Immune Regulation of Metabolic Homeostasis in Health and Disease

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Obesity is an increasingly prevalent disease worldwide. While genetic and environmental factors are known to regulate the development of obesity and associated metabolic diseases, emerging studies indicate that innate and adaptive immune cell responses in adipose tissue have critical roles in the regulation of metabolic homeostasis. In the lean state, type 2 cytokine-associated immune cell responses predominate in white adipose tissue and protect against weight gain and insulin resistance through direct effects on adipocytes and elicitation of beige adipose. In obesity, these metabolically beneficial immune pathways become dysregulated, and adipocytes and other factors initiate metabolically deleterious type 1 inflammation that impairs glucose metabolism. This review discusses our current understanding of the functions of different types of adipose tissue and how immune cells regulate adipocyte function and metabolic homeostasis in the context of health and disease. We also highlight the potential of targeting immuno-metabolic pathways as a therapeutic strategy to treat obesity and associated diseases.

Introduction

Obesity is in an increasingly prevalent metabolic disease characterized by excess accumulation of adipose tissue. Obesity increases the risk of developing a wide variety of diseases including but not limited to type 2 diabetes, cardiovascular diseases, and multiple forms of cancer and has been strongly associated with increased mortality (Prospective Studies Collaboration, 2009; Flegal et al., 2013; Oliveros and Villamor, 2008; Pi-Sunyer, 1999; Pontiroli and Morabito, 2011; Reilly and Kelly, 2011; Rodriguez et al., 2001). In the past few decades, the prevalence of obesity has risen dramatically in both industrialized and less industrialized nations across all continents (Kelly et al., 2008; Ng et al., 2014), and this has been associated with high healthcare expenditures (Withrow and Alter, 2011). For example, in the U.S. in 2009–2010, obesity afflicted 36% of adults (Flegal et al., 2012; Ogden et al., 2012, 2014) and accounted for approximately $190 billion in annual healthcare costs, representing nearly 20% of total national healthcare expenditures that year (Cawley and Meyerhoefer, 2012; Finkelstein et al., 2009). More recent statistics indicate that 35% of adults in the U.S. were obese in 2011–2012 but was as high as 48% in some segments of the population (Ogden et al., 2014). Therefore obesity is a critical problem with major health and economic consequences. Increasing our understanding of the pathways involved in the development of obesity will be critical for the development of new intervention strategies to prevent or treat this disease and its associated co-morbidities.

As in many chronic inflammatory diseases, genetic and environmental factors are important for the development of obesity and associated diseases (Bouchard, 2008; Brestoff and Artis, 2013; McCarthy, 2010; Walley et al., 2009). In addition, emerging studies have implicated various cell types of the immune system as critical regulators of metabolic homeostasis (Jin et al., 2013; Lumeng and Saltiel, 2011; Odegaard and Chawla, 2011, 2013b; Osborn and Olefsky, 2012). Seminal studies connecting the immune system to metabolic dysfunction in obesity indicated that tumor necrosis factor-α (TNF-α) production was upregulated in obese mice and that neutralization of TNF-α improved glucose uptake in murine obesity (Hotamisligil et al., 1993). Subsequent studies revealed that mice lacking TNF-α were protected from high-fat-diet-induced insulin resistance (Uysal et al., 1997). Increased TNF-α production was also observed in human obesity, and weight loss in humans was associated with decreased TNF-α levels (Hotamisligil et al., 1995; Kern et al., 1995). Later, it was discovered that pro-inflammatory macrophages accumulate in adipose of obese mice and that these cells were dominant sources of TNF-α to promote insulin resistance (Weisberg et al., 2003; Xu et al., 2003). Collectively, these studies revealed that obesity is associated with chronic low-grade inflammation and suggested that inflammatory responses can have detrimental metabolic consequences. It is now appreciated that in obesity chronic low-grade inflammation occurs in many organs including but not limited to white adipose tissue (WAT), brown adipose tissue (BAT), pancreas, liver, brain, muscle, and intestine (Cildir et al., 2013). Of these, WAT is the most studied organ in terms of immune-metabolic interactions in obesity.

In WAT, which coordinates metabolism at distant tissues such as the brain, liver, pancreas, and muscle, there is a diverse set of immune cells at steady state (Exley et al., 2014; Ibrahim, 2010; McNelis and Olefsky, 2014; Mraz and Haluzik, 2014). This
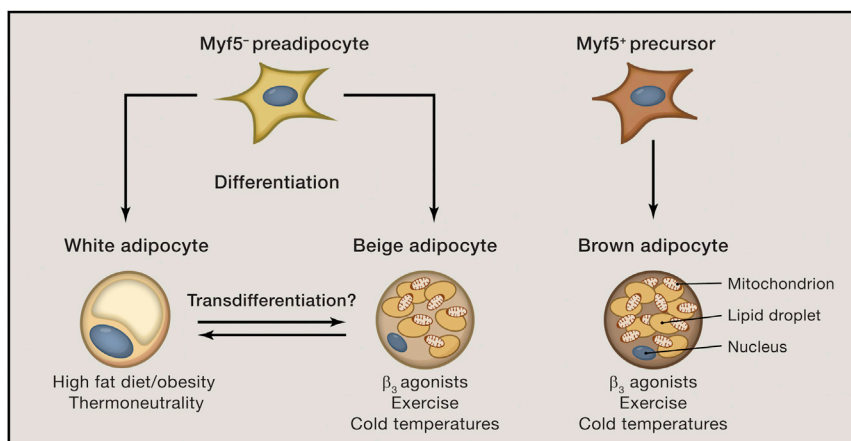
Figure 1. White, Beige, and Brown Adipocytes Are Developmentally and Functionally Distinct Cell Populations

White and beige adipocytes arise from a Myf5⁻ precursor cell population that is bipotent. These pre-adipocytes give rise to white or beige adipocytes depending on the stimulus and physiologic setting. White adipocytes are promoted by high-fat-diet feeding or obesity and by thermoneutrality (30°C in mice). Beige adipocytes are elicited by β₃ adrenergic receptor agonists such as norepinephrine or epinephrine, and are recruited within WAT in the settings of chronic exercise or exposure to cold temperatures. Although white and beige adipocytes emerge from pre-adipocytes via cell differentiation, mature white and beige adipocytes might undergo a process called transdifferentiation, in which one cell type acquires phenotypic characteristics of the other. There is uncertainty about whether transdifferentiation occurs. In contrast, brown adipocytes arise from a Myf5⁺ precursor cell population and are present in discrete brown adipose tissue depots. Despite being developmentally distinct cell populations, beige and brown adipocytes are activated by similar physiologic stimuli, including exercise- and cold temperature-induced hormones and metabolites.

network of immune cells appears to be poised to recognize, integrate, and respond to environmental signals including bacterial products, endogenous lipid species and hormones in order to regulate metabolism (Odegaard and Chawla, 2013a). Changes in immune cell composition and function in WAT have been closely associated with obesity and the regulation of metabolic homeostasis, and disruption of this network of immune cells can have either detrimental or beneficial effects on mammalian health (Exley et al., 2014; Lumeng and Saltiel, 2011; Mraz and Haluzik, 2014; Odegaard and Chawla, 2013b; Osborn and Olefsky, 2012). In addition, recent work has demonstrated that immune-system-associated transcription factors including but not limited to nuclear factor-κ B (NK-κB), c-Jun kinase (JNK), and interferon regulatory factor 4 (IRF4) are key regulators of metabolic homeostasis (Lumeng and Saltiel, 2011; Osborn and Olefsky, 2012). Conversely, metabolite-sensing receptors such as peroxisome proliferator-activated receptor (PPAR)-γ, farnesoid X receptor (FXR), liver X receptor (LXR), G protein coupled receptor 120 (GPR120), and carbohydrate-responsive element binding protein (ChREBP) among others have been shown to regulate immune responses (Brestoff and Artis, 2013; Glass and Saijo, 2010; Hotamisligil and Erbay, 2008; Shoelson et al., 2007; Zelcer and Tontonoz, 2006). Therefore dissecting the complex interactions between immune and metabolic systems will provide important insights into the biology underlying obesity and have implications for understanding how current and future therapeutics might influence metabolism.

The purpose of this review is to describe our current understanding of how immune cells in adipose tissue regulate metabolism. First, we will summarize recent advances in understanding the roles of white, beige, and brown adipose tissues in the regulation of weight gain. Second, we will describe the immune cell composition of adipose tissue at steady state and discuss how these immune cell pathways interact and contribute to the maintenance of metabolic homeostasis. Third, we will discuss immunologic changes that occur in adipose in the setting of obesity and highlight how these changes contribute to metabolic

dysfunction. Finally, we will discuss potential therapeutic implications of targeting the immune system to treat obesity and its associated diseases.

Roles of Adipose Tissues in the Regulation of Obesity

Mammals possess multiple types of adipose tissues including white, brown, and beige adipose. These tissues are found in distinct anatomic locations and are comprised of different adipocyte cell types—white, beige, and/or brown—that have unique developmental and functional properties that are critical for host metabolism (Figure 1) (Bartelt and Heeren, 2014; Cannon and Nedergaard, 2004; Harms and Seale, 2013; Ibrahim, 2010; Peirce et al., 2014; Pfeifer and Hoffmann, 2015; Wu et al., 2013). This section describes white, brown, and beige adipocyte cell types and summarizes their roles in regulating weight gain.

White Adipocytes

WAT is distributed throughout the mammalian body in subcutaneous depots and in association with organs, where it has important roles in insulation and physical protection of the viscera, and is comprised predominantly of white adipocytes (Peirce et al., 2014; Pfeifer and Hoffmann, 2015). These specialized cell types arise from a Myf5⁻ pre-adipocyte lineage and store large amounts of triglycerides in a single large lipid droplet (Pfeifer and Hoffmann, 2015; Sanchez-Gurmaches and Guertin, 2014). In addition to their ability to store triglycerides, white adipocytes respond to hormonal signals to induce lipolysis and release free fatty acids (FFA) into the circulation for oxidation or storage by other cell types (Arner et al., 2011; Bartness et al., 2010). Therefore white adipocytes are critical for regulating both fat storage and release. Beyond this function, white adipocytes produce various adipocyte-specific hormones (also known as adipokines) including but not limited to leptin, resistin, retinol binding protein 4 (RBP4), fibroblast grown factor 21 (FGF21), and adiponectin that regulate metabolic homeostasis by acting on distant organs such as the brain, kidney, liver, pancreas, and skeletal muscle (Allison and Myers, 2014; Itoh, 2014; Kadowaki et al., 2006; Kershaw and Flier, 2004; Kotnik et al., 2011; Lazar, 2007; Ouchi et al., 2011).

In the context of obesity, mature white adipocytes undergo proliferation and become hypertrophic through accumulation of triglycerides to increase the number and size of the adipocyte pool in WAT (Foster and Bartness, 2006; Hausman et al., 2001; Kubota et al., 1999; Spalding et al., 2008). As WAT expands, adipocytes increase production of leptin to suppress food intake and therefore limit the rate of triglyceride accumulation and adipocyte expansion (Allison and Myers, 2014). In obesity, this food intake-suppressive effect of upregulated leptin production is blunted by the development of resistance to leptin action (Park and Ahima, 2015). Leptin also has pro-inflammatory effects by eliciting type 1 effector cytokine production by immune cells (Attie and Scherer, 2009; Gregor and Hotamisligil, 2011; Mraz and Haluzik, 2014; Ouchi et al., 2011). In addition to leptin, the adipokines RBP4 and resistin are increased in obesity and promote insulin resistance in mice (Kotnik et al., 2011; Lazar, 2007; Moraes-Vieira et al., 2014; Norseen et al., 2012; Steppan et al., 2001; Yang et al., 2005). Upregulation of RBP4 expression has been linked to inappropriate sensing of low glucose levels by adipocytes (Yang et al., 2005), whereas resistin production is increased due to elevated levels of insulin and TNF-α among other factors (Lazar, 2007; Song et al., 2002). Both of these factors appear to promote insulin resistance in mice, at least in part, through elicitation of type 1 immune responses in WAT (Jung and Choi, 2014; Ouchi et al., 2011). Thus, leptin, resistin, and RBP4 are pro-inflammatory factors that are increased in obesity and that stimulate type 1 immunity in WAT.

In contrast, adiponectin has anti-inflammatory and insulin-sensitizing effects (Gregor and Hotamisligil, 2011; Kadowaki et al., 2006; Lumeng and Saltiel, 2011). Adiponectin production by white adipocytes is decreased in the context of obesity (Ouchi et al., 2011), and loss of this anti-inflammatory signal may be one factor that contributes to the development of inflammation in WAT in obesity. Other adipokines are also emerging as potential anti-inflammatory factors. In particular, recent work suggests that FGF21 might have immunosuppressive effects through inhibition of the transcription factor nuclear factor-κB (NF-κB) (Yu et al., 2015), a master regulator of inflammatory gene expression. Additional research is needed to determine whether FGF21 regulates inflammation in obesity and whether the immune system regulates expression of FGF21. Other adipokines such as fatty acid binding protein 4 (also known as adipocyte protein 2) and neuregulin 4 (NRG4) that have important roles in regulating metabolism have also been associated with inflammatory markers (Cao et al., 2013; Terra et al., 2011; Wang et al., 2014). Future research will be needed to determine whether these adipokines are direct pro- or anti-inflammatory mediators in WAT. Therefore, white adipocytes appear to link metabolic status of mammals to immune responses in WAT.

Brown Adipocytes

Although brown adipocytes can also produce adipokines, these cells differ from white adipocytes developmentally and functionally and in their anatomic distribution. In mice, brown adipocytes arise from a Myf5$^+$ lineage and are developmentally more closely related to skeletal muscle cells than to white adipocytes (Kajimura et al., 2009; Seale et al., 2008). The primary function of brown adipocytes in both mice and humans is to convert chemical energy into heat via uncoupling protein 1 (UCP1) (Cannon and Nedergaard, 2004). UCP1 is a long chain fatty acid/proton symporter that dissipates the mitochondrial electrochemical gradient, thereby uncoupling energy substrate oxidation from ATP synthesis and resulting in the generation of heat (Fedorenko et al., 2012; Matthias et al., 2000). This process is critical for maintaining core body temperature and in the regulation of weight gain by increasing whole-body energy expenditure. In the latter case, for example, mice that lack UCP1 develop obesity when housed at thermoneutrality (30°C) as compared to UCP1-sufficient controls (Feldmann et al., 2009). Although global deletion of UCP1 impairs thermogenesis in both brown and beige adipocytes (see below), brown adipose tissue (BAT) is believed to be an important regulator of metabolic rate and obesity susceptibility in mice.

Brown adipocytes are found in discrete BAT depots. In mice, the largest BAT depot is present in the interscapular space, and smaller depots are present in the axilla and along the cervical column (Bartelt and Heeren, 2014). In humans, brown adipocytes are abundant in newborns including in the interscapular space (Hondares et al., 2014), whereas in lean adult humans brown adipocytes are reported to be present in the supraclavicular space of the neck and adjacent to the cervical column and heart (van Marken Lichtenbelt et al., 2009; Virtanen et al., 2009). Subsequent studies have determined that supraclavicular neck BAT in healthy adults exhibits a gene expression profile and has morphologic characteristics consistent with those of beige adipocytes (Lee et al., 2014a; Sharp et al., 2012; Wu et al., 2012).

Beige Adipocytes

Like brown adipocytes, beige adipocytes (also known as brown-like or brite adipocytes) express high levels of UCP1 and store triglyceride in one or more lipid droplets, giving rise to a pauciocular or multilocular cell morphology. Although beige and brown adipocytes have similar UCP1-dependent functional characteristics, these cell types differ from each other developmentally and anatomically. Brown adipocytes arise from a Myf5$^+$ precursor and are developmentally related to skeletal muscle cells (Kajimura et al., 2009; Seale et al., 2008), whereas beige adipocytes arise from Myf5$^-$ precursors within WAT and are developmentally related to smooth muscle cells (Long et al., 2014) and/or white adipocytes (Sanchez-Gurmaches and Guertin, 2014). Beige adipocytes may arise from multiple developmental pathways, including differentiation from committed beige pre-adipocytes as well as white-to-beige transdifferentiation in which mature white adipocytes are converted into beige adipocytes (Figure 1) (Barbatelli et al., 2010; Harms and Seale, 2013; Moisan et al., 2015; Sanchez-Gurmaches and Guertin, 2014; Wang et al., 2013b; Wu et al., 2012). While differentiation is a well-accepted developmental pathway for beige adipocytes, white-to-beige transdifferentiation is a controversial topic, and further research is needed to determine whether this process contributes to beige adipogenesis in different physiologic contexts or in response to different stimuli. In mice, beige adipocytes are enriched in subcutaneous WAT compared to visceral fat. However, beige adipocytes are elicited in both types of WAT (Qiu et al., 2014), and future studies will be required to determine whether beige adipocytes in subcutaneous and visceral fat differ from each other developmentally and/or functionally.
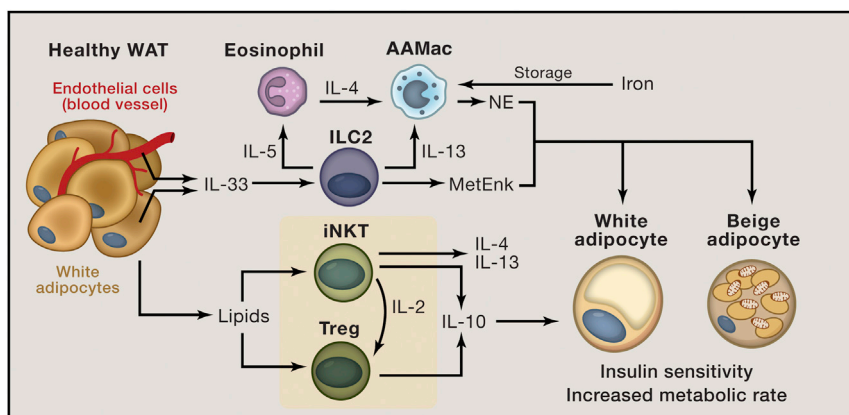
Figure 2. Healthy White Adipose Tissue Is Enriched in Type 2 Cytokine-Associated Immune Cells

In the lean state, adipocytes and endothelial cells in white adipose tissue (WAT) constitutively produce interleukin (IL)-33 that can act on Group 2 innate lymphoid cells (ILC2s) to induce production of IL-5 and IL-13 that sustain eosinophil and alternatively activated macrophage (AAMac) responses, respectively, in WAT. In addition, eosinophils produce IL-4 that is necessary to maintain AAMac responses in WAT. AAMacs have multiple functions to maintain metabolic homeostasis, including storing large amounts of iron, leading to sequestration of this pro-oxidative metal cation from adipocytes to prevent lipid peroxidation, oxidative damage to proteins and mitochondrial dysfunction. In addition, AAMacs produce norepinephrine (NE) that acts on both white and beige adipocytes via the β_3 adrenergic receptor to stimulate lipolysis and elicit beige adipocytes that increase metabolic rate. ILC2s can also promote beiging through production of methionine-enkephalin (MetEnk) peptides. In addition, adipocytes present lipid antigen to invariant natural killer T (iNKT) cells to elicit a unique tissue-specific anti-inflammatory phenotype characterized by increased production of IL-4 and IL-13, which may act on AAMacs, and IL-10. Lipids from adipocytes are also believed to promote regulatory T cell (T_{reg}) responses in WAT to induce production of IL-10. iNKT cells are critical sources of IL-2 and are necessary to sustain T_{regs} in WAT. IL-10 production by iNKT cells, T_{regs} and other cell types promote insulin action in white adipocytes to facilitate maintenance of an insulin-sensitive state. Together, these pathways contribute to metabolically healthy WAT.

Beige adipocytes are elicited in response to environmental stimuli including exposure to cold environmental temperatures or in response to exercise, and these cells are activated or induced to differentiate in response to a range of small molecules and hormones. Factors that stimulate beige adipocyte development or activation include norepinephrine (NE) (Qiu et al., 2014; Rao et al., 2014), adenosine (Gnad et al., 2014), lactate (Carrière et al., 2014), β-aminoisobutyric acid (BAIBA) (Roberts et al., 2014), prostaglandin E_2 (PGE_2) (Madsen et al., 2010), parathyroid hormone-related protein (PTHrp) (Fisher et al., 2012), bone morphogenetic protein 4 (BMP4) (Qian et al., 2013), BMP7 (Schulz et al., 2011), fibroblast growth factor 21 (FGF21) (Fisher et al., 2012), irisin (Wu et al., 2012), and meteorin-like (Rao et al., 2014). Although many factors are known to promote beige adipocyte differentiation or function, it remains unknown whether these factors act on different subsets of beige adipocytes or whether they elicit developmentally or functionally distinct subsets of beige adipocytes. In addition, it is unclear to what extent these factors coordinately regulate beige adipocyte function.

Nonetheless, recent studies indicate that selective deletion of beige but not brown adipocytes results in impaired glucose homeostasis and increased susceptibility to weight gain in response to high fat diet (HFD) feeding (Cohen et al., 2014). Conversely, mice with increased beige adipocytes exhibit increased metabolic rate and decreased obesity (Wang et al., 2013a). Consistent with this finding, 129Sv mice, which are resistant to diet-induced obesity exhibit increased beiging of WAT compared to C57BL/6 mice, which are susceptible to diet-induced obesity (Shabalina et al., 2013). Inhibition of beige adipocytes by supplementing HFD chow with indomethacin resulted in increased weight gain following HFD feeding in 129Sv mice (Madsen et al., 2010). Collectively, these data indicate that impaired beiging is associated with increased weight gain and suggest that elicitation of beige adipocytes can combat obesity in mice.

Recent studies support the relevance of these findings in humans. In the context of human obesity, the incidence of brown/beige adipose tissue (Sharp et al., 2012) is significantly decreased in obese patients compared to lean patients (Saito et al., 2009). In addition, UCP1 expression was found to be higher in cultured beige adipocytes from lean patients compared to obese patients, suggesting that beige adipocyte differentiation or activation is impaired in human obesity (Carey et al., 2014). Consistent with this, ephedrine-induced activation of brown/beige adipose tissue is impaired in human obesity (Carey et al., 2013). While the role of brown/beige adipocytes in the regulation of energy expenditure in humans is unclear, these studies suggest that obesity is associated with loss of beige fat function and raise the possibility that defective beige fat may have deleterious metabolic effects including increased susceptibility to weight gain.

Immune Cell Composition and Function in Lean White Adipose Tissue

White adipose is a heterogeneous tissue comprised of multiple cell types including a diverse array of immune cells. In the steady state, these immune cells tend to be associated with the type 2 immune axis and include alternatively activated macrophages (AAMacs), eosinophils, Group 2 innate lymphoid cells (ILC2s), invariant natural killer T (iNKT) cells, T helper type 2 (Th2) cells, regulatory T (T_{reg}) cells, and other immune cell populations that communicate with each other and participate in cross-talk with adipocytes. As discussed below, the interface between immune cells and adipocytes contributes to the regulation of lipid storage, glucose utilization, redox balance, and energy expenditure (Figure 2). However, in the context of obesity, type 2 immune cells in WAT become dysregulated and, in some cases, acquire a pro-inflammatory phenotype that exacerbates adipose tissue inflammation with deleterious effects on metabolism. In this section, we discuss emerging concepts in the composition and function of immune cells in WAT at steady state and how these cells contribute to protection from diet-induced obesity.
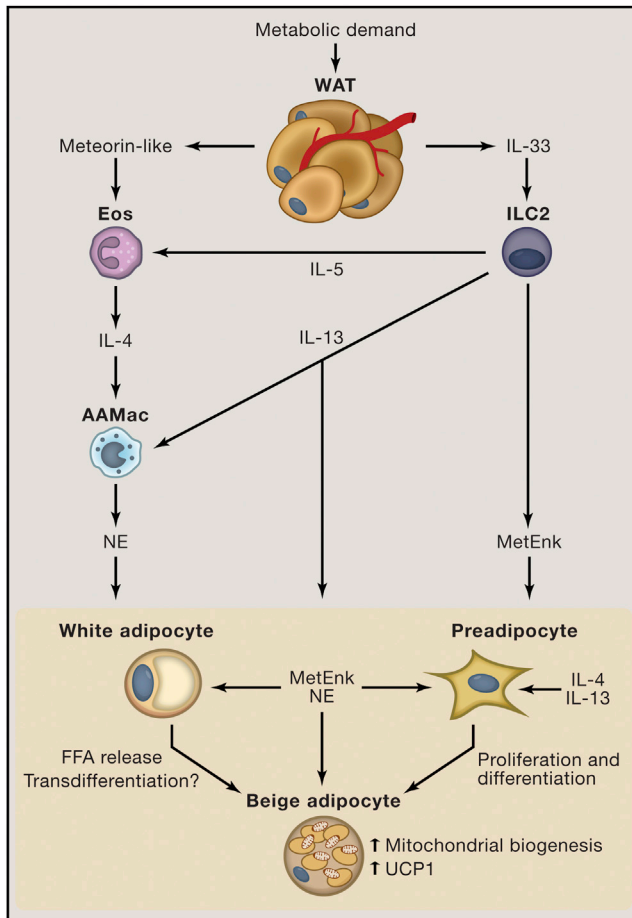
Figure 3. Immunologic Mechanisms That Regulate Beiging
In the context of chronic exposure to cold environmental temperatures or chronic exercise, WAT and muscle produce the adipokine/myokine meteorin-like. This hormone and other factors such as IL-5 promote eosinophil accumulation in WAT. Eosinophils produce IL-4 that sustains alternatively activated macrophages (AAMacs). IL-4 and perhaps IL-13 act on AAMacs to stimulate norepinephrine (NE) production. NE acts to stimulate beiging via differentiation and/or transdifferentiation pathways and to activate existing beige adipocytes, resulting in mitochondrial biogenesis, uncoupling protein 1 (UCP1) upregulation, and UCP1-dependent increases in energy expenditure. In addition, WAT produces the cytokine IL-33 that is critical for maintaining ILC2 responses in WAT. IL-33 stimulates ILC2s to produce IL-5 and IL-13 that sustain the eosinophil/AAMac pathways that can contribute to beiging. In addition, IL-13 can act on pre-adipocytes to promote their proliferation and induce differentiation to beige adipocytes. Further, IL-33 stimulates ILC2s to produce methionine-enkephalin (MetEnk) peptides that can directly promote beiging. Therefore AAMacs and ILC2s both contribute to beiging through production of distinct effector molecules.

The IL-4/Alternatively Activated Macrophage Pathway
AAMacs are IL-4- and IL-13-dependent cells that require signal transducer and activator of transcription 6 (STAT6) to maintain an alternative activation state that is distinct from the classical activation state induced by interferon-γ (IFNγ) (Gordon and Martinez, 2010; Hill et al., 2014; Martinez et al., 2009; Odegaard and Chawla, 2011; Olefsky and Glass, 2010). AAMacs are critical for protective immunity against helminth pathogens and are associated with pathologic allergic inflammation in the lung (Gordon

and Martinez, 2010; Martinez et al., 2009). Recent studies have also implicated AAMacs in the regulation of metabolic homeostasis (Hill et al., 2014; Odegaard and Chawla, 2011; Olefsky and Glass, 2010). Early studies linking AAMacs to metabolism demonstrated that macrophage-specific deletion of Peroxisome proliferator-associated receptor (PPAR)-γ results in decreased AAMacs in WAT in association with increased weight gain, elevated fat accumulation, impaired glucose uptake and insulin resistance following HFD feeding (Odegaard et al., 2007). In addition, deletion of PPAR-δ in leukocytes also impaired AAMac responses and was associated with increased adiposity and insulin resistance (Odegaard et al., 2008). These loss-of-function studies are complemented by gain-of-function approaches indicating that administration of exogenous IL-4 to mice to boost AAMac responses protected mice from HFD-induced obesity and insulin resistance (Chang et al., 2012; Ricardo-Gonzalez et al., 2010). Together, these studies identified a critical role for the IL-4/AAMac axis in the regulation of metabolic homeostasis.

Emerging work has revealed that AAMacs employ a diverse functional repertoire to regulate metabolism. For example, a subset of AAMacs in WAT can express genes involved in iron handling and has the capacity to store large amounts of iron in lean mice (Orr et al., 2014). The capacity of these specialized AAMacs to store iron is diminished in the setting of obesity, leading to abnormal accumulation of iron in adipocytes (Orr et al., 2014) that may lead to iron-initiated production of highly toxic lipid aldehydes that damage cellular proteins, impair adipocyte insulin sensitivity, and lead to mitochondrial dysfunction (Curtis et al., 2010; Curtis et al., 2012). Therefore it appears that specialized iron-storing AAMacs have an essential role in regulating iron homeostasis in WAT to maintain optimal glucose metabolism and mitochondrial function at steady state, and dysregulation of these cells in obesity may have deleterious effects on glucose and energy homeostasis. Consistent with this, treatment of obese mice with the iron chelator deferoxamine is associated with improved glucose tolerance, decreased body weight, lower fat mass, and less inflammation in fat compared to vehicle-treated obese controls (Tajima et al., 2012).

In addition, AAMacs from adipose are capable of producing catecholamines such as norepinephrine (NE) that act on adipocytes via the β3 adrenergic receptor (β3AR) to stimulate lipolysis, activate mitochondrial biogenesis and upregulate expression of UCP1 (Figures 2 and 3) (Liu et al., 2014; Nguyen et al., 2011; Qiu et al., 2014; Rao et al., 2014). AAMac-derived catecholamine production was described in the setting of brown adipocyte activation (Nguyen et al., 2011). Mice that lack IL-4 and IL-13 ($Il4/13^{-/-}$); the shared receptor for these cytokines, IL-4Rα ($Il4ra^{-/-}$); or STAT6, a transcription factor downstream of IL-4Rα signaling ($Stat6^{-/-}$), had defective AAMac responses (Martinez et al., 2009) and exhibited decreased UCP1 expression in BAT (Nguyen et al., 2011). This defect in UCP1 expression in BAT was associated with impaired maintenance of core body temperature following acute exposure to cold environmental temperatures over a 6 hr period compared to wild-type controls (Nguyen et al., 2011). These findings suggested that IL-4/IL-4Rα-dependent activation of AAMacs stimulated production of NE that was necessary for brown adipocyte activation in the setting of short-term cold exposure. However, subsequent

studies indicated that IL-4/IL-4Rα-dependent AAMacs were dispensable for brown adipocyte activation in the setting of more prolonged cold exposure over 72 hr (Qiu et al., 2014). This suggests that there may be time-dependent factors that influence whether the IL-4/AAMac/NE pathway activates brown adipocytes, a topic that should be investigated further.

The IL-4/AAMac/NE pathway is also critical for activating beige adipocytes in WAT (Figure 3) (Qiu et al., 2014; Rao et al., 2014). Mice lacking IL-4/IL-13, IL-4Rα, or STAT6 failed to undergo optimal beiging of WAT and had decreased metabolic rate compared to wild-type controls after 72 hr of exposure to cold environmental temperatures (Qiu et al., 2014; Rao et al., 2014). This phenotype appears to be mediated by macrophage-intrinsic production of NE, as mice that lack the rate-limiting step of catecholamine synthesis, tyrosine hydroxylase (TH), in LysM-Cre-expressing cells such as macrophages exhibit impaired beige adipose development and exhibit a 10%–15% decrease in whole-body oxygen consumption in the setting of chronic exposure to mild (room temperature) or severe (5°C) cold environmental temperatures (Qiu et al., 2014). This defect in metabolic rate suggests that AAMac-derived catecholamines might also be important for limiting weight gain. Consistent with this, mice that lack Receptor interacting protein 140 (RIP140), a transcriptional co-regulator that regulates metabolism in various tissues and that suppresses mitochondrial uncoupling (Rosell et al., 2011), had increased AAMac responses in WAT and increased beiging that was associated with protection from diet-induced obesity (Liu et al., 2014). In addition, treatment of mice with exogenous IL-4 elicits beiging and increases oxygen consumption levels in an UCP1-dependent manner, effects that are associated with decreased severity of diet-induced obesity (Chang et al., 2012; Qiu et al., 2014; Ricardo-Gonzalez et al., 2010). In addition to its effects on AAMacs, IL-4 can act directly on pre-adipocytes to promote beige adipocyte development (Lee et al., 2015). Together, these data suggest that IL-4 in WAT is critical for beiging and regulation of metabolic rate through UCP1-dependent thermogenesis.

Sources of IL-4 in WAT: Eosinophils and Invariant Natural Killer T Cells

The appreciation of AAMacs as critical regulators of metabolic homeostasis sparked interest in determining the cellular sources of IL-4 in WAT. Using the *4get* mouse, a reporter strain that identifies IL-4-competent cells, eosinophils were identified as an abundant immune cell population in WAT and an important source of IL-4 in this compartment at steady state (Wu et al., 2011). Eosinophils are granulocytes that are developmentally dependent on the cytokine IL-5 and the transcription factor GATA-binding protein 1 (GATA-1), and these cells contribute to type 2 immune responses by producing a variety of effector molecules including IL-4 (Rosenberg et al., 2013; Rothenberg and Hogan, 2006). Eosinophils are decreased in WAT of HFD-fed and genetically obese *ob/ob* mice (Wu et al., 2011). ΔDblGata1 mutants or IL-5-deficient mice, both of which lack eosinophils (Rosenberg et al., 2013; Rothenberg and Hogan, 2006), develop more severe obesity and insulin resistance than wild-type controls in association with dysregulated AAMac responses (Wu et al., 2011). Further, mice with elevated numbers of eosinophils

in WAT due to constitutive overexpression of IL-5 or infection with helminth pathogens were protected from diet-induced obesity and insulin resistance (Wu et al., 2011; Yang et al., 2013). Eosinophils are also recruited to WAT in the setting of chronic exposure to cold environmental temperatures, and eosinophil-deficient ΔDblGata1 mice exhibit defective beiging of WAT (Qiu et al., 2014; Rao et al., 2014). These beneficial metabolic effects of eosinophils appear to be mediated by IL-4-dependent AAMac responses in WAT (Wu et al., 2011; Qiu et al., 2014); however, whether eosinophils have other functions in WAT remains unknown.

In addition to eosinophils, iNKT cells that express lipid antigen-specific T cell receptor variants appear to be an important source of IL-4 in WAT (Hams et al., 2013; Lynch et al., 2012). iNKT cells in WAT produce more IL-4 and IL-10 and less IFN-γ than do iNKT cells in the liver and spleen (Lynch et al., 2012), suggesting that iNKT cells in WAT are in an "alternative activation" state. Consistent with this, recent work has shown that mammals produce endogenous lipid antigens such as α-galactosylceramides (αGalCer) that promote production of type 2 cytokines by iNKT cells (Kain et al., 2014; Lynch et al., 2012), and that adipocytes can present lipid antigens to iNKT cells via CD1d (Huh et al., 2013; Rakhshandehroo et al., 2014). iNKT cells are decreased in murine and human obesity, and surgical or dietary treatment of obesity restores iNKT cells in WAT (Lynch et al., 2012). Genetic studies in mice provide further support for the hypothesis that iNKT cells play a critical role in maintenance of body weight and metabolism. Jα18-deficient mice, which lack iNKT cells, exhibit increased body weight and adiposity when fed a HFD compared to wild-type controls, and CD1d-deficient mice, which cannot present lipid antigen to iNKT cells, develop spontaneous obesity on a low-fat diet (Lynch et al., 2012). In addition, mice lacking iNKT cells had more severe glucose intolerance and increased pro-inflammatory macrophages in WAT (Lynch et al., 2012), suggesting that iNKT cells are essential for limiting inflammatory responses in the setting of obesity. Adoptive transfer of iNKT cells induced weight loss and decreased adipocyte size while improving insulin resistance in HFD-fed mice (Hams et al., 2013; Lynch et al., 2012), and treatment of HFD mice with αGalCer recapitulated these effects in an iNKT-dependent manner by increasing IL-4 and IL-10 production by iNKT cells (Lynch et al., 2012). Therefore, eosinophils and iNKT cells may be important sources of IL-4 or other factors that support AAMac function or that directly regulate metabolic homeostasis to limit obesity and insulin resistance.

The IL-33/Group 2 Innate Lymphoid Cell Pathway

ILC2s are recently described immune cells (Moro et al., 2010; Price et al., 2010; Neill et al., 2010) that control eosinophil and AAMac responses (Molofsky et al., 2013; Nussbaum et al., 2013). ILC2s are members of a broader family of ILCs that comprise T-bet-dependent Group 1 ILCs that produce IFN-γ; GATA-3-dependent ILC2s that produce IL4, IL-5, IL-9, IL-13, and amphiregulin; and RORγt-dependent Group 3 ILCs that produce IL-17A and IL-22 (Kim, 2015; Monticelli et al., 2012; Sonnenberg et al., 2013; Spits et al., 2013; Spits and Cupedo, 2012). At barrier surfaces such as the gut, lung, and skin, ILC2s respond to epithelial cell-derived cytokines IL-33, IL-25 and thymic stromal lymphopoietin (TSLP) to initiate type 2

immune responses that protect against helminth infection or that promote pathologic allergic inflammation (Kim, 2015; Monticelli et al., 2012; Sonnenberg et al., 2013; Spits et al., 2013; Spits and Cupedo, 2012). ILC2s were recently shown to be present in murine WAT, where these cells constitutively produce the effector cytokines IL-5 and IL-13 to maintain eosinophil and AAMac responses, respectively, in WAT (Molofsky et al., 2013). Strikingly, eosinophil-deficient mice exhibit decreased energy expenditure and increased obesity compared to eosinophil-sufficient controls (Molofsky et al., 2013; Wu et al., 2011). Recent studies showed that antibody-mediated depletion of ILC2s is associated with increased weight gain and more severe insulin resistance in mice fed a HFD (Hams et al., 2013), and transferring IL-25-elicited ILC2s was sufficient to promote weight loss in diet-induced obese mice (Hams et al., 2013). These data suggest that ILC2s negatively regulate the development of obesity.

Although ILC2s can regulate metabolic homeostasis through their effects on eosinophils and AAMacs, they also have direct effects on metabolism through production of IL-13 and enkephalin peptides (Brestoff et al., 2015; Lee et al., 2015). In the context of exposure to cold environmental temperatures, ILC2-derived IL-13 promotes pre-adipocyte proliferation and differentiation into beige adipocytes in an IL-4Rα-dependent manner (Lee et al., 2015). The ILC2/IL-13/beiging pathway may also be related to young age-associated increases in beiging that may be critical for maintaining core body temperature during mammalian development (Lee et al., 2015). However, whether ILC2-derived IL-13 regulates obesity remains unknown. In this disease context a distinct ILC2-dependent pathway can promote beiging independently of eosinophils or IL-4Rα (Brestoff et al., 2015). Specifically, ILC2s produce methionine-enkephalin (MetEnk) peptides in response to IL-33 stimulation, and MetEnk can act directly on adipocytes from WAT to upregulate *Ucp1* expression levels in vitro and drive the formation of functional beige adipose tissue in vivo (Brestoff et al., 2015). MetEnk was previously shown to stimulate lipolysis in adipocytes (Nencini and Paroli, 1981), a process that is critical for beige adipocyte responses and UCP1 function (Fedorenko et al., 2012; Harms and Seale, 2013; Rosen and Spiegelman, 2014; Wu et al., 2013). Therefore, ILC2s directly contribute to beiging under various physiologic settings by producing IL-13 and MetEnk.

It is possible that ILC2-derived IL-13 and MetEnk, coupled with AAMac-derived NE, cooperatively support optimal beiging to regulate metabolic homeostasis. Consistent with this hypothesis, previous studies have suggested that NE and MetEnk signaling pathways might interact to cooperatively stimulate lipolysis in adipocytes (Nencini and Paroli, 1981). Another possibility is that IL-13, MetEnk and NE elicit distinct populations of beige adipocytes involved in the regulation of metabolic homeostasis in different physiologic contexts or following different environmental stressors. Future studies focused on IL-13, MetEnk, and NE interactions in adipocytes are warranted to better understand the mechanisms by which ILC2s, eosinophils, and AAMacs contribute to the regulation of beiging and metabolic rate.

ILC2-mediated regulation of metabolic processes may be dysregulated in the context of obesity. The cytokine IL-33 is critical for stimulating proliferation and activation of ILC2s (Kim et al., 2014; Molofsky et al., 2013; Monticelli et al., 2011; Moro et al., 2010; Neill et al., 2010; Price et al., 2010) and is expressed at higher levels in WAT of obese mice and humans compared to non-obese controls (Zeyda et al., 2013). However, ILC2s are decreased in murine and human obesity (Brestoff et al., 2015; Molofsky et al., 2013), suggesting that in the obese state ILC2s may be hypo-responsive to IL-33 or have altered cell death, proliferation, or migration. IL-33 was recently shown to be critical for protecting mice from obesity (Brestoff et al., 2015; Miller et al., 2010). Mice lacking IL-33 or the IL-33R exhibit increased obesity and exacerbated impairments in glucose homeostasis, and treatment of obese mice with recombinant IL-33 limited adiposity and improved glucose metabolism in association with enhanced ILC2 and AAMac responses in WAT (Brestoff et al., 2015; Miller et al., 2010). This suggests that targeting the IL-33/ILC2 axis therapeutically could have beneficial metabolic effects that limit obesity and/or associated diseases such as type 2 diabetes.

CD4+ T Helper Cells and Regulatory T Cells
In addition to regulating the ILC2/eosinophil/AAMac pathway, IL-33 also acts on adaptive immune cells such as Th2 cells (Molofsky et al., 2013) and T_{regs} (Schiering et al., 2014). Although Th2 cells are relatively rare in WAT (Molofsky et al., 2013) and remain poorly understood in the context of obesity, T_{regs} in WAT have been shown to be unique members of the T_{reg} pool exhibiting elevated expression of PPAR-γ, Foxp3, and IL-10 compared to T_{regs} in other tissues (Cipolletta et al., 2012; Deiuliis et al., 2011; Feuerer et al., 2009). T_{regs} in WAT contribute to the maintenance of insulin sensitivity in WAT by limiting inflammation and producing insulin-sensitizing factors such as IL-10 (Cipolletta et al., 2012; Feuerer et al., 2009; Ilan et al., 2010). For example, IL-10 suppresses monocyte chemotactic protein-1 (MCP-1) expression by adipocytes to limit inflammatory macrophage infiltration of WAT and inhibits the ability of TNF-α to downregulate glucose transporter 4 (GLUT-4) expression and impair insulin action in adipocytes (Lumeng et al., 2007). In obesity, T_{regs} are decreased in both mice and humans (Cipolletta et al., 2012; Feuerer et al., 2009; Wagner et al., 2013), which may be due to aberrant iNKT cell responses in obese WAT (Lynch et al., 2015). iNKT cells in WAT produce IL-2 to sustain T_{regs} and are an additional source of IL-10 (Lynch et al., 2015; Lynch et al., 2012). Interestingly, recent studies indicate that the anti-diabetic class of drugs known as thiazoladinediones (TZD), which are PPAR-γ agonists, ameliorate insulin resistance in obese mice in part via their effects on T_{regs} (Cipolletta et al., 2012). Therefore promoting T_{reg} responses may be a useful strategy to treat or prevent type 2 diabetes.

Immune Cell Responses in White Adipose Tissue in Obesity
In obesity, WAT undergoes metabolic and inflammatory changes. As white adipocytes accumulate triglycerides and become hypertrophic, the vasculature in WAT becomes rarified leading to hypoxia and oxidative stress (Curtis et al., 2010; Pasarica et al., 2009). In addition, increased oxygen consumption by adipocytes undergoing hypertrophy results in relative local hypoxia that triggers hypoxia-inducible factor 1 α (HIF-1α) activation (Lee et al., 2014b). These changes are associated with increased adipocyte cell death and elevated production of
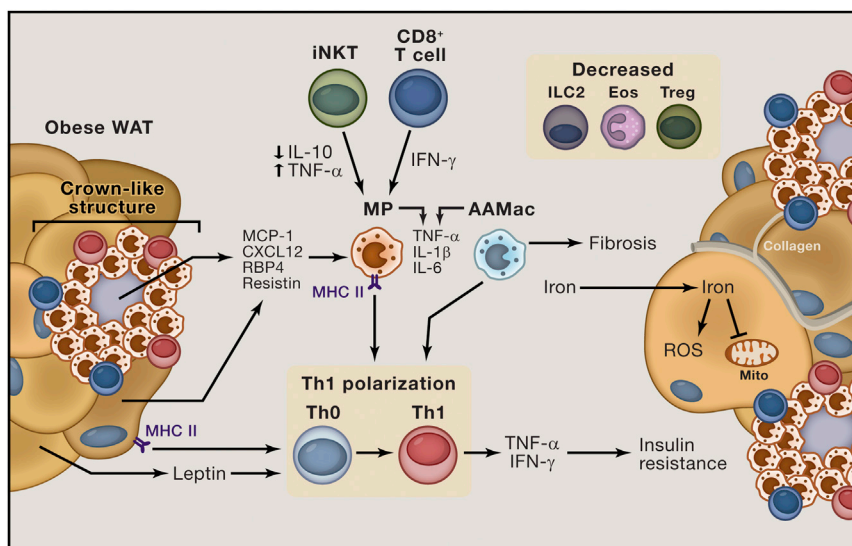
Figure 4. Obese White Adipose Tissue Is Characterized by Type 1 Cytokine-Associated Immune Responses

In obese WAT, adipocyte hypertrophy is associated with hypoxia and adipocyte cell death. Dead and neighboring adipocytes produce pro-inflammatory signals such as Monocyte chemotractant protein 1 (MCP1), C-X-C motif chemokine 12 (CXCL12), retinol binding protein 4 (RBP4) and resistin that are associated with the recruitment of classically activated macrophages (MP) into WAT and MP activation. MP accumulation in WAT is also mediated by pro-inflammatory iNKT cells that exhibit impaired production of IL-10 and upregulated production of tumor necrosis factor-α (TNF-α), and by CD8^{+} cytotoxic T cells that produce interferon (IFN)-γ. These factors also promote MP activation and upregulate major histocompatibility complex class II (MHC II) on MP and adipocytes. MHC II-mediated antigen presentation by MP and adipocytes stimulates polarization of CD4^{+} T cells toward a T helper type 1 (Th1) phenotype. Supporting this process are TNF-α, IFN-γ, IL-1β and IL-6 collectively produced by MP cells, dysregulated AAMacs, iNKT cells and CD8^{+} T cells. In addition, leptin is upregulated in obese WAT, and this factor also promotes Th1 cell polarization. MP cells, CD8^{+} T cells and Th1 cells collectively interact to form crown-like structures (CLS) to facilitate phagocytosis of dead adipocytes (grey cell in center of CLS). This process further promotes antigen presentation and type 1 immune responses, establishing a vicious cycle. Type 1 cytokines such as TNF-α and IFN-γ act directly on adipocytes to impair insulin action, leading to insulin resistance. Dysregulated AAMacs also produce type 1 cytokines in the setting of obesity to contribute to insulin resistance. AAMacs also lose their capacity to store iron, resulting in redistribution of iron to adipocytes. This results in iron-initiated lipid peroxidation that causes reactive oxygen species (ROS) production, insulin resistance, and mitochondrial dysfunction. In addition, AAMacs in obese WAT promote collagen deposition in WAT and fibrosis, leading ultimately to exacerbated hypoxia and inflammation and potentiation of the type 1 immune response. These processes occur in the setting of decreased abundance of regulatory T cells (Treg), Group 2 innate lymphoid cells (ILC2), and eosinophils (Eos) that promote insulin sensitivity and metabolic homeostasis in WAT in the steady state. Mito, mitochondrion.

adipocyte-derived inflammatory mediators, including the adipokines leptin, resistin and RBP4 (Attie and Scherer, 2009; Greenberg and Obin, 2006; Lazar, 2007; McNelis and Olefsky, 2014; Osborn and Olefsky, 2012; Ouchi et al., 2011). As discussed below, these and other pro-inflammatory factors initiate a type 1 immune response in obese WAT that is characterized by increased accumulation of CD4^{+} T helper type 1 (Th1) cells, cytotoxic CD8^{+} T cells, and pro-inflammatory classically activated macrophages (Figure 4). These changes are discussed in this section.

Adipocytes, Macrophages and Type 1 Cytokine-Associated T Cells Participate in a Proinflammatory Positive-Feedback Loop in Obesity

In obesity adipocyte-derived inflammatory mediators such as monocyte chemotactic protein (MCP-1), C-X-C motif chemokine 12 (CXCL12), prostaglandins, leukotrienes, and other factors are increased and promote classically activated monocyte/macrophage activation, proliferation, and infiltration of WAT (Amano et al., 2014; Nomiyama et al., 2007; Oh et al., 2012; Weisberg et al., 2003). These cells engulf dying or dead adipocytes, forming crown-like structures (CLS) that are characterized morphologically as a ring of macrophages and other immune cells surrounding an adipocyte (Murano et al., 2008; Ouchi et al., 2011). The formation of CLS may be an adaptive mechanism to scavenge cellular debris or to limit the release of toxic lipid species when adipocytes undergo cell death via phagocytosis. However, in addition to their phagocytic roles in CLS, classically activated macrophages in WAT of obese mice produce IL-1β, TNF-α, and IL-6 among other factors that potentiate the type 1 inflammatory response (Lumeng et al.,

2007; Nguyen et al., 2007; Zeyda et al., 2010). These cytokines act directly on adipocytes and other cell types in distant tissues such as skeletal muscle to inhibit insulin-dependent glucose uptake (Exley et al., 2014; Gregor and Hotamisligil, 2011; Jin et al., 2013; Osborn and Olefsky, 2012). This pro-inflammatory process is therefore associated with the development of insulin resistance by promoting chronic low-grade type 1 inflammation.

The accumulation of macrophages in obese WAT also appears to be regulated by CD8^{+} T cells (Rausch et al., 2008). These adaptive immune cells are recruited to WAT before infiltration by pro-inflammatory macrophages in the setting of HFD feeding (Nishimura et al., 2009). Deletion of CD8^{+} T cells decreases macrophage accumulation in WAT of obese mice and ameliorates obesity-associated insulin resistance, and adoptive transfer of CD8^{+} T cells to mice fed a HFD is sufficient to promote macrophage infiltration of WAT and exacerbate insulin resistance (Nishimura et al., 2009). In the setting of HFD feeding, CD8^{+} T cells produce IFN-γ that has multiple effects on immune cells in WAT (Revelo et al., 2015). IFN-γ acts on macrophages to upregulate expression of pro-inflammatory effector cytokines and to increase expression of Major histocompatibility complex class II (MHCII) (Schroder et al., 2004). This promotes macrophage antigen presentation to CD4^{+} T cells and induces Th1 cell polarization and proliferation (Cho et al., 2014; Morris et al., 2013). T-bet-dependent CD4^{+} Th1 cells produce TNF-α and IFN-γ to further potentiate insulin resistance in WAT (Cho et al., 2014; Morris et al., 2013; Stolarczyk et al., 2013). Thus, the CD8^{+} T cell/classically activated macrophage pathway in WAT appears to be critical for establishing the pro-inflammatory

environment that influences Th1 cell responses. However, the precise factors that spur this CD8^{+} T cell-dependent response remain to be determined.

Adipocytes also appear to directly contribute to Th1 cell responses in obesity. With increased triglyceride deposition, adipocytes upregulate their expression of leptin, a hormone that limits food intake, as a compensatory mechanism to guard against overly rapid weight gain (Allison and Myers, 2014). While this is a beneficial response to maintain energy homeostasis, in WAT leptin acts on CD4^{+} T cells to induce Th1 polarization and IFN-γ expression to drive a pro-inflammatory immune response that limits insulin sensitivity (Deng et al., 2013). In turn, IFN-γ upregulates CIITA and MHCII expression in adipocytes (Deng et al., 2013) and macrophages (Cho et al., 2014; Morris et al., 2013) to promote adipocyte-mediated antigen presentation to Th1 cells. These MHCII-mediated inflammatory changes in obesity are critical drivers of insulin resistance (Cho et al., 2014; Deng et al., 2013). Therefore it appears that adipocytes, macrophages, CD8^{+} T cells, and CD4^{+} Th1 cells participate in a pro-inflammatory positive-feedback loop with deleterious consequences for WAT inflammation and glucose metabolism.

Alternatively Activated Macrophages Acquire a Classical Activation State in Obesity and Potentiate Type 1 Inflammation in WAT

As discussed above, AAMacs have critical roles for regulating metabolic homeostasis in WAT at steady state. In obesity, however, AAMacs appear to become dysregulated and acquire a pro-inflammatory classically activated-like phenotype that contributes to the development of type 1 inflammatory responses in WAT. For example, in obesity, AAMacs decrease their expression of IL-10 and Arginase 1 and upregulate expression of TNF-α, IL-6, and IL-1β (Han et al., 2013; Lumeng et al., 2007; Moraes-Vieira et al., 2014). This phenotypic switch in AAMacs appears to be driven, at least in part, by RBP4 that is upregulated in obesity and that impairs glucose homeostasis (Graham et al., 2006; Norseen et al., 2012). AAMacs from transgenic mice that overexpress RBP4 exhibit upregulated expression of antigen presentation machinery, TNF-α and IL-1β, and polarize CD4^{+} T cells in WAT toward a Th1 phenotype characterized by increased expression of T-bet and IFN-γ (Moraes-Vieira et al., 2014). Interestingly, this effect was not observed in the liver, suggesting a tissue-specific effect of RBP4 on antigen presenting cells and T cell activation (Moraes-Vieira et al., 2014). In addition, transfer of RBP4-activated bone marrow-derived dendritic cells (DCs) (BMDCs) to lean recipient mice was sufficient to promote Th1 cell polarization in WAT and insulin resistance compared to unactivated BMDCs (Moraes-Vieira et al., 2014). This suggests that AAMacs in WAT become dysregulated in the setting of obesity and acquire a pro-inflammatory classical activation state that supports Th1 cell polarization and the development of insulin resistance.

Perspectives and Conclusions

Adipose tissues are diverse in their structure and function and have multiple roles in the regulation of energy balance and weight gain (Figure 1). WAT is essential for triglyceride storage and regulation of glucose homeostasis, and white adipocytes appear to link mammalian metabolic status to immune cell re-

sponses. In addition, WAT contains beige adipocytes that have been shown to be key regulators of energy expenditure and the development of obesity. In the lean state, WAT is populated by type 2 cytokine-associated immune cells including AAMacs, eosinophils, ILC2s, Th2, and iNKT cells as well as anti-inflammatory cells such as T$_{regs}$. These immune cells participate in a complex dialog to maintain optimal immune and adipocyte function (Figure 2). Although the precise mechanisms by which type 2 immune cells in WAT regulate each other, it appears that elicitation of these cell pathways is associated with increased insulin sensitivity, optimal adipocyte mitochondrial function and in some cases elicitation of beige adipocytes within WAT (Figure 3). Conversely, disruption of these immunologic pathways results in impaired adipocyte function characterized by insulin resistance, oxidative stress, impaired respiratory capacity, and triglyceride deposition resulting in adipocyte hypertrophy and weight gain. Therefore, type 2 immune pathways in WAT appear to have protective roles that support maintenance of metabolic homeostasis and limit the development of obesity. This implies that eliciting type 2 immune cell pathways may be a useful strategy to treat or prevent obesity.

However, in the context of obesity, the immunologic milieu of WAT undergoes a dramatic shift from a type 2 to type 1 cytokine-associated inflammatory environment (Figure 4). Type 2 immune cells are decreased or dysregulated (e.g., ILC2s and eosinophils), and in some cases acquire a pro-inflammatory phenotype (e.g., iNKT cells and AAMacs). As type 2 immune cells tend to be associated with protection against obesity, these alterations in type 2 cytokine-associated immunologic pathways may contribute to the development of obesity and subsequent type 1 inflammatory responses. In addition, in obesity there is recruitment of various granulocytes, monocytes, and lymphocytes to WAT. These cell types produce cytokines such as TNF-α, IFN-γ, and IL-1β among others that potentiate type 1 immune responses and enhance antigen presentation to CD4^{+} T cells, polarizing these cells toward a Th1 cell phenotype. In turn, Th1 cells produce additional TNF-α and IFN-γ, establishing a positive-feedback loop resulting in chronic low-grade type 1 inflammation and dysregulated glucose homeostasis. The precipitating factors that initiate type 1 immune responses in WAT are not well understood but may be related to adipocyte cell death (Spalding et al., 2008), hypoxia (Lee et al., 2014b; Sun et al., 2011), the generation of toxic lipid species (Muoio and Newgard, 2006), direct effects of dietary lipids or carbohydrates (Calder, 2002), and translocation of commensal bacteria to WAT (Amar et al., 2011; Cani et al., 2007) among other factors. The apparent multifactorial nature of the type 1 immune response in WAT suggests that targeting downstream inflammatory mediators such as IFN-γ, TNF-α, or IL-1β might have beneficial therapeutic effects in obesity-associated insulin resistance.

Finally, emerging studies have revealed complex immunomodulatory cross-talk between the type 1 and type 2 immune systems, where type 2 inflammation impairs type 1 responses and vice versa (Osborne et al., 2014; Reese et al., 2014; Stelekati and Wherry, 2012). Given the complex, dramatic shift in the immunologic landscape within obese WAT from a type 2 to type 1 cytokine-associated response, targeting a single immunologic factor may not be sufficient to treat obesity and restore

a normal immunologic profile in WAT. Clinical trials employing biologic agents that inhibit IL-1 (anakinra, canakinumab) or TNF-α (infliximab) in patients with type 2 diabetes or metabolic syndrome have been shown to produce moderate or no improvements in glucose metabolism, as assessed by glycated hemoglobin levels or indices of insulin resistance (Larsen et al., 2007; Ridker et al., 2012; Wascher et al., 2011). However the effects of these therapies on body weight or adiposity is not clear. Further research on immunomodulatory biologic therapy to treat obesity should be considered. In addition, the effectiveness of "two-factor" immunomodulatory therapies (e.g., neutralizing TNF-α antibody plus recombinant IL-33) should be explored as potential anti-obesity regimens. Targeting the immune system with biologics could represent a new strategy to limit food intake and/or increase energy expenditure to treat or prevent obesity and related metabolic diseases such as type 2 diabetes. In addition, understanding how current and future treatments for obesity (e.g., diet, exercise, drugs, and surgery) influence the immune system will be important for understanding their mechanisms of action and the potential side effects of treatment. Therefore, a deeper understanding of how the immune and metabolic systems interact to support metabolic homeostasis will be critical for understanding the biology of obesity and for the development of novel treatment and prevention strategies against this disease.

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