

REVIEW

Immune Regulatory Crosstalk in Adipose Tissue Thermogenesis

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ABSTRACT

Brown adipose tissue (BAT) and thermogenic beige fat within white adipose tissue (WAT), collectively known as adaptive thermogenic fat, dissipate energy as heat, offering promising therapeutic potential to combat obesity and metabolic disorders. The specific biological functions of these fat depots are determined by their unique interaction with the microenvironments, composed of immune cells, endothelial cells, pericytes, and nerve fibers. Immune cells residing in these depots play a key role in regulating energy expenditure and systemic energy homeostasis. The dynamic microenvironment of thermogenic fat depots is essential for maintaining tissue health and function. Immune cells infiltrate both BAT and beige WAT, contributing to their homeostasis and activation through intricate cellular communications. Emerging evidence underscores the importance of various immune cell populations in regulating thermogenic adipose tissue, though many remain undercharacterized. This review provides a comprehensive overview of the immune cells that regulate adaptive thermogenesis and their complex interactions within the adipose niche, highlighting their potential to influence metabolic health and contribute to therapeutic interventions for obesity and metabolic syndrome.

1 | Introduction

Adipose tissue is a complex dynamic organ with key roles in whole-body energy homeostasis, insulin resistance, immune response, and thermogenesis. Brown adipose tissue (BAT) is the main site of mammalian nonshivering thermogenesis, in which energy is dissipated as heat through catabolic processes of energy substrates in specialized fat cells, or adipocytes (Cannon and Nedergaard 2004). This program provides small rodents, and neonates of larger mammals, including humans, body temperature defense independent of muscle activity (Seale et al. 2008; Sanchez-Gurmaches et al. 2012; Wang and Seale 2016; Sanchez-Gurmaches and Guertin 2014). Brown adipocytes possess multiple small multilocular lipid droplets and high amounts of mitochondria, indicative of their capacity to promote the uptake of glucose, lipids, and

other macronutrients to enhance energy expenditure. In addition, brown-like adipocytes appear in white adipose tissue (WAT), and these beige (or brite) adipocytes originate from precursor and white adipocyte lineage but undergo “beiging” or “browning” to exhibit a significant capacity for induction of thermogenesis (Wu, Cohen, and Spiegelman 2013). Hence, both brown and beige adipose adipocytes have thermogenic capacity and are collectively referred to as thermogenic adipocyte. Following its rediscovery in adult humans (Nedergaard, Bengtsson, and Cannon 2007; Virtanen et al. 2009; Cypess et al. 2009), thermogenic adipocyte has gained considerable therapeutic interest as its activity is associated with improved glycemic control, body weight regulation, and cardiometabolic health (Becher et al. 2021; Herz et al. 2022; Stanford et al. 2013). As our understanding of the biological significance and heterogeneity of thermogenic adipose tissue has

evolved to harness its benefits to clinical fruition, so too has our appreciation of the rich hematopoietic niche that sustains and regulates the thermogenic phenomena. Here, we review findings and current perspectives on the diverse resident and infiltrating, innate and adaptive immune cell populations that mediate adipose tissue thermogenesis with an emphasis on emerging evidence related to their developmental origin, functions, and physiopathology.

2 | Obesity and the Adipose Tissue

The condition of obesity is extremely complicated and has been studied intensively because of its major effect on health and disease. Body fat, or adipose tissue, is a dynamic organ that lies at the center of the development and progression of obesity. Fat is not simply an energy reservoir; it is also an active endocrine organ that regulates metabolism and exerts a variety of effects on the obesity-related pathophysiology (Guerreiro, Carvalho, and Freitas 2022; Sam and Mazzone 2014). The complex connection between obesity and adipose tissue is essential for comprehending the mechanisms that lead to obesity-related problems. Adipose tissue produces several different molecules and hormones, collectively referred to as adipokines, that influence not just metabolism but also inflammation that is sometimes part of metabolic diseases (Silveira Rossi et al. 2022; Yao, Wu, and Qiu 2022). Obesity causes significant changes in the structure and function of adipose tissue, leading to dysregulation of adipokine secretion and a breakdown of metabolic homeostasis. With the metabolic dysregulation of adipose tissue, fat cells, or adipocytes, become dysfunctional and coordinate signals that propagate a body-wide inflammatory response. In coordination with the signaling pathways of dysfunctional adipose tissue leads not only to the development of insulin resistance but to other metabolic diseases associated with obesity (Ye 2013; Chait and den Hartigh 2020; Zhang et al. 2023). In addition, obesity is a state of chronic low-grade inflammation, a condition sometimes referred to as “meta-inflammation.” This condition is marked by the infiltration of immune cells and by a change in the production of cytokines in the adipose tissue (Charles-Messance et al. 2020; Hotamisligil 2006) (Figure 1). Obesity leads to improperly regulated fat tissue that serves as a depot for immune cells. These cells, particularly T cells and macrophages, release pro-inflammatory factors that contribute to a state of systemic inflammation and metabolic dysfunction. The inflammatory environment in fat tissue exacerbates insulin resistance and the progression of obesity-related diseases (Kawai, Autieri, and Scalia 2021; Trim, Turner, and Thompson 2018).

Adipose tissue is a complex, metabolically active tissue that plays many roles in addition to energy storage. Beyond simply being a place where the body can store excess energy, adipose tissue acts as an energy thermostat. It stores excess energy, and then it can also release energy when needed (Landecho et al. 2019; Luo and Liu 2016). Adipose tissue can be classified into several types based on its various functions and characteristics. The main types are white adipose tissue (WAT), brown adipose tissue (BAT), and beige adipose tissue (Chang et al. 2012; Hanssen et al. 2015; Min et al. 2016; Noriega, Yang, and Wang 2023; Wu et al. 2012) (Figures 2 and 3).

3 | White Adipose Tissue

WAT is an organ comprising mature adipocytes and preadipocytes, as well as various other cell types including macrophages, neutrophils, lymphocytes, dendritic cells, mast cells, and T- and B-lymphocytes (Zhang et al. 2023; Corvera 2021; Lenz et al. 2020; Sun et al. 2020; Wang et al. 2013). Typically, white adipocytes are spherical and contain a large, central lipid droplet that displaces other organelles, including the nucleus, to the cell's periphery. Adipocytes constitute approximately 20%–40% of the total volume of adipose tissue (Corvera 2021), primarily functioning to store triglycerides in unilocular lipid droplets and release them as needed (Lee, Wu, and Fried 2013; Lee et al. 2015). Beyond their role in lipid storage, adipocytes also secrete adipokines, which position adipose tissue as a dynamic endocrine organ (Lehr et al. 2012; Fain et al. 2004).

WAT depots are categorized by their anatomical locations as either subcutaneous or visceral. In humans, visceral fat resides within the peritoneal cavity, including the omental and mesenteric regions (Meza-Perez and Randall 2017; Bjørndal et al. 2011). Subcutaneous fat is located beneath the skin and typically makes up 80% or more of total fat mass, with major concentrations in the abdominal and gluteofemoral areas (Karastergiou and Fried 2017). Visceral fat, situated around the liver, intestines, and other organs, is stored in the omentum, an apron-like structure beneath the abdominal muscles that envelops the intestines. As the omentum fills with fat, it becomes denser and thicker. Although visceral fat constitutes a smaller proportion of total body fat, it significantly impacts various health conditions (Ferrannini et al. 2008; Wajchenberg 2000).

Mice and rats possess analogous visceral (mesenteric, perirenal, and gonadal) and subcutaneous (inguinal and axillary) fat depots. A key difference is that murine gonadal fat drains into the systemic circulation, whereas human visceral fat drains into the portal circulation (Rytka et al. 2011). In humans, subcutaneous fat develops in the abdominal region (abWAT), as well as the femoral (thigh) and gluteal regions, especially in women. Human abdominal subcutaneous fat can be divided into superficial and deep layers, a distinction likely absent in mice. Notably, subcutaneous fat serves as the primary storage site for meal-derived lipids, and upon reaching its storage limit, excess lipids start accumulating in visceral fat. This phenomenon is observed in lipodystrophy, where genetically induced loss of subcutaneous fat, particularly in the gluteal and femoral regions, replicates many metabolic syndrome features, regardless of visceral fat quantity. In mice, subcutaneous fat is divided into posterior and anterior depots. Clinical research indicates that the subcutaneous depot provides metabolic protection. The visceral depot, located around vital organs within the rib cage and abdominal cavity, protects and supplies energy to these organs (Chusyd et al. 2016).

3.1 | White Adipocytes

White adipocytes exhibit a highly variable size, with diameters ranging from 10–20 to 70–100 μm in mice, and are approximately 20–300 μm in humans (Suzuki et al. 2011; Klötting et al. 2010). A defining feature of adipocytes is the large lipid droplet that

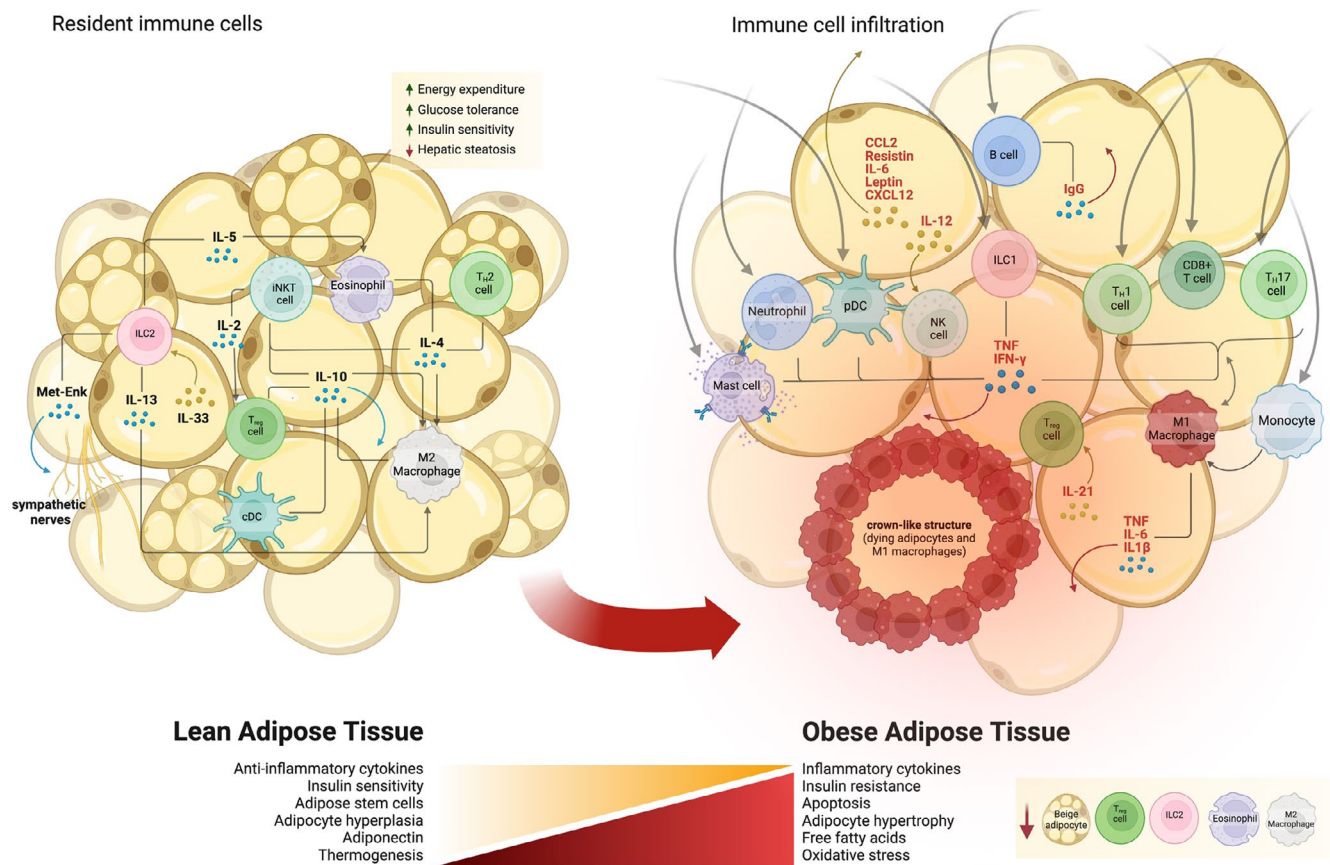


FIGURE 1 | Immune spectrum in lean and obese adipose tissue. Lean adipose tissue contains immune cells that support an anti-inflammatory state, which is essential for maintaining metabolic homeostasis and thermogenic capacity. M2 macrophages, regulatory T cells (Tregs), invariant natural killer T (iNKT) cells, eosinophils, conventional dendritic cells (cDCs), and type 2 innate lymphoid cells (ILC2s) are enriched in lean white adipose tissue (WAT). These cells predominantly secrete anti-inflammatory cytokines, including interleukin (IL)-4, IL-13, and IL-10. IL-33 produced by adipose tissue stimulates ILC2s to release IL-5 and IL-13, which sustain eosinophil activity and M2 macrophage polarization, respectively. Beige adipocytes, interspersed within lean WAT, contribute to thermogenesis and energy balance, driven by intact sympathetic innervation and adrenergic signaling supported by ILC-2-derived methionine-enkephalin (MetEnk). However, in the context of obesity, the adipose tissue microenvironment transitions to a pro-inflammatory state marked by increased infiltration of immune cells, including M1 macrophages, monocytes, neutrophils, dendritic cells, type 1 helper T (Th1) cells, CD8⁺ T cells, natural killer (NK) cells, type 1 innate lymphoid cells (ILC1s), plasmacytoid dendritic cells (pDCs), and B cells. These immune cells secrete elevated levels of pro-inflammatory cytokines such as tumor necrosis factor- α (TNF- α), IL-6, IL-1 β , immunoglobulin G (IgG), and interferon-gamma (IFN- γ). The reduction in eosinophils, ILC2s, and Tregs diminishes M2 macrophage polarization and exacerbate inflammation, further hindering thermogenic activity and energy expenditure. Illustration created using BioRender.

displaces the nucleus to the cell's periphery. The cytoplasm forms a thin layer surrounding the lipid droplet and contains various organelles, with the mitochondrion being the most prominent. These mitochondria are typically small, elongated, and have randomly oriented cristae (Kuri-Harcuch et al. 2019; Mota de Sá et al. 2017). Several markers have been identified in white adipocytes including adiponectin and leptin. There are other markers that has been identified such as Solute carrier family 7 member 10 (SLC7a10/Asc-1 neutral amino acid transporter, y⁺ system) and Serpina3k, Wdnm1-like, Hoxc9, Mpzl2, Ebf3, and Fbox31, Tcf 21, Resistin, and Lpl (Cypess et al. 2013; Gesta, Tseng, and Kahn 2007; Pilkington, Paz, and Wankhade 2021) (Figure 3). Adipocytes are closely associated with and interact with immune cells to maintain metabolic homeostasis and regulate lipid handling and storage. Key immune cells involved include invariant natural killer T (iNKT) cells, regulatory T (Treg) cells, eosinophils, IgM-producing B cells, and alternatively activated M2 macrophages (Feuerer et al. 2009; Lynch et al. 2007; Mantell

et al. 2011; Winer et al. 2011; Wu et al. 2011). The roles of these immune cells will be discussed in detail later in this review.

3.2 | Beige Adipocytes

Beige adipocytes are another crucial cell type in white adipose tissue (Figures 2 and 3). These inducible, multilocular cells can express UCP1 and are thermogenic (Harms and Seale 2013). The term “beige” reflects their intermediate status between brown and white adipocytes (Zhang et al. 2018). In their basal state, beige cells resemble conventional white adipocytes, expressing very low levels of UCP1 and displaying minimal thermogenic activity (Kalinovich et al. 2017). While significant research demonstrates the thermogenic potential of beige adipocytes in rodents, it is critical to acknowledge notable species differences. For instance, in human WAT, while UCP1 mRNA expression increases with cold exposure, there is no corresponding rise in UCP1 protein levels or

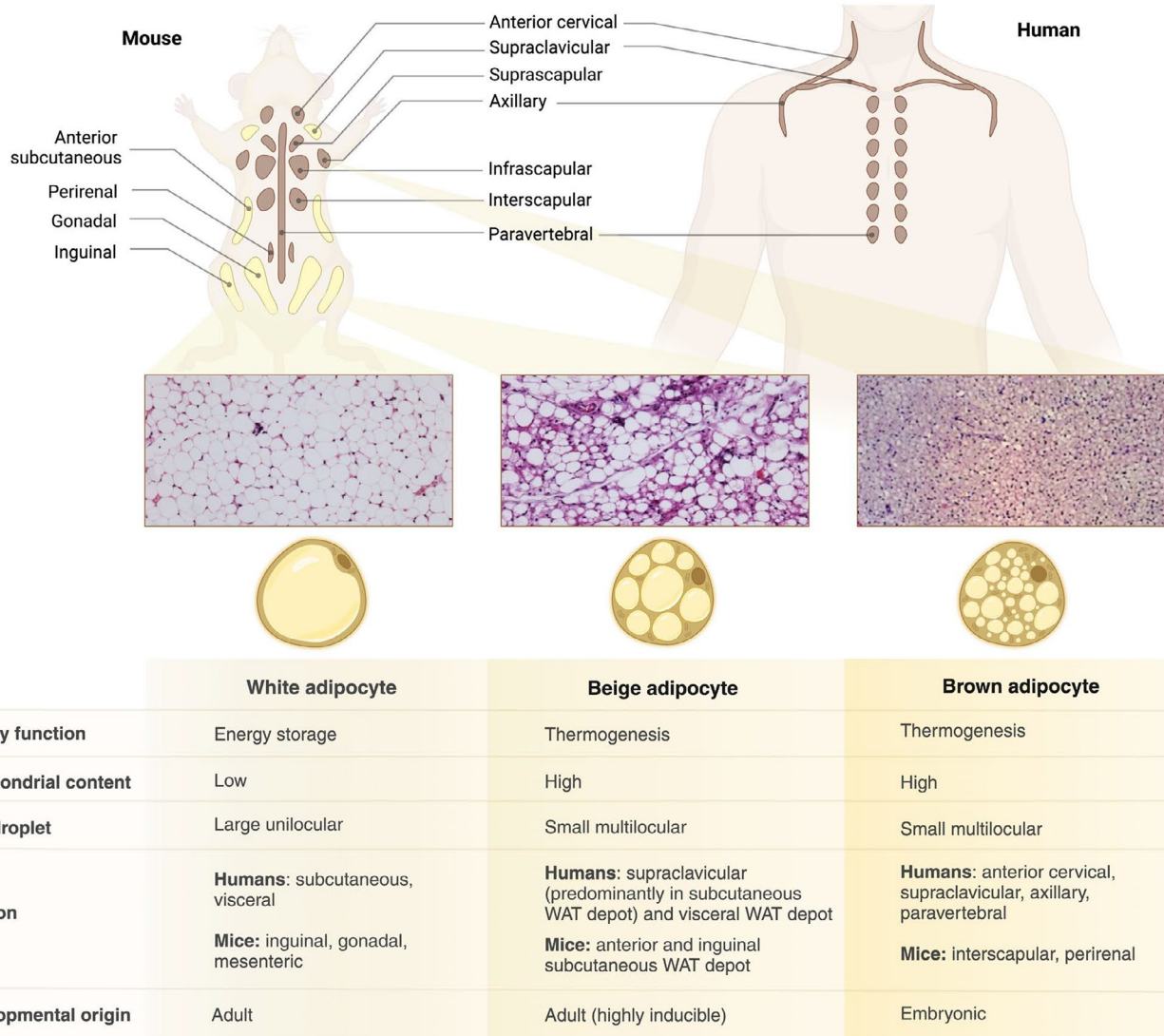


FIGURE 2 | Schematic overview of brown, white, and beige adipocytes. In mice, brown adipose tissue (BAT) development is established during embryogenesis before other depots and maintained in adult mice. Adult mice possess several depots of BAT (Zhang et al. 2018), with the main depots located in the dorsal anterior region and including the interscapular, axillary, and cervical BAT. In addition to these depots, cold and certain other stimuli promote the emergence of beige adipocytes in mice subcutaneous and inguinal white adipose tissue (WAT). Infant humans also possess interscapular BAT anatomically analogous to classical rodent BAT (Lidell et al. 2013). Additional human BAT depots are identified in supraclavicular, axillary, cervical, mediastinal, paraspinal, and abdominal regions (Leitner et al. 2017). The histological section and cartoon representations show that brown and beige adipocytes share many morphological and functional similarities, including many small lipid droplets (multilocular) and densely packed cristae-dense mitochondria with high levels of iron, which give the tissue containing these adipocytes its characteristic brown color. WAT, in contrast, is broadly distributed across the body with adipocytes comprised of large unilocular lipid droplets and fewer mitochondria. Illustration created using BioRender.

measurable WAT activity via PET/CT imaging. Additionally, exercise has not been shown to impact UCP1 mRNA or protein levels in human WAT biopsies, nor is UCP1 expression significantly correlated with BMI in humans (Dinas et al. 2020). These findings underscore that, while immune cell-adipocyte crosstalk facilitates thermogenesis in rodents, human WAT may contribute less substantially to thermogenic processes, necessitating further research to bridge this gap. Beige precursor activation or transdifferentiation of white adipocyte to beige adipocyte occurs in response to stimuli such as cold exposure, β 3-adrenergic receptor agonists, thiazolidinediones (TZDs), and various peptides and hormones (Wang et al. 2013; Lim et al. 2012; Xiao et al. 2015). Several characteristics distinguish beige adipocytes from white and brown adipocytes.

For instance, in mice, they express markers such as CD137, T-box1 (TBX1), and transmembrane protein 26 (TMEM26), which are not highly expressed in white or brown adipocytes (Wu et al. 2012). Additionally, beige adipocytes expressing CD137 and TMEM26 show high expression of genes associated with mitochondria and thermogenesis, including *Cox7a*, *Cox8b*, *Prdm16*, and *Fgf21* (Wu et al. 2012; Sharp et al. 2012; Ussar et al. 2014). Beige adipocytes, being WAT cells, derive from *Myf5*⁻ precursors that express *Pax3*, *Cd81*, *Pdgfra*, and *Acta2* which differentiate when induced, although some may arise from transdifferentiated white adipocytes after the same adrenergic stimulation (Sanchez-Gurmaches and Guertin 2014; Berry, Jiang, and Graff 2016; Lee et al. 2012; Vishvanath et al. 2016) (Figure 2). WAT beiging—adaptive

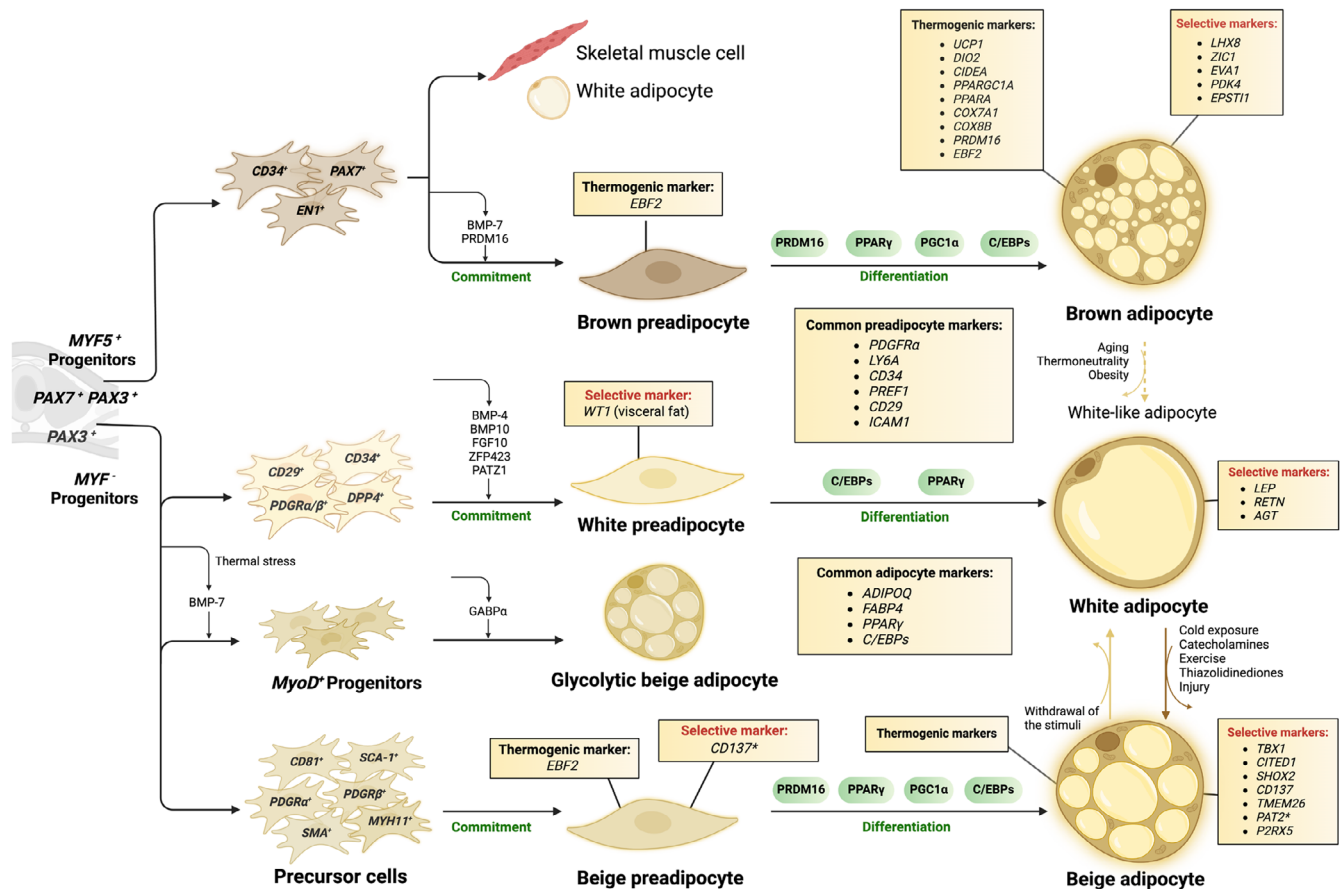


FIGURE 3 | Legend on next page.

thermogenic fat biogenesis from a $PDGFR\alpha^+$ $SCA1^+$ $CD81^+$ precursor cell subset (Oguri et al. 2020) can be stimulated by binding of sympathetic neuron-released CL to β -adrenergic receptors (β -AR) in adipocytes as well as adenosine binding the A_{2A} receptor (Gnad et al. 2014), and factors like thiazolidinediones and fibroblast growth factor (FGF21) (Wang and Seale 2016).

4 | Brown Adipose Tissue

Brown adipose tissue (BAT) is a constitutively thermogenically active type of fat that regulates body temperature; in mice, it exists in periaortic, perirenal, axillary, subscapular, and interscapular depots (Frontini and Cinti 2010; Cinti 2005; de Jong et al. 2015; Waldén et al. 2012) (Figures 2 and 3). In human infants, BAT is predominantly interscapular, which diminishes with age, and thereafter exists mostly in supraclavicular and paravertebral depots (Nedergaard, Bengtsson, and Cannon 2007; Ouellet et al. 2012; Yoneshiro et al. 2011). BAT develops from precursor lineages distinct from WAT adipocytes (Figure 3), but human supraclavicular BAT is more similar to the thermogenically active beige adipocytes—so called because of the darker color conferred by the proliferation of mitochondria—that arise in WAT than the classical BAT in mice (Cypess et al. 2013; Sharp et al. 2012; Jespersen et al. 2013; Lidell et al. 2013) (Figure 2). Brown adipocyte precursor cells, unlike white adipocyte precursors, develop in the embryonic dermomyotome and express *En1*, paired-box protein 7 (*Pax7*), *Pax3*, and myogenic factor 5 (*Myf5*), of which *Pax3* and *Myf5* are sufficient to differentiate

human iPSCs into brown adipocytes (Seale et al. 2008; Lepper and Fan 2010; Rao et al. 2023). BAT can be stimulated by binding of sympathetic neuron-released catecholamines (CL) to β -adrenergic receptors (β -AR) as well as adenosine binding the A_{2A} receptor, and factors like thiazolidinediones and FGF21.

5 | Adipose Tissue Thermogenesis

BAT activity is facilitated by UCP1, a mitochondrial protein that uncouples respiration from ATP synthesis at the ETC by equalizing the H^+ gradient across the inner membrane, driving fatty acid processing toward β -oxidation and heat generation (Cogliati, Enriquez, and Scorrano 2016; Heden et al. 2019; Kopecký et al. 1996). Lipolysis and the thermogenic program marked by UCP1 can be activated by the binding of norepinephrine released by sympathetic neurons during cold exposure to adrenergic receptors (Cho, Patel, and Rajbhandari 2023). Beige adipocytes express UCP1 and generate heat in response to sympathetic activation, under which they proliferate chiefly in subcutaneous WAT (sqWAT) in response to chronic exposure to cold and other β -adrenergic stimulation (Wang and Seale 2016; Harms and Seale 2013; Isler, Hill, and Meier 1987; McCormack 1982; Vallerand, Pérusse, and Bukowiecki 1987).

UCP1 expression, however, is not uniform in thermogenic adipose tissue, so that some thermogenic adipocytes generate heat in a UCP1-independent manner, through mechanisms like futile creatine cycling (Kazak et al. 2015; Shabalina et al. 2013).

FIGURE 3 | Source of thermogenic adipocytes in adipose tissues. *De novo* differentiation and transdifferentiation trajectories of major adipocyte populations involve designated adipocyte progenitors or precursors (APCs) which commit to becoming preadipocytes and subsequently differentiate into mature adipocytes. The current model of adipocyte development traces the shared embryonic precursors and progenitors of adipose tissue as the multipotent mesenchymal stem cells of the mesoderm (Sanchez-Gurmaches and Guertin 2014; Chau et al. 2014; Sebo et al. 2018; Sebo and Rodeheffer 2019). Functionally separating APCs from the heterogeneous stromal vascular fraction (SVF) cell populations, through fluorescence-activated cell sorting (FACS) or single-cell profiling by the consensus precursor cell surface markers unique to the adipocyte fate (such as CD34⁺CD29⁺Sca1⁺CD81⁺CD24^{+/-}), has enabled the identification of multiple adipocyte subtypes originating from multiple lineages. For instance, distinct subpopulations of beige adipocytes: glycolytic beige adipocytes that arise from MyoD⁺ progenitors in inguinal WAT depots in a manner dependent on GA-binding protein- α (GABP α) (Chen et al. 2019), and cold-induced α SMA-derived beige adipocytes were recently identified (Jiang, Berry, and Graff 2017). Beige adipocytes also arise from a unique subset of APCs positive for platelet-derived growth factor receptor- α (PDGFR α), stem cell antigen 1 (SCA1), and myosin heavy chain 11 (MYH11⁺) in subcutaneous white adipose tissue (WAT) marked by cell surface protein CD81 (Oguri et al. 2020). During prenatal development, BAT depots form before other adipose tissue depots and emerge from the dermomyotomal progenitors expressing somite markers myogenic factor 5 (MYF5), paired box 7 (PAX7), and engrailed homeobox 1 (EN1) that also give rise to myocytes and a subset of white adipocytes (Seale et al. 2008; Sanchez-Gurmaches et al. 2012; Wang and Seale 2016; Sanchez-Gurmaches and Guertin 2014; Lepper and Fan 2010; Sebo and Rodeheffer 2019). Secretory factors, including transcriptional factor PR domain zinc finger protein 16 (PRDM16) and morphogenetic protein (BMP)-7, induce APCs commitment to brown preadipocytes, whereas BMP-4, BMP-10, and fibroblast growth factor 10 (FGF10) induce MYF5-cell commitment to white preadipocytes. Early B-cell factor 2 (EBF2) expression defines thermogenic adipocyte precursors and regulates the expression of transcriptional factor PRDM16 in tandem with peroxisome proliferator activated receptor- γ (PPAR γ) (Wang et al. 2014). As the major regulators of adipocyte cell fate, transcription factors PPAR γ and CCAAT/enhancer-binding protein α and β (C/EBPs) are involved in all types of preadipocyte differentiation, whereas brown and beige adipocytes require additional factors including PPAR γ co-activator-1 alpha (PGC-1 α). Key molecular markers common in beige, brown, and white preadipocytes such as preadipocyte factor 1 (PREF1) (Sul 2009), the recently identified CD29 (also known as integrin β 1) (Xue et al. 2015) and intercellular adhesion molecule (ICAM1) (Chen et al. 2023) are indicated as common adipocyte markers. Thermogenic markers are found in both beige and brown fat, but not in white fat. Selective markers include wims tumor 1 (*WT1*), which is expressed only in visceral white preadipocyte (Chau et al. 2014); LIM homeobox protein 8 (LHX8), zinc finger protein of the cerebellum 1 (ZIC1), epithelial V-like antigen 1 (EVA1), pyruvate dehydrogenase kinase 4 (PDK4) and epithelial stromal interaction 1 (EPSTI1) which are BAT selective (versus in beige) (Wu et al. 2012; Sharp et al. 2012; Petrovic et al. 2010). Beige-fat-selective markers include T-box 1 (TBX1), Cbp/p300-interacting transactivator with Glu/Asp-rich carboxy-terminal domain 1 (CITED1), short stature homeobox 2 (SHOX2), CD137, transmembrane protein 26 (TMEM26), proton-coupled amino acid transporter 2 (PAT2) and P2X purinoceptor 5 (P2RX5) (Wu et al. 2012; Sharp et al. 2012; Ussar et al. 2014; Lidell et al. 2013; Petrovic et al. 2010). ADIPOQ, adiponectin; AGT, angiotensinogen; C1Q, collagen domain containing; CD, cluster of differentiation; CIDEA, cell death-inducing DFFA-like effector A; COX, cytochrome c oxidase; DIO2, deiodinase, iodothyronine, type II; FABP4, fatty acid-binding protein 4; LEP, leptin; LY6A, lymphocyte antigen 6 complex, locus A; PATZ1, POZ/BTB and AT hook containing zinc finger 1; RETN, resistin; UCP1, uncoupling protein 1; ZFP423, zinc finger protein 423. *Cell surface markers. Illustration created using BioRender.

Interscapular BAT cells can be further differentiated into groups expressing high adiponectin, high β 3-AR gene (*Adrb3*), and accordingly high *Ucp1*, or low adiponectin and displaying large lipid droplets, low mitochondrial number, and higher basal oxygen consumption rate. This latter group of cells, like lipid-scavenging white adipocytes, express more fatty acid uptake genes than their more thermogenically active counterparts (Chang et al. 2012; Warner et al. 2016; Zhao et al. 1994; Song et al. 2020). Conversely, aging and the removal of thermogenic signals—such as housing at room temperature or the cessation of an acute chemical stimulus—can lead BAT adipocytes to acquire white adipocyte morphology and become less thermogenically active, although such whitened cells can revert to a brown phenotype upon signal reappearance (Berry, Jiang, and Graff 2016; Félix-Soriano et al. 2021; Gonçalves et al. 2017; Raiko et al. 2020).

In humans, the thermogenic activity of BAT is critical in the non-shivering thermogenic response to cold, and higher BAT activity and the consequent higher resting energy expenditure are associated with lower white adiposity and improved metabolic health with age (Becher et al. 2021; Herz et al. 2022; Raiko et al. 2020). Blood circulation through BAT accordingly increases upon exposure to cold, facilitating uptake of glucose and free fatty acids (FFA), which are used to generate heat along with the triglycerides stored in the cells (Virtanen et al. 2009; Orava et al. 2011). Cold exposure induces PDGFR α ⁺ stromal cell proliferation and

adipogenesis from a *Gdf10*-, *Clec11a*-, *Fbln1*-expressing subset in BAT, in which β 1-adrenergic signaling is normal in vivo although β 3-adrenergic stimulation alone is sufficient to induce immune cell accumulation and neogenesis (Burl et al. 2022).

6 | Immune Cells in the Adipose Tissue Microenvironment

The immune cells residing within the microenvironment of the adipose tissue play pivotal role in the modulation of metabolic functions and the development of specific diseases related to obesity (Figure 1). Adipose tissue is not just a body fat reserve but also is an active endocrine organ that coordinates metabolism business with the release of adipokines and controls the immune responses. In individuals with a normal weight, there is an increased number of mostly resident and adaptive immune cells present in the adipose tissue that support metabolic homeostasis and limit inflammation (Feuerer et al. 2009; Wu et al. 2011; Lumeng, Bodzin, and Saltiel 2007; Nishimura et al. 2009; Rocha et al. 2008a).

7 | Innate Immune Cells

The innate immune cells found within the surrounding environment of adipose tissues have been shown to be instrumental in

regulating metabolic equilibrium, especially in the clinical situations of obesity and the associated metabolic complications. Among these cells are the macrophages, which are the most populous and heterogeneous cells in the adipose tissue immune cell compartment. In lean adults, most of tissue macrophages in the adipose tissue (ATMs) have an M2 phenotype mainly related to insulin sensitivity and anti-inflammatory agents (Figure 1). Such M2 macrophages synthesizing anti-inflammatory cytokines are often associated with promotion of tissue healing (Lumeng, Bodzin, and Saltiel 2007; Park and Kim 2018; Suganami and Ogawa 2010).

However, during the transition to obesity, this phenomenon is quickly shifted toward an M1 macrophage dominated by the synthesis of pro-inflammatory mediators like TNF- α and IL-6 (Figure 1). The causes of this transition include pathological expansion of adipocytes and dysfunction of adipose tissue leading to local lower oxygen tension and differential expression of monocyte chemotactic protein succeeded in embedding mononuclear cells within the adipose tissues (Feuerer et al. 2009; Lumeng, Bodzin, and Saltiel 2007; Gericke et al. 2015; Hotamisligil, Shargill, and Spiegelman 1993; Lumeng et al. 2007; Weisberg et al. 2003; Xu et al. 2003).

The process of macrophage infiltration into adipose tissue is not merely a passive process, it is subject to the metabolic landscape of the tissue. In obesity, the enlargement of adipocytes and the ensuing remodeling of the tissue creates an inflammatory milieu conducive to the recruitment and activation of macrophages. Depending on the specific niche, these macrophages may exhibit a diversity of functional characteristics that are modulated by nutrients and interaction with other immune cells (Cho et al. 2016; Morris et al. 2013; Vandannagsar et al. 2011) (Figure 1). Moreover, besides the macrophages, other cells of innate immunity like neutrophils, eosinophils, and innate lymphoid cells also shape the immune architecture of the adipose tissue. Neutrophils are among the first effector cells recruited to adipose tissues in response to inflammatory mediators and have the potential to aggravate inflammation through the generation of reactive oxygen species and pro-inflammatory cytokines (Guzik et al. 2017; LaMarche, Kohlgruber, and Brenner 2018; Mraz and Haluzik 2014).

Mast cells (MCs) are innate immune cells found in various tissues, including WAT. They produce a variety of pro-inflammatory cytokines. These granular, long-lived cells originate from CD34+/CD117+ pluripotent progenitor cells (Poglio et al. 2010; Ribatti 2016). Eosinophils, on the other hand, have been shown to promote the accumulation of alternatively activated macrophages (M2) and help maintain tissue homeostasis in lean adipose tissue (Wu et al. 2011). It has also been shown that the presence of ILCs, especially type 2 ILCs, can contribute to the metabolism of the adipose tissue since these cells are capable of producing cytokines that can lead to M2 macrophage differentiation and enhance tissue repair processes (Abe et al. 2022; Oishi and Manabe 2016; Yin, Zhao, and Pei 2022).

In summary, innate immune cells, particularly macrophages, play a central role in the adipose tissue microenvironment, influencing both local and systemic metabolic processes. The transition from a lean to an obese state is marked by significant changes in the composition and function of these immune cells,

leading to a chronic low-grade inflammatory state that contributes to insulin resistance and other metabolic disorders.

8 | Adaptive Immune Cells

The adaptive immune cells present in the adipose tissue microenvironment play a significant role in modulating inflammation and metabolic processes, particularly in the context of obesity. Among these cells, T cells and B cells are the primary components of the adaptive immune response, and their interactions with adipocytes and innate immune cells are critical for maintaining homeostasis and regulating inflammation (Figure 1). T cells, which include various subsets such as CD4+ helper T cells, CD8+ cytotoxic T cells, and regulatory T cells (Tregs), are abundant in adipose tissue and are involved in both pro-inflammatory and anti-inflammatory responses (Onodera et al. 2015; Priceman et al. 2013; Yang et al. 2010). In lean individuals, T_{regs}, which can account for a substantial proportion of T cells in adipose tissue, helps to maintain an anti-inflammatory environment by producing cytokines such as IL-10 and TGF- β , which promote tissue repair and metabolic homeostasis (Vignali, Collison, and Workman 2008; Munoz-Rojas and Mathis 2021).

B cells also play a crucial role in the adaptive immune response within adipose tissue. They are involved in the production of antibodies and can contribute to the inflammatory milieu by secreting pro-inflammatory cytokines (Boothby, Hodges, and Thomas 2019). Recent studies have shown that B cell accumulation in adipose tissue occurs early in the progression of obesity and is associated with the activation of T cells and macrophages (Winer et al. 2011; Ioan-Facsinay et al. 2013; McLaughlin et al. 2014; Oleinika et al. 2022). This B-cell-mediated inflammation can further exacerbate insulin resistance and metabolic dysfunction, highlighting the interconnectedness of different immune cell types in adipose tissue (Oleinika et al. 2022).

Natural killer T (NKT) cells are a unique subset of T cells that exhibit characteristics of both T cells and natural killer (NK) cells, and they play a significant role in regulating inflammation and metabolism, particularly within adipose tissue. These cells can produce regulatory cytokines known to promote M2 macrophage polarization and enhance insulin sensitivity. The activation of NKT cells in adipose tissue has been shown to improve systemic glucose tolerance and mitigate the adverse effects of obesity, indicating their protective role in metabolic health (Ji et al. 2012; Martin-Murphy et al. 2014). To provide a more comprehensive overview of the immune cells and cytokines within the adipose tissue microenvironment, a summary of reported immune cells within adipose tissue and their secretion profiles is presented in Table 1 and Figure 4.

9 | Immune Cells and Their Roles in Adipose Thermogenesis

Adipose tissues are the foremost energy storage and management tissues, and adaptive and innate immune cells are also known to contribute to adipose homeostasis by regulating adipose tissue thermogenesis and energy expenditure through the generation of heat, or non-shivering thermogenesis (Figure 4).

TABLE 1 | Summary of reported immune cell population dynamics and their functions in thermogenic adipose tissue.

Immune cell type	Lineage	Cell type	Subsets	Cell secretion factors	Functions in thermogenic adipose tissue
Innate immunity	Myeloid	Macrophage	M1	TNF- α IL-6 IL-1 β IL-18 (Weisberg et al. 2003)	Release of pro-inflammatory cytokines suppress the induction of <i>UCPI</i> gene expression in WAT and TAT, impairing thermogenic potential (Sakamoto et al. 2013; Shan et al. 2017; Gonzalez-Hurtado et al. 2018)
			M2	acetylcholine (Knights et al. 2021) CCL22 (Yuan et al. 2024) IL-10 (Kim et al. 2004; Blüher et al. 2005) Slit-3 (Wang, Tang, et al. 2021) TGF- β 1 (Sciaretta et al. 2024)	Macrophage population is widely heterogeneous in their functions: SAMs suppress thermogenic activation via NE transporter SLC6A2 and the enzyme MAOA (Pitrzalska et al. 2017); ATM was found to degrade NE in an NLRP3 inflammasome-dependent manner (Camell et al. 2017); LAM-derived TGF- β 1 suppresses brown adipocyte identity (Sciaretta et al. 2024), whereas ChAMs secrete acetylcholine in β 2-AR activation dependent manner for increased beige adipocyte biogenesis and thermogenesis (Jun et al. 2020, 2018). M2 macrophages maintain adipocyte turnover (Nawaz et al. 2017), and promote cold-induced differentiation of beige adipocytes from <i>PDGFRα</i> + stromal cells (Qiu et al. 2014; Rao Rajesh et al. 2014). Macrophage-derived Slit-3 and CCL22 enhance thermogenesis by binding to ROBO1 receptor on sympathetic neurons (Wang, Tang, et al. 2021) and CCR4 for eosinophil recruitment (Yuan et al. 2024), respectively. Independent of the SNS, macrophages block <i>ETS1</i> expression in adipocyte progenitors to facilitate beige adipogenesis (Wu et al. 2024)
		Monocyte	Classical, Non-classical, Intermediate	CCL2/Mcp-1 (Kanda et al. 2006)	Support M2 macrophage polarization (Rosina et al. 2022), and TAT homeostasis by promoting tissue expansion (Gallerand et al. 2021)
		Mast cell	—	IL-6 IL-16 IL-1 β IL-1Ra (Divoux et al. 2012)	Mast cells engage in direct communication with progenitor cells via molecules such as histamine and serotonin. However, it remains to be determined whether this interaction enhances or impairs TAT functions (Finlin et al. 2017; Zhang et al. 2019)
		Neutrophil	—	Neutrophil gelatinase-associated lipocalin S100A8/A9 (Feng et al. 2023; Wang et al. 2024)	Inhibition of thermogenic activity by proteins potentially secreted by neutrophils could suppress thermogenesis (Ishii et al. 2017; Feng et al. 2023; Wang et al. 2024)
		Eosinophil	—	IL-4 IL-13 (Wu et al. 2011) Metnl IL-33 (Knights et al. 2020)	Induce M2 macrophage polarization and enhance WAT innervation (Meng et al. 2022). Release of IL-4 promotes beige adipocyte biogenesis along with IL2-derived IL-13 (Lee et al. 2015; Qiu et al. 2014). Mice lacking eosinophils or eosinophil dependent signaling exhibit impaired thermogenesis and energy expenditure (Wu et al. 2011; Molofsky et al. 2013)

(Continues)

TABLE 1 | (Continued)

Immune cell type	Lineage	Cell type	Subsets	Cell secretion factors	Functions in thermogenic adipose tissue
Adaptive immunity	Lymphoid	Innate Lymphoid Cell (ILC)	ILC1 ILC2 ILC3	IL-5 IL-13 (Molofsky et al. 2013) MetEnk (Brestoff et al. 2015)	IL-33 induces ILC2 secretion of MetEnk peptides that bind to OPRD1 (higher expression in WAT) and OGR1 (higher expression in BAT) to upregulate <i>UCPI</i> expression and promote browning of WAT (Brestoff et al. 2015). ILC2 also activates and recruits M2 macrophages and eosinophils (Lee et al. 2015; Molofsky et al. 2013; Brestoff et al. 2015)
		NKT cell	Type 1 Type 2 NKT-like	IL-2 (Lynch et al. 2015) IL-4 IL-10 (Lynch 2014) fgf21 (Lynch et al. 2016)	Modulation of Treg homeostasis and function occurs through IL-2 secretion, while the induction of fgf21 production promotes WAT browning by stimulating adipocyte glucose uptake (Lynch et al. 2016, 2015)
		$\gamma\delta$ T cell	V δ 1 V δ 2	IL-17F (Kohlgruber et al. 2018) TNF- α (Mehta, Nuotio-Antar, and Smith 2015)	δ T-cell-derived IL-17F stimulates innervation of TAT and promotes browning and thermogenesis signaling through upregulating the expression of tyrosine hydroxylase via adipocyte IL-17RC (Kohlgruber et al. 2018; Hu et al. 2020)
		CD8 ⁺ T cell	Tc	IFN- γ (Moysidou et al. 2018)	Inhibition of <i>UCPI</i> expression and cold-induced thermogenesis through IFN signaling (Moysidou et al. 2018)
		CD4 ⁺ T cell	Th Treg Th17	IFN- γ IL-4 IL-17 IL-10 (Winer et al. 2009) CCL18 (Duncan et al. 2003; Subramanian et al. 2023)	CD4 ⁺ T cells in TAT differentiate toward Tregs when subjected to cold exposure (Kälén et al. 2017; Becker et al. 2019), and Tregs promote browning through A2aR pathway (Kong et al. 2023). T cells are a source of IL-10, which has been shown to inhibit thermogenesis (Rajbhandari et al. 2018, 2019)
		S100A8/A9+ T cell	—	—	Inhibit sympathetic innervation and thermogenic capacity by suppressing genes involved in axon guidance in brown adipocytes (Feng et al. 2023)
		B cell	B2 cell Breg cell	IgG (Winer et al. 2011) IL-10 (Nishimura et al. 2013)	B cells comprise more than 20% of the immune cell population in TAT, and their numbers are suggested to increase with obesity (Peterson, Flaherty, and Hasty 2017). B cells also produce IL-10, an antithermogenic cytokine (Rajbhandari et al. 2018, 2019)

Abbreviations: A2aR, adenosine A2a receptor; ATM, adipose tissue macrophage; Breg, regulatory B cells; CCL, chemokine C-C motif ligand; cDCs, conventional dendritic cells; ChAM, cholinergic adipose macrophage; CXCL, chemokine C-X-C motif ligand; FGF-21, fibroblast growth factor 21; IFN- γ , interferon gamma; IgG, immunoglobulin G; IL, interleukin; IL-17RC, IL-17 receptor C; IL-17, IL-17 receptor C; IL-17C, IL-17 receptor C; IL-17, invariant natural killer T cell; LAM, lipid-associated macrophages; Mcp-1, monocyte chemoattractant protein-1; MetEnk, methionine-enkephalin; METKNL, meteorin-like, cometin and subfatin; MOAO, monoamine oxidase a; NE, norepinephrine; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; OGR1, opioid growth factor receptor; OPRD1, δ 1 opioid receptor; pDCs, plasmacytoid dendritic cells; ROBO1, roundabout guidance receptor 1; SAM, sympathetic neuron associated macrophage; SLC6a, solute carrier family 6; SLIT-3, slit guidance ligand 3; SNS, sympathetic nervous system; TAT, thermogenic adipose tissue; TGF- β , transforming growth factor beta; Th, helper T cell; Treg, T regulatory T cells; *UCPI*, uncoupling protein 1; WAT, white adipose tissue; β 2-AR, β 2 adrenergic receptor; β 3-AR, β 3 adrenergic receptor; $\gamma\delta$ T cell, gamma-delta T cells.

CD4⁺ T helper WAT plays a crucial role in whole-body metabolic disorders; in humans with cardiovascular disease, Type II diabetes, or both, bactericidal chemotactic protein C–C motif chemokine ligand 18 (CCL18) and the dendritic, helper-T, naive-T, CD4⁺ CD8-T cells that it attracts accumulate in WAT. CCL18 yields no direct effect on mature adipocytes, but treating CD4⁺ T cells with CCL18 in vitro induces the release of high levels of IFN γ and TGF- β into the culture media, which increases glycerol release in adipocytes treated with that conditioned media (Duncan et al. 2003; Subramanian et al. 2023).

Foxp3⁺ T_{reg} cells in visceral white adipose tissue (VAT) arise from conventional CD4⁺ T cells that invade from lymphoid tissues, then mature in the presence of antigen presentation by MHCII on AT-resident macrophages and expand under soluble mediators like IL33, produced by a mesenchymal stromal cell subset distinct from adipocyte precursor cells (APCs) (Torres et al. 2024). In the absence of CD40 in mice, VAT-resident macrophage MHCII expression decreases, as does CD3⁺ CD4⁺ Foxp3⁺ T-cell recruitment, although CD3⁺ CD4⁺ Foxp3⁺ T_{reg} number remains unchanged. In humans with Type II diabetes, CD40 expression correlates positively with CD80 and CD86, indicating a role in controlling MHCII and CD86 expression in macrophages and consequent CD4⁺ T-cell expansion, unlike in mice (Morris et al. 2016).

In obese mice, the introduction of IL33 induces T_{reg} expansion in VAT and an improvement in metabolic health. The differentiation of these T_{reg} cells and maintenance of transcriptional architecture depends on IL33 signaling via myeloid differentiation factor MyD88 and the ST2 receptor, which is evolutionarily conserved between T_{reg} cells in mouse VAT and human omental AT (Vasanthakumar et al. 2015). IL33 produced by PDGFR α ⁺ Pdpn⁺ mesenchymal stem cells regulates the expansion and activity of ILC2s and T_{reg} cells, with IL33-dependent T_{reg} cells being more abundant in males, presumably because of testosterone's facilitation of MSC differentiation (Spallanzani et al. 2019).

12 | Effects on WAT

The induction of T_{reg} cell differentiation by AT-resident macrophages differs by metabolic state, with macrophages from lean AT inducing PPAR γ ^{high} T_{reg} cells in vitro and obese AT macrophages inducing PPAR γ ^{low} T_{reg} cells (Onodera et al. 2015). This is likely due in part to differing proportions of M1 inflammatory and M2 anti-inflammatory macrophages between obese and more metabolically active WAT. Mice homozygous for the *Fas*^{lpr} lymphoproliferation spontaneous mutation are used ordinarily for their development of systemic autoimmunity. They also exhibit lower fat mass, smaller adipose depot size, better glucose tolerance, lower HFD-induced obesity susceptibility, and higher basal body temperature, indicative of thermogenic fat loss which can also be attributed to the proliferation of aberrant T cells. The WAT of MRL/lpr (*Fas*^{lpr}-homozygous) mice shows higher tyrosine hydroxylase (TH), UCP1, IL4, and IL10 under HFD, with more acute UCP1 upregulation and tissue beiging after cold challenge, indicating that T cells support a preexisting thermogenic state more sensitive to further adrenergic activation. IL4 and IL10 also increase M2 macrophage polarization, so that MRL/lpr mice display a lower M1:M2 ratio in WAT relative to

MRL/Mpj controls carrying WT *Fas*, further promoting beiging (Choi et al. 2020).

AT-resident regulatory and conventional T cells can be activated by AT dendritic cells, identified as CD11c⁺ CD64⁻ (to distinguish from CD11c⁺ CD64⁺ M1 macrophages) or CD11b⁻ CD11c⁺ expressing higher MHCII than CD11b⁺ CD11c⁺ M (Cho et al. 2016). T-cell regulation by MHCII includes its expression on adipocytes, where its absence decreases adipocytes' capacity to stimulate IFN γ expression by Th1 cells, thereby releasing IFN γ inhibition of IL33 and increasing adipose T_{reg} abundance under HFD (Molofsky et al. 2015). In HFD-induced obesity, MHCII increases the expression in obese VAT T_{reg} cells of inhibitory coreceptors like cell death protein 1 and OX40, inducing AT inflammation and suppressing metabolism (Bradley et al. 2022).

CD56⁻ NKp46⁺ EOMES⁺ iNKT cells present in AT also regulate adipose tissue function by modulating the proliferation of immunosuppressive T-regulatory cells (T_{reg}) via IL2 (Chinen et al. 2016; Haugstøyl et al. 2023; McQuaid et al. 2020). Interrupting this signal with subcutaneous injection of IL2-mAb complexes causes selective expansion of Foxp3⁺ T_{reg} cells and a resulting increase in expression of canonical thermogenic genes in sqWAT, especially *Ucp1*, *Pgc1a*, *Prdm16*, and *Cidea*, as well as genes related to lipolysis (including *Lipe* and *Plin1*) and fatty acid β -oxidation (such as *Acox1* and *Acs1l*) (Kälin et al. 2017).

T_{reg} expansion is also regulated by $\gamma\delta$ T cells, an innate subcutaneous adipose tissue-resident PLZF⁺ population that produces IL17A and TNF. In the absence of $\gamma\delta$ T cells or either cytokine, production of IL33 by PDGFR α ⁺ and Pdpn⁺ stromal cells is reduced, and conversely ST2⁺ T_{reg} cells fail to accumulate (Kohlgruber et al. 2018). T_{reg} activation is potentiated by β -adrenergic stimulation, via cold exposure or a direct β 3-adrenergic receptor (β 3-AR) agonist like mirabegron. In humanized mice, short-term cold exposure activates expression of *BORCS6* (encoding Ragulator-interacting protein C17orf5) in CD4⁺ T cells, blocking mTORC1 signaling and lending naïve T cells from subcutaneous white fat (sqWAT) a greater capacity to be induced in vitro into T_{reg} cells (Becker et al. 2019). Three days at 4°C is sufficient to increase B, NK, and CD4⁺ B cells in WAT relative to room temperature, but direct β 3-AR stimulation with catecholamines (CL 316,243; CL) recruits more lymphoid-origin immune cells, chiefly CD19⁺ B and CD8⁺ and CD4⁺ T, demonstrating that the use of CL injection as a thermogenic stimulus may be sufficient for adipocytes—the different patterns of remodeling nevertheless result in the same proportion of UCP1⁺ cells—but cannot mobilize and mimic the complete immune response seen under cold challenge (Becker et al. 2019).

CD4⁺ activation is dependent on STAT6 signaling, as demonstrated by increased *Stat6* expression in WAT CD4⁺ cells in vivo following cold exposure or direct CL treatment, and existing higher *Stat6* levels in CD4⁺ cells in BAT. Pharmacological inhibition of STAT6 in vivo and *Stat6*^{-/-} knockout blunt both T_{reg} induction and expression of *Ucp1* in response to β 3-AR stimulation, indicating the importance of STAT6 to T_{reg} responsiveness to CL or cold challenge, and the importance of T_{reg} cells to adipocytes' responses to the same β 3-AR stimulation (Kälin et al. 2017). This capacity to reduce WAT mass and support metabolic health likely comes from T_{reg} cells' amplification of β 3-AR stimulation

in sqWAT, but not VAT. Adoptive transfer of T_{reg} cells enhances beige adipogenesis and thermogenic gene expression in sqWAT in response to 7 days' CL injection, specifically by suppressing M1 macrophage markers *Tnfa*, *iNos*, *Il6*, and *Ip10* and activating M2 markers *Mrc1*, *Arg1*, and *Il10* in sqWAT in vivo and in bone marrow-derived macrophages in vitro. Adoptive transfer of T_{regs} from healthy female mice to obese females reduces gWAT mass without additional thermogenic signals, and in the presence of CL reduces sqWAT mass, indicating a role in amplifying systemic thermogenic fat loss (Fang et al. 2020).

β 3-AR stimulation also induces beige adipogenesis and thermogenesis in VAT, in which $ST2^+ KLRG1^+ T_{reg}$ cells modulate the production of anti-inflammatory IL10 by B-lymphocyte-induced maturation protein 1 (Blimp-1) and inhibit WAT thermogenesis (Beppu et al. 2021). The loss of IFN β -mediated IL10 expression in the WAT of IRF3 $^{-/-}$ mice results in increased M1 macrophage accumulation, which is associated with increased PPAR γ activity and adipogenesis, and an obesity-prone state with little thermogenesis (Tang et al. 2021).

A potential thermogenic-suppressive effect of some T-cells is further indicated by increased catecholaminergic input, beige adipogenesis, and consequent energy dissipation in the sqWAT of *Rag1* $^{-/-}$ mice, in which both B and T cells fail to mature. The selective ablation of CD8 $^+$ T cells and blockage of IFN γ signaling are independently sufficient to produce this effect (Moysidou et al. 2018). Knockout of the mitochondrial chaperone protein disulfide-bond A oxidoreductase-like protein (DsbA-L) in adipose-resident T cells likewise reduces HFD-induced obesity and enhances thermogenesis in BAT by reducing the IFN γ production in the fat pad and increasing PKA activation and the resultant lipolysis, mitochondrial biogenesis, and heat generation (Zhou et al. 2021).

This obesogenic effect persists even after fat mass has been lost; CD4 $^+$, CD8 $^+$, and T_{reg} cells maintain an 'obesity memory' in WAT, accelerating weight regain in previously obese mice relative to weight gain in lean controls. After removal from HFD and a return to normal weight, previously obese mice retain the insulin insensitivity and fatty acid oxidation dependence characteristic of the disease, due to increased T-cell count and expression of T-cell receptor, toll-like receptor, JAK/STAT pathway, and inflammatory genes—including IFN γ —in their gonadal and inguinal WAT. Impaired B- and/or T-cell maturation in *Rag1* $^{-/-}$ and *H2A* $^{-/-}$ mice or immunosuppression with dexamethasone in WT mice ablates this memory, as does CD4 $^+$ and CD8 $^+$ T-cell deficiency in TCR β $^{-/-}$ mice, which revert to normal insulin sensitivity and glucose metabolism after weight loss. Previously obese WT epididymal WAT shows markedly higher CD4 $^+$ T cell counts; the introduction of these cells to *Rag1* $^{-/-}$ mice induces obesity memory, and their depletion with anti-CD4 antibodies reduces memory. Therefore, CD4 $^+$ T cells act to preserve an obese state by persistent suppression of metabolic activity, including thermogenic fat loss (Zou et al. 2018).

13 | Effects on BAT

FACS and microexpression assay analysis of T_{reg} cells from mouse BAT and spleen following 3 days at 30°C or 2 days at

12°C showed upregulation of 430 genes in BAT T_{reg} cells relative to splenic, 222 significantly in triplicate. Classic T_{reg} markers such as *Foxp3* were overrepresented; *CXCL1* and 2 and anti-inflammatory IL10 were overexpressed. Using the top 30 upregulated and bottom 10 downregulated genes from this analysis, unsupervised hierarchical clustering showed BAT T_{reg} cells to have a unique expression profile relative to splenic and WAT T_{reg} , as well as T_{conv} from BAT and spleen; 11 genes, including disheveled associated activator of morphogenesis 2 (*Daam2*), zinc finger protein 668 (*Zfp668*), and RNA polymerase I polypeptide A (*Polr1a*), also defined an expression profile unique to cold-exposed BAT (Medrikova et al. 2015).

Mice expressing diphtheria toxin receptor (DTR) under *Foxp3* experience systemic depletion of T_{reg} cells after DT administration. Forty-eight hours after T_{reg} depletion, an additional 48 h at room temperature showed no change in O $_2$ consumption, but T_{reg} depletion reduced VO $_2$ and heat production after mice were exposed to 4°C for 48 h. Markers of lipolysis such as serum FFA remained unchanged relative to T_{reg} -proficient controls, indicating a specificity of T_{reg} action to supporting thermogenic BAT activation. Corroborating this, canonical thermogenic genes such as *UCP1*, *Cidea*, and *PPAR γ* were downregulated in T_{reg} -deficient cold-challenged BAT but not WAT; inflammatory indicators such as *Ccl2* and *Tnfa* expression and macrophage infiltration were also observed (Kälin et al. 2017).

Microarray analysis of T_{reg} -deficient BAT show upregulation of 107 genes, especially immune-related genes like CC chemokines *Ccl2*, 3, 6, 7, and 9; macrophage marker *Cd68*; and Toll-like receptors *Tlr7*, 8, and 13. Downregulation of aldolase A (*Aldoa*) and solute carrier family 2, member 5 (*Slc2a5*) indicated impaired glycolysis and glucose transport, supported by noticeable but not significant downregulation of other glycolytic pathway genes. Gene Set Enrichment Analysis accordingly showed upregulation of pro-inflammatory cell proliferation and activation pathways and ATP metabolic processes in T_{reg} -deficient BAT (Medrikova et al. 2015).

P38 also plays a role in T_{reg} cells that impairs BAT activation and browning during obesity through mTOR pathway-mediated regulation of IL-35 production. IL-35 treatment increases BAT temperature by activating ATF-2 and upregulating *UCP1* and *FGF21* in mice. IL-35 expression is significantly lower in the visceral fat of obese individuals. Single-cell analysis in T and T_{reg} cells shows upregulation of p38 α , *MKK3*, and ATF-2 in obese humans, whereas *DUSP1* is downregulated. Blocking p38 expression in T cells reduces obesity and improves metabolic features, confirming the obesogenic role of p38. P38 activation in T_{reg} cells decreases IL-35 expression. Targeting p38 in T_{reg} cells could be a therapeutic strategy for metabolic diseases by regulating IL-35 and promoting AT browning through the ATF-2/*UCP1*/*FGF21* axis (Nikolic et al. 2024).

14 | Complement System and Thermogenesis

The complement system is a vital component of the immune system, comprising over 30 proteins that facilitate interactions between innate and adaptive immunity (Dunkelberger and Song 2010). The specific roles of the complement receptors C3aR

and C5aR in regulating adipocyte browning and diet-induced obesity are particularly intriguing (Shim et al. 2020). Activation of the complement cascade results in the cleavage of C3 and C5 into C3a and C5a, which subsequently bind to their receptors C3aR and C5aR, initiating immune responses.

Previous studies have demonstrated that signaling through C3a/C3aR and C5a/C5aR downregulates Foxp3 expression in Tregs, thereby inhibiting their immune-suppressive capabilities (Kwan et al. 2013). The double knockout (DKO) of C3aR and C5aR has been shown to promote the differentiation of Foxp3+ Tregs from CD4+ T cells (Strainic et al. 2013). Blocking either C3aR or C5aR reduces pro-inflammatory adipokines in adipose tissue and enhances insulin sensitivity in cases of diet-induced obesity (Abe et al. 2022; Kaye et al. 2017; Lim et al. 2013; Mamane et al. 2009; Phielers et al. 2013).

In a recent study, it has been identified the effects of the combined loss of C3aR and C5aR on adipocyte browning and metabolic health. It has been found that C3aR and C5aR DKO mice exhibited increased cold-induced adipocyte browning and reduced diet-induced obesity. This enhancement in browning was linked to elevated Treg activation in subcutaneous white adipose tissue (sWAT) (Kong et al. 2023). Activated Tregs in the DKO mice produced adenosine, which was subsequently converted to inosine by adipocyte-derived adenosine deaminases (ADA). Inosine then promoted adipocyte browning and mitigated diet-induced obesity and metabolic dysfunction by activating the adenosine A2a receptor (A2aR). Flow cytometric analysis revealed a significant increase in the percentage of CD4+Foxp3+ Tregs in the sWAT of DKO mice following cold exposure compared to wild-type (WT) mice. Treg depletion in vivo blocked the cold-induced adipocyte browning, indicating the necessity of Treg activation for the observed browning effects in C3aR/C5aR-deficient mice. DKO Tregs had increased expression of CD39 and CD73, which are crucial for adenosine production. The released adenosine was converted to inosine by ADA, which then promoted adipocyte browning through the A2aR pathway. Elevated inosine levels in the sWAT and serum of DKO mice confirmed this mechanism (Kong et al. 2023). Significant IL17 is also produced by $\gamma\delta$ T cells. $\gamma\delta$ T-deficient mice are less capable of thermoregulation after cold challenge in part due to the resultant lack of T_{reg} cells, indicating one role of $\gamma\delta$ T cells and IL17 in facilitating responsiveness of thermogenic activation to environmental temperature, another may involve the promotion of sympathetic innervation of fat pads via parenchymal cell IL17 receptor C. Ablating IL17RC on adipocytes reduces their TGF β 1 expression, impairing local sympathetic innervation and contributing to obesity and defective non-shivering adaptive thermogenesis (Hu et al. 2020).

Examination of obese human tissue indicates that some of the effects of IL17 on WAT may have the inverse effect and originate from nontissue-resident T cells such as mucosal-associated invariant T (MAIT) cells. Frequencies of these cells and their production of IFN γ , TNF α , and IL17 are higher in obese children; their participation in the maintenance of an insulin-resistant obese phenotype is demonstrated by the inhibition by IL17 in vitro of pAkt and ERK activity in adipocytes (Bergin et al. 2022).

Predominant among the CD4+ T-cells found in previously obese mouse eWAT are Th1 and Th17 cells, an IL17A-producing subset in which successful differentiation and the DNA-binding of ROR γ t is regulated by obesity-induced acetyl-CoA carboxylase 1 (ACC1) (Endo et al. 2015; Rocha et al. 2008b). Blockage of IL17A signaling via ubiquitous IL17RA knockout in mice (*Il17ra*^{-/-}) or inhibition of IL17-producing ROR γ t⁺ cells with digoxin improves metabolic health, increasing beige adipogenesis, thermogenesis, and energy expenditure in WAT and suppressing obesity under an HFD. IL17 supports HFD-induced obesity by inducing the CDK5-dependent phosphorylation of PPAR γ at serine 273, promoting adipogenesis and the expression of obesity-associated genes, a pattern observed in the WAT of morbidly obese humans (Teijeiro et al. 2021). Obesity is characterized by deficient thermogenesis and a persistent inflammatory state, and an increased frequency of dead adipocytes in epididymal WAT. iNKTs are associated with the inflammation and metabolic dysregulation associated with obesity. In female human omental WAT, the accumulation of IFN γ -producing CD56⁻ NKp46⁺ EOMES⁺ NK cells is positively associated with inflammatory gene expression and higher serum glucose levels (Mogilenko et al. 2021).

15 | Invariant Natural Killer T (iNKT) Cells in Adipose Thermogenesis

iNKTs are also known to congregate around dead and hypertrophic, pro-inflammatory Fas-positive adipocytes, suggesting a possible cytotoxic effect responsible for fat cell death (Park et al. 2019). Fas-L positivity—indicating this cytotoxic capacity—increases in eWAT iNKTs when mice are fed HFD; when iNKT-deficient *J α 18* KO mice are fed HFD, eWAT mass increases and dead adipocyte fraction decreases relative to HFD-fed wild-type (WT) mice, indicating that Fas-L positive iNKTs play a cytotoxic role in adipocyte turnover in diet-induced obesity in mice, helping to preserve a metabolically active state (Maricic et al. 2018).

After adipocyte turnover, insulin sensitivity improves due to iNKT activation by the prototypic ligand α -galactosylceramide (α GalCer), triggering the production of fibroblast growth factor 21 (FGF21) and direct effects on adipose tissue metabolism. iNKT activation or adoptive transfer in both BAT and WAT induces FGF21 and thermogenesis (Lynch et al. 2016). In lean subcutaneous WAT, FGF21 induces beige adipogenesis and consequent increases in body temperature, VO₂, VCO₂, and fatty acid oxidation in vivo without changing food intake or activity. The necessity of FGF21 to the thermogenic stimulation of adipocytes under α GalCer activation of iNKTs was demonstrated by the loss of this effect in FGF21 null mice, and its absence if iNKTs are activated by the GLP-1 receptor agonist liraglutide, which does not stimulate FGF21 production (Lynch et al. 2016). The role of iNKTs in the regulation of adipose tissue function, particularly through their cytotoxic effects on dysfunctional adipocytes and their ability to enhance FGF21-mediated thermogenesis, is a promising strategy for targeted therapeutic interventions and preventing obesity and related metabolic disorders. Understanding and manipulating the mechanisms by which iNKTs control adipose tissue metabolism may lead to the development of strategies that enhance or reduce inflammation and

provide metabolic changes effectively. For effective interventions, it is essential to comprehend the complex interactions that occur within adipose tissue between T cells and other immune system components. It may be possible to improve metabolic outcomes in obese individuals by improving thermogenesis, restoring the health of adipose tissue, and targeting these immune pathways.

16 | B Cells in Adipose Tissue

16.1 | Pro-Inflammatory and Regulatory Roles

B lymphocytes have a great impact on adipose tissue immune response and controlling inflammation within the organ. The role of B lymphocytes in adipose tissue metabolism was covered extensively by Shinoda and the group previously (Fernandez and Shinoda 2022). Previous research indicated that B cells are the most prominent antigen presenting cells in the adipose tissue niche and play an important role in generating immunoglobulins (Ying et al. 2016). For example, in conditions like obesity, there is an increase in B-cell populations which invade adipose tissues leading to metabolic homeostasis (Camell et al. 2019). Moreover, regulatory B cells were identified as endogenous suppressors of inflammatory responses in adipose tissue, thus demonstrating their role in maintaining the equilibrium of this organ (Nishimura et al. 2013). As well as T cells, macrophages, and neutrophils among other immune cell types, B cells are found within the adipose tissue where they can influence general metabolism through several mechanisms (Grant and Dixit 2015). In murine adipose tissue, B1 cells (CD5+ B1a and CD5– B1b) are self-renewing, fetal liver-derived innate-like producers of natural antibodies in the absence of antigens and T-cell responses to microbial antigens or oxidative stress. B2 cells are conventional adaptive immune cells that arise in adult bone marrow and migrate to secondary lymphoid organs (like AT) as immature B cells expressing specific IgM, then differentiate into the marginal zone or predominantly follicular B, which differentiate further during adaptive responses (Muri et al. 2019). These are the first immune cells to accumulate in eWAT under HFD, increasing at 3 weeks and contributing to inflammation and insulin resistance; T cells increase at 6 weeks and macrophages at 12 (Guzik et al. 2017; Fernandez and Shinoda 2022; Lee et al. 2011; Bénézech et al. 2015; Shimobayashi et al. 2018).

Overall B lymphocyte abundance is highest in omental VAT, where the B1:B2 ratio is nearly 1:1, as in the peritoneal cavity; the splenic ratio is closer to 0.1:1, mirroring much lower B1 proportions in non-adipose tissues, suggesting a unique B1 role in fat. Omental fat in mice concentrates B1 cells and macrophages in encapsulated “milky spots,” where macrophages regulate the trafficking of both cell types to and from the pleural and peritoneal cavities via CXCL13 (Rangel-Moreno et al. 2009). B220+ B cells constitute 20%–30% of BAT immune cells, and increase in number as BAT mass increases under HFD-induced obesity but undergo no change as mice age (Peterson, Flaherty, and Hasty 2017). They segregate with CD4+ T cells and CD11b+ myeloid cells in fat-associated lymphoid clusters (FALCs) in mesenteric, mediastinal, gonadal, and pericardial VAT (Bénézech et al. 2015).

16.2 | Effects of B Cell on Adipose Thermogenesis

Both AT-resident and systemic B cells impact adipose metabolism: whole-body B-cell depletion in aged mice increases pHSL and total ATGL—markers of active lipolysis—and restores their ability to maintain core body temperature after cold challenge, indicating a suppressive effect of B cells on normal beige cell function and the nonshivering thermogenic adaptive response to cold (Camell et al. 2019). The best-indicated secreted factor for this B cell activity is IL10.

Both effector and regulatory B cells produce cytokines; constitutively, IL10-producing B_{reg} cells (Carter et al. 2011) or B10 cells have been characterized as CD1d^{low} CD5^{-/low} CD11b^{low} CD21/CD35^{low} CD23^{-/low} CD25⁺ CD69⁺ CD72^{high} CD185⁻ CD196⁺ IgM⁺ IgD⁺ in murine eWAT and sqWAT, and CD22⁺ CD19⁺ CD45R⁺ in both human and murine WAT, especially sqWAT (Nishimura et al. 2013). B_{reg} IL10 and TGFβ production is observed in the spleen in B1a, marginal zone (MZ), and transitional-2 MZ precursor B cells, and in the peritoneum in B1 cells, only after stimulation; therefore, constitutive IL10 production in AT is unique. B10 cells constitute only a small antigen-dependent inflammation-suppressing subset in lymphoid tissues and bone marrow, while being nearly absent in the spleen, in which IL10 is produced only by 1%–2% of B cells after stimulation (DiLillo, Matsushita, and Tedder 2010; Vitale, Mion, and Pucillo 2010).

The impact of T- and B-cell-derived IL10 on thermogenesis in murine sqWAT has been studied in detail. Full-body *Il10*^{-/-} mice, despite having body weights similar to WT mice on a chow diet, have higher serum FFA and darker iWAT exhibiting higher adipocyte counts and smaller, more multilocular lipid droplets, all visible signs of active beigeing. Both aging and HFD-induced obesity-induced markedly less weight gain in *Il10*^{-/-} mice, which body composition MRI confirmed was due to reduced fat mass. Lower triglyceride and cholesterol levels in both serum and liver, protection against HFD-induced hepatic steatosis, and increased glucose tolerance and adipocyte pAKT—indicating better insulin sensitivity—indicated an overall improved metabolic state in *Il10*^{-/-} mice relative to WT (Rajbhandari et al. 2018).

Indirect calorimetry measured higher VO₂ and energy expenditure in *Il10*^{-/-} mice under both chow and HFD, corroborated by increased respiration in mitochondria isolated from IL10-deficient mice and increased electron flow in complexes I—IV isolated from those mitochondria. RNA sequencing of *Il10*^{-/-} iWAT under room temperature and cold conditions showed significant upregulation of such known thermogenic genes as *Ucp1*, *Cidea*, and *Pm20d1*, while obesity-associated and white adipogenic genes such as *Mmp12*, *Trem2*, *Celec4d*, and *Atp6v0d2* were downregulated, indicating that the energy expenditure and qualitative changes to iWAT in *Il10*^{-/-} mice were due to induction of a thermogenic profile. That bone marrow-derived cells ordinarily produce IL10 was demonstrated by the capacity of WT bone marrow transplantation into *Il10*^{-/-} mice to reconstitute WT levels of VO₂, energy expenditure, thermogenic gene expression, and mitochondrial respiration (Rajbhandari et al. 2018).

It was found that iWAT adipocytes begin to express *Il10ra* during differentiation and increase expression under the white

adipogenic conditions in aging and genetic and HFD-induced obesity, which also induced an increase in serum IL10; that this axis was responsible for thermogenic gene suppression was confirmed by the downregulation of *Ucp1*, *Cidea*, and *Pgc1α* in beige-differentiated white preadipocytes and *Il10ra*-expressing brown preadipocytes in vitro. Primary and enhancer RNAs for *Ucp1* were found to be downregulated in adipocytes treated with IL10, suggesting that the mechanism by which IL10 suppresses thermogenesis in adipocytes is a change in chromatin architecture, as seen in macrophages; indeed assay for transposase-accessible chromatin sequencing (ATAC-seq) revealed a decrease in chromatin accessibility in enhancer/promoter regions of *Ucp1*, *Cidea*, and other thermogenic genes. Accordingly, chromatin immunoprecipitation quantitative PCR (ChIP-qPCR) and sequencing (ChIP-seq) showed that IL10 inhibited the recruitment of transcription factors C/EBPβ, PGC1α, and ATF-2 to *Ucp1* enhancer regions and C/EBPβ DNA occupancy at the regulatory regions of brown differentiation genes (Rajbhandari et al. 2018).

Therefore, an adipocyte-specific *Il10ra* lox/Cre knockout mouse line was generated by crossing a *Il10ra^{fl/fl}* line with mice carrying *Cre* under the white and beige adipogenesis marker adiponectin (*AdipoQ*) (Rajbhandari et al. 2019). These AdIL10Rα KO mice exhibited lower fat mass than their WT littermates (*Il10ra^{fl/fl}* without *Cre*), and their iWAT displayed the darker color observed in the more thermogenically active iWAT of systemic *Il10^{-/-}* mice. Similarly, when AdIL10Rα KO mice were challenged with 4°C for 24 h. or CL at 1 mg/kg for 4 days, expression of *Ucp1*, *Elovl3*, *Pgc1α*, and other thermogenic genes were upregulated relative to controls.

Single-nuclei adipocyte RNA sequencing (SNAP-seq) of iWAT from cold-challenged WT mice revealed 14 adipocyte subtypes, of which one—designated Type 9—displayed enriched β3-AR, lipase, and beige/brown marker expression, and increased in proportion among iWAT cells after cold stress and CL treatment, suggesting a role as a cold-responsive beige preadipocyte compartment. Accordingly, Type 9 preadipocytes constitute a higher proportion of iWAT cells in AdIL10Rα KO mice and proliferate more acutely under cold stress or CL, demonstrating increased beige adipogenesis and more sensitive adaptive thermogenesis in the absence of IL10 signaling. Single-cell RNA sequencing (scRNA-seq) on the stromal vascular fraction (SVF) of cells from CL-treated WT iWAT revealed markedly increased B cell frequency and *Il10* expression following β3-adrenergic stimulation. Therefore, thermogenesis in iWAT must be suppressed by IL10-producing T or B cells; T- and B-cell-deficient SCID mice treated with CL or exposed to 24 h. Accordingly 4°C exhibited higher energy expenditure and VO₂ (Rajbhandari et al. 2019).

B cells are crucial, in tissue as they help regulate the response and inflammation within the AT. Research indicates that B cells play a role as antigen presenting cells in tissue producing immunoglobulins and impacting metabolic balance in metabolic diseases. Regulatory B cells are players in suppressing responses in adipose tissue contributing to the organ's overall equilibrium. These cells along with cell types such as T cells and macrophages are present in adipose tissue and influence metabolism through various mechanisms. Moreover, it has been observed that IL10

produced by B cells affects thermogenesis in tissue leading to improved metabolic profiles in IL10 mice. The knockout mouse model with IL10Rα to adipocytes further confirmed the impact of IL10 signaling on thermogenesis within these cells. In summary B lymphocytes play a role in regulating inflammation, immune responses, and metabolic processes, within tissue through their cytokine production and regulatory functions.

16.3 | Myeloid Cells

Myeloid cells are the most abundant adipose tissue-resident immune cells. Tissue-resident macrophages derive from the yolk sac and are the first immune cells to seed adipose tissue, where they undergo local expansion (Hassnain Waqas et al. 2017; Schulz et al. 2012).

16.4 | Macrophages in Adipose Thermogenesis

The adipose tissue is a microenvironment that is composed with multiple immune cells, adipose progenitors, endothelial cells, and neuronal cells (Shamsi, Wang, and Tseng 2021). Macrophages constitute the immune cell population in adipose tissue that has undergone the most extensive research. Although the prevailing classification in adipose tissue literature simplifies macrophages into the binary M1/M2 (pro-inflammatory/anti-inflammatory), it is important to recognize that macrophages have diverse functions and subtypes. Numerous additional subtypes can be characterized based on a diverse range of markers and functions (Martinez and Gordon 2014; Chavez-Galan et al. 2015). Adipose tissue macrophages (ATMs) are a heterogeneous population with many subtypes, although conventionally divided into two subtypes M1 (pro-inflammatory) and M2 (anti-inflammatory) cells (Thomas and Apovian 2017). M1 macrophages are recruited by pro-inflammatory factors such as LPS (Lipopolysaccharides) and IFN-γ (interferon-gamma) and are known to secrete IL-1β (Interleukin 1 beta), IL-6, IL-12, IL-23, and TNF-α (tumor necrosis factor-alpha). On the other hand, M2 macrophages are recruited by anti-inflammatory responses and secrete IL-4, IL-10, IL-33, and TGF-β (transforming growth factor-beta) (Li, Yun, and Mu 2020; Castoldi et al. 2015). In obese adipose tissue, the polarization of macrophages is known to shift to the activation of M1 macrophages in contrast to lean adipose tissue to activate and shift to M2 macrophages. The polarization of M1 macrophages is known to lead to insulin resistance and metabolic dysfunction to the host. Not only does M1/M2 macrophages affect glucose homeostasis but also is known to be related to the brown/beige adipose differentiation and activation that leads to thermogenesis and energy expenditure. Evidence of association with macrophages and brown adipose tissue-induced thermogenesis has been highlighted in many studies such as through C-X-C motif chemokine ligand 14 (CXCL14). CXCL14 is released from brown adipose tissue which leads to the recruitment of M2 macrophages and thermogenesis (Cereijo et al. 2018). Although the association of macrophages and thermogenesis in BAT has been reported the direct mechanism still are not established.

Initially, M2 macrophages were documented as contributors to adaptive thermogenesis by generating catecholamines in

cold-induced conditions (Nguyen et al. 2011). This introduced a novel perspective to explore immune cell-mediated modulation of thermogenesis in adipose tissue (Qiu et al. 2014; Nguyen et al. 2011). However, studies have shown that macrophages do not secrete catecholamines (Fischer et al. 2017).

16.5 | Catecholamine Processing by Macrophages in Adipose Thermogenesis

A subset of macrophages known as sympathetic neuron-associated macrophages (SAMs) has been proposed to process catecholamines by means of expressing the norepinephrine (NE) transporter solute carrier family 6 member 2 (SLC6A2) and the degrading enzyme monoamine oxidase A (MAOA) (Pirzgalska et al. 2017). It was also observed that macrophages engage in the degradation of NE through the activation of the NLR family pyrin domain containing 3 (NLRP3) inflammasome (Camell et al. 2017). The discordant findings might stem from the role of macrophages in supporting sympathetic innervation. While they do not directly synthesize NE (Fischer et al. 2017; Pirzgalska et al. 2017; Blaszkiewicz et al. 2020), macrophages could potentially influence the local NE levels generated by sympathetic neurons within thermogenic adipose tissue through direct interactions (Wang, Tang, et al. 2021; Wolf et al. 2017). In a more recent study, a study highlighted CX3CR1+ SAMs could express IL-27, a factor that has been demonstrated to play a role in promoting thermogenesis and energy expenditure (Wang, Li, et al. 2021). The capability of M2 macrophages to induce browning without relying on the participation of sympathetic neurons was demonstrated in a *Fasn*^{-/-} mouse model (Henriques et al. 2020). Additionally, macrophages can express UCP1 and contribute to the remodeling of beige adipose tissue following cold exposure (Finlin et al. 2021). Additionally, in response to adipocyte death induced by CL, CD44⁺ M2 macrophages are recruited and generate elevated quantities of 9-hydroxyoctadecadienoic acid (9-HODE) and 13-HODE (Lee et al. 2016). These compounds are recognized PPAR γ ligands, and they facilitate the transformation of platelet-derived growth factor receptor alpha (PDGFR α ⁺) progenitor cells into beige adipocytes (Lee et al. 2016). Furthermore, osteopontin (OPN) originating from macrophages stimulates the recruitment of PDGFR α ⁺ progenitor cells, which play a role in the process of beige adipocyte generation (Lee, Petkova, and Granneman 2013).

Catecholamine-induced lipolysis, which is vital for energy production through triglyceride hydrolysis, diminishes with age, resulting in increased visceral fat, reduced exercise capacity, and impaired thermoregulation (Camell et al. 2017). Despite normal catecholamine signaling in adipocytes, aged mice exhibit reduced catecholamine-induced lipolysis. While fasting boosts catecholamine levels and promotes lipolysis in young mice, aged mice show decreased release of free fatty acids (FFA) and glycerol, indicating impaired lipolysis. The number of F4/80+CD11b+ ATMs in visceral adipose tissue (VAT) decreases with age. Aged ATMs inhibit noradrenaline-induced lipolysis in young adipocytes, whereas young ATMs partially restore lipolysis in aged VAT explants, suggesting age-specific defects in ATMs. Transcriptome analysis indicates that aging upregulates genes involved in catecholamine degradation, such as MAOA,

through an NLRP3 inflammasome-dependent mechanism. Deleting NLRP3 in aged mice reinstates catecholamine-induced lipolysis by downregulating MAOA and other catecholamine catabolic enzymes. Activation of the NLRP3 inflammasome in macrophages inhibits lipolysis by upregulating catecholamine degradation machinery, growth differentiation factor-3 (GDF3), which is highly upregulated in aged ATMs, inhibits lipolysis and is downregulated when NLRP3 is deleted. GDF3 deficiency in inflammasome-activated macrophages enhances lipolysis by lowering MAOA and caspase-1 levels. Treating aged mice with clorgiline, an MAOA inhibitor, restores fasting-induced lipolysis, increases the expression of HSL and ATGL, and raises noradrenaline levels in VAT. This study shows that age-related chronic inflammation, driven by NLRP3 inflammasome activation in macrophages, hampers catecholamine-induced lipolysis by increasing catecholamine degradation. Targeting macrophage activity and catecholamine bioavailability presents new strategies to address metabolic impairments and functional decline associated with aging (Camell et al. 2017).

A recent study investigated the role of lipid-associated macrophages (LAMs) in the transformation of BAT during obesity (Sciarretta et al. 2024). Employing a multilayered approach that combined single-cell RNA-sequencing (scRNA-seq) and deep immunophenotyping, the research provides critical insights into BAT cell dynamics in the context of obesity and type 2 diabetes (T2D). The study revealed a substantial increase in LAMs within the BAT of obese mice. These macrophages were characterized by their lipid-handling and lysosomal gene expression profiles. This increase was evident in both genetic (db/db mice) and dietary models of obesity. Metabolically stressed brown adipocytes release extracellular vesicles (EVs) containing damaged lipids and mitochondria, which macrophages scavenge via the CD36 receptor, driving the LAM phenotype. LAMs secrete transforming growth factor beta 1 (TGF- β 1), which promotes the loss of brown adipocyte identity by inducing aldehyde dehydrogenase 1 family member A1 (Aldh1a1). This process contributes to the conversion of brown fat to white fat, a phenomenon observed in obesity. CD36-deficient macrophages showed increased expression of brown fat genes in adipocytes, indicating that CD36 is crucial for the lipid-scavenging function of LAMs and their role in BAT remodeling. The secretion of TGF- β 1 by LAMs correlates with increased Aldh1a1 expression in brown adipocytes, promoting the loss of brown adipocyte characteristics and enhancing white fat gene expression. These findings suggest that targeting macrophage activity and TGF- β 1 signaling could be a promising therapeutic strategy to preserve BAT function and combat obesity-related metabolic disorders (Sciarretta et al. 2024).

M2 macrophages have been shown to promote the beiging of WAT independently of the SNS (Wu et al. 2024). This challenges the traditional view that the SNS is the sole regulator of adipose tissue thermogenesis (Jiang et al. 2017). A recent study delved into the intricate relationship between immune cells, particularly M2 macrophages, and beige adipogenesis within adipose tissue, shedding light on the mechanisms underlying metabolic regulation (Wu et al. 2024). One key aspect highlighted in the study is the role of M2 macrophages in promoting beige adipogenesis through the modulation of mitochondrial biogenesis via transcriptional regulation. The application of cold exposure or a

β 3-adrenergic receptor (β 3-AR) agonist is shown to significantly increase mitochondrial biogenesis through transcriptional modulation, emphasizing the impact of environmental cues on metabolic processes. Furthermore, it highlighted the importance of transcriptional regulation in mitochondrial biogenesis within beige adipocytes, with a specific focus on the role of transcription factor Ets1 as a mitochondrial repressor that influences both mitochondrial degradation and biogenesis (Wu et al. 2024). This finding is significant as it highlights the dual role of M2 macrophages in boosting mitochondrial numbers in adipocytes while also regulating the quality control of thermogenic fat metabolism by removing damaged mitochondria.

Moreover, the distinct effects of Ets1 on beige adipocytes compared to BAT, pointing out that Ets1 has a more pronounced impact on Ucp1 expression and thermogenic marker gene activation in beige adipocytes than in BAT. This distinction underscores the unique regulatory mechanisms governing beige adipogenesis and highlights the need for further research to elucidate the differences in cellular responses between beige and brown adipocytes. Additionally, the signaling pathways involved in the regulation of beige adipocytes by immune cells, emphasize the role of factors like meteorin-like hormone (METRNL) secreted by skeletal muscle in activating resident eosinophils in fat pads, leading to the promotion of M2 macrophage polarization and beige adipogenesis (Rao Rajesh et al. 2014). This signaling cascade highlights the intricate communication network between different cell types within adipose tissue to regulate metabolic processes and underscores the multifaceted nature of immune cell-mediated metabolic regulation (Wu et al. 2024).

IL-11, a pro-inflammatory cytokine belonging to the IL-6 family, has been shown to adversely affect age-associated diseases and reduce lifespan in mice (Widjaja et al. 2024). During aging, IL-11 is upregulated in cells and tissues, promoting cellular and tissue aging via the ERK-AMPK-mTORC1 pathway. Deletion of IL-11 provides protection against metabolic syndrome. Treatment with anti-IL-11 improves metabolism and muscle function while also decelerating aging by reducing biomarkers associated with aging. Transcriptome analysis of visceral WAT indicated that Ucp1 was the most upregulated gene following anti-IL-11 treatment, which is essential for the development of thermogenic “beige” adipocytes within WAT deposits.

The process of beiging in WAT is closely associated with the presence of anti-inflammatory M2-like macrophages (Sakamoto et al. 2016). Although this link is well established, the exact mechanisms by which M2-like macrophages drive the beiging process are not yet fully elucidated. A recent study has identified Slit3 as a cold-sensitive protein secreted by M2 macrophages, which plays a crucial role in enhancing the thermogenic capacity of inguinal white adipose tissue (iWAT) during cold exposure (Wang, Tang, et al. 2021). Slit3 functions by activating the SNS within iWAT, which promotes the growth and activity of sympathetic nerves. This activation is mediated through the transmembrane protein Roundabout (ROBO1) receptor, identified as the primary receptor for Slit3 in adipocytes (Brose et al. 1999). The binding of Slit3 to ROBO1 on sympathetic neurons initiates the activation of the PKA/CaMKII pathway, resulting in increased phosphorylation of tyrosine hydroxylase (TH) and subsequent

synthesis of NE. NE then activates the PKA signaling pathway in adipocytes, promoting lipolysis and the expression of thermogenic genes such as UCP1. This cascade of events underscores the integrated role of immune cells and sympathetic neurons in regulating adipose tissue function. Targeting the Slit3-ROBO1 pathway offers a potential approach to enhance the beiging of WAT and improve metabolic health. These findings also emphasize the broader role of M2 macrophages in adipose tissue remodeling and thermogenesis, underscoring their importance beyond conventional immune functions. By understanding and manipulating these pathways, therapeutic interventions could be developed to utilize the thermogenic potential of beige adipose tissue, thereby addressing obesity and related metabolic disorders (Wang, Tang, et al. 2021).

A recent study also revealed the essential role of local lymph nodes (LNs) in the beiging process of iWAT (Yuan et al. 2024). It was discovered that removing inguinal LNs disrupts cold-induced beiging, but this can be reversed by injecting M2 macrophages or CCL22 into iWAT. This finding highlights the importance of LNs in mediating adaptive thermogenesis in response to cold exposure. The study shows that cold exposure increases sympathetic nervous system (SNS) activity in LNs, promoting the release of (IL-33), which subsequently activates type 2 innate lymphoid cells (ILC2s). These cells are crucial for the formation of beige adipocytes. It has been shown that CCL22, a chemokine produced by M2 macrophages, as a key factor in this process. CCL22 binds to its receptor CCR4, which is primarily expressed on eosinophils, facilitating their recruitment to iWAT. Eosinophils, in turn, promote adipocyte beiging by secreting IL-4, which activates the STAT6 signaling pathway in adipocyte progenitor cells (APCs) (Qiu et al. 2014). The study provides detailed mechanistic insights into how CCL22 and CCR4 signaling facilitates adipose tissue beiging. During cold exposure, CCL22 levels increase in iWAT, promoting the recruitment and activation of eosinophils. This process relies on the focal adhesion kinase (FAK)/p65 signaling pathway within eosinophils, which is activated when CCL22 binds to CCR4. This cascade of events illustrates the critical role of the immune system in regulating adaptive thermogenesis in adipose tissue (Yuan et al. 2024).

It has been demonstrated that metabolically stressed white adipocytes release damaged mitochondrial proteins through EVs (Crewe et al. 2021). Brown adipocytes physiologically produce mitochondrial ROS (mtROS) to sustain thermogenesis (Chouchani et al. 2016; Lettieri-Barbato 2019; Mills et al. 2018). A recent study demonstrated macrophages regulate the thermogenic function of BAT by removing damaged mitochondria released from brown adipocytes during thermogenesis (Rosina et al. 2022). Brown adipocytes expel oxidatively damaged mitochondrial proteins via mitochondrial-derived vesicles (MDVs) into the extracellular vesicle (EV) pathway, similar to white adipocytes. The research highlighted that PINK1 played a critical role in generating MDVs under oxidative stress. These MDVs are then incorporated into EVs for extracellular release. Also, inhibiting lysosomal degradation increases the release of damaged mitochondrial proteins, suggesting that lysosomal and EV pathways collaborate to maintain mitochondrial quality. Overall, M2 macrophages have

roles directly related to thermogenesis and will lead to the overall understanding of metabolism.

16.6 | Monocytes

Monocytes are a specialized type of immune cells that have been recently identified as powerful regulators of thermogenesis in the adipose tissue. While the precise role of monocytes in adipose tissue thermogenesis continues to be defined, one can study how infiltrated monocytes may affect downstream effects due to their inflammatory nature. Yet, they are known to recruit other immune cells particularly M2 macrophages that have been identified as the predominantly recruited cell type in adipose tissue supporting thermogenesis. The recruitment of monocytes to adipose tissue modulates the inflammatory milieu and thereby influences metabolic homeostasis, which impacts the thermogenic pathway (Qiu et al. 2014). The activation of thermogenesis in adipose tissue is a complex process that requires precise coordination between multiple cellular and molecular pathways. Monocytes have been identified as potential cellular effectors capable of regulating immune responses and promoting a metabolic environment in AT. Cytokines, free fatty acids, and other substances were brought by these studies upon as key components that control thermogenic activity in adipocytes (Ye et al. 2024). As described above, cold exposure triggers the recruitment of monocytes and their differentiation into brown adipose tissue macrophages (bMACs), which are essential for sustaining BAT's thermogenic function (Rosina et al. 2022). The study observed an increase in patrolling monocytes and a shift toward a less inflammatory macrophage phenotype in response to cold stress. Furthermore, CD36 was identified as a key receptor mediating the uptake of mitochondrial EVs by macrophages. Inhibiting CD36 reduces EV internalization, underscoring its role in the mitochondrial quality control process (Rosina et al. 2022). A recent study demonstrated that monocytes play a crucial role in the expansion and maintenance of BAT during conditions of increased metabolic demand, such as cold exposure (Gallerand et al. 2021). Using scRNA-seq, the study revealed a diverse population of immune cells, including distinct macrophage and monocyte subsets within BAT. The authors show that monocytes are recruited to BAT to replenish the macrophage pool, especially during tissue remodeling. In a genetic mouse model with adipocyte-specific ATGL deficiency, which leads to significant BAT expansion, monocyte recruitment was found to be critical for maintaining macrophage diversity and promoting tissue remodeling, specifically in lipid metabolism and matrix restructuring. Depletion of monocytes impaired BAT expansion and altered tissue architecture, confirming their essential role. Additionally, the study identified Podoplanin engagement as a necessary mechanism for BAT expansion, with its blockade preventing tissue growth. These findings highlight the pivotal role of monocytes in supporting BAT's functional adaptation and expansion, emphasizing their importance in thermogenic processes. Together, these studies implicate monocytes as an emerging axis that regulates thermogenesis in adipose tissues and could dictate the crosstalk between immunity, metabolic homeostasis, and energy expenditure. Unraveling the function of monocytes in adipose tissue thermogenesis is a central question that strongly relates to immune metabolic cross-talk and mitochondrial-uncoupling pathway.

16.7 | Eosinophils and Type 2 Innate Lymphoid Cells

The classical roles of eosinophils and type 2 innate lymphoid cells (ILC2s) typically inhabit mucosal tissues and play roles in responses to helminthic infections and allergic reactions (Bochner 2018; Bartemes and Kita 2021). However, their functions exhibit a broader range and are contingent upon their specific anatomical placements within the body (Marichal, Mesnil, and Bureau 2017). In adipose tissue, eosinophils are characterized by elevated levels of Siglec-F expression and have the capacity to generate IL-4 and IL-13, thereby facilitating the polarization of M2 macrophages (Wu et al. 2011). The genetic removal of eosinophils or disruption of the IL4/IL13-IL4R α -STAT6 pathway has been associated with compromised cold-induced browning due to the diminished polarization of M2 macrophages (Qiu et al. 2014). As a result, the broader impact of M2 macrophages on thermogenic adipose tissue functions and browning seems to be influenced at an earlier stage by the existence of eosinophils and/or signaling through IL-4 and IL-13 (Qiu et al. 2014). Upon stimulation through IL-33, ILC2s stimulate the proliferation of PDGFR α ⁺ adipocyte precursors and encourage their dedication to the beige lineage by means of IL-4R α (Lee et al. 2015). IL-4, IL-13, and IL-33, pivotal constituents of type 2 cytokines, have all been shown to facilitate thermogenesis and lipolysis (Lee et al. 2015; Qiu et al. 2014). A recent study integrated neuroendocrinology and immunometabolism, previously separate fields of obesity research. LepR-expressing Sympathetic Perineurial Cells (SPCs) produce IL-33 (Haberman et al. 2024), a crucial factor for the maintenance and recruitment of Tregs and eosinophils in AT. In mice lacking IL-33 in SPCs (SPC IL-33 KO), BAT exhibits significantly fewer Tregs and eosinophils, leading to BAT inflammation. This finding suggests that IL-33 plays a protective role in diet-induced obesity, independent of food intake. Furthermore, SPC IL-33 KO mice demonstrate impaired adaptive thermogenesis and do not respond to leptin-induced metabolic adaptation (Haberman et al. 2024). A recent study showed that timed feeding promotes adipose tissue browning through ILC2 pathways (Mattar et al. 2024). In this study, the authors show that twice-a-night (TAN) feeding creates biphasic oscillations of insulin and leptin, driving cellular and metabolic changes in sWAT and increasing energy expenditure. Single-cell RNA-sequencing and flow cytometry revealed that insulin and leptin surges recruit ILC2 through APC IL-33 production, promoting sWAT browning. Disruption of sWAT denervation, insulin/leptin signaling, or ILC2 recruitment reduced TAN-induced sWAT remodeling. Moreover, mimicking insulin and leptin oscillations with daily timed injections was sufficient to induce sWAT remodeling. Overall, this study showed that timed feeding reorganizes immune and nutrient-sensitive pathways, driving sWAT remodeling, beiging, and its metabolic benefits.

16.8 | Dendritic Cells

Dendritic cells (DCs) are crucial elements of the immune system. They are mainly known for initiating adaptive immune reactions through antigen presentation. Their contribution to thermogenesis regulation in adipose tissue has been recently brought to light (Soedono and Cho 2021). This emerging perspective suggests that dendritic cells may influence immune responses and play a critical

role in metabolic processes, particularly in the context of energy expenditure and thermogenic activity in adipose tissue. The relationship between adipocytes and dendritic cells is intricate and includes multiple signal transduction pathways. Some investigations have shown that they can change the differentiation as well as the functioning of adipocytes within a thermogenesis context. Dendritic cells have been a point of debate in association with adipose tissue homeostasis. This is because these cells are difficult to differentiate from macrophages and monocytes. Under normal circumstances, dendritic cells can be distinguished by high levels of CD11c and MHCII, but typical, dendritic cell markers can also be expressed by activated macrophages and monocytes in adipose tissue (Patsouris et al. 2008; Stefanovic-Racic et al. 2012). A recent study used Zbtb46 reporter mice that allow the unequivocal identification of conventional DC (cDCs) among other myeloid cells (Satpathy et al. 2012). This study indicated that both type 1 and type 2 conventional dendritic cells (cDC1s and cDC2s) produce IL-10 as an anti-inflammatory cytokine in lean adipose tissue. Hence, both resident macrophages as well as conventional DCs are involved in maintaining the homeostasis of fat tissues (Maddougall et al. 2018).

16.9 | Neutrophils

Neutrophils, as key components of the innate immune system, are traditionally recognized for their roles in host defense and acute inflammation. However, emerging evidence suggests that neutrophils also play significant roles in metabolic tissues, including adipose tissue, where they influence processes such as inflammation, energy metabolism, and thermogenesis (Mansuy-Aubert et al. 2013). In adipose tissue, neutrophils are among the first immune cells to infiltrate during stress or metabolic challenges, such as obesity or cold exposure, where they can shape the local immune environment through cytokine release and interaction with other immune cells. This emerging field provides evidence that neutrophils might be crucial for controlling energy consumption as well as thermogenic activity, especially during cases of obesity and metabolic diseases (Talukdar et al. 2012).

Regarding thermogenesis, neutrophils may impair the browning of WAT. Studies have shown that genes related to this process are likely to be expressed due to the inflammatory environment created by neutrophils and thus decrease the thermogenic potential of WAT. Neutrophil-derived factors, including neutrophil gelatinase-associated lipocalin (NGAL), have been shown to directly impact BAT function. NGAL exerts antithermogenic effects by suppressing BAT activity and promoting obesity in murine models (Ishii et al. 2017). Additionally, the accumulation of immune cells, including neutrophils, in BAT during aging disrupts thermogenic capacity, exacerbating metabolic decline (Feng et al. 2023). Beyond thermogenesis, the whitening of BAT, characterized by a loss of thermogenic potential, has been shown to inhibit osteogenic differentiation through the secretion of S100A8/A9, further underscoring the complex role of BAT in systemic health (Wang et al. 2024). These findings highlight a dynamic role for neutrophils in adipose tissue biology, particularly in regulating BAT function and systemic energy metabolism, positioning them as potential therapeutic targets for addressing obesity, aging, and related metabolic disorders.

17 | Conclusion

In summary, this review comprehensively underscores the integral cross talk between immune cells and adipocytes in the regulation of AT thermogenesis and overall metabolic homeostasis. BAT and beige WAT, driven by UCP1, play a crucial role in heat generation through β -oxidation of fatty acids, especially during cold exposure and sympathetic activation. The microenvironment of adipose tissue includes innate and adaptive immune cells, such as macrophages, eosinophils, T cells, and dendritic cells, which influence thermogenic responses. M2 macrophages, eosinophils, and regulatory T cells promote tissue homeostasis and support thermogenic processes by driving the browning of white adipose WAT and enhancing BAT function. In contrast, during obesity, pro-inflammatory immune cells like M1 macrophages and neutrophils dominate, contributing to metabolic dysfunction and impaired thermogenesis. The recruitment and function of immune cells, including monocytes and dendritic cells, play a significant role in maintaining metabolic homeostasis, with monocytes supporting BAT expansion and dendritic cells contributing to immune balance. Targeting immune-mediated pathways offers potential therapeutic strategies to enhance adipose tissue thermogenesis and combat metabolic disorders.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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