

REVIEW

Chronic tissue inflammation and metabolic disease

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Obesity is the most common cause of insulin resistance, and the current obesity epidemic is driving a parallel rise in the incidence of T2DM. It is now widely recognized that chronic, subacute tissue inflammation is a major etiologic component of the pathogenesis of insulin resistance and metabolic dysfunction in obesity. Here, we summarize recent advances in our understanding of immunometabolism. We discuss the characteristics of chronic inflammation in the major metabolic tissues and how obesity triggers these events, including a focus on the role of adipose tissue hypoxia and macrophage-derived exosomes. Last, we also review current and potential new therapeutic strategies based on immunomodulation.

Insulin resistance is a key feature of obesity and type 2 diabetes mellitus (T2DM). Since obesity is the most common cause of insulin resistance in humans, the obesity epidemic is the major cause of the rising global incidence of T2DM. In nondiabetic subjects with obesity, hyperinsulinemia usually compensates for the underlying insulin resistance, maintaining glucose homeostasis within normal or near normal levels. When compensatory hyperinsulinemia fails and insulin levels decline due to development of a β -cell defect, hyperglycemia and the typical T2DM state ensues, indicating that both insulin resistance and β -cell dysfunction are needed for the full development of this disease. In obesity, chronic tissue inflammation is a well-reported key contributor to decreased insulin sensitivity, particularly in adipose tissue and the liver. However, several recent reports have shown obesity-associated inflammatory responses in pancreatic islets (Zhao et al. 2003; Warren et al. 2006; Ehses et al. 2007; Böni-Schnetzler et al. 2008; Richardson et al. 2009; Mahdi et al. 2012; Jourdan et al. 2013; Kamada et al. 2013; Butcher et al. 2014; Hasnain et al. 2014; Ying et al. 2019), suggesting that chronic islet inflammation can also lead to β -cell dysfunction in the context of obese T2DM subjects.

Although there are a number of potential, and sometimes overlapping, mechanisms that can contribute to insulin resistance and β -cell dysfunction, in this current review we focus on the role of chronic tissue inflammation in these metabolic defects. The reader is referred to other excellent reviews on possible causes of insulin resistance and β -cell dysfunction, independent of chronic tissue inflammation (Halban et al. 2014; DeFronzo et al. 2015; Czech 2017; Newgard 2017; Guilherme et al. 2019; Kahn et al. 2019; Roden and Shulman 2019; Scherer 2019; Alonge et al. 2021; Sangwung et al. 2020).

The interconnections between inflammation and metabolic dysfunction are often described by the term immunometabolism (Hotamisligil 2017). Immunometabolism includes the effects of immune cells on the regulation of systemic metabolism, as well as the effects of metabolism within immune cells on inflammation. Both of these mechanisms are of importance, but in this review we focus our attention on the role of chronic inflammation in the etiology of disordered glucose homeostasis.

Chronic inflammation in adipose tissue, the liver, the central nervous system, the gastrointestinal (GI) tract, pancreatic islets, and muscle have all been described in obese/T2DM states, indicating the complex, multiorgan crosstalk network involved in these disorders. The general metabolic consequences of obesity-induced tissue inflammation are summarized in Table 1. These concepts are mostly derived from mouse studies, and among all these contributing tissues, adipose tissue inflammation in obesity has been the most extensively studied.

Although the contribution of chronic inflammation in T2DM in obesity has been suggested for many years, in the past two decades a number of studies have been published, bringing out underlying physiologic and molecular mechanisms as to how obesity-associated inflammation leads to insulin resistance and glucose intolerance. One of the earliest studies was reported by Grunfeld and Feingold (Feingold et al. 1989) who showed that treatment of rodents with TNF α leads to hyperglycemia. An additional key early study showed increased TNF α levels in the adipose tissue of obese mice and showed that neutralization

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Table 1. The metabolic effects of obesity-associated tissue inflammation

Tissue	Metabolic Effects of Inflammation
Adipose Tissue	<ul style="list-style-type: none"> ↑ Lipolysis (SFAs), ↓ Glucose Uptake (Insulin Resistance) ↓ Adaptive Thermogenesis (in beige, brown adipocytes) Adipokine Dysregulation Δ Exosomal Cargoes (adipocytes, ATMs)
Liver	<ul style="list-style-type: none"> ↑ Lipogenesis, ↑ Glucose Production ↑ FetuinA (and other hepatokines) Insulin Resistance
Skeletal muscle	<ul style="list-style-type: none"> ↓ Glucose Uptake (Insulin Resistance)
Beta Cell	<ul style="list-style-type: none"> ↓ GSIS ↑ Beta Cell Proliferation
GI Tract (Dysbiosis)	<ul style="list-style-type: none"> ↑ Endotoxemia (LPS) ↑ N-Formyl Peptide → ↓ GLP1 secretion Δ Microbial Metabolites (SCFAs, 2^o bile acids)

of TNF α ameliorates insulin resistance (Hotamisligil et al. 1993). Numerous studies have identified various molecules within the inflammatory signaling cascade that can impair insulin signaling, such as JNK, IKK β , and various cytokines (Xia et al. 2015; Goldfine and Shoelson 2017; Hotamisligil 2017; Zhao et al. 2018; Donath et al. 2019; Hall et al. 2020). Many reports have identified a mechanistic link between chronic inflammation and insulin resistance in rodent studies by use of various genetic gain- and loss-of-function studies (Lee et al. 2018). For example, mice engineered to globally deplete IKK β , JNK, CCR2, or CCL2/MCP-1 show improved insulin sensitivity in obesity (Hirosumi et al. 2002; Arkan et al. 2005; Weisberg et al. 2006). Adipocyte or hepatocyte KO of JNK, HIF-1 α , NEMO, or TLR4 also produce enhanced insulin sensitivity (Sabio et al. 2008; Wunderlich et al. 2008; Jia et al. 2014; Lee et al. 2014). In contrast, adipocyte-specific overexpression of *Ccl2* or *Hif1a* induces insulin resistance and glucose intolerance on a normal chow diet (Kanda et al. 2006; Halberg et al. 2009). Most importantly, a large number of macrophage (or hematopoietic cell)-specific KOs of inflammatory molecules have been reported that all lead to protection from insulin resistance and glucose intolerance (Saber et al. 2009; Olefsky and Glass 2010; Han et al. 2013; Hill et al. 2014; Takikawa et al. 2016; Desai et al. 2017). However, while there are a number of studies in human adipose tissue (Lofgren et al. 2000; Fabbrini et al. 2013; Hill et al. 2018), the liver (Senn et al. 2002; Ghazarian et al. 2017), primary adipocytes (Liu et al. 1998), skeletal muscle (Austin et al. 2008), and pancreatic islets (Maedler et al. 2002) that are supportive of this immunometabolism process (Pickup et al. 1997), the concept that chronic inflammation causes insulin resistance and β -cell dysfunction still remains to be validated in humans.

Association between T2DM and genetic variations associated with inflammation

While the contribution of chronic inflammation to the development of insulin resistance and T2DM remains to be

validated in humans, recent advances in genome-wide association studies (GWAS) suggest that inflammation might be causally related to the incidence of T2DM in humans. While early GWASs showed that T2DM is associated with genetic variations in genes associated with insulin secretion and β -cell function (McCarthy et al. 2010; Dimas et al. 2014), later studies found that genes involved in peripheral insulin sensitivity and adipose tissue function such as *PPARG* and *KLF14* are also associated with the incidence of T2DM (Voight et al. 2010). Moreover, variations in genes regulating T-cell (e.g., *PTPRJ* and *CMIP*) or macrophage (e.g., *MAEA*) function or inflammatory signaling pathways (e.g., *WVVOX*, *MAP8IP1*, *IFNGR1*, *ST6GAL1*, *JAZF1*, *MAP3K1*, *MACROD1*, *NFE2L3*, and *TLR4*) are also associated with the incidence of T2DM (Waeber et al. 2000; Kooner et al. 2011; Cho et al. 2012; Manning et al. 2012; Locke et al. 2015; Shungin et al. 2015; Flannick et al. 2019; Liao et al. 2019; Diedisheim et al. 2020). While more inclusive GWAS and whole-exome sequencing studies are being updated (Mahajan et al. 2018; Flannick et al. 2019), many genetic variations associated with the incidence of T2DM are found in non-coding DNA regions. Moreover, heterogeneity in the etiology of T2DM (Philipson 2020) may dilute the contribution of specific genetic variations to disease pathology. One should take these factors into consideration when interpreting GWAS results.

Inflammation in obesity

Adipose tissue

Chronic adipose tissue inflammation is a characteristic feature of obesity, and two early studies published simultaneously in 2003 (Weisberg et al. 2003; Xu et al. 2003) showed that this was largely due to the increased accumulation of proinflammatory macrophages in both human and mouse adipose tissue. Many subsequent reports have documented this accumulation of adipose tissue macrophages (ATMs) in obese adipose tissue and have further characterized these macrophages with respect to surface markers, biological effects, and transcriptomic phenotypes. In addition to macrophages, other innate and adaptive immune cell types participate in obese adipose tissue inflammation (summarized in Fig. 1). However, macrophages are the dominant cell type mediating insulin resistance and metabolic dysfunction in obese adipose tissue. Thus, macrophages are the most abundant immune cell type accumulating in obese adipose tissue and liver. Moreover, these cells are the main immune cells secreting most of the inflammatory cytokines, galectin-3, and exosomes (Weisberg et al. 2003; Zeyda et al. 2007; Li et al. 2016; Ying et al. 2017a), and depletion of macrophages corrects insulin resistance and glucose tolerance in obese mice (Huang et al. 2010; Chatenoud et al. 2011; Lee et al. 2011b; Bu et al. 2013).

Adipose tissue macrophages In lean mice, macrophages account for 5%–10% of stromal vascular cells in visceral adipose tissue. As early as 3 d after feeding a high fat diet

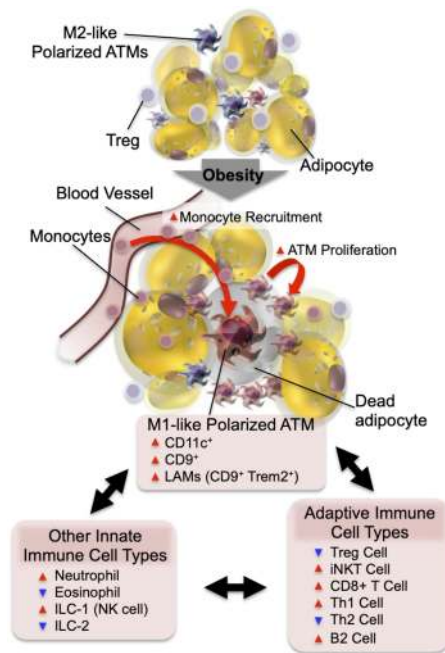


Figure 1. Adipose tissue inflammation in obesity. In the normal state, resident ATMs mostly show an M2-like polarized phenotype. Factors released from Tregs and eosinophils support ATMs to maintain this anti-inflammatory state. In obesity, increased adipocyte chemokine production induces increased blood monocyte recruitment, as well as ATM proliferation. The majority of monocyte-derived ATMs express CD11c and/or CD9 and the M1-like polarized phenotype. The decreased number of eosinophils and Tregs and the increased number of neutrophils, ILC1, CD8+ T cells, Th1 cells, and B2 cells enhance M1-like ATM polarization and adipose tissue inflammation.

(HFD), increased proinflammatory cytokine expression and macrophage infiltration can be observed in visceral adipose tissue (Lee et al. 2011b). These changes gradually increase during the development of obesity, along with progressive deterioration of insulin sensitivity and glucose tolerance until obesity is fully stabilized and these changes start to plateau. In obesity, ATMs accumulate, becoming the most abundant immune cell type in adipose tissue, and can comprise up to 40% of all stromal vascular cells. Along with the obesity-induced quantitative changes in ATM content, ATMs also undergo phenotypic switching from M2-like polarized anti-inflammatory cells to the M1-like polarized proinflammatory state (Lumeng et al. 2007a). M1 macrophages are considered to represent the “classically activated” proinflammatory phenotype of macrophages, and these macrophages produce proinflammatory cytokines, reactive oxygen species, and nitric oxide that eliminate pathogens. M2 cells represent the “alternatively activated” anti-inflammatory phenotype of macrophages, which generally promote tissue repair and remodeling (Jakubzick et al. 2017; Koelwyn et al. 2018). In obesity, while the number of both M1- and M2-like polarized ATMs is increased, the increase in M1-like polarized ATMs is much greater, skewing the balance to-

ward a tissue proinflammatory state. The majority of M1-like polarized ATMs are derived from circulating monocytes and express CD11c on the surface, whereas the majority of M2-like polarized ATMs are resident and do not display CD11c expression (Lumeng et al. 2007b). The inflammatory state of ATMs can also be modified by various lipid species. Saturated fatty acids (SFAs) derived from either dietary sources or adipocyte triglyceride hydrolysis can drive M1-like ATM polarization through a toll-like receptor 4 (TLR4)-dependent mechanism (Saber et al. 2009; Holland et al. 2011; Orr et al. 2012; Tao et al. 2017). On the other hand, omega-3 FAs inhibit proinflammatory activation of ATMs through a GPR120-dependent mechanism (Oh et al. 2010).

The terms M1- and M2-like are often used to describe ATMs in lean and obese states as a matter of convenience. However, the concept of M1 and M2 macrophages was first introduced based on the immunologic differences between mouse strains that preferentially promote Th1 or Th2 responses. They are specifically defined as bone marrow progenitor cells polarized to an M1 or M2 state in culture by incubating with LPS/IFN γ or IL-4/IL-13, respectively (Mills et al. 2000). In the in vivo setting, ATMs do not exist within these narrow categories but actually span across a polarization spectrum similar to, but distinct from, M1 or M2 macrophages (Li et al. 2019). Thus, studies using single-cell RNA sequencing (scRNA-seq) analyses revealed that the transcriptomic profiles of ATMs are highly heterogeneous in obese adipose tissue. ATMs in obesity display a proinflammatory profile that is overlapping but different compared with in vitro generated M1 cells (Kratz et al. 2014; Hill et al. 2018; Jaitin et al. 2019). Moreover, they show unique metabolic gene expression profiles, including activation of lysosome-dependent lipid metabolism, collectively termed the “metabolic activation state” (Xu et al. 2013; Kratz et al. 2014; Coats et al. 2017). Hill et al. (2018) reported two subpopulations of ATMs depending on CD9 expression, and the number of CD9⁺ ATMs increases during the development of obesity. These CD9⁺ ATMs show unique functional, morphological, and locational features: They express high levels of proinflammatory cytokines, contain intracellular lipid droplets, secrete exosomes, and are located within crownlike structures surrounding dying adipocytes. In addition, a subset of ATMs expresses the monocyte marker Ly6C and also accumulates in obese adipose tissue. Since Ly6C is a marker for monocytes, the Ly6C⁺ ATMs most likely represent newly recruited monocyte-derived macrophages undergoing differentiation. As found in aortic wall macrophages, these Ly6C⁺ cells lose expression of Ly6C as they fully differentiate into mature macrophages (Jakubzick et al. 2017). The Ly6C⁺ ATMs are found outside of crownlike structures and can stimulate adipocyte differentiation (Hill et al. 2018). Many of the transcriptomic signature genes of CD9⁺ or Ly6C⁺ ATMs are distinct from in vitro differentiated M1 or M2 macrophages or from each other. Jaitin et al. (2019) conducted unbiased scRNA-seq analyses and found that ATMs can be divided into three subpopulations: one showing transcriptomic signatures of perivascular macrophages and another two subsets with

CD9 expression. In line with the findings of Hill et al. (2018), they reported that the number of CD9⁺ ATMs expands in obesity and can be found within crownlike structures. They further characterized CD9⁺ ATMs using lineage tracing and found that ~80% of the CD9⁺ ATMs are bone marrow derived. Interestingly, CD9⁺ ATMs can be divided into two subpopulations, depending on the expression of the lipid receptor Trem2. Trem2⁺ CD9⁺ ATMs abundantly express genes associated with phagocytosis and lipid metabolism. They termed these cells lipid-associated macrophages (LAMs), and showed that obesity-induced LAM expansion is TREM2 dependent and that *Trem2* KO mice show increased weight gain, glucose intolerance, and dyslipidemia on a HFD, suggesting that TREM2-dependent LAM ATMs can mitigate obesity and metabolic dysregulation.

These CD9⁺ Trem2⁺ ATMs display functional similarities to CD11c⁺, M1-like polarized ATMs, and CD9 expression correlates with CD11c expression, although CD11c⁺ and CD9⁺ populations are not identical (Hill et al. 2018). This suggests that both the CD9⁺ and CD11c⁺ populations might be functionally heterogeneous. Additional studies are required to further define CD11c and CD9 double and single positive and negative populations.

ATMs and the control of local catecholamine levels

Chawla and his colleagues suggested that M2-like polarized ATMs synthesize catecholamines (Nguyen et al. 2011; Qiu et al. 2014). However, this concept was challenged by other groups who reported that ATMs do not produce physiologically relevant levels of catecholamines and do not express the enzyme tyrosine hydroxylase, which is necessary for catecholamine synthesis. Moreover, these groups found IL-4 treatment does not alter energy expenditure and body weight either in cold, ambient, or thermoneutral temperatures (Fischer et al. 2017). As an alternative mechanism for how macrophages might modulate local catecholamine levels, a subset of macrophages, termed sympathetic neuron-associated macrophages (SAMs), are capable of extracellular catecholamine uptake and catabolism (Pirzgalska et al. 2017). SAMs represent another subset of ATMs found in proximity to sympathetic nerves in adipose tissue. In obesity, the number of SAMs increases, contributing to reduced adaptive thermogenic activity. The concept of macrophage-mediated catecholamine catabolism in adipose tissue was also reported by Dixit and his colleagues (Camell et al. 2017), who showed that aging-induced catecholamine resistance is associated with increased ATM catecholamine catabolism. In support of the concept that ATMs regulate local catecholamine levels, systemic depletion of tissue macrophages using clodronate liposomes, but not sympathetic denervation, blocks inguinal WAT beigeing in adipocyte *Fasn* KO mice (Henriques et al. 2020).

Mechanisms of macrophage accumulation The mechanism by which macrophages accumulate in obese adipose tissue involves (1) increased monocyte/macrophage chemotaxis (increased blood monocyte immigration) and decreased ATM emigration (or increased retention), and (2)

higher rates of resident ATM proliferation. In vivo labeling of blood monocytes or resident ATMs have shown that blood monocyte migration into adipose tissue increases in obesity (Lumeng et al. 2007a; Oh et al. 2012). This increase is associated with monocytoysis (Nagareddy et al. 2014) and increased production of chemokines such as CCL2/MCP-1 and leukotriene B4 (LTB4) in visceral adipose tissue (Li et al. 2015). Adipocyte-specific depletion of CCL2 reduces obesity-induced ATM accumulation (Kanda et al. 2006). Moreover, genetic deletion or pharmacological inhibition of the receptors for the chemokines CCL2 (CCR2) or LTB4 (LTB4R) blocks obesity-induced ATM accumulation (Lumeng et al. 2007a; Li et al. 2015). This shows that monocyte chemotaxis into adipose tissue is largely mediated by the CCL2/CCR2 and LTB4/LTB4R systems. In addition to increased chemotaxis, the levels of factors associated with macrophage retention, such as Netrin1 and Sema3E, are increased in obese adipose tissue, inhibiting emigration of ATMs (Shimizu et al. 2013; Wanschel et al. 2013; Ramkhelawon et al. 2014).

In addition to chemotaxis into adipose tissue, ATM accumulation is also due to increased resident ATM proliferation, which can be stimulated by CCL2 (Amano et al. 2014). In subsequent studies, increased ATM proliferation in obese adipose tissue was confirmed by separate groups (Zheng et al. 2016).

Other innate immune cells Although relatively small in number, changes in other innate immune cell types also contribute to the development of adipose tissue inflammation, mainly by regulating ATM polarization and function. For example, innate lymphoid cell type 1 (ILC1) cells, including natural killer cells, reside in normal/lean adipose tissue and contribute to adipose tissue homeostasis (Lee et al. 2016; Boulenouar et al. 2017; Theurich et al. 2017). In obesity, the number of ILC1 cells increases and ILC1-derived cytokines, including IFN γ , stimulate proinflammatory activation of ATMs. On the other hand, the number of ILC2 cells producing Th2 cytokines decreases in obesity (Molofsky et al. 2013; Nussbaum et al. 2013). ILC2-derived cytokines support immigration and maturation of eosinophils in adipose tissue, which produce IL-4 and IL-13 that stimulate M2-like macrophage polarization (Wu et al. 2011). In obese adipose tissue, decreased ILC2 cells are associated with decreased local eosinophil numbers. Finally, the recruitment of neutrophils into adipose tissue increases in obesity, and factors released from neutrophil granules, such as neutrophil elastase and myeloperoxidase, can contribute to the development of insulin resistance (Talukdar et al. 2012; Tam et al. 2020).

Adaptive immune cells Several types of adaptive immune cells are also involved in adipose tissue inflammation. In obesity, the number of adipose tissue CD8⁺ T cells increases, and factors released from these cells can facilitate ATM differentiation and chemotaxis (Nishimura et al. 2009). Among CD4⁺ T cells, the number of proinflammatory T helper (Th) 1 cells increases (Nishimura et al. 2009), whereas the adipose tissue content of anti-inflammatory Th2 cells decreases in obesity,

contributing to increased adipose tissue interferon γ (IFN γ) levels and inflammation (Winer et al. 2009). Tregs (CD3⁺CD4⁺FOXP3⁺) are another CD4⁺ T-cell subset well studied in adipose tissue (Feuerer et al. 2009; Li et al. 2020). There are only a small number of these cells in young mice, but they start to accumulate in visceral adipose tissue at the age of 10–15 wk, due to increased proliferation and decreased turnover. Tregs represent the major CD4⁺ T-cell subset (40%–80% of total CD4⁺ T cells) by 20–30 wk of age in normal mice (Bapat et al. 2015). Tregs control the activity of other T cells and restrain the innate immune system by inhibiting monocyte immigration and proinflammatory polarization. In obesity, the number, or proportion, of adipose tissue Treg cells decreases, contributing to increased adipose tissue inflammation (Feuerer et al. 2009). Adipose tissue Tregs show a unique transcriptional profile distinct from Tregs in other sites, which is largely regulated by peroxisome proliferator-activated receptor γ (PPAR γ). Indeed, >80% of adipose tissue Tregs express PPAR γ , which is unique to adipose Tregs, and Treg PPAR γ mediates a component of the anti-inflammatory effects of thiazolidinediones (TZDs) in obese mice (Cipolletta et al. 2012). $\gamma\delta$ T cells abundant in adipose tissue of normal mice support sympathetic innervation and Treg expansion by releasing IL-17 (Kohlgruber et al. 2018; Hu et al. 2020).

Invariant natural killer T (iNKT) cells account for 10%–30% of all adipose tissue-resident T cells (Huh et al. 2013). These are innate-like $\alpha\beta$ T cells that are specifically stimulated by lipid antigens through the major histocompatibility complex (MHC)-like molecule CD1d (Huh et al. 2013; Lynch 2014). iNKT cells release IL-10, IL-4, IL13, and IL-2, potentiating M2-like polarization of ATMs. The number of adipose tissue iNKT cells decreases in obesity, and this could contribute to the development of inflammation. However, other reports cast doubt on the beneficial effects of iNKT cells. For example, Satoh et al. (2016) and Wu et al. (2012b) have shown proinflammatory and negative metabolic effects of iNKT cells in obese mice. As a possible explanation for these contradicting results, scRNA-seq analysis found that adipose tissue iNKT cells can be functionally divided into two subsets, depending on NK1.1 expression: NK1.1⁺ iNKTs are proinflammatory and produce IFN γ , whereas NK1.1[−] iNKTs are anti-inflammatory and produce IL-10 (LaMarche et al. 2020).

B lymphocytes account for 3%–10% of SVCs in normal adipose tissue and increase up to twofold in obesity or 10-fold in aged mice (Camell et al. 2019). Compared with the spleen and bone marrow, adipose tissue B cells show a higher B1:B2 ratio in normal mice. However, in obesity, the B1:B2 ratio decreases with increased recruitment of proinflammatory B2 cells (Ying et al. 2017b). B2 recruitment into obese visceral adipose tissue is mainly mediated by the LTB4/LTB4R1 system (Ying et al. 2017b; Srikakulapu and McNamara 2020), and these cells can contribute to adipose tissue inflammation and metabolic dysfunction in obesity.

Acute versus chronic inflammation While numerous studies have shown the detrimental effects of chronic adi-

pose tissue inflammation on the development of systemic insulin resistance in obesity, inflammation is a physiological process necessary for defense against pathogenic invasion or tissue damage and repair. Acute inflammation is necessary to maintain normal adipose tissue function by mediating healthy adipose tissue remodeling to safely accommodate excess lipids into adipose tissue (Wernstedt Asterholm et al. 2014). For example, Zhu et al. (2020) reported that inhibition of inflammatory pathways by inducible overexpression of an adenoviral protein, called RID α/β (which blocks several inflammatory signaling pathways) reduces weight gain and adiposity and exacerbates glucose and insulin intolerance in HFD/obese mice. Therefore, it is likely that acute adipose tissue inflammation is necessary for adipose tissue homeostasis, whereas chronic inflammation contributes to the development of insulin resistance and adipose tissue dysfunction.

Liver

Hepatic macrophages Obesity, or a HFD, leads to hepatic steatosis commonly referred to as nonalcoholic fatty liver disease (NAFLD), which can proceed to a condition termed nonalcoholic steatohepatitis (NASH). Obesity is also associated with increased hepatic inflammation, and macrophages are the major source of the proinflammatory cytokines (Stienstra et al. 2010; Xu et al. 2014). Injection of gadolinium or intravenous clodronate liposomes selectively depletes hepatic macrophages owing to the fenestrated hepatic sinusoidal structure. Selective depletion of hepatic macrophages improves insulin resistance and liver steatosis in obese mice or rats (Huang et al. 2010; Lanthier et al. 2010; Lee et al. 2011b; Reid et al. 2016). Liver macrophages can be divided into two major subsets based on their developmental origin: These include yolk-sac-derived resident Kupffer cells (KCs) and bone marrow-derived recruited hepatic macrophages (RHMs). In normal liver, hepatic macrophages account for ~10% of all hepatic cells, and the majority of them are KCs (Bouwens et al. 1986). In obesity, the number of KCs is unchanged, whereas circulating monocyte chemotaxis and differentiation into macrophages (RHMs) increase, largely through the CCL2/CCR2 system (Obstfeld et al. 2010; Morinaga et al. 2015). While both KCs and RHMs are highly heterogeneous, RHMs express higher levels of M1-like polarized macrophage markers and proinflammatory gene expression, which is exacerbated in obesity (Arkan et al. 2005; Morinaga et al. 2015; Seidman et al. 2020). These results suggest that a major component of obesity-induced liver inflammation can be attributed to increased monocyte infiltration and macrophage differentiation (summarized in Fig. 2).

Recently, single-cell analyses of transcriptomic and epigenetic changes in hepatic macrophages (e.g., scRNA-seq and scATAC-seq) combined with monocyte tracking and KC depletion studies have further elucidated hepatic macrophage phenotypes (Seidman et al. 2020). Thus, in mice fed a NASH-prone HFD, KCs undergo partial loss of their identifying gene expression patterns while gaining a scar-

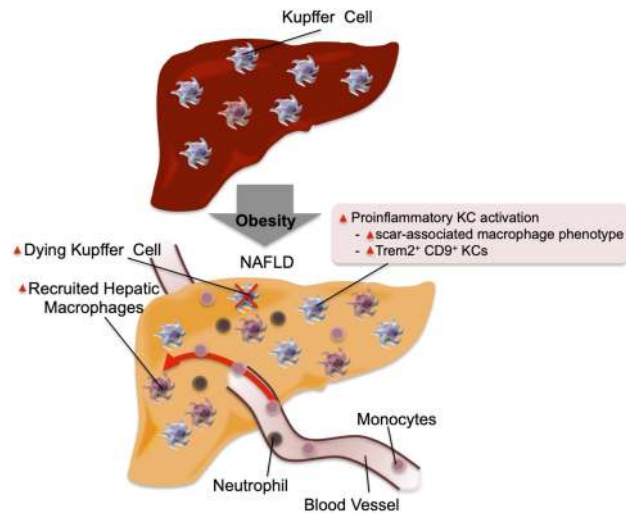


Figure 2. Inflammation in the liver. In the normal physiological state, KCs account for ~10% of all liver cells. In addition, they scavenge pathogens and show M2-like polarized anti-inflammatory phenotype. In obese steatotic livers, KCs can show increased expression of genes associated with tissue repair and inflammation. These genes include *Cd9* and *Trem2*. This is accompanied by increased KC apoptosis, and a component of KC death is compensated for by increased recruitment of blood monocytes, which differentiate into KC-like macrophages. Chemokines released by steatotic hepatocytes cause increased recruitment of blood monocytes into the liver, which differentiate into proinflammatory macrophages (RHMs) and produce factors that can cause insulin resistance. The recruitment of neutrophils also increases, and the molecules released from neutrophil granules such as neutrophil elastase and myeloperoxidase can induce insulin resistance in hepatocytes.

associated macrophage phenotype with *Trem2* and *Cd9* expression. These changes are accompanied by increased KC apoptosis. As these KC numbers decline, they are replaced by monocyte-derived macrophages that undergo convergent epigenomic and transcriptomic changes and become new KC-like cells.

Other hepatic immune cells The number of neutrophils is also increased in the liver of obese mice compared with lean/normal mice (Talukdar et al. 2012), and neutrophil-derived cytokines and chemokines contribute to the development of obesity-induced liver inflammation. Moreover, NE released from neutrophils can be taken up by hepatocytes and cause degradation of IRS-2, promoting decreased insulin sensitivity.

Among adaptive immune components, the number of CD8⁺ cytotoxic T cells increases in the liver of obese mice compared with lean mice through an IFN γ -dependent signaling pathway (Ghazarian et al. 2017). On other hand, the numbers of CD4⁺ T cells, Tregs, and $\gamma\delta$ T cells decrease or remain unchanged in obesity.

Communication between liver cell types Obesity-induced changes in the liver leading to the development of insulin resistance and NASH involve interactions be-

tween intrahepatic cell types such as hepatocytes, various immunocytes, and hepatic stellate cells (Koyama and Brenner 2017). For example, activation of hepatocyte JNK, IKK β , or IKK ϵ or the unfolded protein response (ER stress) increases production of chemokines and other hepatokines, stimulating KC proinflammatory activation and circulating monocyte and neutrophil recruitment (Arkan et al. 2005; Seki et al. 2012; Reilly et al. 2013; Lee et al. 2018). The incoming immune cells are highly proinflammatory (Morinaga et al. 2015; Seidman et al. 2020), enhancing liver inflammation. Hepatocyte and immunocyte-derived factors such as TGF β can activate quiescent stellate cells and induce secretion of collagen, leading to liver fibrosis (Hellerbrand et al. 1999; Koyama and Brenner 2017). Moreover, activated stellate cell-derived cytokines and chemokines can enhance liver inflammation, exacerbating liver steatosis and fibrosis (Weiskirchen and Tacke 2014). Please see Koyama and Brenner (2017) and Arab et al. (2018) for excellent reviews on the pathophysiology of NAFLD and NASH.

Muscle

Skeletal muscle accounts for the majority of in vivo insulin-stimulated glucose disposal, and this is decreased in obesity/T2DM, contributing to the development of compensatory hyperinsulinemia and glucose intolerance. Several mechanisms such as mitochondrial dysfunction, microvascular dysfunction, and ectopic fat accumulation (or lipotoxicity) have been proposed as causes of this defect and are well reviewed elsewhere (Serné et al. 2007; Roden and Shulman 2019; Sergi et al. 2019). While relatively less studied compared with adipose tissue and liver, proinflammatory pathways are enhanced with increased macrophage infiltration in skeletal muscle of obese mice and T2DM patients compared with normal mice or human subjects (Fink et al. 2014). Systemic depletion of macrophages or genetic modifications suppressing proinflammatory activation of macrophages improves insulin sensitivity in skeletal muscle in mice (Patsouris et al. 2008; Han et al. 2013), suggesting that inflammation plays a causative role in the development of muscle insulin resistance. Consistent with this, treatment with proinflammatory cytokines induces insulin resistance in cultured myocytes or skeletal muscle in vivo (de Alvaro et al. 2004; Plomgaard et al. 2005). On the other hand, the anti-inflammatory cytokine, IL-10, can play a protective role. For example, muscle-specific overexpression of IL-10 mitigates and muscle-specific deletion of *Il10* exacerbates obesity-induced muscle inflammation and insulin resistance (Hong et al. 2009; Dagdeviren et al. 2016).

With respect to mechanisms of muscle inflammation, intermyocellular adipose tissue (IMAT) or perimuscular adipose tissue (PMAT) have been implicated (Khan et al. 2015). Thus, in obesity, IMAT and PMAT expand and show macrophage accumulation, similar to visceral adipose tissue. As in visceral adipose tissue, the majority of macrophages infiltrated into obese skeletal muscle are CD11c⁺ M1-like polarized macrophages. Moreover, the

changes in the proportion of different T-cell subsets (e.g., increased Th1 cells and decreased Tregs) show similar patterns as seen in visceral adipose tissue (Wu and Ballantyne 2017).

Pancreatic islets

β -Cell dysfunction is a critical etiologic component of T2DM, and a variety of mechanisms for this defect have been identified (for reviews, see Halban et al. 2014; Hudish et al. 2019). Several reports have shown islet inflammation can also be etiologically important in causing β -cell dysfunction in T2DM. The expression of proinflammatory cytokines (such as IL-1 β , IL-33, IL-23, and IL-24) and macrophage infiltration is increased in the islets of obese/T2DM patients compared with normal subjects (Ehshes et al. 2007; Böni-Schnetzler et al. 2008; Richardson et al. 2009; Mahdi et al. 2012; Butcher et al. 2014; Hasnain et al. 2014; Kamata et al. 2014; Schludi et al. 2017). Treatment of isolated human islets with proinflammatory cytokines reduces glucose-induced intracellular Ca²⁺ levels and GSIS (Corbett et al. 1993; O'Neill et al. 2013), and induces β -cell death (Brozzi et al. 2015). Unlike T1DM islets, obesity- or T2DM-associated islet inflammation is dominated by macrophages and does not involve T-cell infiltration (Ehshes et al. 2007). The concept that islet inflammation induces β -cell dysfunction was more extensively tested in rodent studies. Systemic depletion of macrophages by intraperitoneal injection of clodronate liposomes potentiates glucose-stimulated insulin secretion (GSIS), as well as insulin sensitivity in obese mice (Eguchi et al. 2012). *Ex vivo* depletion of macrophages within primary islets isolated from HFD/obese mice enhances GSIS (Eguchi et al. 2012; Ying et al. 2019). Treatment of primary mouse islets with proinflammatory cytokines (e.g., IL-1 β , IL-23, IL-24) reduces GSIS (Mahdi et al. 2012; Jourdan et al. 2013; Hasnain et al. 2014). Moreover, Myd88 or TLR4 KO mice are protected from β -cell dysfunction induced by subchronic lipid infusion (lipotoxicity) (Eguchi et al. 2012), while β -cell-specific IL-1 receptor antagonist (IL-1Ra) KO mice develop β -cell dysfunction (Böni-Schnetzler et al. 2018).

While similar to adipose tissue and liver inflammation in causing functional defects in parenchymal cells (in this case, β cells), there is a sharp difference in the mechanism for macrophage accumulation in obese islets compared with liver and adipose tissue. Thus, in the liver and adipose tissue, macrophage expansion largely involves recruitment of circulating monocytes (Weisberg et al. 2003; Morinaga et al. 2015; Jaitin et al. 2019; Seidman et al. 2020a), with a smaller component due to resident macrophage proliferation (Amano et al. 2014). In islets, macrophage accumulation is largely mediated by resident islet macrophage proliferation (Ying et al. 2019). Blood monocytes are recruited to the peri-islet region but do not enter the islet capsule (Eguchi et al. 2012; Ying et al. 2019).

In islets, there are two resident macrophage populations (intraislet and peri-islet macrophages) showing distinct anatomical distribution, phenotypes, and functional prop-

erties (Ying et al. 2019). These islet macrophages show a unique transcriptomic profile distinct from M1- or M2-like polarized macrophages or other tissue resident macrophages. Intraislet macrophages substantially proliferate in obesity, whereas peri-islet macrophages lining the islet capsule do not. Moreover, intraislet macrophages, but not peri-islet macrophages, inhibit β -cell insulin secretion. This effect of intraislet macrophages is mediated by a cell-cell contact-dependent mechanism, involving the engulfment of β -cell insulin secretory vesicles. In addition, proinflammatory cytokines produced from islet macrophages also suppress β -cell GSIS (Maedler et al. 2002; Eguchi et al. 2012). For example, IL-1 β produced from islet macrophages binds to the IL-1 receptor (IL-1R), which is abundantly expressed on β cells, leading to decreased GSIS through stimulation of the JNK and NF- κ B signaling pathways (Kwon et al. 1998; Larsen et al. 2005; Ortis et al. 2006; Wang et al. 2009). Furthermore, islet macrophages (both intraislet and peri-islet) release growth factors such as PDGF and IGF-1, simulating β -cell proliferation (Ying et al. 2019; Nackiewicz et al. 2020). Therefore, it is likely that obesity-associated islet inflammation induces decreased β -cell GSIS and promotes the β -cell proliferation that exists in obese islets. This results in changes to islet function favoring increased basal insulin secretion and decreased GSIS.

One can question whether increased β -cell proliferation by islet macrophages is necessarily detrimental to metabolic homeostasis. Indeed, although adverse effects of islet inflammation on GSIS and β function were reported in chronic obese inflammatory states, inflammation is a physiological process, and acute islet inflammation may be beneficial for the maintenance of islet function in the normal state (Banaei-Bouchareb et al. 2004; Geutskens et al. 2005; Yano et al. 2007; Kayali et al. 2012; Lee et al. 2013; Dror et al. 2017; Burke et al. 2018; Riopel et al. 2018; Ying et al. 2019). Therefore, it is possible that acute inflammation is necessary to maintain islet function, whereas chronic inflammation contributes to the development of β -cell dysfunction.

GI tract

Recent advances in our understanding of the gut microbiota have provided potential new insights as to how obesity affects tissue inflammation and metabolic defects. In both human and rodent obesity, the composition of the gut microbiota changes (dysbiosis), which can modify the host immune system and metabolism. HFD/obese WT mice display increased proinflammatory cytokine expression and IL17-producing $\gamma\delta$ T cells, Th1 cells, CD8⁺ T cells, macrophages, and dendritic cells, along with decreased Tregs, ILC3 cells, and eosinophils in the intestinal lamina propria (Johnson et al. 2015; Monteiro-Sepulveda et al. 2015; Winer et al. 2016). Fecal transplantation experiments and clinical trials further showed that dysbiosis contributes to the development of inflammation and insulin resistance in obesity. For example, transplantation of germ-free mice with fecal preparations from human twins discordant for obesity showed that the obese gut

microbiota can induce increased weight gain, adipose tissue mass, and glucose intolerance (Ridaura et al. 2013). Moreover, a clinical study found that administration of intestinal microbiota from lean donors to recipients with metabolic syndrome improved insulin sensitivity (Vrieze et al. 2012). These studies suggest that a component of the obesity-associated metabolic phenotype is due to dysbiosis. Nonetheless, it should be noted that the effects of fecal transplantation were small, and healthy gut microbiome transfer does not normalize the metabolic defects induced by obesity.

In this context, several gut microbiota-derived molecules/mechanisms that can modify host immune tone and metabolism have been reported. For example, in obesity or shortly after a HFD, gut permeability increases, allowing bacterial translocation across the intestinal barrier (Neal et al. 2006; Amar et al. 2011; Ha et al. 2020). Moreover, increased gut permeability also allows gut microbiota-derived molecules, such as lipopolysaccharide (LPS), to leak into the blood circulation (Erridge et al. 2007; Kumar et al. 2011). Increased LPS-stimulated TLR4 induces proinflammatory responses in various immune cells, gut epithelial cells, and insulin target cells, resulting in insulin resistance and glucose intolerance (Shi et al. 2006; Saberi et al. 2009; Guo et al. 2013; Tao et al. 2017). Plasma levels of another gut microbiota-derived molecule, formyl-methionyl-leucyl-phenylalanine (*N*-formyl peptides), are also elevated in HFD/obese mice. Genetic deletion or pharmacological inhibition of the *N*-formyl peptide receptor Fpr1 improves glucose tolerance by increasing glucagonlike peptide 1 secretion from enteroendocrine L cells with a subsequent increase in β -cell GSIS. Of the bioactive metabolites produced by the gut microbiota, short chain fatty acids (SCFAs) are among the most abundant (Stevens and Hume 1998). SCFAs activate G-protein-coupled receptors (GPCRs), including GPR41 and GPR43, which are expressed in adipocytes, enterocytes, immune cells, and pancreatic β cells. Several reports showed beneficial effects of GPR43 activation to reduce adiposity and improve insulin sensitivity, as well as β -cell GSIS in obese mice (Tolhurst et al. 2012; Kimura et al. 2013; McNelis et al. 2015). However, conflicting results were also reported (for review, see Ang and Ding 2016): For example, β -cell-specific depletion of both GPR41 and GPR43 increases GSIS and improves glucose tolerance in mice (Tang et al. 2015). In addition to SFAs, secondary and tertiary bile acids produced by gut microbes alter the composition of the bile acid pool (Brufau et al. 2010; Suhre et al. 2010; Haeusler et al. 2013; Ridaura et al. 2013; Yoshimoto et al. 2013) and modulate inflammation and metabolism by stimulating the bile acid receptor 1 (TGR5) and farnesoid X receptor (FXR) (Pols et al. 2011; Wollam and Antebi 2011).

Taken together, the GI tract plays a role in obesity-associated chronic tissue inflammation and metabolic dysregulation. One obvious mechanism is that the development of obesity leads to increased gastrointestinal permeability, such that proinflammatory bacterial products (e.g., LPS), and even bacteria themselves, gain access to surrounding lymph nodes and the systemic circulation.

In addition, the dysbiosis of obesity provides another potential mechanism in which specific GI bacterial species, or combinations of species, can contribute to meta-inflammation. The latter is clear in mice but will require further translational validation in humans. This is a promising field, since further studies could identify specific factors that might be useful in drug discovery.

Hypoxia as initiating event

As noted above, it is well known that obesity leads to an accumulation of proinflammatory macrophages in adipose tissue in both mice and humans. These ATMs are key drivers of the development of insulin resistance and glucose intolerance. Areas of current active interest focus on how macrophage accumulation is initiated at the onset of obesity and how do proinflammatory ATMs cause systemic metabolic dysfunction. Several studies have been published, providing important insights into these questions. In this section, we attempt to integrate these new insights into an overall sequential hypothesis.

For years, it has been known that adipose tissue oxygen tension is decreased in obesity in both mice and humans (Hosogai et al. 2007; Halberg et al. 2009; Pasarica et al. 2009, 2010; Lawler et al. 2016; Seo et al. 2019; Smith et al. 2019). The initial view was that this adipose tissue hypoxic state was due to an imbalance between expanding adipose tissue mass and the available oxygen delivery. However, tissue oxygen tension is maintained by the balance between oxygen supply and demand, and more recent data show that obesity leads to increased adipocyte oxygen consumption (Lee et al. 2014). This increased consumption accounts for ~40% of the decrease in interstitial oxygen tension in obesity (Seo et al. 2019). The remaining component of the decreased interstitial oxygen tension is not due to decreased arterial oxygen delivery (blood flow into adipose depot and blood O₂ saturation) but is explained by decreased functional capillary density in obese adipose tissue (Lee et al. 2014). Therefore, there are two components, decreased capillary density and increased adipocyte oxygen consumption, that contribute to the relative hypoxia of adipose tissue in obesity. As a general matter, hypoxic conditions lead to greater expression of the adipocyte HIF-1 α transcription factor, triggering the downstream hypoxia transcriptome response. However, the induction of HIF-1 α does not occur until oxygen tensions fall to $\leq 1\%$ (Seo et al. 2019). Therefore, the decrease in extracellular adipose tissue oxygen tension described in obesity is probably not enough to trigger the HIF-1 α hypoxic response. On the other hand, the increase in adipocyte oxygen consumption is quite marked in obesity, bringing the intra-adipocyte oxygen concentration down to levels below ~1.4%. This is adequate to induce adipocyte HIF-1 α expression and the downstream effects mediated by this transcription factor (Hosogai et al. 2007; Halberg et al. 2009; Lee et al. 2014). This view is supported by the finding that hypoxia-induced pimonidazole adducts in obese adipose tissue are confined to adipocytes (Lee et al. 2014). Taken together, obesity-induced

increased adipocyte oxygen consumption is likely the major contributor to the intracellular adipocyte hypoxic response, whereas the decreased interstitial oxygen tension probably plays a contributory or permissive role to exaggerate the impact of increased adipocyte oxygen consumption.

The mechanisms by which intracellular oxygen levels regulate HIF-1 α have been well described and occur mainly at the protein level with smaller effects on mRNA expression (Ivan and Kaelin 2017; Schödel and Ratcliffe 2019; Semenza 2019). In normoxic conditions, prolyl hydroxylase domain proteins (PHDs) bind to HIF-1 α , and PHD-dependent hydroxylation of HIF-1 α leads to ubiquitin-dependent proteasomal degradation of the protein. Under hypoxia, PHDs are inactivated, which results in HIF-1 α protein stabilization, causing increased HIF-1 α protein expression. Although this is the major driver for regulation of HIF-1 α expression, in obesity, modest increases in HIF-1 α mRNA have also been reported as a contributing factor (Lee et al. 2014).

This induction of adipocyte HIF-1 α plays an important role in mediating overall adipose tissue inflammation (Lee et al. 2014). This can occur through multiple mechanisms. For example, several chemokines are downstream transcription targets of HIF-1 α , and expression of these chemokines is increased in obesity and other hypoxic conditions. These chemokines serve to recruit monocytes into the hypoxic adipose tissue, which then predominantly differentiate into proinflammatory, M1-like ATMs. As discussed in more detail above, the increase in M1-like ATMs is a key mechanism for the metabolic dysfunction characterized by insulin resistance and glucose intolerance in obesity (Fig. 3). There are many studies in which various proinflammatory genes have been deleted in macrophages, and all of these studies consistently show amelioration of obesity-induced metabolic dysfunction (Arkan et al. 2005; Weisberg et al. 2006; Saberi et al. 2009; Han et al. 2013; Li et al. 2015). Consistent with this formulation, the central role of HIF-1 α in the proinflammatory responses leading to insulin resistance has been shown through cell type-specific knockout studies (Jiang et al. 2011; Lee et al. 2011a, 2014; Krishnan et al. 2012; Sun et al. 2013). Thus, adipocyte-specific HIF-1 α knockout largely prevents obesity-induced ATM accumulation, adipose tissue inflammation, glucose intolerance, and insulin resistance but does not cause any change in overall body weight. This highlights the importance of HIF-1 α in the overall adipose tissue inflammatory response, consistent with the idea that obesity-induced intracellular adipocyte hypoxia leads to HIF-1 α induction, which in turn promotes ATM accumulation, inflammation, and subsequent glucose intolerance and insulin resistance.

The mechanisms underlying obesity-induced increased adipocyte oxygen consumption are also of interest. Adenine nucleotide translocase (ANT) 2 is a mitochondrial inner-membrane protein that pumps protons from the intermembrane space into the mitochondrial matrix (Bertholet et al. 2019). Therefore, an increase in ANT2 activity results in proton leakage from the intermembrane

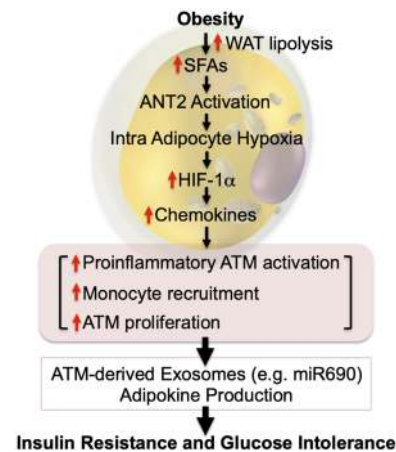


Figure 3. Intracellular adipocyte hypoxia triggers inflammation and insulin resistance. In obesity, increased intracellular FFAs stimulate ANT2-dependent increased mitochondrial uncoupled respiration in adipocytes. Combined with decreased functional capillary density, this leads to intracellular hypoxia and HIF-1 α stabilization. HIF-1 α induces increased chemokine production, leading to increased immune cell infiltration, including monocytes, and increased ATM proliferation. These changes critically affect ATM exosome secretion, as well as adipocyte exosome and adipokine production, causing systemic insulin resistance. Most of these sequential events have been shown in mouse models. This hypothesis remains to be validated in humans.

space, leading to uncoupled mitochondrial respiration with enhanced O₂ consumption. It should be noted that another important uncoupling protein, UCP1, is not expressed in white adipocytes (Cousin et al. 1992; Wu et al. 2012a). Adipose tissue SFA levels are elevated in obesity, and SFAs can activate ANT2-dependent uncoupling of oxidative metabolism, leading to increased adipocyte oxygen consumption (Lee et al. 2014). In theory, increased fatty acid oxidation could also lead to greater oxygen consumption, but more detailed studies have shown that this component is rather negligible compared with the direct effect of SFAs to activate ANT2 protein. To further solidify this overall concept, deletion of ANT2 in adipocytes can reverse all of these hypoxic responses. Thus, adipocyte-specific ANT2 KO is sufficient to block the obesity-induced increased adipocyte O₂ consumption, ameliorating the adipocyte hypoxia response and preventing HIF-1 α induction (Seo et al. 2019). This mitigates the development of adipose tissue inflammation with reduced proinflammatory ATM content and decreased expression of inflammatory pathway genes. This is accompanied by a robust improvement in glucose tolerance and insulin sensitivity in obese mice without any changes in body weight.

How does adipose tissue inflammation cause insulin resistance?

The fact that increased obesity-induced proinflammatory ATM content can directly cause insulin resistance is well

established, at least in mice, but precisely how M1-like macrophages lead to decreased insulin sensitivity is not entirely clear and has been the subject of intense investigation. A logical presumption is that proinflammatory macrophages release factors that can cause paracrine or systemic effects on insulin target cells to impair insulin signaling. Classically, M1-like polarized macrophages release a variety of cytokines and chemokines. Chemokines act by providing a concentration gradient in which monocytes and other types of immune cells can migrate down that gradient toward the chemokine source; this is the operational definition of chemotaxis. In obese states, some of these chemokines produced in adipose tissue can leak into the circulation. However, circulating chemokines are not able to generate a differential concentration gradient to promote chemotaxis of monocytes out of the circulation into inflamed tissues. In addition, the circulating levels of chemokines due to this “spillover” are generally much lower than the biologically effective concentrations, so they will not have meaningful systemic physiologic effects. Even if a particular chemokine can cause decreased insulin signaling in vitro (Sartipy and Loskutoff 2003), it would still be a challenge to conclude that such a chemokine could act systemically, since the circulating systemic concentrations are so low.

More attention has been placed on secreted cytokines, since it is well known that certain cytokines (e.g., TNF α) have potent effects to cause decreased insulin signaling. TNF α can cause local tissue effects to decrease insulin action (Hotamisligil et al. 1994) by several mechanisms. TNF α can reduce *Irs2* and *Glut4* expression, promote inhibitory phosphorylation of insulin receptor substrate (IRS) proteins, enhance adipocyte lipolysis (FFA release) and ceramide synthesis, and inhibit PPAR γ expression (Stephens et al. 1997; Guilherme et al. 2008). This phenomenon could occur in the various adipose tissue depots, which become enlarged and inflamed during the course of obesity (TNF α is used as an example, since it is the most well studied immune cell-derived cytokine). However, systemic insulin resistance requires decreased insulin sensitivity in muscle and the liver, as well as adipose tissue, and unless muscle and the liver are generating high levels of tissue cytokines, it is unlikely that TNF α or other cytokines that leak out of obese adipose tissue could cause systemic effects. Thus, the circulating concentrations of TNF α and other cytokines are substantially below the levels needed to exert biologic effects in tissues (Stephens et al. 1997; Amar et al. 2007; McGillicuddy et al. 2011). In contrast, adipose tissue levels of cytokines can be quite elevated in obesity, and this could cause local effects. If one administers large amounts of TNF α in vivo, raising circulating levels far higher than they normally exist in obesity, then an insulin-resistant state ensues (Lang et al. 1992). However, this does not mirror the actual pathophysiologic state in obesity in which cytokine levels in the blood, while higher than in normals, are not elevated to levels at which they exert substantial biologic effects. IL-6 may be an exception to this general principle, since the levels of IL-6 that enter the circulation in obesity have been reported to be biologically active. However,

studies of IL-6's metabolic activities are mixed with some studies showing insulin-like actions to improve insulin sensitivity, while others report that it inhibits insulin action (Carey et al. 2006; Franckhauser et al. 2008).

Given the above discussion, many laboratories have been trying to identify other factors that are elaborated from M1-like macrophages that could cause metabolic dysfunction. One such factor is Galectin-3. Galectin-3 is produced almost exclusively from macrophages, and in both human and mouse obesity, blood levels are quite high compared with normals and are in the range where they exert biologic effects (Li et al. 2016). Indeed, in humans, circulating levels of Galectin-3 are elevated compared with normal subjects, and the degree of the increase in Galectin-3 levels is correlated with the magnitude of obesity and the degree of insulin resistance. In vitro studies show that Galectin-3 treatment of insulin target cells can directly cause decreased insulin signaling by interfering with the ability of insulin to properly activate the insulin receptor at the cell surface. Loss-of-function studies have been performed by analyzing macrophage-specific Galectin-3 KO mice. Depletion of macrophage Galectin-3 protects HFD mice from the development of glucose intolerance and insulin resistance, while weight gain is entirely normal. Additional gain- and loss-of-function studies with Galectin-3 are consistent with this formulation, suggesting that macrophage-derived circulating Galectin-3 can contribute to the development of insulin resistance in obesity.

The above considerations have led to a search for additional factors that can enter the circulation from obese adipose tissue and cause systemic insulin resistance. Indeed, recent studies suggest that ATM-derived exosomes might fulfill this role. Exosomes are small nanoparticles (~150 nm) produced by most cell types (Pegtel and Gould 2019). They can be secreted into the interstitial space where they then enter the circulation leading to both paracrine and endocrine-like effects. Exosomes contain a variety of cargo constituents including proteins, lipids, microRNAs (miRNAs), and mRNAs, as well as a number of other RNA species. Recent studies have shown that exosomes derived from ATMs in obese mice can directly cause insulin resistance in vitro when applied to adipocytes, primary hepatocytes, or myocytes (Ying et al. 2017a). These “obese” ATM-derived exosomes can be harvested and administered intravenously to lean mice. When this was done, the lean recipient mice developed glucose intolerance, hyperinsulinemia, and insulin resistance comparable with that seen in the obese state. Importantly, eating behavior and body weight do not change as a result of in vivo exosome treatment. On the other side of this coin, ATM exosomes harvested from chow-fed lean mice produce the opposite phenotype. Treatment of adipocytes, myocytes, or primary hepatocytes with “lean” ATM exosomes directly leads to increased insulin signaling. More importantly, when obese mice were treated with “lean” ATM-derived exosomes for a period of 3 wk, these mice showed markedly improved glucose tolerance with an increase in insulin sensitivity. In a very real sense, these “lean” ATM exosomes produce a therapeutic

response, mitigating metabolic dysfunction in obesity. With respect to mechanisms, these studies also showed that the biologic effects of obese and lean ATM exosomes are entirely mediated by their miRNA cargo, since depletion of exosomal miRNAs prevents all of these exosome-mediated actions (Fig. 4).

Recent studies have honed in on the specific miRNAs that can produce these beneficial “therapeutic” effects in mice. By conducting complete sequencing of M2-like ATM-derived exosomes, coupled with a bioinformatics approach and screening of specific mRNAs upregulated in lean ATM-derived exosomes, miR-690 was identified as an insulin-sensitizing miRNA. Thus, deletion of miR-690 prevents the beneficial effects of M2-like macrophage exosomes, and an artificial miR-690 mimic reproduces the beneficial effects of lean ATM exosomes on insulin sensitivity and glucose intolerance. In addition, an inhibitor (antagomir) of miR-690 completely blocks the effects of the miR-690 mimic. Thus, miR-690 emerges as a bona fide insulin-sensitizing molecule in both mouse and human cells, and if translational studies are successful, this molecule could potentially lead to an insulin-sensitizing therapeutic.

A comprehensive study from Thomou et al. (2017) identified the presence of several hundred miRNAs in blood exosomes in WT mice. When they studied adipocyte-specific Dicer KO mice, to deplete all miRNAs from any adipocyte-derived exosomes that enter the circulation, they

found that ~60% of the circulating miRNAs were reduced, indicating that adipocytes make important quantitative contributions to the circulating exosome pool. This study also found that miR-99b is highly expressed in exosomes released from brown adipocytes and that miR-99b can inhibit hepatic expression of FGF21, and suggested that the decrease in circulating FGF21 levels is linked to the improved glucose tolerance they observed in the adipocyte Dicer KO mice. Based on miRNA sequencing studies, it is important to note that there is a marked difference in miRNA composition between ATM versus adipocyte-derived exosomes, with only an ~20% overlapping concordance (Thomou et al. 2017; Ying et al. 2017a). This further emphasizes the necessity to understand the function of cell type-specific exosomes in metabolic disease.

Exosomes are a component of a more diverse group of secreted particles termed extracellular vesicles (EVs). There are several additional published studies showing results consistent with the view that EVs/exosomes-derived from obese adipose tissue can affect insulin sensitivity (Kita et al. 2019). For example, obese human adipose tissue EV/exosome preparations displayed differential expression of several miRNAs that can impact insulin signaling. Exosomes harvested directly from obese adipose tissue impair insulin sensitivity, and one study implicated miR141-3P as playing a causative role (Kranendonk et al. 2014; Dang et al. 2019). It should be noted that in studies using adipose tissue-derived exosomes, one does not know which cell type within adipose tissue is producing the biologically active particles.

Taken together, the above studies lead to the model depicted in Figure 3. This model shows a general sequential hypothesis in which obesity leads to increased SFA activation of ANT2, causing uncoupled respiration with enhanced adipocyte oxygen consumption. This leads to a state of relative hypoxia within the adipocyte, causing HIF-1 α induction and downstream inflammatory responses, including recruitment and accumulation of ATMs and increased expression of a variety of proinflammatory genes. This inflammatory state then can drive the generation of insulin and glucose intolerance, and ATM-derived exosomal miRNAs (particularly miR-690) are at least one mechanism leading to the metabolic dysfunction that characterizes the obese state.

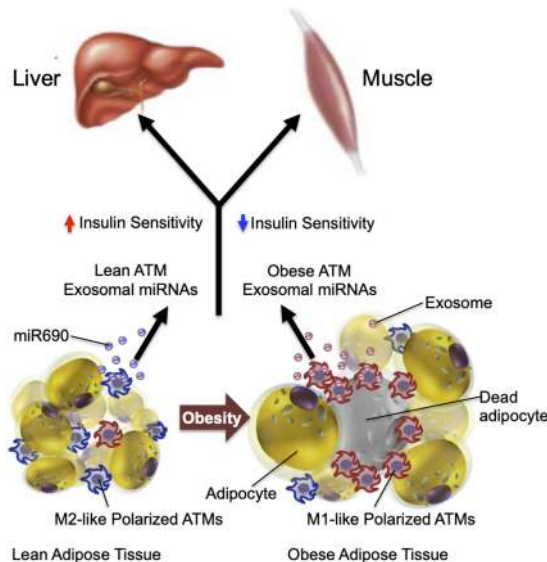


Figure 4. Systemic effect of ATM exosomes. ATMs can regulate systemic insulin sensitivity by releasing miRNA-containing exosomes. Injection of exosomes released from lean mouse ATMs increases insulin sensitivity in obese mice, whereas injection of obese mouse ATM-derived exosomes induces insulin resistance in lean mice. In addition, direct *in vitro* treatment of insulin target cells with “lean” or “obese” exosomes directly causes insulin sensitivity or resistance, respectively. Most of these sequential events have been shown in mouse models. This hypothesis remains to be validated in humans.

Clinical implications

While various genetic gain- and loss-of-function experiments in mice have clearly shown the importance of chronic tissue inflammation in the etiology of insulin resistance and glucose intolerance, the concept remains to be definitively validated in humans. Since these kinds of gene manipulation studies are not possible in humans, we will need to rely on various anti-inflammatory pharmacologic treatment modalities to definitively test this overall concept in humans.

As we refine our mechanistic understanding of the effects of chronic inflammation, more precise tools to test

these overall concepts in humans will hopefully emerge. While this remains to be done, there are currently a number of clinical studies providing data that relate to this issue. For example, there are several reports using inhibitory antibodies directed against TNF α in patients with metabolic disease. These agents obviously have great clinical success in the treatment of rheumatoid arthritis and inflammatory bowel disease (Lin et al. 2020; Vulliamoz et al. 2020), and many patients treated for these other conditions are obese or have T2DM. Some of these patients have been analyzed, and small-scale clinical studies have been reported. Unfortunately, the results of these studies have been variable with no clear-cut conclusions emerging. Some reports note modest improvement in glycemia or insulin sensitivity (Kiortsis et al. 2005; Gonzalez-Gay et al. 2006), whereas others find no effects (Ofei et al. 1996; Paquot et al. 2000; Dominguez et al. 2005; Bernstein et al. 2006; Wascher et al. 2011). Large-scale, randomized, double-blind clinical trials will be necessary to sort out any possible effects of TNF α inhibition in metabolic disease. Perhaps the most promising findings are from a meta-analysis study showing that TNF- α antibody treatment might reduce the risk of developing T2DM (Burska et al. 2015), although, again, this would have to be demonstrated in a prospective study for translational validation. Based on the available data, it is reasonable to suggest that the effects of anti-TNF α treatment may not be clinically robust in metabolic disease, with a number of studies showing marginal or no effects. In the absence of large prospective studies, it is useful to consider why TNF α inhibition might not be highly effective in humans, as it has been in obese mice. One possibility is that in humans, TNF α is not as important for insulin resistance as it appears to be in mice, and this remains to be tested. Another scenario is that cytokines like TNF α work predominantly at the tissue level, rather than through circulating TNF α effects, and it is possible that anti-TNF α biologics do not penetrate adipose tissue at high enough concentrations to sufficiently block the high tissue levels of TNF α in obesity.

Inhibitory antibodies directed against another inflammatory cytokine, IL-1 β , have also been reported. Some of these studies have been larger scale and prospective and have shown small, but consistent, decreases in glucose and HbA1c levels as a result of IL-1 β inhibition (Larsen et al. 2007; Everett et al. 2018). However, these beneficial effects appear to be due to enhanced insulin secretion and β -cell function, rather than an improvement in insulin sensitivity. This may point to the fact that IL-1 β plays a significant role in the development of β -cell dysfunction in T2DM but is not mechanistically relevant to the generation of inflammation-induced insulin resistance. A large-scale prospective clinical study, termed the Cantos trial, has been reported for the treatment of CVD, this study showed clinically meaningful reductions in CV events in the IL-1 β antibody-treated patients (Ridker et al. 2017). Although there were some significant unwanted side effects related to infections, this study does highlight the potential usefulness of anti-inflammatory therapy in atherosclerosis.

Another potential anti-inflammatory mechanism using salicylic acid derivatives has also been studied in the context of insulin resistance and T2DM. Early smaller-scale studies showed promising effects of salsalate treatment to improve insulin sensitivity and reduce glycemia in T2DM (Goldfine et al. 2008). A subsequent larger-scale prospective study has also shown modest reductions on the order of 0.3%–0.5% in HbA1c in diabetes (Goldfine et al. 2010). While these were encouraging, there has been little progress in clinical studies over the past several years with salicylic acid derivative treatment. Furthermore, it should be noted that while salicylates were initially thought to be anti-inflammatory by inhibiting IKK β (Yuan et al. 2001), other studies have questioned whether this is the mechanism of action of this class of drugs. Thus, some reports have shown that salicylates may activate AMPK, accounting for metabolic improvement (Hawley et al. 2012).

Other possible approaches have been suggested. These include development of a small molecule agonist for GPR120 to harness the anti-inflammatory, insulin-sensitizing effects of this signaling cascade. Perhaps inhibitors of circulating Galectin-3 or selective inhibition of monocyte chemotaxis into adipose tissue and/or the liver might also prove useful. Although possible in the future, no clinical development programs related to these mechanisms have yet appeared.

Since hepatic inflammation is an important component of NASH pathophysiology, it is useful to briefly summarize the status of specific anti-inflammatory treatments in this disease. There have been two anti-inflammatory mechanisms tested in NASH: ASK1 inhibition (Harrison et al. 2020) and CCR2/5 inhibition (Ratziu et al. 2020). Although the long-term phase 3 clinical studies failed to show any improvement in fibrosis or NASH scores, it is important to point out that while these might be “potential anti-inflammatory” treatments, in fact, they did not cause any anti-inflammatory effects in the clinical trials. In other words, the NASH scores, which include lobular inflammation, were unchanged in the ASK1 and CCR2/5 inhibitor-treated patients. In grading NASH, inflammation is scored separately on a scale of 1–4 and the average value in these studies was \sim 2. An effective therapy should lower the inflammation score by at least one point in treated subjects, and in these reports, it did not. Therefore, just as in the failure of “anti-inflammatory” treatments for insulin resistance, one must understand that simply referring to a treatment as anti-inflammatory and finding no effect on NASH or insulin resistance does not mean that the treatment was actually anti-inflammatory. The published clinical data simply have not provided an effective anti-inflammatory mechanism to test the hypothesis. In other words, the absence of positive data is not the same as the presence of negative data.

From a translational point of view, it is important to keep in mind that inhibiting inflammatory responses might lead to suppression of specific aspects of the immune system, which might lead to unwanted safety consequences. This needs to be carefully monitored in any clinical development program involving an anti-

inflammatory approach to treat metabolic disease. This also informs the kinds of strategies used to identify drug targets, or drugs, that produce insulin-sensitizing, anti-inflammatory effects. Proximal proinflammatory signals typically activate a number of overlapping and interconnected inflammatory pathways, raising the possibility that targeting a specific distal inflammatory event might have inadequate efficacy if redundant proinflammatory signaling systems are still intact. On the other side of the coin, inhibiting the wider network of inflammatory pathways would probably carry the risk of increased unwanted side effects. In this context, it would be more advantageous to direct a therapy at a specific aspect of the inflammatory response critical to the development of insulin resistance. Obviously, if a drug delivery method were developed that provides tissue selectivity, this would be of great advantage in preventing insulin resistance with less risk of unwanted side effects.

Thiazolidinediones (TZDs) are a highly efficacious class of anti-diabetic drugs that stimulate PPAR γ and ameliorate insulin resistance. TZDs have anti-inflammatory effects by directly inhibiting proinflammatory activation of macrophages, promoting differentiation toward the anti-inflammatory M2-like state (Jiang et al. 1998; Ricote et al. 1998; Bouhlef et al. 2007; Nelson et al. 2018). In addition, TZDs can act on PPAR γ within Tregs, stimulating these cells to restrict inflammation induced by the innate immune system (Cipolletta et al. 2012). On the other hand, TZDs have been studied for many years, and a number of additional mechanisms for TZD/PPAR γ -induced insulin sensitivity have been identified (Tontonoz and Spiegelman 2008). These include stimulation of adiponectin release (Yu et al. 2002; Xia et al. 2018), redistribution of adipose tissue fat storage (de Souza et al. 2001), and induction of direct PPAR γ genes (such as Glut-4) (Young et al. 1995), which mediate insulin signaling. In the *in vivo* clinical situation, it is currently not possible to identify the degree to which TZD-mediated anti-inflammatory effects contribute to the overall insulin-sensitizing, anti-diabetic actions of these agents.

Since obesity is a key pathophysiologic factor in the development of chronic tissue inflammation, insulin resistance, and ultimately T2DM and/or NASH, it is evident that sustained weight loss is a straightforward preventative or treatment modality for these conditions. Unfortunately, while this method of treatment may be straightforward, it is far from easy. There are bariatric surgical approaches, several anti-obesity drug therapies, and numerous forms of lifestyle intervention combining various diets with exercise. Unfortunately, weight loss effects are often short lived, and weight regain (recidivism) is a major unresolved problem with current pharmacologic and lifestyle approaches. Even weight loss after bariatric surgery can wane over time, although, in general, the weight reduction achieved through surgical approaches is far more durable than with lifestyle and drug treatment. Despite the above-mentioned difficulties of sustaining long-term weight loss, it is abundantly clear that weight reduction leads to large therapeutic effects, with respect to decreased tissue inflammation,

amelioration of T2DM, and either prevention or reversal of NAFLD/NASH. Since weight loss leads to these multiple beneficial effects concomitantly, it is not possible to dissect out the contributions of tissue inflammation to the overall metabolic improvement induced by weight loss, since multiple factors are changed with any reduction in adiposity.

As discussed earlier, the presence of increased proinflammatory ATMs, as well as other immune cells, has been well documented in human obesity, as is the presence of increased inflammatory responses in the liver, pancreatic islets, and gastrointestinal tract. At this point, the translational findings are associations and correlations and do not prove causality. Since genetic manipulations are not possible in humans, an effective anti-inflammatory modality will be necessary to test this overall concept. As summarized above, a small number of potential anti-inflammatory approaches have been tried, with limited success. Therefore, the field awaits further specific anti-inflammatory treatments to better understand the role of chronic tissue inflammation in the etiology of metabolic dysregulation in obese humans.

Competing interest statement

The authors declare no competing interests.

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