Gao *et al. J Cardiovasc Aging* 2024;4:5
DOI: 10.20517/jca.2023.38

The Journal of Cardiovascular Aging

Review

Open Access

Adipose tissue lymphocytes and obesity

Feng Gao, Benjamin Litchfield, Huaizhu Wu

Department of Medicine, Baylor College of Medicine, Houston, TX 77030, USA.

Correspondence to: Prof. Huaizhu Wu, Department of Medicine, Baylor College of Medicine, One Baylor Plaza, MS BCM285, Houston, TX 77030, USA. E-mail: hwu@bcm.edu

How to cite this article: Gao F, Litchfield B, Wu H. Adipose tissue lymphocytes and obesity. *J Cardiovasc Aging* 2024;4:5. https://dx.doi.org/10.20517/jca.2023.38

Received: 23 Oct 2023 **First Decision:** 15 Nov 2023 **Revised:** 1 Dec 2023 **Accepted:** 6 Dec 2023 **Published:** 1 Jan 2024

Academic Editor: Leila Rouhi **Copy Editor:** Fangyuan Liu **Production Editor:** Fangyuan Liu

Abstract

Obesity is associated with chronic inflammation in adipose tissue (AT), mainly evidenced by infiltration and phenotypic changes of various types of immune cells. Macrophages are the major innate immune cells and represent the predominant immune cell population within AT. Lymphocytes, including T cells and B cells, are adaptive immune cells and constitute another important immune cell population in AT. In obesity, CD8+ effector memory T cells, CD4+ Th1 cells, and B2 cells are increased in AT and promote AT inflammation, while regulatory T cells and Th2 cells, which usually function as immune regulatory or type 2 inflammatory cells, are reduced in AT. Immune cells may regulate the metabolism of adipocytes and other cells through various mechanisms, contributing to the development of metabolic diseases, including insulin resistance and type 2 diabetes. Efforts targeting immune cells and inflammation to prevent and treat obesity-linked metabolic disease have been explored, but have not yielded significant success in clinical studies. This review provides a concise overview of the changes in lymphocyte populations within AT and their potential role in AT inflammation and the regulation of metabolic functions in the context of obesity.

Keywords: Obesity, adipose tissue, insulin resistance, T cells, B cells

INTRODUCTION

Obesity, which is mainly caused by positive energy imbalance and is associated with aging, has become a global health problem and increases the risk for type 2 diabetes mellitus, cardiovascular diseases, and many other diseases[1]. Studies have indicated that low-grade chronic inflammation characterized by immune cell

infiltration and phenotypic changes in adipose tissue (AT) and other tissues occurs in obesity and may contribute to obesity-associated diseases[2-9]. Macrophages are the most abundant immune cells in AT, can change to classically activated (M1)- or metabolically activated-like phenotypes in obesity, and play an important role in AT inflammation by secreting proinflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β)[10-17].

In addition to macrophages, lymphocytes, including T lymphocytes and B lymphocytes, are another type of immune cells in AT that play a crucial role in AT inflammation and may contribute to insulin resistance (IR)[6,18-24]. In this review, we summarize the current knowledge of T cells and B cells in AT and their potential roles in obesity-linked metabolic disease, aiming to provide a new perspective on targeting these immune cells to prevent obesity and related IR.

T cells and B cells

T cells and B cells are both adaptive immune cells responsive to antigens. While T cells are responsible for cellular immunity mainly by producing cytokines or via cell interactions, B cells mediate humoral immunity mainly by producing antibodies.

Based on T cell receptors (TCR_s), T cells can be categorized into αβT cells and γδT cells, both of which play a crucial role in immune functions[25,26]. The majority of T cells in most tissues are αβT cells, which express α and β TCR chains[25]. γδT cells possess a TCR consisting of γ and δ chains[26]. TCRαβ and TCRγδ share some similarities but are also different in several aspects. Although the variable (V) regions of TCRαβ and TCRγδ exhibit a similar structure, the distance between the immunoglobulin-like domains and the disulfide bond in the connecting peptide is longer in TCRγδ compared to TCRαβ. In addition to polar amino acids located in the transmembrane (TM) region, the sequence of other amino acids in the TM region of TCRγδ and TCR αβ differs greatly. TCRαβ can recognize foreign or mutated peptides presented on major histocompatibility complex (MHC) molecules, whereas the majority of TCRγδ does not recognize MHC molecules[25].

Within the αβT cell population, CD4+ T cells can differentiate into T helper cells (Th) after antigen stimulation. Depending on stimuli and environment, CD4+ T cells can polarize into type 1 (Th1), type 2 (Th2), type 17 (Th17), or other types of T helper cells, which are different in numerous surface markers and released cytokines and therefore play different roles in inflammation [Table 1]. CD4+ T cells also contain a special regulatory subset known as regulatory T cells (Tregs), which are characterized by the expression of CD25 and Foxp3 and exhibit immunoregulatory functions mainly by inhibition of activation of conventional T cells, B cells, and natural killer (NK) cells. Tregs are involved in the maintenance of tissue homeostasis and self-tolerance, or contribute to the pathogenesis of some morbidities by downregulating immune responses[21]. Of the αβT cell population, CD8+ T cells predominantly mediate cell killing by secreting granzymes and perforin and are therefore also known as cytotoxic T lymphocytes (CTLs). In addition, CD8+ T cells can mount immune responses through the secretion of cytokines.

Similar to T cells, B cells are heterogeneous and consist of several distinct subsets. Broadly, B cells have been identified as B1, B2, and regulatory B cells (Bregs), which differ in originations, phenotypes, locations, and functions[27,28]. B1 cells primarily originate from the fetal liver and can be further classed into B1a and B1b cells, which are both $CD19^{high}$, $B220^{-/low}$, IgM^{high}, IgD^{low}, $CD23^{-}$, $CD43^{+}$, and $CD1d^{mid}$, but different in CD5 with B1a being $CD5^{+}$ and B1b being $CD5^{-}$[28]. B1 cells are abundant in mucosal tissues, peritoneal cavities, omentum, and fat pads near the peritoneal cavity[29,30]. B2 cells are mainly derived from the bone marrow and are $CD19^{+}$, $B220^{+}$, $CD21^{high}$, $CD43^{-}$, and $CD5^{-}$[27,28]. B2 cells constitute the major B cell population in secondary lymphoid organs and play a pivotal role in adaptive immune responses[27,28]. In contrast, Bregs primarily function to restrain immune responses by producing cytokines such as IL-10[27,28].

Table 1. Major AT lymphocytes and their roles in obesity

Cell phenotypes				Markers		Major cytokines secreted	Changes in obesity and role in IR
αβ T	CD4+	T helper[120-123]	Th1	Surface	$CD3^+$, $CD4^+$, $CD8^-$, $CCR1^+$, $CCR5^+$, IL-12 R $\beta2^+$, IL-27 R α^+, IFN-γ $R2^+$, IL-18 $R\alpha^+$, and $CXCR3^+$	INF-γ, IL-2, TNF-α, and TNF-β	Increase in obesity; promote IR[19,32,34-36,38,40]
				Intracellular	$STAT1^+$, $STAT4^+$, and T-bet^+		
			Th2	Surface	$CD3^+$, $CD4^+$, $CD8^-$, $CCR3^+$, $CCR4^+$, $CCR8^-$, $CD14^-$, $CD19^-$, $CXCR4^+$, IL-4 R α^+, IL-17RB$^+$, ST2/IL-33R$^+$, and TSLP R^+	IL-4, IL-5, IL-9, IL-10, IL-13, and IL-21	Decrease in obesity; alleviate IR[23,40,44,45]
				Intracellular	GATA-3$^+$, IRF4$^+$, STAT5$^+$, and STAT6$^+$		
			Th17	Surface	$CD3^+$, $CD4^+$, $CD8^-$, $CCR4^+$, $CCR6^+$, $CD14^-$, $CD19^-$, IL-1 RI$^+$, IL-6 R α^+, IL-21 R^+, IL-23 R^+, and TGF-β RII$^+$	CCL20, IL-17A, IL-17F, IL-21, and IL-22	Increase in obesity; promote IR[48-50]
				Intracellular	Batf$^+$, IRF4$^+$, RORα^+, RORC2$^+$, and STAT3$^+$		
		Treg[124,125]		Surface	$CD3^+$, $CD4^+$, $CD5^+$, $CD14^-$, $CD19^-$, $CD25^+$, $CD39^+$, $CD103^+$, $CD127^{low}$, CTLA-4^+, folate receptor 4^+, GITR$^+$, $CD223^+$, LAP$^+$, LRRC32$^+$, BDCA-4$^+$, OX40$^+$, and $CD62^+$	Galectin-1, IL-10, IL-35, and TGF-β	Decrease in diet-induced obesity, but increase with aging; alleviate IR in diet-induced obesity[59,64,65,67], promote obesity and IR with aging[71]
				Intracellular	FoxP3$^+$ and $STAT5^+$		
	CD8+[126]			Surface	$CD3^+$, $CD4^-$, $CD8^+$, $CD28^+$, $CCR4^+$, $CCR6^+$, $CD69^+$, $CD103^+$, and KLRB1$^+$	TNFα, INF-γ, IL-2, IL-4, IL-5, IL-9, IL-10, and IL-17	Increase in obesity; promote IR[18,22]
				Intracellular	TBX21$^+$, GATA3$^+$, IRF4$^+$, and RORC$^+$		
	NKT[127]			Surface	$CD3^+$, $CD4^{+/-}$, $CD8^{+/-}$, $CD56^+$, $CD161^+$, $CD1d^+$, NK1.1$^+$ (in mice) and $CD94^+$	IFN-γ and IL-4	Increase in obesity; promote IR[80-82] Decrease in obesity; alleviate IR[79,83,84]
				Intracellular	T-bet and Eomes		
γδ T[26]				Surface	Vγ7^+, Vγ1^+, Vγ4^+, Vγ5^+, Vγ6^+, $CD27^{+/-}$, CD45RB$^+$ and NK1.1$^+$	IL-17A	Increase in obesity; promote IR[75] Increase in obesity; alleviate IR[77,128]
B Cells	B1[28,129]			Surface	$CD19^{high}$, $B220^{-/low}$, IgM^{high}, IgD^{low}, $CD23^-$, $CD43^+$, and $CD1d^{mid}$	IL-10 and IgM	Decrease in obesity; alleviate IR[24,29,90]
	B2[130]			Surface	$CD19^+$, $B220^+$, $CD21^{high}$, $CD11b^{low}$, $CD43^-$, and $CD5^-$	IFN-γ, IL12, IL10, IL4 and IgG	Increase in obesity; promote IR[24,90]
	Breg[130]			Surface	$CD1d^{high}$, $CD5^+$, $CD19^+$, $CD40^+$, $CD21^+$ $CD24^+$, IgD$^+$, and IgM$^+$	IL-10, IL-35, and TGF-β	Decrease in obesity; alleviate IR[27,28,97]
				Intracellular	EBF-1^+, E2A$^+$, Oct2^+, and Pax5^+		
	T-bet+			Surface	$CD19^+$, IgM^+CD11c^+ $CD21^-$ and $CD23^-$	IgG2a/c	Increase in obesity; promote IR[100]
				Intracellular	T-bet^+		

T cells in adipose tissue

In obesity and IR conditions, the proportions of Th1 cells are increased, whereas Th2 and Tregs are decreased in both humans and mice[6,19,21-23,31]. Animal studies indicated that Th1 cells and IFN-γ, the signature cytokine of Th1 cells, promote and Th2 cells and Tregs protect against IR in obesity [Table 1][6,19,21,23,32].

Th1 subset

The proportion of AT Th1 cells and the Th1 signature cytokine, IFN-γ, highly correlate with body mass index[23,33] and are positively associated with AT inflammation and IR both in mice and humans[19,34]. The accumulation and polarization of Th1 cells in AT in obesity may be induced by the increased expression of class II major histocompatibility complex (MHC II) and costimulatory molecules on macrophages and adipocytes[34-36]. MHC II on either macrophages or adipocytes is sufficient to promote Th1 cell polarization and IFN-γ production[35,36]. In addition, AT macrophage- or dendritic cell-released IL-12 promotes Th1 differentiation and IFN-γ expression via activating signal transducer and activator of transcription 4 (STAT4)[37].

Ablation of Th1 cells or IFN-γ in mice attenuates obesity-linked AT inflammation and IR, supporting a promoter role of Th1 cells and IFN-γ in AT inflammation and IR[19,32,38]. Mechanistically, Th1 cells may adversely regulate adipocyte or preadipocyte metabolism including impairing insulin signaling possibly via IFN-γ[19,20,39]. Th1 cells and IFN-γ may also contribute to AT inflammation and IR by inducing recruitment and M1-like phenotypic changes of macrophages in AT with obesity[19,32,40]. Deficiency of IFN-γ or its signaling molecule, STAT1, inhibits M1-like macrophage recruitment and TNF-α levels in AT and improves IR with obesity[32,40]. In addition, CD40L (CD154) expressed on Th1 cells may contribute to the accumulation of M1-like macrophages and the production of proinflammatory cytokines via interaction with CD40 expressed on macrophages in obese mice. CD40L deficiency in mice attenuates obesity-linked AT inflammation and hepatic steatosis and increases systemic insulin sensitivity[41].

Th2 subset

Th2 cells can be identified by the expression of cytokines such as IL-4, IL-5, IL-9, and IL-13 and induce macrophage polarization into M2 phenotypes[42]. The proportion of Th2 cells is decreased in AT of obese humans and mice[43]. A previous study revealed that after adoptive transfer into obese T cell-deficient mice, CD4+ T cells from wild-type mice polarized into Th2 cells, which were associated with reversal of enhanced weight gain and IR in recipient T cell-deficient mice. In contrast, the transfer of T cells from Stat6-deficient mice, which have impairment in Th2 cell polarization, did not have these effects[23]. These data support a protective role of Th2 in the development of obesity and its related IR. Th2 cells and related cytokines may protect against obesity and metabolic complications by directly regulating adipocyte metabolism or by impacting other immune cells, such as M2 macrophages and eosinophils, both of which may have beneficial effects on obesity-related metabolism[40,44,45].

Th17 subset

Th17 cells can be distinguished from other T cell subtypes by expression of IL-17[46]. IL-17 interacts with IL-17 receptor (IL-17R) expressed on other immune cells and epithelial cells and activates several signaling cascades such as NFκB, mitogen-activated protein kinases (MAPKs), and the CCAAT-enhancer-binding proteins (C/EBPs) cascades in these cells to produce inflammatory molecules. Th17 cells have been implicated in various autoimmune disorders and inflammation[47]. However, the role of Th17 cells in obesity and IR remains largely unexplored. An elevated proportion of Th17 cells is observed in AT, peripheral blood, spleen, and lymph nodes in both humans and mice with obesity[48,49]. The accumulation of Th17 cells

in AT positively correlates with AT inflammation and IR, and studies in mice with the absence of IL-17 support the proinflammatory role of IL-17 in AT[50]. IL-17 may promote AT inflammation but inhibit adipocyte differentiation through TANK-binding kinases 1 (TBK1) and I-kappa-B kinase epsilon (IKBKE)[50].

In AT, Th17 cells interact with and are regulated by other immune cells and adipocytes[51,52]. A distinct subset of dendritic cells characterized by being $CD11c^{high}F4/80^{low}CX3CR1^{+}$ has been shown to correlate with Th17 differentiation in AT[53]. Adipose-derived stem cells (ASCs) from human subjects with obesity have been demonstrated to enhance IL-17 release by Th17 cells but inhibit the expression of IFN-γ and TNF-α by Th1 cells[54]. Furthermore, dysregulation of Tregs in obesity may contribute to the increase in Th17 in AT. Under healthy conditions, Th17 and Tregs cells are balanced; however, imbalance occurs in inflammatory conditions such as obesity and IR[55]. Th17 cells are susceptible to suppression by naïve and memory Tregs, which inhibit the production of IL-17, IL-22, and CXCL8[56]. Rab4b, a small GTPase governing endocytic trafficking in T cells, exhibits decreased expression in individuals with obesity, which may also contribute to the elevation of Th17 cells and reduction of Tregs within AT in obesity[57].

Tregs

Tregs are usually a small portion of CD4+ T cells but are enriched in visceral AT (VAT) in lean conditions[21,58]. VAT enrichment of Tregs shows sexual dimorphism, with more Treg enrichment in male than female VAT[58]. AT Tregs exhibit elevated expression levels of CTLA-4, GITR, OX40, peroxisome proliferator-activated receptor (PPAR)-γ, and IL-10[59]. Obesity diminishes accumulation of Tregs in both VAT and subcutaneous AT (SAT) in mice and humans[21,59] and changes VAT Treg signature. Depletion of Tregs in mice leads to increased gene expression of inflammatory mediators, including TNF-α, IL-6, and CCL5, and impaired metabolic signaling pathways within VAT, and expansion of Tregs improves insulin sensitivity in mice fed high-fat diet (HFD)[21,60], supporting a protective role of Tregs in AT inflammation and IR associated with diet-induced obesity.

Tregs also participate in the regulation of adipocyte browning[61]. Brown AT or white AT browning facilitates nonshivering thermogenesis, representing a capacity for energy expenditure and holding potential for the treatment of obesity[62]. A unique subset of Tregs characterized by the expression of $CD73^{hi}ST2^{lo}$ in AT exerts IR-improving effects by promoting white AT beiging through the augmentation of adenosine production[63].

Although the mechanisms responsible for the enrichment and function of Tregs in lean VAT have not been fully elucidated, several factors are considered crucial for Tregs accumulation in AT. PPAR-γ, the "master regulator" of adipocyte differentiation, is an essential regulator of the phenotype and function of Treg accumulation in VAT and contributes to Treg upregulation in conjunction with Foxp3. In obesity, the phosphorylation of PPAR-γ at Ser273 leads to the disappearance of this VAT Treg signature[59,64,65]. The enzyme hydroxyprostaglandin dehydrogenase (HPGD), which exhibits high expression levels in VAT Tregs, plays a pivotal role in maintaining VAT homeostasis and metabolic regulation and contributes significantly to the suppressive capabilities of VAT Tregs, which are partially induced by PPAR-γ[66]. Furthermore, adipocytes and other immune cells within AT also contribute to the accumulation, phenotype, and function of VAT Tregs. MHCII molecules are highly expressed on adipocytes and negatively correlated with Tregs in AT. The specific knockout of MHCII in adipocytes promotes Treg accumulation and M2-like macrophage polarization, possibly by inhibiting IFN-γ production in Th1 cells[67]. Costimulatory B7 molecules (CD80 and CD86) on antigen-presenting cells (APCs) may be important in maintaining Tregs in AT. CD80/CD86 double knockout in mice reduces AT Tregs, with

enhanced AT inflammation and IR, while adoptive transfer of Tregs effectively mitigates IR and AT inflammation in CD80/CD86 double-knockout mice[68]. In addition, ST2, the IL-33 receptor, is highly expressed on VAT Tregs from humans and mice; IL-33 drives VAT Treg proliferation and is able to rescue VAT Treg numbers in obese mice, along with improving AT inflammation and IR[69,70].

In contrast to the changes and role in diet-induced obesity, AT Tregs are increased with aging and may play an adverse role in age-associated immune responses and IR.[71]

CD8+ T cells

CD8+ T cells increase early and mainly accumulate in VAT in obesity[22] and may participate in the progression of obesity-associated AT inflammation and IR[18,19,22]. Along with macrophages, CD8+ T cells participate in crown-like structure formation[22,36]. In obesity, AT CD8+ T cells polarize into an effector memory phenotype, with elevated expression of IFN-γ and granzyme B[18,22]. The accumulation and activation of CD8+ T cells may be induced by elevated IL-12 and IL-18 in obese AT[18]. Similar to Th1 cells, CD8+ T cells promote AT inflammation and IR[18,22]. CD8+ T cell deficiency in mice improves IR in obesity, associated with reduced macrophage infiltration and decreased M1-like macrophage recruitment[22,72]. In addition, blocking CD4+ and CD8+ T cell activation in mice with anti-CD40L antibody reduces weight gain, mitigates VAT inflammation, and alleviates obesity-induced IR, also supporting the role of T cell activation in the development of obesity and IR[73,74]. CD8+ T cells may contribute to the development of obesity and IR through inhibition of beige adipogenesis[72].

γδT cells

Similar to αβT cells, γδT cells accumulate within AT during obesity and play a role in AT inflammation and macrophage recruitment[75]. Mice with a deficiency of γδT cells have reduced M1-like macrophage accumulation and increased M2-like macrophage enrichment in VAT[75]. Upon activation, γδT cells mainly function through the production of cytokines and growth factors[76]. γδT cells are one major source of IL-17A in AT[75], thereby contributing to AT inflammation, adipogenesis, and glucose metabolism. γδT cell-secreted IL-17 may also promote AT sympathetic innervation and thermogenesis through the IL-17 receptor C/TGFβ1 pathway in adipocytes[77]. Further, based on the BTB-POZ transcription factor, PLZF, γδT cells can be distinguished into two distinct populations with differences in IL-17A production[78]. Mice lacking γδT cells or IL-17A exhibit a low abundance of ST2+ Tregs and IL-33 in VAT and have impaired capacity to regulate core body temperature when exposed to cold[69,78], supporting a role of AT resident γδT cells in the maintenance of AT immune homeostasis and control of body temperature.

NKT cells

Natural killer T (NKT) cells are characterized by the co-expression of NK cell markers (NK1.1 or CD56) and T cell marker (αβTCR)[79]. NKT cells primarily identify glycolipid antigens presented by the MHC class I-like molecule CD1d and can be categorized into two main types: type I and type II NKT cells[6]. Both NKT subtypes can produce Th1 and Th2 cytokines such as IFN-γ and IL-4 and contribute to the regulation of adaptive immunity. Type I NKT cells express the invariant TCRα (Vα14-Jα18 in mice, Vα24-Jα18 in humans) and are also named invariant NKT (iNKT)[6]. While some initial studies indicated that obesity in mice increased VAT NKT cells, including iNKT, and that NKT cells may promote obesity-linked AT inflammation[80-82], others reported that iNKT cells are highly enriched in AT of lean humans and mice and are decreased in AT of obese individuals[79,83,84].

The presence and activation of iNKT cells in AT depend on their interaction with CD1d molecules expressed on adipocytes[79]. In normal conditions, adipocytes with high CD1d expression act as APCs that

present lipid antigens to iNKT cells, thereby sustaining iNKT cell populations and promoting their activation within AT[84]. Obesity is associated with a decrease in CD1d expression in both human and mouse AT, resulting in a reduction of iNKT cells in AT[85].

AT iNKT cells have a unique transcriptional program and produce IL-2 and IL-10, which may promote M2-like macrophage polarization and control the proliferation and suppressive function of Tregs in AT[86]. While some studies showed that iNKT cell deficiency in mice did not impact weight gain[81,86], with no effects on glucose tolerance[86] or with improved insulin resistance[81], another study showed that mice with iNKT cell deficiency had increased weight gain and exacerbated insulin resistance, along with proinflammatory macrophage infiltration[83]. The reasons for the data discrepancy are not clear. Differences in housing conditions and environment may have contributed to the discrepancy.

B cells in adipose tissue

Similar to T lymphocytes, B cells infiltrate VAT and undergo functional and phenotypic changes in response to diet-induced obesity and IR[24,87-90]. B1 cells negatively correlate with AT inflammation and IR, whereas B2 cells are positively associated with AT inflammation and IR [Table 1][24,89,90].

B1 cells

Of the B1 cells, B1a cells are recognized as the primary producers of natural IgM antibodies, while B1b cells are responsible for initiating adaptive humoral immune responses against T cell-independent antigens[91]. In AT, B1 cells constitute a small portion of B cells, accounting for ~20%-30% of total B cells[24,29,90]. Reports on changes in AT B1 cells in obesity were not consistent, with some studies[29,90] showing reductions but another study[24] showing slight increases in AT B1 cells in mice with obesity. B1a cells are identified as the major producers of B cell-derived IL-10, which exerts anti-inflammatory functions in obesity-induced AT inflammation[29]. Adaptive transfer of B1a cells or IL-10 rapidly improves insulin resistance and glucose tolerance, supporting the protective role of B1a and IL-10 in IR[29]. B1b cells in AT reduce cytokine production by M1-like macrophages, and adoptive transfer of B1b cells exerts anti-inflammatory effects in AT[89]. Further, B-1b cells protect against the development of obesity-associated glucose intolerance in an IgM-dependent manner[89]. In addition, B1 cell-produced IgM antibodies exhibit cross-reactivity with membrane lipids and circulating oxidized low-density lipoprotein (oxLDL)[92]. The neutralization of oxLDL by natural IgM antibodies has been demonstrated to protect against inflammation associated with atherosclerosis[93].

B2 cells

B2 cells produce specific antibodies in response to T cell-dependent antigens[94]. Depending on the microenvironment, B2 cells also possess the capacity to differentiate into effector cells, which can produce proinflammatory cytokines such as IFN-γ and IL-12 and anti-inflammatory cytokines including IL-10 and IL-4[95]. In AT, B2 cells account for ~70%-80% of total B cells and are significantly increased in VAT of mice with HFD-indued obesity[24,90]. B cell deficiency in mice reduces obesity-induced AT inflammation and improves IR, with impacts on weight gain, and adoptive transfer of AT B2 cells from wild-type mice restores AT inflammation and insulin resistance in mice with B cell deficiency[24,90], indicating a promoting role of B2 cells in the development of AT inflammation and IR in obesity. B2 cells may promote IR and AT inflammation by activating macrophages and T cells through cytokine production and antigen presentation and by producing pathogenic IgG antibodies[24,96]. The recruitment and activation of B2 cells in AT in obesity may be mediated by the interaction of leukotriene B4 (LTB4) and its receptor LTB4R1, which is highly expressed on AT B2 cells[90].

Breg cells

Bregs are characterized by producing IL-10 and transforming growth factor-β (TGF-β) and have anti-inflammatory effects[27,28,97]. However, various other B cell subsets, including B1a and B1b, are able to produce IL-10[27-29]. Nishimura *et al.* reported that B cells in AT, but not in the spleen, in old normal chow-fed mice express IL-10 and that these IL-10-expressing B cells in AT are distinct from other known IL-10-expressing B cell subsets and are considered Bregs[97]. Diet-induced obesity in mice reduces IL-10 expression in AT B cells[97]. The frequencies of Bregs are also diminished in AT of individuals with overweight and obesity compared to individuals with normal weight[98]. B cell-specific IL-10 deletion aggravates AT inflammation and IR in obese mice, whereas adaptive transfer of AT Bregs ameliorates these effects[97], supporting a protective role of IL-10-expressing Bregs in obesity-linked inflammation and IR.

T-bet+ B cells

T-bet+ B cells are a subset of B cells that express T-bet and CD11c but lack CD21 and CD23, and expand during chronic inflammation[99]. The frequencies of T-bet+ B cells are elevated in AT of humans and mice with obesity[100,101]. The increased frequencies of AT T-bet+ B in obesity rely on iNKT cells and TLR7 stimulation[100-102]. Mice with ablation of T-bet in B cells are protected from AT inflammation and IR with obesity, while the adaptive transfer of T-bet+ B cells aggravates IR in obesity, suggesting a proinflammatory and pathological role of T-bet+ B cells in obesity-linked inflammation and metabolic complications[100]. T-bet+ B cells may contribute to inflammation through the production of IgG2c during obesity. Along with the reductions in inflammatory cytokines and macrophages in AT, mice with ablation of T-bet in B cells have reduced serum levels of IgG2c[100].

Conclusion and perspective

Obesity is mainly caused by an energy imbalance between energy intake and energy expenditure and is associated with aging[103]. It has been well recognized that obesity is associated with low-grade chronic AT inflammation, with changes in the numbers and phenotypes of various types of immune cells[4-9]. While macrophages are the immune cells first reported in AT[10,17], lymphocytes including T cells and B cells also reside in AT and undergo numeric and phenotypic changes in obesity[20,24]. Obesity increases $CD8^+$ effector memory T cells, $CD4^+$ Th1 cells, and B2 cells, but reduces Treg and Th2 cells, in AT[18,19,21-24,90].

Many studies mainly performed in rodent models have demonstrated that AT inflammation and immune cells may play a role in the development of obesity-associated metabolic complications, including IR and type 2 diabetes, through various mechanisms. Therefore, efforts targeting immune cells and inflammation have been explored to prevent and treat obesity-related diseases[104-106]. The classical generic anti-inflammatory drugs, salicylates, have been shown to lower blood glucose levels in humans with obesity and/or type 2 diabetes[104,107-109]. Another generic anti-inflammatory drug, methotrexate, reduces hemoglobin A1c levels in patients with rheumatoid arthritis[110]. Several large clinical trials have shown the efficacy of therapies targeting inflammation in the prevention of atherosclerotic cardiovascular diseases over the past few years[111-113]. However, targeting inflammation or immune cells has not proven very successful for the prevention and treatment of obesity-related metabolic disease in large clinical trials. A significant barrier to the development of effective immune therapies for obesity and its metabolic complications is our limited knowledge of the mechanisms that regulate immune responses specific to obesity and the precise pathways through which immune cells influence metabolism.

The JAK/STAT pathways play critical roles in inflammation and have recently been active therapeutic targets for inflammatory diseases. Several JAK inhibitors have been approved by the US Food and Drug Administration (FDA) for the treatment of inflammatory diseases such as rheumatoid arthritis and

psoriasis[114]. The JAK/STAT pathways are also activated early and persistently in AT with obesity and may contribute to AT inflammation and IR in obesity[39,40,115]. Therefore, we and others tested the effects of targeting the JAK/STAT pathways on immune and metabolic phenotypes in mouse models of HFD-induced obesity. Of note, treatment with baricitinib, an FDA-approved JAK1/JAK2 inhibitor for rheumatoid arthritis, reduces Th1 cells in AT and improves insulin sensitivity in mice fed HFD[34,116,117]. A phase 2 randomized controlled clinical trial involving 129 participants showed that baricitinib treatment (for 24 weeks) of humans with type 2 diabetes and diabetic kidney disease reduced inflammation, improved renal functions, and lowered hemoglobin A1c levels[118], indicating a potential of repurposing FDA-approved medications to treat obesity- and/or diabetes-related complications. Another example is auronofin, another FDA-approved rheumatoid arthritis drug, which exerts beneficial effects on obesity-associated metabolic abnormalities in mouse models of diet-induced obesity[119]. Future studies will need to focus on deeper insights into the roles and mechanisms of immune cells in metabolic diseases, which could potentially unveil innovative paths for identifying new pharmacological targets and agents for the prevention and treatment of metabolic diseases, including type 2 diabetes.

DECLARATIONS

Acknowledgment

We thank Kerrie Jara for editorial assistance.

Author's contribution

Design of the figure: Gao F

Manuscript conception, writing, and editing: Gao F, Litchfield B, Wu H

Availability of data and materials

No original data were generated for this review article.

Financial support and sponsorship

This work was supported by National Institutes of Health grants R01DK121348 and R01AG065197 (Wu H), American Heart Association award 968367 (Wu H), and American Diabetes Association postdoctoral fellowship award 11-23-PDF-75 (Gao F).

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate.

Not applicable.

Consent for publishing.

Not applicable.

REFERENCES

1. SantaCruz-Calvo S, Bharath L, Pugh G, et al. Adaptive immune cells shape obesity-associated type 2 diabetes mellitus and less prominent comorbidities. *Nat Rev Endocrinol* 2022;18:23-42. DOI
2. Srikakulapu P, McNamara CA. B lymphocytes and adipose tissue inflammation. *Arterioscler Thromb Vasc Biol* 2020;40:1110-22. DOI PubMed PMC
3. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked

insulin resistance. *Science* 1993;259:87-91. DOI PubMed
4. Wu H, Ballantyne CM. Skeletal muscle inflammation and insulin resistance in obesity. *J Clin Invest* 2017;127:43-54. DOI PubMed PMC
5. Wu H, Ballantyne CM. Metabolic inflammation and insulin resistance in obesity. *Circ Res* 2020;126:1549-64. DOI PubMed PMC
6. Wang Q, Wu H. T cells in adipose tissue: critical players in immunometabolism. *Front Immunol* 2018;9:2509. DOI PubMed PMC
7. Lumeng CN, Saltiel AR. Inflammatory links between obesity and metabolic disease. *J Clin Invest* 2011;121:2111-7. DOI PubMed PMC
8. Chavakis T, Alexaki VI, Ferrante AW Jr. Macrophage function in adipose tissue homeostasis and metabolic inflammation. *Nat Immunol* 2023;24:757-66. DOI PubMed
9. Rohm TV, Meier DT, Olefsky JM, Donath MY. Inflammation in obesity, diabetes, and related disorders. *Immunity* 2022;55:31-55. DOI PubMed PMC
10. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW Jr. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest* 2003;112:1796-808. DOI PubMed PMC
11. Lumeng CN, Bodzin JL, Saltiel AR. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. *J Clin Invest* 2007;117:175-84. DOI PubMed PMC
12. Lumeng CN, DelProposto JB, Westcott DJ, Saltiel AR. Phenotypic switching of adipose tissue macrophages with obesity is generated by spatiotemporal differences in macrophage subtypes. *Diabetes* 2008;57:3239-46. DOI PubMed PMC
13. Schaum N, Lehallier B, Hahn O, et al. Ageing hallmarks exhibit organ-specific temporal signatures. *Nature* 2020;583:596-602. DOI
14. Russo L, Lumeng CN. Properties and functions of adipose tissue macrophages in obesity. *Immunology* 2018;155:407-17. DOI PubMed PMC
15. Liu K, Zhao E, Ilyas G, et al. Impaired macrophage autophagy increases the immune response in obese mice by promoting proinflammatory macrophage polarization. *Autophagy* 2015;11:271-84. DOI PubMed PMC
16. Kratz M, Coats BR, Hisert KB, et al. Metabolic dysfunction drives a mechanistically distinct proinflammatory phenotype in adipose tissue macrophages. *Cell Metab* 2014;20:614-25. DOI PubMed PMC
17. Xu H, Barnes GT, Yang Q, et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J Clin Invest* 2003;112:1821-30. DOI
18. Jiang E, Perrard XD, Yang D, et al. Essential role of CD11a in $CD8^+$ T-cell accumulation and activation in adipose tissue. *Arterioscler Thromb Vasc Biol* 2014;34:34-43. DOI PubMed PMC
19. Khan IM, Dai Perrard XY, Perrard JL, et al. Attenuated adipose tissue and skeletal muscle inflammation in obese mice with combined CD4+ and CD8+ T cell deficiency. *Atherosclerosis* 2014;233:419-28. DOI PubMed PMC
20. Wu H, Ghosh S, Perrard XD, et al. T-cell accumulation and regulated on activation, normal T cell expressed and secreted upregulation in adipose tissue in obesity. *Circulation* 2007;115:1029-38. DOI
21. Feuerer M, Herrero L, Cipolletta D, et al. Lean, but not obese, fat is enriched for a unique population of regulatory T cells that affect metabolic parameters. *Nat Med* 2009;15:930-9. DOI PubMed PMC
22. Nishimura S, Manabe I, Nagasaki M, et al. CD^{8+} effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity. *Nat Med* 2009;15:914-20. DOI
23. Winer S, Chan Y, Paltser G, et al. Normalization of obesity-associated insulin resistance through immunotherapy. *Nat Med* 2009;15:921-9. DOI PubMed PMC
24. Winer DA, Winer S, Shen L, et al. B cells promote insulin resistance through modulation of T cells and production of pathogenic IgG antibodies. *Nat Med* 2011;17:610-7. DOI PubMed PMC
25. Morath A, Schamel WW. αβ and γδ T cell receptors: similar but different. *J Leukoc Biol* 2020;107:1045-55. DOI PubMed
26. Ribot JC, Lopes N, Silva-Santos B. γδ T cells in tissue physiology and surveillance. *Nat Rev Immunol* 2021;21:221-32. DOI PubMed
27. Wang Y, Liu J, Burrows PD, Wang J. B cell development and maturation. In: Wang J, editor. B Cells in Immunity and Tolerance. Singapore: Springer; 2020. pp. 1-22. DOI
28. Baumgarth N. The double life of a B-1 cell: self-reactivity selects for protective effector functions. *Nat Rev Immunol* 2011;11:34-46. DOI PubMed
29. Shen L, Chng MH, Alonso MN, Yuan R, Winer DA, Engleman EG. B-1a lymphocytes attenuate insulin resistance. *Diabetes* 2015;64:593-603. DOI PubMed PMC
30. Jennbacken K, Ståhlman S, Grahnemo L, Wiklund O, Fogelstrand L. Glucose impairs B-1 cell function in diabetes. *Clin Exp Immunol* 2013;174:129-38. DOI PubMed PMC
31. Bradley D, Smith AJ, Blaszczak A, et al. Interferon gamma mediates the reduction of adipose tissue regulatory T cells in human obesity. *Nat Commun* 2022;13:5606. DOI PubMed PMC
32. Rocha VZ, Folco EJ, Sukhova G, et al. Interferon-gamma, a Th1 cytokine, regulates fat inflammation: a role for adaptive immunity in obesity. *Circ Res* 2008;103:467-76. DOI PubMed PMC
33. Kintscher U, Hartge M, Hess K, et al. T-lymphocyte infiltration in visceral adipose tissue: a primary event in adipose tissue inflammation and the development of obesity-mediated insulin resistance. *Arterioscler Thromb Vasc Biol* 2008;28:1304-10. DOI
34. Khan IM, Perrard XY, Brunner G, et al. Intermuscular and perimuscular fat expansion in obesity correlates with skeletal muscle T

cell and macrophage infiltration and insulin resistance. *Int J Obes* 2015;39:1607-18. DOI PubMed PMC

35. Morris DL, Cho KW, Delproposto JL, et al. Adipose tissue macrophages function as antigen-presenting cells and regulate adipose tissue CD4+ T cells in mice. *Diabetes* 2013;62:2762-72. DOI PubMed PMC
36. Deng T, Lyon CJ, Minze LJ, et al. Class II major histocompatibility complex plays an essential role in obesity-induced adipose inflammation. *Cell Metab* 2013;17:411-22. DOI PubMed PMC
37. Dobrian AD, Galkina EV, Ma Q, et al. STAT4 deficiency reduces obesity-induced insulin resistance and adipose tissue inflammation. *Diabetes* 2013;62:4109-21. DOI PubMed PMC
38. Strissel KJ, DeFuria J, Shaul ME, Bennett G, Greenberg AS, Obin MS. T-cell recruitment and Th1 polarization in adipose tissue during diet-induced obesity in C57BL/6 mice. *Obesity* 2010;18:1918-25. DOI PubMed PMC
39. McGillicuddy FC, Chiquoine EH, Hinkle CC, et al. Interferon gamma attenuates insulin signaling, lipid storage, and differentiation in human adipocytes via activation of the JAK/STAT pathway. *J Biol Chem* 2009;284:31936-44. DOI PubMed PMC
40. Antony A, Lian Z, Perrard XD, et al. Deficiency of Stat1 in $CD11c^+$ cells alters adipose tissue inflammation and improves metabolic dysfunctions in mice fed a high-fat diet. *Diabetes* 2021;70:720-32. DOI PubMed PMC
41. Poggi M, Engel D, Christ A, et al. CD40L deficiency ameliorates adipose tissue inflammation and metabolic manifestations of obesity in mice. *Arterioscler Thromb Vasc Biol* 2011;31:2251-60. DOI
42. Zhu J. Transcriptional regulation of Th2 cell differentiation. *Immunol Cell Biol* 2010;88:244-9. DOI PubMed PMC
43. McLaughlin T, Liu LF, Lamendola C, et al. T-cell profile in adipose tissue is associated with insulin resistance and systemic inflammation in humans. *Arterioscler Thromb Vasc Biol* 2014;34:2637-43. DOI PubMed PMC
44. Qiu Y, Nguyen KD, Odegaard JI, et al. Eosinophils and type 2 cytokine signaling in macrophages orchestrate development of functional beige fat. *Cell* 2014;157:1292-308. DOI PubMed PMC
45. Wu D, Molofsky AB, Liang HE, et al. Eosinophils sustain adipose alternatively activated macrophages associated with glucose homeostasis. *Science* 2011;332:243-7. DOI PubMed PMC
46. Sumarac-Dumanovic M, Stevanovic D, Ljubic A, et al. Increased activity of interleukin-23/interleukin-17 proinflammatory axis in obese women. *Int J Obes* 2009;33:151-6. DOI
47. Li X, Bechara R, Zhao J, McGeachy MJ, Gaffen SL. IL-17 receptor-based signaling and implications for disease. *Nat Immunol* 2019;20:1594-602. DOI PubMed PMC
48. Wang M, Chen F, Wang J, Zeng Z, Yang Q, Shao S. Th17 and treg lymphocytes in obesity and type 2 diabetic patients. *Clin Immunol* 2018;197:77-85. DOI
49. Fabbrini E, Cella M, McCartney SA, et al. Association between specific adipose tissue CD4+ T-cell populations and insulin resistance in obese individuals. *Gastroenterology* 2013;145:366-74.e3. DOI PubMed PMC
50. Lee SH, Jhun J, Byun JK, et al. IL-17 axis accelerates the inflammatory progression of obese in mice via TBK1 and IKBKE pathway. *Immunol Lett* 2017;184:67-75. DOI
51. Ip B, Cilfone NA, Belkina AC, et al. Th17 cytokines differentiate obesity from obesity-associated type 2 diabetes and promote TNFα production. *Obesity* 2016;24:102-12. DOI PubMed PMC
52. Chang YC, Hee SW, Chuang LM. T helper 17 cells: a new actor on the stage of type 2 diabetes and aging? *J Diabetes Investig* 2021;12:909-13. DOI PubMed PMC
53. Bertola A, Ciucci T, Rousseau D, et al. Identification of adipose tissue dendritic cells correlated with obesity-associated insulin-resistance and inducing Th17 responses in mice and patients. *Diabetes* 2012;61:2238-47. DOI PubMed PMC
54. Eljaafari A, Robert M, Chehimi M, et al. Adipose tissue-derived stem cells from obese subjects contribute to inflammation and reduced insulin response in adipocytes through differential regulation of the Th1/Th17 balance and monocyte activation. *Diabetes* 2015;64:2477-88. DOI
55. Croce S, Avanzini MA, Regalbuto C, et al. Adipose tissue immunomodulation and Treg/Th17 imbalance in the impaired glucose metabolism of children with obesity. *Children* 2021;8:554. DOI PubMed PMC
56. Crome SQ, Clive B, Wang AY, et al. Inflammatory effects of ex vivo human Th17 cells are suppressed by regulatory T cells. *J Immunol* 2010;185:3199-208. DOI
57. Gilleron J, Bouget G, Ivanov S, et al. Rab4b deficiency in t cells promotes adipose Treg/Th17 imbalance, adipose tissue dysfunction, and insulin resistance. *Cell Rep* 2018;25:3329-41.e5. DOI
58. Vasanthakumar A, Chisanga D, Blume J, et al. Sex-specific adipose tissue imprinting of regulatory T cells. *Nature* 2020;579:581-5. DOI PubMed PMC
59. Cipolletta D, Feuerer M, Li A, et al. PPAR-gamma is a major driver of the accumulation and phenotype of adipose tissue Treg cells. *Nature* 2012;486:549-53. DOI PubMed PMC
60. Ilan Y, Maron R, Tukpah AM, et al. Induction of regulatory T cells decreases adipose inflammation and alleviates insulin resistance in ob/ob mice. *Proc Natl Acad Sci USA* 2010;107:9765-70. DOI PubMed PMC
61. Fang W, Deng Z, Benadjaoud F, Yang D, Yang C, Shi GP. Regulatory T cells promote adipocyte beiging in subcutaneous adipose tissue. *FASEB J* 2020;34:9755-70. DOI
62. Schulz TJ, Tseng YH. Brown adipose tissue: development, metabolism and beyond. *Biochem J* 2013;453:167-78. DOI PubMed PMC
63. Li Y, Lu Y, Lin SH, et al. Insulin signaling establishes a developmental trajectory of adipose regulatory T cells. *Nat Immunol* 2021;22:1175-85. DOI

64. Cipolletta D. Adipose tissue-resident regulatory T cells: phenotypic specialization, functions and therapeutic potential. *Immunology* 2014;142:517-25. DOI PubMed PMC
65. Cipolletta D, Cohen P, Spiegelman BM, Benoist C, Mathis D. Appearance and disappearance of the mRNA signature characteristic of Treg cells in visceral adipose tissue: age, diet, and PPARγ effects. *Proc Natl Acad Sci USA* 2015;112:482-7. DOI PubMed PMC
66. Schmidleithner L, Thabet Y, Schönfeld E, et al. Enzymatic activity of HPGD in treg cells suppresses tconv cells to maintain adipose tissue homeostasis and prevent metabolic dysfunction. *Immunity* 2019;50:1232-48.e14. DOI
67. Deng T, Liu J, Deng Y, et al. Adipocyte adaptive immunity mediates diet-induced adipose inflammation and insulin resistance by decreasing adipose Treg cells. *Nat Commun* 2017;8:15725. DOI PMC
68. Zhong J, Rao X, Braunstein Z, et al. T-cell costimulation protects obesity-induced adipose inflammation and insulin resistance. *Diabetes* 2014;63:1289-302. DOI PubMed PMC
69. Vasanthakumar A, Moro K, Xin A, et al. The transcriptional regulators IRF4, BATF and IL-33 orchestrate development and maintenance of adipose tissue-resident regulatory T cells. *Nat Immunol* 2015;16:276-85. DOI
70. Han JM, Wu D, Denroche HC, Yao Y, Verchere CB, Levings MK. IL-33 reverses an obesity-induced deficit in visceral adipose tissue $ST2^+$ T regulatory cells and ameliorates adipose tissue inflammation and insulin resistance. *J Immunol* 2015;194:4777-83. DOI PubMed
71. Bapat SP, Myoung Suh J, Fang S, et al. Depletion of fat-resident Treg cells prevents age-associated insulin resistance. *Nature* 2015;528:137-41. DOI PubMed PMC
72. Moysidou M, Karaliota S, Kodela E, et al. CD8+ T cells in beige adipogenesis and energy homeostasis. *JCI Insight* 2018;3:95456. DOI PubMed PMC
73. Montes VN, Turner MS, Subramanian S, et al. T cell activation inhibitors reduce CD8+ T cell and pro-inflammatory macrophage accumulation in adipose tissue of obese mice. *PLoS One* 2013;8:e67709. DOI PubMed PMC
74. Yi Z, Bishop GA. Regulatory role of CD40 in obesity-induced insulin resistance. *Adipocyte* 2015;4:65-9. DOI PubMed PMC
75. Mehta P, Nuotio-Antar AM, Smith CW. γδ T cells promote inflammation and insulin resistance during high fat diet-induced obesity in mice. *J Leukoc Biol* 2015;97:121-34. DOI PubMed PMC
76. Fay NS, Larson EC, Jameson JM. Chronic Inflammation and γδ T Cells. *Front Immunol* 2016;7:210. DOI PubMed PMC
77. Hu B, Jin C, Zeng X, et al. γδ T cells and adipocyte IL-17RC control fat innervation and thermogenesis. *Nature* 2020;578:610-4. DOI PubMed PMC
78. Kohlgruber AC, Gal-Oz ST, LaMarche NM, et al. γδ T cells producing interleukin-17A regulate adipose regulatory T cell homeostasis and thermogenesis. *Nat Immunol* 2018;19:464-74. DOI PubMed PMC
79. Huh JY, Park J, Kim JI, Park YJ, Lee YK, Kim JB. Deletion of CD1d in adipocytes aggravates adipose tissue inflammation and insulin resistance in obesity. *Diabetes* 2017;66:835-47. DOI
80. Ohmura K, Ishimori N, Ohmura Y, et al. Natural killer T cells are involved in adipose tissues inflammation and glucose intolerance in diet-induced obese mice. *Arterioscler Thromb Vasc Biol* 2010;30:193-9. DOI
81. Wu L, Parekh VV, Gabriel CL, et al. Activation of invariant natural killer T cells by lipid excess promotes tissue inflammation, insulin resistance, and hepatic steatosis in obese mice. *Proc Natl Acad Sci USA* 2012;109:E1143-52. DOI PubMed PMC
82. Satoh M, Andoh Y, Clingan CS, et al. Type II NKT cells stimulate diet-induced obesity by mediating adipose tissue inflammation, steatohepatitis and insulin resistance. *PLoS One* 2012;7:e30568. DOI PubMed PMC
83. Lynch L, Nowak M, Varghese B, et al. Adipose tissue invariant NKT cells protect against diet-induced obesity and metabolic disorder through regulatory cytokine production. *Immunity* 2012;37:574-87. DOI PubMed PMC
84. Huh JY, Park YJ, Kim JB. Adipocyte CD1d determines adipose inflammation and insulin resistance in obesity. *Adipocyte* 2018;7:129-36. DOI PubMed PMC
85. Huh JY, Kim JI, Park YJ, et al. A novel function of adipocytes in lipid antigen presentation to iNKT cells. *Mol Cell Biol* 2013;33:328-39. DOI PubMed PMC
86. Ji Y, Sun S, Xu A, et al. Activation of natural killer T cells promotes M2 Macrophage polarization in adipose tissue and improves systemic glucose tolerance via interleukin-4 (IL-4)/STAT6 protein signaling axis in obesity. *J Biol Chem* 2012;287:13561-71. DOI PubMed PMC
87. Winer DA, Winer S, Chng MH, Shen L, Engleman EG. B Lymphocytes in obesity-related adipose tissue inflammation and insulin resistance. *Cell Mol Life Sci* 2014;71:1033-43. DOI PubMed PMC
88. Oleinika K, Slisere B, Catalán D, Rosser EC. B cell contribution to immunometabolic dysfunction and impaired immune responses in obesity. *Clin Exp Immunol* 2022;210:263-72. DOI PubMed PMC
89. Harmon DB, Srikakulapu P, Kaplan JL, et al. Protective role for B-1b B cells and IgM in obesity-associated inflammation, glucose intolerance, and insulin resistance. *Arterioscler Thromb Vasc Biol* 2016;36:682-91. DOI PubMed PMC
90. Ying W, Wollam J, Ofrecio JM, et al. Adipose tissue B2 cells promote insulin resistance through leukotriene LTB4/LTB4R1 signaling. *J Clin Invest* 2017;127:1019-30. DOI PubMed PMC
91. Haas KM, Poe JC, Steeber DA, Tedder TF. B-1a and B-1b cells exhibit distinct developmental requirements and have unique functional roles in innate and adaptive immunity to S. pneumoniae. *Immunity* 2005;23:7-18. DOI
92. Ait-Oufella H, Herbin O, Bouaziz JD, et al. B cell depletion reduces the development of atherosclerosis in mice. *J Exp Med* 2010;207:1579-87. DOI PubMed PMC
93. Kyaw T, Tay C, Khan A, et al. Conventional B2 B cell depletion ameliorates whereas its adoptive transfer aggravates atherosclerosis.

J Immunol 2010;185:4410-9. DOI
94. Cyster JG, Allen CDC. B cell responses: cell interaction dynamics and decisions. *Cell* 2019;177:524-40. DOI PubMed PMC
95. Vazquez MI, Catalan-Dibene J, Zlotnik A. B cells responses and cytokine production are regulated by their immune microenvironment. *Cytokine* 2015;74:318-26. DOI PubMed PMC
96. DeFuria J, Belkina AC, Jagannathan-Bogdan M, et al. B cells promote inflammation in obesity and type 2 diabetes through regulation of T-cell function and an inflammatory cytokine profile. *Proc Natl Acad Sci USA* 2013;110:5133-8. DOI PubMed PMC
97. Nishimura S, Manabe I, Takaki S, et al. Adipose natural regulatory B cells negatively control adipose tissue inflammation. *Cell Metab* 2013;18:759-66. DOI
98. García-Hernández MH, Rodríguez-Varela E, García-Jacobo RE, et al. Frequency of regulatory B cells in adipose tissue and peripheral blood from individuals with overweight, obesity and normal-weight. *Obes Res Clin Pract* 2018;12:513-9. DOI
99. Myles A, Sanz I, Cancro MP. T-bet$^+$ B cells: a common denominator in protective and autoreactive antibody responses? *Curr Opin Immunol* 2019;57:40-5. DOI PubMed PMC
100. Hägglöf T, Vanz C, Kumagai A, et al. T-bet$^+$ B cells accumulate in adipose tissue and exacerbate metabolic disorder during obesity. *Cell Metab* 2022;34:1121-36.e6. DOI PubMed PMC
101. Enslow B, Vanz C, Dudley EA, Hägglöf T, Leadbetter EA. Diet-induced obesity promotes CD11c$^+$ T-bet$^+$ B cell expansion in liver and adipose tissue. *J Immunol* 2022; 208 (1_Supplement):160.09. DOI
102. Weisel NM, Joachim SM, Smita S, et al. Surface phenotypes of naive and memory B cells in mouse and human tissues. *Nat Immunol* 2022;23:135-45. DOI PubMed PMC
103. Roderka MN, Puri S, Batsis JA. Addressing obesity to promote healthy aging. *Clin Geriatr Med* 2020;36:631-43. DOI PubMed PMC
104. Donath MY, Dinarello CA, Mandrup-Poulsen T. Targeting innate immune mediators in type 1 and type 2 diabetes. *Nat Rev Immunol* 2019;19:734-46. DOI PubMed
105. Goldfine AB, Shoelson SE. Therapeutic approaches targeting inflammation for diabetes and associated cardiovascular risk. *J Clin Invest* 2017;127:83-93. DOI PubMed PMC
106. Murphy AJ, Febbraio MA. Immune-based therapies in cardiovascular and metabolic diseases: past, present and future. *Nat Rev Immunol* 2021;21:669-79. DOI PubMed
107. Fleischman A, Shoelson SE, Bernier R, Goldfine AB. Salsalate improves glycemia and inflammatory parameters in obese young adults. *Diabetes Care* 2008;31:289-94. DOI PubMed PMC
108. Goldfine AB, Silver R, Aldhahi W, et al. Use of salsalate to target inflammation in the treatment of insulin resistance and type 2 diabetes. *Clin Transl Sci* 2008;1:36-43. DOI PubMed PMC
109. Faghihimani E, Aminorroaya A, Rezvanian H, Adibi P, Ismail-Beigi F, Amini M. Reduction of insulin resistance and plasma glucose level by salsalate treatment in persons with prediabetes. *Endocr Pract* 2012;18:826-33. DOI PubMed
110. de Rotte MC, de Jong PH, den Boer E, et al. Effect of methotrexate use and erythrocyte methotrexate polyglutamate on glycosylated hemoglobin in rheumatoid arthritis. *Arthritis Rheumatol* 2014;66:2026-36. DOI
111. Ridker PM, Everett BM, Thuren T, et al; CANTOS Trial Group. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med* 2017;377:1119-31. DOI PubMed
112. Tardif JC, Kouz S, Waters DD, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. *N Engl J Med* 2019;381:2497-505. DOI PubMed
113. Nidorf SM, Fiolet ATL, Mosterd A, et al; LoDoCo2 Trial Investigators. Colchicine in patients with chronic coronary disease. *N Engl J Med* 2020;383:1838-47. DOI
114. Tanaka Y, Luo Y, O'Shea JJ, Nakayamada S. Janus kinase-targeting therapies in rheumatology: a mechanisms-based approach. *Nat Rev Rheumatol* 2022;18:133-45. DOI PubMed PMC
115. Cox AR, Chernis N, Bader DA, et al. STAT1 dissociates adipose tissue inflammation from insulin sensitivity in obesity. *Diabetes* 2020;69:2630-41. DOI PubMed PMC
116. Lian Z, Perrard X, Ballantyne CM, Wu H. 1205-P: baricitinib inhibition of Jak/STAT pathway changed immune composition in adipose tissue and improved metabolism in diet-induced obese mice. *Diabetes* 2021;70:1205-P. DOI
117. Collotta D, Hull W, Mastrocola R, et al. Baricitinib counteracts metaflammation, thus protecting against diet-induced metabolic abnormalities in mice. *Mol Metab* 2020;39:101009. DOI PubMed PMC
118. Tuttle KR, Brosius FC 3rd, Adler SG, et al. JAK1/JAK2 inhibition by baricitinib in diabetic kidney disease: results from a phase 2 randomized controlled clinical trial. *Nephrol Dial Transplant* 2018;33:1950-9. DOI PubMed PMC
119. Cox AR, Masschelin PM, Saha PK, et al. The rheumatoid arthritis drug auranofin lowers leptin levels and exerts antidiabetic effects in obese mice. *Cell Metab* 2022;34:1932-46.e7. DOI PubMed PMC
120. Zacharias ZR, Houtman JCD. OMIP-099: 31-color spectral flow cytometry panel to investigate the steady-state phenotype of human T cells. *Cytometry A* 2023;105:10-5. DOI
121. Kare AJ, Nichols L, Zermeno R, Raie MN, Tumbale SK, Ferrara KW. OMIP-095: 40-color spectral flow cytometry delineates all major leukocyte populations in murine lymphoid tissues. *Cytometry A* 2023;103:839-50. DOI PubMed
122. Watanabe S, Yamada Y, Murakami H. Expression of Th1/Th2 cell-related chemokine receptors on CD4$^+$ lymphocytes under physiological conditions. *Int J Lab Hematol* 2020;42:68-76. DOI PubMed
123. Martinez GJ, Nurieva RI, Yang XO, Dong C. Regulation and function of proinflammatory TH17 cells. *Ann N Y Acad Sci*

2008;1143:188-211. DOI PubMed PMC

124. Santegoets SJ, Dijkgraaf EM, Battaglia A, et al. Monitoring regulatory T cells in clinical samples: consensus on an essential marker set and gating strategy for regulatory T cell analysis by flow cytometry. *Cancer Immunol Immunother* 2015;64:1271-86. DOI PubMed PMC
125. Yu N, Li X, Song W, et al. $CD4^+CD25^+CD127^{low/-}$ T cells: a more specific Treg population in human peripheral blood. *Inflammation* 2012;35:1773-80. DOI
126. Topham DJ, Reilly EC. Tissue-resident memory $CD8^+$ T Cells: from phenotype to function. *Front Immunol* 2018;9:515. DOI PubMed PMC
127. Cooper MA, Fehniger TA, Caligiuri MA. The biology of human natural killer-cell subsets. *Trends Immunol* 2001;22:633-40. DOI PubMed
128. Goldberg EL, Shchukina I, Asher JL, Sidorov S, Artyomov MN, Dixit VD. Ketogenesis activates metabolically protective γδ T cells in visceral adipose tissue. *Nat Metab* 2020;2:50-61. DOI PubMed PMC
129. Duan B, Morel L. Role of B-1a cells in autoimmunity. *Autoimmun Rev* 2006;5:403-8. DOI PubMed
130. Browne P, Petrosyan K, Hernandez A, Chan JA. The B-Cell transcription factors BSAP, Oct-2, and BOB.1 and the Pan-B-Cell Markers CD20, CD22, and CD79a are useful in the differential diagnosis of classic hodgkin lymphoma. *Am J Clin Pathol* 2003;120:767-77. DOI PubMed