while others suggest that IL-6 have insulin-like actions with improved insulin sensitivity (Carey et al., 2006; Franckhauser et al., 2008). Another prominently released cytokine is IL-1β. It is well known that islet macrophage-derived IL-1β impairs insulin secretion contributing to the development of glucose intolerance and T2D (Eguchi et al., 2012; Maedler et al., 2002). Further, IL-1β was also shown to promote IR (Stienstra et al., 2010; Vandanmagsar et al., 2011; Wen et al.,

2011; Zhou et al., 2010). In adipose tissue, IL-1β impairs adipocyte insulin signaling (Jager et al., 2007; Lagathu et al., 2006; Stienstra et al., 2010). In humans, IL-1β release from visceral ATMs is enhanced with glycemic deterioration and decreases after gastric bypass surgery (Dalmas et al., 2014). However, clinical evidence for a role of IL-1β in IR remains to be clarified. In a clinical study of IL-1Ra in patients with T2D no changes in insulin sensitivity could be found, although HbA1c decreased (Larsen et al., 2007). However, insulin sensitivity was only assessed in a small patient subgroup in this study. In contrast, in an elegant study in patients with T1D who also have IR caused by obesity, treatment with IL-1Ra improved insulin sensitivity and glycemic control (van Asseldonk et al., 2012). Finally, in a recent study of patients with rheumatoid arthritis and diabetes, IL-1Ra improved insulin sensitivity (Ruscitti et al., 2019). Therefore, it is likely that IL-1β plays also a role in IR.

Galectin-3, a member of the lectin family, is a factor which is exclusively macrophage-derived and achieves biologically effective concentrations in the circulation of obese mice and humans (Li et al., 2016). Studies have shown that galectin-3 can directly cause macrophage chemotaxis and impaired insulin signaling, while myeloid-specific deletion of galectin-3 inhibits HFD-induced glucose intolerance and IR (Li et al., 2016).

ATMs release exosomes which work locally in a paracrine fashion and can also enter the circulation in sufficient concentrations to have distal effects on insulin sensitive tissues. Exosomes are a component of secreted extracellular vesicles (EVs) with a diameter of ~150nm and can be produced by almost all cell types (Pegtel and Gould, 2019). Exosomal cargo consists of a large number of proteins, lipids, micro RNAs (miRNAs), mRNAs, and noncoding RNA species. EV/exosome preparations obtained from obese human adipose tissue express increased levels of several miRNAs that negatively interact with the insulin signaling pathway (Kita et al., 2019). Consistent with this, exosomes prepared from obese adipose tissue cause IR and miR-141–3p has been implicated in this process (Dang et al., 2019; Kranendonk et al., 2014). However, since all of the cell types within adipose tissue release exosomes, studies using exosome preparations derived from whole adipose tissue do not reveal which cell type produces the biologically relevant exosomal particles. Recent studies, specifically focused on macrophages, have shown that ATM-derived exosomes isolated from obese mice directly cause decreased insulin signaling in adipocytes, myocytes, or primary hepatocytes *in vitro* (Ying et al., 2017) (Figure 2 adipose tissue). These “obese” exosomes contain high levels of miR-155, which represses PPAR-γ expression, thereby contributing to IR. Lean mice treated intravenously with these “obese” ATM exosomes develop glucose intolerance, hyperinsulinemia and IR comparable to obese mice, without changes in body weight. Interestingly, lean chow-fed mice produce ATM exosomes which cause the opposite effects. In other words, “lean” ATM exosomes directly enhance insulin signaling *in vitro* and, when given to obese mice, markedly improve insulin sensitivity and glucose tolerance. These effects were entirely attributed to the miRNA cargo of the exosomes, and miRNA-690 was identified as the predominant miRNA within M2-like macrophage exosomes causing these beneficial effects (Ying et al., 2021). Indeed, *in vivo* treatment with a miR-690 mimic recapitulates the insulin sensitizing effects of “lean” ATM exosomes, whereas treatment with an antagomir blocks miR-690-mediated effects. In this

way, M2-like macrophage exosomes and miR-690 mimics have emerged as promising insulin sensitizers.

Hepatic inflammation

Obesity characteristically leads to hepatic steatosis and liver inflammation, commonly termed nonalcoholic fatty liver disease (NAFLD)(Polyzos et al., 2019). This is a very common condition and some estimates suggest one billion NAFLD patients worldwide (Younossi et al., 2019). Hepatocyte lipid accumulation is multi-factorial. In obesity adipocytes become insulin resistant, leading to impaired suppression of lipolysis with increased free fatty acid release. This enhanced influx of adipocyte-derived free fatty acids, as well as dietary fat entering the liver via gastrointestinal-derived chylomicrons are important pro-steatotic mechanisms (Donnelly et al., 2005; Meex and Watt, 2017). In addition, within the hepatocyte, *de novo* lipogenesis pathways are increased in obesity and this is coupled with decreased fatty acid oxidation (Song et al., 2018). All of these factors drive steatosis and NAFLD.

There are two major categories of liver macrophages: Kupfer cells (KCs) and recruited hepatic macrophages (RHMs) (Morinaga et al., 2015; Seidman et al., 2020). KCs are the resident liver macrophages and are derived from the embryonic yolk sac (Naito et al., 1989; Perdiguero et al., 2015) (Figure 1, lean liver). A second category of hepatic macrophages are bone marrow-derived and arise from circulating monocytes which enter the liver in response to chemokines, primarily CCL2/MCP-1, which can be secreted from steatotic hepatocytes and KCs (Morinaga et al., 2015; Obstfeld et al., 2010). These monocytes differentiate into M1-like pro-inflammatory macrophages, termed RHMs (Morinaga et al., 2015; Seidman et al., 2020). In obesity, KC numbers are relatively unchanged, but there is a large increase in RHMs (Morinaga et al., 2015; Obstfeld et al., 2010) (Figure 1, NAFLD). RHMs also produce chemokines, setting up a feed-forward loop, in which newly arrived RHMs produce chemokines, which attract additional monocytes into the liver (Morinaga et al., 2015). KCs perform scavenger and phagocytic functions, such as removing senescent red blood cells to ensure iron conservation, filtering gut-derived factors like LPS, and participate in tissue homeostasis and repair (Nguyen-Lefebvre and Horuzsko, 2015). These cells comprise up to 10 % of all liver cells and their transcriptomic profile does not fall into typical M1 or M2 categories (Bouwens et al., 1986; Morinaga et al., 2015). In obesity, RHMs are predominantly pro-inflammatory and are responsible for the major component of obesity-mediated hepatic inflammation (Morinaga et al., 2015). KCs and RHMs participate in intrahepatic signaling, since cytokines derived from hepatic macrophages can stimulate hepatocyte *de novo* lipogenesis and ceramide biosynthesis (Chavez and Summers, 2012; Holland et al., 2011; Sanders and Griffin, 2016). Macrophages are not the only immune cells participating in hepatic inflammation, since obesity also leads to an increase in liver neutrophils and $CD8^+$ T-cells (Ghazarian et al., 2017; Talukdar et al., 2012). Neutrophil elastase can be released and taken up into hepatocytes (Talukdar et al., 2012), promoting intracellular degradation of insulin receptor substrate 2 (IRS-2) and thus potentiating hepatocyte IR.

Some estimates indicate that up to 37 % of obese NAFLD subjects progress to nonalcoholic steatohepatitis (NASH) (Abrams et al., 2004; Gholam et al., 2007; Machado et al., 2006; Ong et al., 2005), which potentially leads to cirrhosis with severely impaired liver function (Loomba et al., 2021). Further, NASH is increasingly recognized as a common complication of obesity (Akshintala et al., 2000). Given the commonality of obesity to NASH and T2D, NASH can also be thought of as a complication of T2D and studies have indicated that 20–40% of subjects with diabetes also have NASH (Younossi et al., 2019). Inflammation and ER stress are important drivers of NAFLD and the progression to NASH (Puri et al., 2008; Rutkowski et al., 2008). Fu et al. reported that hepatic ER stress is caused by significant changes in ER fatty acid and lipid composition, resulting in inhibition of calcium ATPase (SERCA) activity (Fu et al., 2011). In addition, the progression of NASH is partially dependent on pro-inflammatory hepatic macrophages producing TNF (Nakagawa et al., 2014; Todoric et al., 2020).

Recent studies using a variety of monocyte tracking techniques coupled with RNA-sequencing have revealed new insights into the phenotypes of KCs and RHMs in NASH (Seidman et al., 2020). As NASH develops, the original resident yolk sac-derived KCs undergo gradual apoptosis and are replaced by monocyte-derived RHMs which accumulate in NASH livers. These RHMs can enter the sinusoidal niche where they respond to local environmental clues and develop a KC-like transcriptomic profile. These “KC-like” cells in NASH livers are similar, but not identical, to original healthy KCs. Thus, apoptosis and defects in normal KC function represent an important feature of NASH. The exact pathophysiologic consequences of this form of KC dysfunction are currently unknown.

A key element of the NASH liver phenotype is collagen accumulation (Loomba et al., 2021; Loomba et al., 2018). Thus, it is important to understand the various determinants which convert normal stellate cells from the quiescent or inactive state into activated cells which proliferate and elaborate excess collagen that deposits in the extracellular matrix. Transforming growth factor beta (TGF-β) and connective tissue growth factor (CTGF) can be released by hepatocytes or hepatic macrophages and stimulate the stellate cell fibrogenic program (Gressner and Gressner, 2008; Hellerbrand et al., 1999). Indeed, a subpopulation of $CD9^{+}Trem2^{+}$ bone marrow-derived hepatic macrophages are found in close proximity to collagen fibrils and have been termed scar-associated macrophages (SAMs)(Seidman et al., 2020). These cells may play a role in promoting collagen production by stellate cells (Fallowfield et al., 2007). Hepatocytes under early HFD stress (4 weeks HFD) release exosomes that promotes insulin sensitizing effects via miR-3075 (Ji et al., 2021) (Figure 2 liver). In addition, several reports have shown that exosomes released by steatotic hepatocytes stimulate stellate cell fibrogenesis through their exosomal cargo, including miR-128-3p which suppress PPAR-γ signaling (Povero et al., 2015) and miR-1 via activation of the NF-κB pathway (Jiang et al., 2020). Apart from these intrahepatic signals, it is also likely that extrahepatic signals impinge on the liver to promote the NASH phenotype. For example, obesity is a frequent concomitant in subjects with NASH, and it is well known that obesity leads to a “leaky” gut (see section on intestinal inflammation), allowing LPS and other bacterial byproducts, or perhaps bacteria themselves to enter the bloodstream and target the liver. Normally, KCs filter out gut-derived products, but it is possible that the dysfunctional KCs observed in NASH livers are deficient in this function

(Bennett et al., 2020). In this case, these gut-derived products may provide signals to other cells in the liver to promote NASH. Furthermore, adipose tissue is well-known to secrete adipocytokines such as leptin, adiponectin, and galectin-3, all of which influence steatosis and hepatic inflammation.

Muscle inflammation

The skeletal muscle (SM) is a key organ in the development of metabolic disease since it is responsible for the majority (70–80%) of insulin-stimulated glucose disposal (Ferrannini et al., 1988). Therefore, IR in SM is an important determinant of metabolic dysregulation in T2D (DeFronzo and Tripathy, 2009). Proposed mechanisms for SM IR include mitochondrial defects, ectopic fat accumulation, and intrinsic dysregulation of insulin action and these have been reviewed elsewhere (Di Meo et al., 2017; Samuel and Shulman, 2016). In this section, we will focus on the role of muscle inflammation as a possible mediator of IR. This subject is less well-studied compared to fat tissue and liver, but several reports suggest a role of chronic SM inflammation in IR (Boon et al., 2015; Varma et al., 2009). These reports demonstrated increased inflammatory markers, activated pro-inflammatory pathways as well as immune cell accumulation in SM in obesity and diabetes (Fink et al., 2014; Hong et al., 2009; Patsouris et al., 2014). Similar to visceral fat, muscle macrophages are increased in obesity in the intermyocellular/intermuscular adipose tissue (IMAT) between the muscle fibers as well as in perimuscular adipose tissue (PMAT) (Khan et al., 2015). These IMAT and PMAT macrophages exhibit a $CD11c^+$ pro-inflammatory, M1-like phenotype (Fink et al., 2014; Khan et al., 2015; Patsouris et al., 2014). SM Th1, $CD4^+$ and $CD8^+$ T cells are also more abundant while Tregs are decreased, all of which characterize chronic SM inflammation and point to similar mechanisms as observed for visceral fat (Khan et al., 2015). These immune cells contribute to higher levels of pro-inflammatory cytokines, such as TNFα, IL-6, IL-1β and CCL2/MCP-1 in SM. SM can also be a secretory organ. Exercise and muscle contraction leads to increased secretion of “myokines” such as IL-6 with potential beneficial effects on lipid metabolism and inflammation (Eckardt et al., 2014; Pedersen and Febbraio, 2012). In the presence of the high SFA levels in obesity, myocyte TLR-2 and TLR-4 are stimulated (Wei et al., 2008). This causes them to secrete increased levels of chemokines, promoting monocyte migration and SM inflammation. In support of this, deletion of TLR-4 from cultured myocytes protects them from lipid-induced IR both *in vitro* and *in vivo* (Radin et al., 2008). IL-6 is probably the most well-studied myocyte cytokine and is a mediator of macrophage infiltration and polarization, as well as muscle repair (Munoz-Canoves et al., 2013). Several studies show that IL-6 has pro-inflammatory effects and can induce IR in obesity (Rehman et al., 2017; Rotter et al., 2003). However, acute IL-6 treatment increases both basal and insulin-stimulated SM glucose uptake and improves systemic glucose homeostasis (Carey et al., 2006; Pedersen and Febbraio, 2012). *In vitro*, TNFα, or conditioned media from Th1 cells or pro-inflammatory macrophages induce IR in myocyte cultures (de Alvaro et al., 2004). TNFα infusion in healthy humans also results in SM IR (Plomgaard et al., 2005). Interestingly, the anti-inflammatory cytokine IL-10 protects myocytes from the development of IR. Indeed, muscle-specific IL-10 expression attenuates muscle inflammation and IR *in vivo*, while genetic deletion of IL-10 promotes these metabolic abnormalities (Dagdeviren et al., 2016; Hong et al., 2009).

Intestinal inflammation

Obesity leads to several pro-inflammatory alterations in the gastrointestinal tract. The gut contains an extensive microbiome repertoire, which is altered in human and mouse obesity, a finding termed dysbiosis. Different analyses of microbiota composition have been extensively reported and the reader is referred to several excellent reviews on this subject (Choi et al., 2020; Fan and Pedersen, 2021; Khan et al., 2021).

The first mechanical barrier, preventing entry to the systemic circulation, is the intestinal epithelia, a single layer of cells, joined by tight junctions, as well as a mucosal layer, produced by goblet cells. In obesity, leakage of microbial factors or bacterial products, such as LPS occurs due to higher intestinal permeability (Amar et al., 2011; Cani et al., 2007; Cani et al., 2008; de La Serre et al., 2010). These microbial products and metabolites, such as short-chain FAs can activate G-protein-coupled receptors (GPCRs), or inflammasomes, triggering inflammation and impaired glucose metabolism (Kim et al., 2012; Kimura et al., 2013; Tolhurst et al., 2012). For instance, bile acids improve glucose and insulin sensitivity in obese and diabetic mice through activation of the nuclear farnesoid X receptor (FXR) and Takeda G-protein receptor (TGR5) (Swann et al., 2011; Thomas et al., 2009).

As the gut is the first organ exposed to food and microbial antigens, it contains a robust and complex immune system, located in the subepithelial lamina propria. Several changes in adaptive and intestinal innate immunity have been reported in obesity. IFN-γ and IL-1β-producing immune cells increase barrier permeability in obesity, while IL-22-secreting innate lymphoid cells (ILCs) and Tregs promote production of mucin and anti-microbial immunoglobulin A (IgA) (Al-Sadi and Ma, 2007; Cong et al., 2009; Luck et al., 2015; Wang et al., 2014). Furthermore, depletion of intestinal eosinophils by HFD points towards a protective function of these cells on the gut barrier (Johnson et al., 2015). In addition, HFD induces a pro-inflammatory shift in T cells, characterized by higher INF-γ^+ Th1 and CD8$^+$ T cells, along with reduced IL-10$^+$ Tregs and IL17$^+$ Th17 cells (Luck et al., 2015). Obese subjects also display an accumulation of intraepithelial CD8$\alpha\beta^+$ T cells (Monteiro-Sepulveda et al., 2015). A lower level of IgA$^+$ antibody-secreting cells and B cells in HFD-fed mice causes a reduction in colonic secretory IgA$^+$ and might promote IR (Luck et al., 2019). Obesity is also associated with reduced IL-22- and IL-17-secreting intestinal group 3 innate lymphoid cells (ILC3s), which are important for barrier integrity (Luck et al., 2015). In contrast, ILC2s seem to have a detrimental effect, since mice deficient in ILC2 are resistant to diet-induced obesity (Sasaki et al., 2019). In humans, intestinal ILC1 and ILC2 numbers negatively correlate with body-mass index (Yudanin et al., 2019). Recent reviews (Febbraio and Karin, 2021; Herman and Birnbaum, 2021) suggest that fructose is a metabolic toxin causing impaired intestinal barrier integrity and endotoxemia. Fructose was thought to be exclusively metabolized in the liver, but it is now known that it can also be metabolized at its site of absorption in the small intestine (Goncalves et al., 2019; Jang et al., 2020; Taylor et al., 2021). Fructose enhances nutrient absorption (Taylor et al., 2021) and induces dyslipidemia and hepatic ER stress, contributing to steatosis and NASH via the gut-liver axis (see section on hepatic inflammation) (Jang et al., 2020; Todoric et al., 2020; Zhao et al., 2020).

HFD leads to a lack of $CD103^+CD11b^+$conventional dendritic cells (DCs) (Stagg, 2018) and a reduction in intestinal innate-like T cells, called mucosal-associated invariant T (MAIT) cells (Toubal et al., 2020). These MAIT cells regulate intestinal barrier function and the activated $CD44^+$ phenotype of these cells in obesity promotes both intestinal and adipose tissue inflammation (Toubal et al., 2020; Varelias et al., 2018).

As in other tissues, intestinal macrophages are heterogeneous and are sub-grouped based on phenotypic markers, and functional differences. After circulating blood monocytes enter the gut lumen, they initially display high expression levels of Ly6C and CCR2, but gradually differentiate towards resident mature macrophages, losing Ly6C/CCR2 and gaining CD64/MHII expression (Bain et al., 2014; Bain and Mowat, 2014; Bain et al., 2013; Tamoutounour et al., 2013; Tamoutounour et al., 2012). These “monocyte-like” transition cells are characterized by upregulation of TNFα, IL-1β, or IL-6 and hyper-responsiveness to inflammatory stimuli (Bain et al., 2014; Bain et al., 2013). In obese mice, these gut $CCR2^+$ pro-inflammatory monocytes/macrophages increase (Kawano et al., 2016; Rohm et al., 2017). In contrast, resident intestinal macrophages display anti-inflammatory features, such as IL-10 secretion, phagocytic activity, tissue repair, and anergy towards TLR stimulation (Bain et al., 2013). Mature $CX3CR1^+$ macrophages are reduced in obesity (Hong et al., 2017; Luck et al., 2019). One of the initiating signals priming obesity-induced monocyte recruitment into the gut is mediated by the chemokine gradient generated by epithelial cells, which produce higher levels of CCL2/MCP-1. This was demonstrated in mouse models where macrophages lacked CCR2 and intestinal epithelial cells lacked CCL2/MCP-1, resulting in reduced colonic macrophage accumulation, intestinal permeability, inflammasome activation, and improved glucose metabolism (Kawano et al., 2016). In human obese subjects, $CD14^{hi}$ pro-inflammatory macrophages accumulate along the gastro-intestinal tract, due to higher blood monocyte recruitment (Rohm et al., 2021). Moreover, greater body-mass index or waist-to-height ratio, as well as sedentary lifestyle, positively correlate with intestinal inflammation (Rohm et al., 2021). This correlation was confirmed by colon-specific macrophage depletion improving insulin sensitivity and glucose intolerance in obese mice (Rohm et al., 2018). Bacteria might be a prerequisite for intestinal inflammation and glucose dysregulation since germ-free mice display lower colonic macrophage numbers (Bain et al., 2014) and are partially protected from adiposity and glucose intolerance (Backhed et al., 2004; Backhed et al., 2007).

Islet inflammation and impaired insulin production

Chronic low-grade inflammation in pancreatic islets is a hallmark of T2D, characterized by an increased number of innate immune cells, cytokines, and chemokines (Ehses et al., 2007; Maedler et al., 2002) (Figure 3). Following these initial reports, immunohistological and flow cytometric analysis confirmed and further characterized islet immune subsets in T2D (Butcher et al., 2014; Kamata et al., 2014; Martino et al., 2015; Nordmann et al., 2017; Richardson et al., 2009; Rodriguez-Calvo et al., 2014). Most cells express markers of M1-like macrophages but low numbers of other immune cells such as T and B cells may also be increased in islets in T2D (Boni-Schnetzler and Meier, 2019; Butcher et al., 2014; Ehses et al., 2007; Kamata et al., 2014; Martino et al., 2015; Nordmann et al., 2017; Richardson et al., 2009; Rodriguez-Calvo et al., 2014). Interestingly, increased frequency of immune cells

(mostly CD8+ T cells) was also reported in the exocrine pancreas (Rodriguez-Calvo et al., 2014). Rodent models of obesity and T2D confirm these observations. Goto-Kakizaki rats, leptin receptor-deficient db/db mice and HFD-fed wildtype or KKAy mice show increased insulitis (Eguchi et al., 2012; Homo-Delarche et al., 2006). In the setting of HFD, the major mechanisms of increased intra-islet macrophage numbers seems to be proliferation of resident macrophages (Ying et al., 2019).

These immune cells secrete cytokines and the first one described in islets from patients with T2D was IL-1β (Maedler et al., 2002). Islet IL-1β is derived from NLRP3 inflammasomes in intra-islet macrophages and in the setting of T2D mostly glucose, free fatty acids and islet amyloid polypeptide activate this sensor of metabolic stress (Boni-Schnetzler et al., 2009; Maedler et al., 2002; Masters et al., 2010; Wen et al., 2011). Further, insulin was shown to promote IL-1β maturation in a glucose-dependent manner (Dror et al., 2017). Blocking IL-1 signaling in human islet cultures using IL-1Ra prevents the induction of IL-6, IL-8, CXCL1, and TNF-α and the chemokine CCL2/MCP-1, suggesting that these pro-inflammatory mediators are downstream of IL-1 receptor activation (Boni-Schnetzler et al., 2009; Igoillo-Esteve et al., 2010). Thus, it makes sense that inhibition of IL-1 signaling also prevents immune cell infiltration into the islet (Ehses et al., 2009; Sauter et al., 2015). Immune cell-derived cytokines, such as IL-1β activate the highly expressed IL-1R1 on neighboring insulin-producing β-cells. Although, IL-1β acutely potentiates insulin secretion (Dror et al., 2017), prolonged activation of the IL-1 system in β-cells impairs insulin secretion and has a negative impact on β-cell mass, leading to β-cell failure and eventually hyperglycemia. Important for this concept, macrophage depletion, IL-1 and, to a certain extent, TNF-α blockade improve β-cell function and reduce glycemia in rodent models (Eguchi et al., 2012; Ehses et al., 2009; Nordmann et al., 2017; Sauter et al., 2015). This effect was also observed in a human study, in which the IL-1 pathway was blocked with IL-Ra (Larsen et al., 2007, 2009). This led to an increase in the ratio of circulating insulin/proinsulin in patients with T2D, indicative for improved β-cell function.

Islet resident macrophages are in a preactivated state even under normal conditions and IL-1β induces its own expression. Further, β-cell expression of the counterregulatory IL-1R antagonist (IL-1Ra) is reduced in T2D (Maedler et al., 2004), tilting the IL-1/IL-1Ra balance towards a pro-inflammatory state. Supporting this concept, β-cell-specific IL-1Ra ablation reduces β-cell proliferation and mass, and impairs insulin secretion (Boni-Schnetzler et al., 2018). Further, in response to inflammatory stimuli, β-cells secrete exosomes and miR-21-5p was identified to induce apoptosis in surrounding cells (Guay et al., 2015; Javeed et al., 2021; Lakhter et al., 2018) (Figure 2 pancreatic islet).

An important aspect of islet inflammation in the context of T2D is islet amyloidosis. The β-cell product islet amyloid polypeptide is a strong inducer of IL-1β in islets. It triggers the NLRP3 inflammasome to release mature IL-1β (Masters et al., 2010) and has the propensity to aggregate and form amyloid deposits. These are found in most patients with T2D (Clark et al., 1988) and are associated with β-cell apoptosis and a reduction in β-cell mass (Jurgens et al., 2011). Islet amyloid polypeptide secretion is increased in prediabetes because it is functionally coupled to the increased insulin demand. It not only activates immune cells but also recruits additional immune cells to the islet by triggering chemokine release from

β-cells. Interestingly, in a human T2D study, only amyloid-positive islets showed increased immune cell infiltration (Kamata et al., 2014). The contribution of islet amyloidosis is generally underappreciated, as rodents do not show amyloid deposits due to differences in the polypeptide sequence. In support of this, transgenic expression of human islet amyloid polypeptide leads to increased chemokine and cytokine expression in a rodent model of long-term HFD feeding (Meier et al., 2014). Importantly, IL-1 blockade is able to mitigate islet amyloid pathogenesis (Westwell-Roper et al., 2015).

Taken together, in T2D islets show increased immune cell infiltration and cytokine release which in turn directly impairs β-cell mass and function. So far, IL-1β is identified as the major cytokine to mediate these pathologies since blocking IL-1 activation prevents deterioration of β-cell mass and function and improves glycemia. A detailed review of islet inflammation comparing human and rodent data was recently published (Boni-Schnetzler and Meier, 2019).

Beneficial physiological effects of inflammation on metabolism

Metabolism and the immune system are usually considered as two distinct entities. However, their functions are physiologically linked, supporting the concept of immunometabolism. Indeed, a key aspect of the immune system is to secure tissue integrity and repair, preserving homeostasis. In this function, immune cells consume a substantial amount of energy that needs to be mobilized and transported to these cells. Beyond the supply of energy, glucose also has a signaling function, activating a response to pathogens (Bantug et al., 2018; Murphy and O'Neill, 2018). If food is not available in sufficient quantities, as in starvation, glucose concentrations may be too low to support an immune response, thus saving energy at the risk of uncontrolled infection. Conversely, the immune system needs to control metabolism to secure its energy supply. Using infection as an example, an important component of the innate immune response to pathogens, is mediated through IL-1β, which is a strong stimulator of adrenocorticotropic hormone and cortisol release (Bataillard et al., 1992). Cortisol will induce IR with subsequent increased glucose concentrations that can fuel immune cells.

This competition or optimization of the distribution of cell nutrients regulated by the immune and endocrine-metabolic systems is apparent under several physiological situations such as during a meal or exercise. Indeed, following food ingestion, the gut flora and glucose stimulate the release of IL-1β by peritoneal macrophages (Dror et al., 2017; Traba et al., 2015). IL-1β then potentiates glucose-induced insulin secretion (Dror et al., 2017; Hajmrle et al., 2016; Maedler et al., 2002). Next, both insulin and IL-1β can regulate glucose disposal, since IL-1β facilitates glucose uptake into immune cells. Thereby, IL-1β alerts and fuels the immune system, possibly to prevent the dissemination of microorganisms contained in the food. Concomitantly, insulin signals the availability of glucose and regulates its distribution to the skeletal muscle, while surplus calories are stored as fat (Dror et al., 2017).

Another example of adaptive cross-talk between metabolism and immunity is the role of IL-6 during exercise. Beyond its function as a cytokine, IL-6 can be viewed as a myokine, since it is produced and released by contracting skeletal muscle during exercise (Pedersen

and Febbraio, 2008). Interestingly, IL-6 released during physical activity also increases circulating GLP-1 levels (Adam and Westerterp-Plantenga, 2004; Ellingsgaard et al., 2011; Traub et al., 2017). Indeed, IL-6 stimulates GLP-1 secretion from intestinal L-cells and re-programs pancreatic α-cells to process proglucagon to GLP-1 via upregulation of the prohormone convertase 1/3 (Ellingsgaard et al., 2011; Traub et al., 2017). Thus, during exercise, IL-6-induced GLP-1 leads to metabolic adaptation by reducing gut motility and appetite. This also provides a trophic effect on the islets to prepare them for the insulin secretion needed for the expected following meal. Additionally, exercise-mediated mobilization of visceral fat requires IL-6 signaling (Wedell-Neergaard et al., 2018).

Several other cytokines contribute to the physiological regulation of metabolism. For example, IL-33 promotes insulin secretion via islet-resident group 2 innate lymphoid cells (Dalmas et al., 2017). Another example is IL-22, which contributes to the preservation of the gut mucosal barrier and, thus, mitigates endotoxemia-induced IR (Wang et al., 2014). Furthermore, IL-22 protects β-cells from oxidative and endoplasmic reticulum stress (Hasnain et al., 2014).

Finally, intra- and peri-islet macrophages participate in the adaptive increase of β-cell mass in response to high calorie intake by promoting β-cell proliferation (Ying et al., 2018). M2-like macrophages may promote β-cell replication by up-regulation of SMAD7 (Cao et al., 2014; Xiao et al., 2014).

Chronic effects of inflammation on the complications of diabetes

In contrast to the early beneficial regulatory effects of the immune system on metabolism described above, prolonged and exaggerated metabolic stress can lead to deleterious inflammatory reactions and precipitate autoinflammatory diseases. Although specific to each organ, a similar pattern is seen in many tissues affected by metabolic stress. Thus, increased nutrient exposure leads to cytokine and chemokine release, followed by immune cell recruitment and/or proliferation. In some cases, disproportional expansion of the tissue (e. g. adipocytes) or microvascular occlusions (retina, peripheral neurons), will lead to hypoxia and trigger an immune response. The inflammasome is a critical sensor of all these changes. Indeed, the NLRP3 inflammasome is activated by increased levels of glucose, fatty acids, cholesterol, and uric acid as well as by hypoxia (Duewell et al., 2010; Guo et al., 2015; Martinon et al., 2002; Martinon et al., 2006; Stienstra et al., 2010; Tschop and Thomas, 2006; Zhou et al., 2010). Depending on the specific tissue involved, this will lead to distinct pathologies, but the pattern of metabolic stress-induced inflammation remains similar. As detailed below, this can be observed in cardiovascular disease (CVD), NAFLD, retinopathy, nephropathy, neuropathy, and Alzheimer's disease, among others.

Inflammation and cardiovascular disease

Almost 200 years ago, Carl von Rokitansky and Rudolf Virchow described atherosclerosis as an inflammatory process (Mayerl et al., 2006). Over the years, this view has been confirmed. Indeed, recent studies show that atherosclerosis is not only a complication of type 2 diabetes as part of the metabolic syndrome, but also shares a similar pattern

of metabolic stress-induced inflammation. Myeloid cells play a critical role in CVD inflammation, and an initiating trigger can be the IL-1 system in sensing metabolic changes.

Early in the development of atherosclerosis, monocytes adhere to the endothelial surface and then migrate into the artery wall, where they can become foam cells that accumulate around endothelial lesions (Gerrity, 1981). This is initiated by the NLRP3 inflammasome, which is activated by crystalline cholesterol and SFAs, whereas, replacement of saturated by monounsaturated FAs reduces IL-1β priming and secretion (Bevilacqua et al., 1985; Duewell et al., 2010; Finucane et al., 2015; Libby et al., 1985; Wen et al., 2011). IL-β can then modulate chemotaxis and adhesion of monocytes (Dinarello, 2009). Further proof for the role of IL-1β in CVD has been generated by the CANTOS study (see below).

The role of IL-1α is less clear, although it has been implicated in the development of vascular smooth muscle cell senescence as a contributor to atherosclerosis (Gardner et al., 2015). IL-1α may also promote later stage development of ischaemic events (Cohen et al., 2010). Therefore, the beneficial effects of IL-1 receptor blockade after acute myocardial infarction may be due to antagonism of both IL-1β and IL-1α (Abbate et al., 2008).

The role of IL-6 in metabolism and in the context of CVD is complex (Febbraio, 2014). Since circulating IL-6 is elevated during obesity and correlates with the onset of diabetes (Spranger et al., 2003), it is often thought to have a negative effect on metabolism. This is supported by studies showing that IL-6 induces hepatic IR (Klover et al., 2003a; Klover et al., 2003b; Lagathu et al., 2003). This is in apparent contradiction to the physiological release of IL-6 by skeletal muscle cells in response to muscle contraction (Febbraio and Pedersen, 2002), since IR decreases with exercise (Wojtaszewski et al., 2000). Furthermore, IL-6 is associated with reduced visceral adipose tissue mass and blocking IL-6 leads to dyslipidemia (Wedell-Neergaard et al., 2018). A large-scale CV outcomes trial with an anti-IL-6 antibody is ongoing and should provide further answers on this subject (DOI: 10.1016/S0140-6736(21)00520-1).

In summary, the role of inflammation in CVD with a particular role for macrophages and IL-1β has been demonstrated. It is likely that other cytokines also contribute and ongoing clinical trials will provide further insights.

Inflammation and retinopathy, nephropathy, neuropathy and wound healing

The role of inflammation in the pathogenesis of diabetic retinopathy and macular edema is well established (Joussen et al., 2004; Mesquida et al., 2019). Chronic retinal inflammation is detectable from the early phases to the sight-threatening advanced stages of diabetic retinopathy (Rubsam et al., 2018). Key cytokines important to this process include IL-1β, IL-1 dependent IL-6, IL-8, and TNF-α, as well as monocyte adhesion to the endothelial wall followed by chemotaxis into the subendothelial space (Dong et al., 2013; Joussen et al., 2004; Simo-Servat et al., 2012). Important factors promoting these processes appear to be hypoxia due to microvasculature occlusions and hyperglycemia. The induced cytokines can damage the retinal vasculature, disrupting the blood-retinal barrier with subsequent macular edema and retinal neovascularization. A key mediator of these events is vascular endothelial growth factor (VEGF), which may be directly induced via hypoxia, IL-1β, IL-6, insulin,

insulin-like growth factor-1 (IGF-1) and fibroblast growth factor (FGF) (Nagineni et al., 2012; Simo et al., 2014). The importance of cytokines in this process may explain why VEGF is overexpressed in diabetic macular edema despite the absence of overt hypoxia (Simo et al., 2014).

Innate immunity is also involved in the development and progression of diabetic nephropathy (Tang and Yiu, 2020). Mechanistically, TLR4 is overexpressed in kidneys of patients with T2D and correlates positively with HbA1c levels and negatively with renal function (Lin et al., 2012). Furthermore, animal studies support the participation of TLR2 and TLR4 in diabetic kidney disease (Jialal et al., 2014; Lin et al., 2012; Ma et al., 2014a; Ma et al., 2014b). In addition, NLRP3 inflammasome activation of IL-1β plays an important role by sensing metabolic stress in the diabetic kidney (Fang et al., 2013; Shahzad et al., 2016; Tang and Yiu, 2020; Vilaysane et al., 2010).

Although diabetic polyneuropathy has major clinical consequences such as diabetic foot ulcers and amputation, research on its pathogenesis is limited. Traditionally, diabetic neuropathy is classified as non-inflammatory in contrast to neuropathies such as Guillain–Barré syndrome or demyelinating neuropathy (Herder et al., 2019). However, several recent studies have uncovered strong correlations between inflammation and diabetic neuropathy (Bonhof et al., 2019; Herder et al., 2018; Herder et al., 2017; Herder et al., 2019). Nevertheless, mechanistic data are limited.

Wound healing is delayed in T2D and worldwide approximately 20% of patients with T2D develop diabetic wounds. Overactive pro-inflammatory cytokine pathways are a major contributor to this T2D co-morbidity (Geng et al., 2021).

Inflammation and Alzheimer’s disease

The correlation between T2D and the risk of Alzheimer’s disease (AD) is well-known and some have suggested that AD could be considered Type 3 Diabetes (Nguyen et al., 2020). Two major mechanisms have been widely reported in regards to the etiology of Alzheimer’s. One is the aggregation of Aβ monomers into amyloid fibrils or plaques following extracellular proteolytic cleavage of β-amyloid precursor protein (APP) (Braak and Braak, 1991; Kocahan and Dogan, 2017; Murphy and LeVine, 2010; Selkoe, 1994). Secondly, hyperphosphorylation of TAU leads to the formation of extracellular tangles as well as neuronal microtubular dysfunction (Alonso et al., 1996; Alonso et al., 1994; Alonso et al., 2018; Alonso et al., 1997). Chronic neuroinflammation is now recognized as an additional feature of Alzheimer’s and this is due to activation of brain resident macrophages, termed microglia (Akiyama et al., 2000; Kinney et al., 2018; Leng and Edison, 2021). These microglia release a variety of cytokines and other factors that might play a functional role in the pathogenesis of AD and have been referred to as disease associated microglia (Keren-Shaul et al., 2017). Although neuroinflammation with microglia activation may not be the initiating mechanism for AD, they appear to play a role in augmenting the Aβ and TAU etiologies (Dani et al., 2018; Hanisch, 2002; Hayes et al., 2002).

In the normal state, microglia are inactive and function to assess the local microenvironment for harmful molecules and communicate to neuronal cells (Arcuri et al., 2017). The

increased presence of Aβ may serve as an activating signal for microglia and these cells then help clear excessive Aβ from the brain. During the chronically inflamed and activated state, the ability of the microglia to clear Aβ declines, which would promote the development of fibrils and plaques (Bolmont et al., 2008; Heneka et al., 2015a; Hickman et al., 2008). Several genetic studies show that a large proportion of the AD risk alleles are associated with genes that are primarily or exclusively expressed in microglia (Hansen et al., 2018). Most of these variants are located in noncoding areas and might function to promote the AD phenotype due to effects on enhancer and or promoter activity (Nott et al., 2019). Many of these genes reside in microglial pathways that involve phagocytosis, autophagy or lysosomal function (Nott et al., 2019). Reduced activity of these pathways can be a cause of increased cytokine production by microglia. There is also evidence that neuroinflammation can cause bone marrow-derived macrophage recruitment into the brain and participate in AD pathology (Theriault et al., 2015). These concepts are supported by the identification of genetic variants in the macrophage receptor TREM2 which cause enhanced risk for AD development (Guerreiro et al., 2013; Jonsson et al., 2013; Jonsson and Stefansson, 2013; Sims et al., 2017). TREM2 is highly expressed in microglia, but the exact mechanisms underlying the enhanced risk for AD remains unclear (Keren-Shaul et al., 2017). Since TREM2 is a receptor for a yet to be identified lipid species, it is possible that activation of TREM2 with a ligand or an activating antibody could represent a potential therapeutic approach.

Similar to macrophages throughout the body, activated microglia also release a number of cytokines which may participate in AD pathogenesis (Del Bo et al., 1995; Hanisch, 2002; Heneka et al., 2015b; Heneka et al., 2013; Smith et al., 2012). IL-1β might be the most important cytokine released in this context and is elevated in the brains of AD patients (Liu and Quan, 2018). IL-1β can cause increased secretion of Aβ precursor APP and promote enhanced processing to Aβ, further increasing fibril and plaque formation (Dash and Moore, 1995). Since Aβ also activates the NLRP3 inflammasome in microglia promoting the release of IL-1β, this could provide a feed-forward mechanism sustaining or increasing AD (Goldgaber et al., 1989; Yates et al., 2000). TNF-α and IL-6 are also released by activated microglia and lead to increased APP production, hyperphosphorylation of TAU and conversion of APP to Aβ by promoting β-secretase production (Chen et al., 2012a; Quintanilla et al., 2004). In addition to microglia, astrocytes can play a role in neuroinflammation, since activated microglial cells release cytokines that promote the development of reactive astrocytes that actively participate in neuronal cell death and damage (Liddelow et al., 2017).

The prevailing view is that Aβ monomers derived from APP proteolysis and hyperphosphorylated TAU protein are the prevailing mechanisms underlying the tangles and amyloid plaques which define AD brain pathology. However, the resident microglia, as well as brain astrocytes, appear to be important in promoting the processes which ultimately lead to AD and all of its clinical sequalae.

Additional obesity and diabetes-related inflammatory disorders

As discussed above, obesity and T2D have strong inflammatory components and chronic activation of the innate immune system may induce or precipitate other conditions driven by inflammation. Some examples are given below.

Polycystic ovary syndrome (PCOS) is a common disease defined by a combination of androgen excess and ovarian dysfunction, leading to hirsutism, anovulation and infertility (Escobar-Morreale, 2018). Interestingly, PCOS is strongly associated with IR and diabetes. A possible explanation for this is that inflammation might participate in PCOS. Indeed, women with PCOS show increased circulating markers of inflammation (Kelly et al., 2001). Furthermore, the ovary expresses IL-1β and IL-1 receptor type 1 with peri-ovulatory changes compatible with the notion that it has effects on ovulation (Kol et al., 1999). This is supported by several studies showing the impact of IL-1β on steroidogenesis (Popovic et al., 2019). Clinical intervention studies to determine whether IL-1β is causative in PCOS are ongoing (https://clinicaltrials.gov/ct2/show/NCT03578497).

Similar to the association of PCOS with T2D in women, obesity and T2D in men are frequently associated with hypogonadism (Rao et al., 2013). The association between low testosterone and T2D might also be partly explained by inflammation. Thus, TNF-α, IL-6 and IL-1β can indirectly inhibit the secretion of testosterone by reducing hypothalamic-pituitary gonadotropin production and can also directly inhibit testicular and androgen production (Jones and Kennedy, 1993). This idea has recently been supported by a clinical study showing that treatment with an IL-1 antagonist increased testosterone levels in obese men with testosterone deficiency (Ebrahimi et al., 2018).

Some inflammatory diseases with an aetiology unrelated to T2D may be exacerbated or precipitated by the concomitant occurrence of both conditions. A striking example is rheumatoid arthritis. Its primary pathology is autoimmune joint inflammation (Klareskog et al., 2009). Although the aetiology of rheumatoid arthritis is unrelated to T2D, the prevalence of both conditions together is increased (Ruscitti et al., 2017a; Ruscitti et al., 2017b). The molecular mechanism could involve cytokines, such as TNF-α and IL-1β, promoting both rheumatoid arthritis and T2D (Dinarello, 2011). Interestingly, monocytes from patients with rheumatoid arthritis and T2D display increased production of IL-1β via NLRP3-inflammasome activation compared to monocytes from patients with only one of the two conditions (Ruscitti et al., 2015). Accordingly, a recent clinical study of IL-1 antagonism in patients with rheumatoid arthritis and T2D showed a remarkable improvement in both glycemia, and joint disease activity [(Ruscitti, 2019), for details, see below]. Autoimmune skin diseases such as psoriasis are also associated with a profound increase in prevalence of T2D. A large longitudinal study found a prevalence of 11.4% of T2D in patients with psoriasis (Holm et al., 2019). Other examples of diseases which may be exacerbated by T2D, are gout, and Crohn’s disease (Donath, 2014).

An unexpected role of inflammation has been reported in postprandial hypoglycemia after bariatric surgery. This condition presents acutely after meal ingestion with disabling neuroglycopenic symptoms. This may result in a long-term increase in food intake and subsequent weight regain. The underlying mechanism is related to the rapid transit of food

without gastric delay due to the anatomical changes, leading to an early peak in glycemia. This, in turn, causes an exaggerated induction of the postprandial rise in IL-1β-induced insulin secretion [see (Dror et al., 2017; Maedler et al., 2002) and above], leading to an overshoot of the insulin response, followed by hypoglycemia. This is supported by a proof-of-concept clinical study, which tackled this process at two steps (Hepprich et al., 2020). The initial hyperglycemic peak was reduced via SGLT-2-inhibition while the effect of IL-1β was blocked with an IL-1 receptor antagonist. Both drugs reduced postprandial insulin release and prevented episodes of hypoglycemia.

Therapeutic approaches, targeting inflammation

The first clinical evidence for the beneficial effect of anti-inflammatory treatment in diabetes was published in 1876 (Ebstein, 1876). This empirical study showed that sodium salicylate improved glycemia in patients with diabetes. More than a hundred years later, Shoelson and colleagues showed that this anti-diabetic effect is mediated via inhibition of the NF-κB pathway (Yuan et al., 2001). They went on to validate the effectiveness of salsalate to improve glycemia in proof-of-concept studies (Fleischman et al., 2008; Goldfine et al., 2008; Koska et al., 2009) (Faghihimani et al., 2013; Goldfine et al., 2013a) followed by larger placebo-controlled studies (Goldfine et al., 2013b; Goldfine et al., 2010). The only safety signal was a small increase in low-density lipoprotein cholesterol levels and a reversible rise in urinary albumin. These clinical studies add to the evidence for a role of chronic inflammation in diabetes.

The initial discovery by Hotamisligil and Spiegelman on the effect of TNF-α in IR (Hotamisligil et al., 1993) was followed by a rapid attempt to translate the findings into the clinic. Unfortunately, these studies were not adequately designed, with low sample size and duration of treatment e. g. a single dose in 7–10 patients for a few days. (Bernstein et al., 2006; Dominguez et al., 2005; Ofei et al., 1996; Paquot et al., 2000). Taking into account the number of variable factors that can influence a metabolic response, including genetic background, body weight, food intake, and exercise, it is likely that the design of these studies was insufficient to detect changes, explaining the apparent lack of metabolic effects of TNF-α antagonism. For details on the limitations of these studies, see (Donath, 2014). However, indirect evidence supports the clinical potential of TNF-α antagonists in T2D. Thus, these drugs improve glycemia in obese subjects without diabetes as well as in patients with psoriasis, rheumatoid arthritis and Crohn’s disease (Gonzalez-Gay et al., 2006; Huvers et al., 2007; Kiortsis et al., 2005; Marra et al., 2007; Stanley et al., 2011; Timper et al., 2013; Yazdani-Biuki et al., 2006; Yazdani-Biuki et al., 2004). Furthermore, TNF-α antagonism reduces the incidence of T2D in patients with rheumatoid arthritis or psoriasis (Antohe et al., 2012; Solomon et al., 2011). However, it is unclear whether the beneficial effect on glycemia was direct or due to an improvement in the underlying disease with subsequent enhanced exercise capacity. On the other hand, a recent study directly compared TNF-α versus IL-1 blockade in patients with rheumatoid arthritis and T2D. TNF-α antagonism failed to decrease glycemia (Ruscitti, 2019). Therefore, a well-designed diabetes-focused study of TNF antagonism, ideally with clinically relevant outcomes, such as CVD, is warranted.

The most advanced clinical translation of inflammation and T2D has been achieved with IL-1 antagonism. An initial trial in patients with T2D showed that anakinra (a recombinant human IL-1Ra) improved β-cell secretory function and reduced glycemia (Larsen et al., 2007). The ability of IL-1 inhibitors to improve insulin secretion was confirmed in several follow up studies using anakinra (van Asseldonk et al., 2011; van Poppel et al., 2014). Similarly, treatment of T2D subjects with neutralizing anti-IL-1β antibodies demonstrated beneficial effects, although the magnitude varied depending on baseline HbA1c levels and sample size (Cavelti-Weder et al., 2012; Rissanen et al., 2012; Ruscitti, 2019; Sloan-Lancaster et al., 2013).

In a large CV outcome study (CANTOS), treatment with an anti-IL-1β antibody prevented CV events (Ridker et al., 2017a). A sub-analysis showed that blocking IL-1β also significantly decreased HbA1c during the first 6–9 months of treatment, with waning effect towards the end of the study (Everett et al., 2018b). This attenuation of the glucose lowering effect may be due to the design of the study, which allowed for lifestyle interventions and adaptations of standard anti-diabetic drugs. Supporting this assumption, in the non-diabetic patients, anti-IL-1β treatment decreased HbA1c for the duration of the study. Furthermore, IL-1 antagonism prevented new onset of diabetes for about 4 years. After 4 years, the number of patients followed decreased by 90% and the effect of anti-IL-1β could no longer be detected. The observed prevention of diabetes suggests an ongoing islet inflammatory process in patients with prediabetes. Most importantly, this outcome study showed that in a patient population with T2D, CV complications can be prevented (Everett et al., 2018b). An additional beneficial effect of IL-1β inhibition was prevention of heart failure, particularly in patients with higher body mass index and diabetes (Everett et al., 2018a), confirming previous clinical proof- of-concept studies (Abbate et al., 2015; Abbate et al., 2010; Van Tassell et al., 2017; Van Tassell et al., 2018). Although the CANTOS study showed the overall safety of prolonged IL-1β inhibition, in patients with severe infections necessitating inpatient treatment, IL-1β antagonism was associated with a higher incidence of fatal infections, which warrants caution in patients at risk.

Following these studies, a meta-analysis involving 2921 cases with 2TD treated with IL-1 blocking therapy, demonstrated a highly significant reduction in HbA1c ($P<0.00001$) (Kataria et al., 2019).

Recently, a new designer ligand for the gp130 receptor with CNTF-like properties that signals in a IL-6-receptor-dependent manner was shown to improve glycemia and prevent body weight gain in high-fat-diet-fed mice (Findeisen et al., 2019) showing that designer approaches targeting specific pathways but avoiding activation of others have great potential for future human studies.

A list of anti-inflammatory clinical trials targeting T2DM and its associated pathologies is given in Table 1.

CONCLUDING REMARKS

At this point, the only antidiabetic drugs demonstrating improvement in macrovascular disease are GLP-1 analogs (Marso et al., 2016) while SGLT-2 inhibitors are the only drug class demonstrating protective effects against heart failure and nephropathy (Zinman et al., 2015). This explains why these two classes of drugs are currently often used as first line antidiabetic treatment as opposed to insulin, sulfonylureas and DPP-4 inhibitors which only lower glucose. An anti-inflammatory drug may provide additional benefits beyond improving glycemia. Indeed, as detailed above, IL-1β antagonism mitigated β-cell dysfunction and improved glycemia, CV complications and heart failure (Abbate et al., 2015; Abbate et al., 2010; Cavelti-Weder et al., 2012; Donath, 2014; Everett et al., 2018a; Larsen et al., 2007; Ridker et al., 2017; Ridker et al., 2018b; Rissanen et al., 2012; Ruscitti, 2019; Sloan-Lancaster et al., 2013; Van Tassell et al., 2017; Van Tassell et al., 2018). Future studies are needed to determine whether anti-inflammatory treatment may counteract other complications of diabetes, including NASH, nephropathy, fatigue, polyneuropathy, retinopathy and macular oedema (Cavelti-Weder et al., 2011; Febbraio et al., 2018; Herder et al., 2013; Herder et al., 2018; Herder et al., 2017; Herder et al., 2009; Lehrskov et al., 2018; Mesquida et al., 2014; Schlesinger et al., 2018; Stahel et al., 2015; Sun and Karin, 2012; Tesch, 2017). Beyond IL-1β antagonism, other immunomodulatory drugs, either alone or in combination, may be more effective. However, the choice of an anti-inflammatory drug should be based on a pathophysiologic mechanistic understanding and not on a nonspecific effect, as with methotrexate, which did not decrease IL-1β and failed to prevent CV complications in patients with metabolic syndrome (Ridker et al., 2018a). An overview of validated and potential future pro-inflammatory targets in human T2DM and associated diseases is given in Figure 4.

The association of diabetes with other inflammatory diseases such as gout or rheumatoid arthritis allows treatment of two conditions with one therapeutic agent. This has been demonstrated by Ruscitti and Giacomelli in patients with rheumatoid arthritis and T2D (Ruscitti, 2019). Treatment of these patients with anakinra was highly effective, achieving a decrease in HbA1c by > 1% after 6 months, while simultaneously reducing rheumatoid disease activity. Therefore, anti-inflammatory treatment can improve both conditions and is already doable in countries where IL-1 antagonism is approved for rheumatoid arthritis or gout.

Several companies are developing inhibitors of the NLRP3-IL-1β pathway, including small molecules that can be taken orally, avoiding injection site reactions of IL-1Ra. The short half-life of these oral agents would also help in the management of severe infections. Hopefully, in the near future, these inhibitors will be tested in patients with T2D and associated complications. An encouraging phase 1b study using an oral NLRP3 inhibitor, dapansutrile, showed signs of improved heart failure and significantly decreased blood glucose levels (Wohlford et al., 2020).

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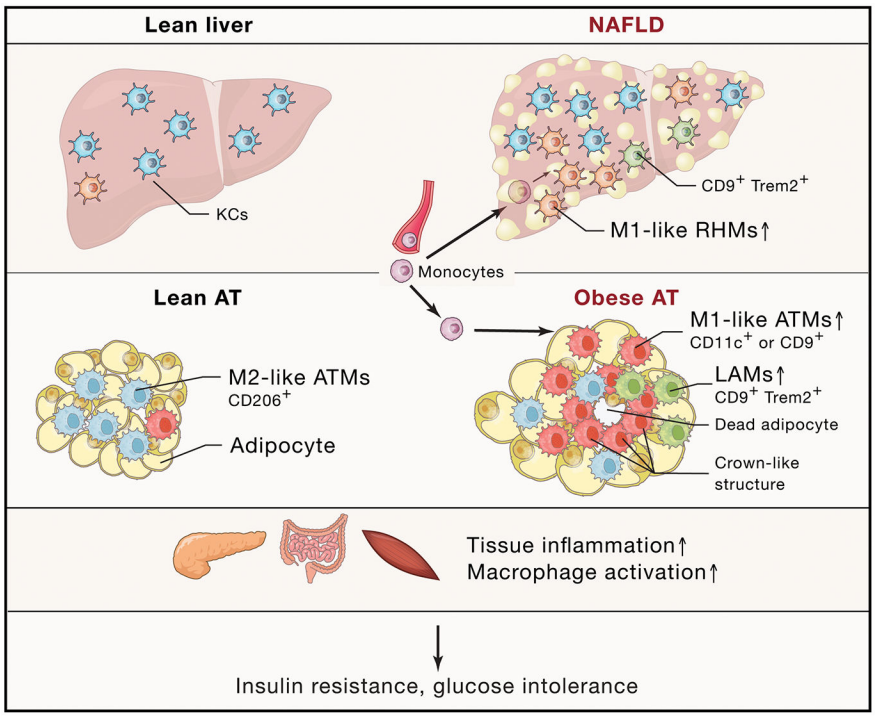

Figure 1. Chronic tissue inflammation in obesity.

In normal lean conditions, tissue macrophages in the liver, adipose tissue, pancreatic islets, intestine, and muscle generally display an anti-inflammatory M2-like (blue) polarization state. Obesity induces monocyte recruitment into the tissue and resident macrophage proliferation with a switch toward a more pro-inflammatory M1-like state (red), promoting systemic IR and glucose intolerance. Obesity also causes accumulation of lipid associated macrophages (green; $Trem2^{+}CD9^{+}$ LAMs). In the lean liver, Kupffer cells (KCs) represent ~10% of all cells. Obesity increases the recruitment of monocytes also into the liver, which differentiate into M1-like recruited hepatic macrophages (RHMs). In the progression to non-alcoholic steatohepatitis (NASH), KC genes involved in tissue repair, inflammation, and lipid metabolism, such as Trem2 and CD9, are upregulated.

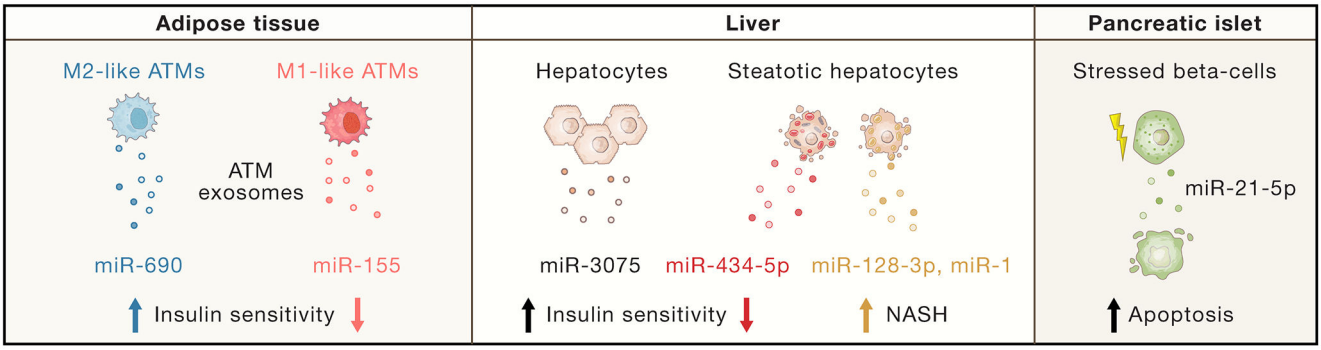

Figure 2. Exosomes as regulators of intercellular and interorgan crosstalk in metabolism.

The release of exosomes from adipose tissue macrophages (ATMs), hepatocytes and islet β-cells have systemic metabolic effects. Exosomal miRNA (miR)-690 from M2-like ATMs improves insulin sensitivity, while miR-155 from M1-like ATMs can cause insulin resistance. In early stage HFD, hepatocytes secrete exosomes containing miR-3075, which produces beneficial metabolic effects. In contrast, the hepatocyte exosomes in chronically obese mice contain miR-434-5p, which promotes inflammation and insulin resistance. Exosomes from steatotic hepatocytes also contain pathogenic miRs, such as miR-128 and miR-1, that can induce inflammation or cause hepatic stellate cell activation, promoting NASH. β-cells stressed by pro-inflammatory stimuli release exosomes containing miR-21-5p, which can induce apoptosis in neighboring β-cells.

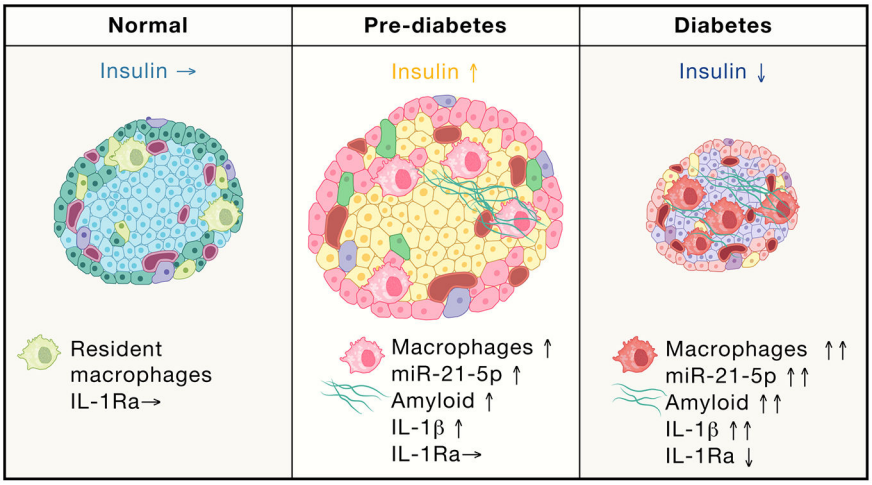

Figure 3. Islet inflammation.

In a normal state, pro-inflammatory cytokines released from macrophages and the anti-inflammatory IL-1 receptor antagonist (IL-1Ra) released from immune- and β-cells keep the IL-1 system balanced. In pre-diabetes, islet function is increased, the number of immune cells increases and the overall inflammatory balance is tilted towards pro-inflammation. A self-amplified prolonged pro-inflammatory milieu and amyloid polypeptide promotes deterioration of β-cell mass and function, eventually leading to type 2 diabetes.

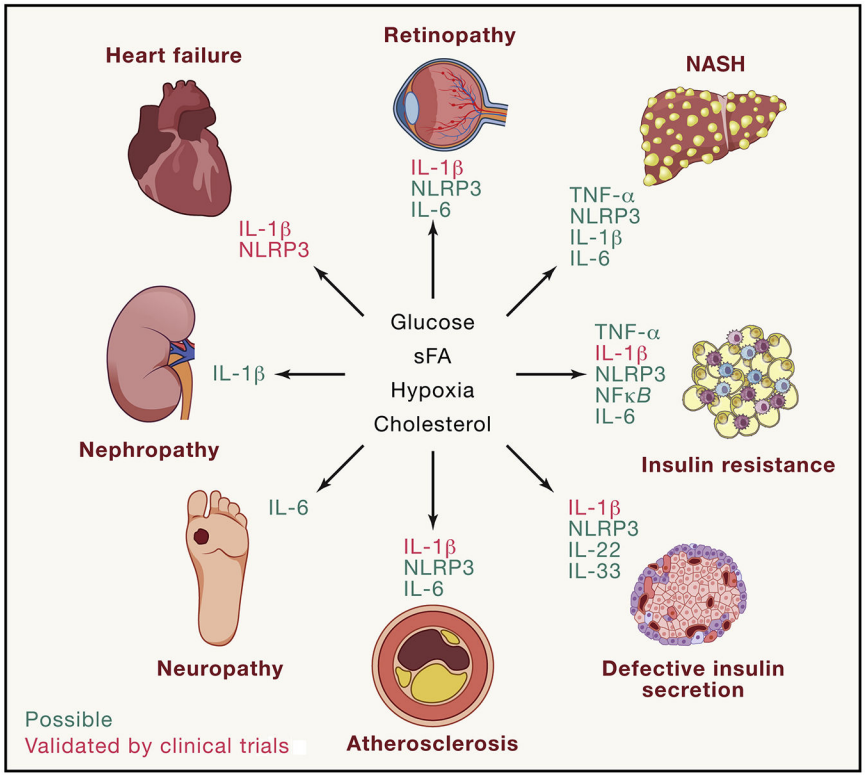

Figure 4. Immunomodulatory targets for the treatment of diabetes and its complications.

Targeting the IL-1 pathway in patients with type 2 diabetes was shown to have beneficial effects on insulin sensitivity and secretion as well as atherosclerosis, heart failure and retinopathy. Future clinical studies building on preclinical work blocking TNF-α, the IL-1 system or other pro-inflammatory mediators may uncover novel routes to counteract type 2 diabetes and its complications.

Table 1.

Clinical studies of anti-inflammatory treatments in patients with type 2 diabetes and associated complications

	Targets	Drugs	References
Glycemia	NF-κB	Salsalate	(Faghihimani et al., 2013; Fleischman et al., 2008; Goldfine et al., 2013a; Goldfine et al., 2013b; Goldfine et al., 2010; Goldfine et al., 2008; Koska et al., 2009)
	TNFα	Etanercept Remicade (mixed results)	(Bernstein et al., 2006; Dominguez et al., 2005; Gonzalez-Gay et al., 2006; Huvers et al., 2007; Kiortsis et al., 2005; Marra et al., 2007; Ofei et al., 1996; Paquot et al., 2000; Ruscitti, 2019; Stanley et al., 2011; Timper et al., 2013; Yazdani-Biuki et al., 2006; Yazdani-Biuki et al., 2004)
	IL-1β NLRP3	Anakinra Canakinumab Gevokizumab LY2189102 Diacerein Dapansutrile	(Cavelti-Weder et al., 2012; Everett et al., 2018b; Kataria et al., 2019; Larsen et al., 2007; Ramos-Zavala et al., 2011; Rissanen et al., 2012; Ruscitti, 2019; Sloan-Lancaster et al., 2013; van Asseldonk et al., 2011; van Poppel et al., 2014; Wohlford et al., 2020)
β-cell function	IL-1β	Anakinra Diacerein	(Larsen et al., 2007; Ramos-Zavala et al., 2011; van Asseldonk et al., 2011; van Poppel et al., 2014)
Insulin resistance	NF-κB	Salsalate	(Faghihimani et al., 2013; Fleischman et al., 2008; Goldfine et al., 2013a; Goldfine et al., 2013b; Goldfine et al., 2010; Goldfine et al., 2008; Koska et al., 2009)
	TNFα	Etanercept Remicade (mixed results)	(Bernstein et al., 2006; Dominguez et al., 2005; Gonzalez-Gay et al., 2006; Huvers et al., 2007; Kiortsis et al., 2005; Marra et al., 2007; Ofei et al., 1996; Paquot et al., 2000; Ruscitti, 2019; Stanley et al., 2011; Timper et al., 2013; Yazdani-Biuki et al., 2006; Yazdani-Biuki et al., 2004)
	IL-1β	Anakinra	(Ruscitti et al., 2019; van Asseldonk et al., 2012)
Cardiovascular complications	IL-1β	Canakinumab	(Ridker et al., 2017)
Heart failure	IL-1β NLRP3	Anakinra Canakinumab Dapansutrile	(Abbate et al., 2015; Abbate et al., 2010; Everett et al., 2018a; Van Tassell et al., 2017; Van Tassell et al., 2018; Wohlford et al., 2020)
Gout	IL-1β NLRP3	Anakinra Canakinumab Dapansutrile	(Kluck et al., 2020; Martinon et al., 2006; So et al., 2007; Vitale et al., 2015)
Rheumatoid arthritis	IL-1β	Anakinra	(Ruscitti, 2019)
Retinopathy	IL-1β	Canakinumab	(Stahel et al., 2015)