

Review Article



OPEN ACCESS

Received: Nov 30, 2021
Revised: Jan 9, 2022
Accepted: Jan 10, 2022
Published online: Feb 7, 2022

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Conflict of Interest

The authors declare no potential conflicts of interest.

Abbreviations

α -GalCer, α -galactosylceramide; AT, adipose tissue; ATM, adipose tissue macrophage; BAT, brown adipose tissue; GF, germ-free; GLP-1, glucagon-like peptide; HFD, high fat diet; iNKT cells, invariant natural killer T cells; IELs T cells, Intraepithelial T cells; MAIT cells, mucosal-associated invariant T cells M1 ATMs, classical

The Role of T Cells in Obesity-Associated Inflammation and Metabolic Disease

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ABSTRACT

Chronic inflammation plays a critical role in the development of obesity-associated metabolic disorders such as insulin resistance. Obesity alters the microenvironment of adipose tissue and the intestines from anti-inflammatory to pro-inflammatory, which promotes low grade systemic inflammation and insulin resistance in obese mice. Various T cell subsets either help maintain metabolic homeostasis in healthy states or contribute to obesity-associated metabolic syndromes. In this review, we will discuss the T cell subsets that reside in adipose tissue and intestines and their role in the development of obesity-induced systemic inflammation.

Keywords: T cells; Obese mice; Obesity-associated inflammation; Metabolic diseases; Insulin resistance

INTRODUCTION

The prevalence of obesity has significantly grown over the last several decades and is now considered a worldwide epidemic. The World Health Organization estimates that at least 2.8 million people die each year due to complications of being overweight or obese. Obesity increases the prevalence of multiple metabolic and non-metabolic diseases including insulin resistance, type 2 diabetes, hyperglycemia, dyslipidemia, cardiovascular disease, fatty liver, hypertension, and cancer (1).

It is now understood that obesity is accompanied by a chronic low-grade systemic inflammation as a result of expanded adipose tissue (AT). This systemic inflammation impairs glucose metabolism and has a role in the pathogenesis of obesity-related metabolic disorders (2-5). AT itself serves as an important link between immune cells and metabolic dysfunction in the setting of obesity. Hypertrophied adipocytes secrete inflammatory cytokines and chemokines (4), such as MCP-1 (CCL2). This triggers the accumulation of various pro-inflammatory immune cells (M1 macrophage, CD8⁺ T cells, and Th1 cells) and a concomitant decrease in anti-inflammatory immune cells (M2 macrophage, Th2 cells, invariant natural killer T [iNKT] cells, and Treg). In addition to AT, other organs, including the liver, muscle, pancreas, heart, brain, and small and large intestines, display low-grade

activated ATMs; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; WAT, white adipose tissue.

Author Contributions

Supervision: Shastri N; Writing - original draft: Park CS; Writing - review & editing: Park CS, Shastri N.

inflammation that may contribute to obesity-induced insulin resistance. In this review, we would focus on the role of various T cell subsets in the development of obesity-related systemic inflammation.

THREE TYPES OF AT

AT can classically be divided into two major subsets: white AT (WAT) and brown AT (BAT) (6,7). In rodents, WAT is widely distributed through the body and includes subcutaneous AT (SAT) and visceral AT (VAT) in the mesentery, gonads, and omentum. In contrast, “classical” BAT exists predominantly in discrete anatomic depots, such as the interscapular region. Functionally, WAT serves as energy storage to maintain whole-body energy homeostasis. Dietary excess of fats is converted to triglyceride and stored in a single lipid droplet inside WAT cells in a process called lipogenesis (8). VAT has been linked to obesity and metabolic disorders, while SAT is considered to play a metabolically protective role (9,10).

BAT specializes in burning fat and is the main site for heat production through non-shivering thermogenesis by oxidizing fatty acid and glucose in the mitochondria (11). BAT highly expresses the thermogenic uncoupling protein-1, a transport protein of the inner mitochondria membrane that plays a central role in non-shivering thermogenesis (12). BAT is rich in mitochondria and possesses multiple droplets to maximize its thermogenesis capacity. Under certain conditions, BAT specific gene pathways are induced in WAT, in a process called “browning”. This browning process creates a third type of AT known as beige or brite adipocyte tissue, which are typically interspersed in WAT (13). The beige adipocyte tissue has features midway between WAT and BAT and can be induced by many stimuli such as prolonged cold exposure, exercise, cytokine, gut microbiota, and β 3-adrenergic agonists (14).

INFLAMMATION IN OBESITY AND METABOLIC DISORDERS

Obesity has been recognized as a state of chronic low-grade inflammation (2,4). The relationship between inflammation, obesity, and metabolic syndrome was first suggested by the observation by Hotamisligil et al. (15) that the proinflammatory cytokine TNF- α is overexpressed in the AT of obese rodents. They also observed a strong positive correlation between TNF- α expression and insulin resistance in obese rodents and humans (15,16). Further studies by this group showed that obese mice deficient in TNF- α or TNF receptors have higher insulin sensitivity in muscle and fat tissues than WT obese control animals (17). In addition, neutralization of TNF- α in obese rats increases insulin sensitivity (15). Obese mice also have elevated insulin level, caused by impaired insulin sensitivity (18). Improvement in insulin sensitivity after weight loss is accompanied by a decreased expression of proinflammatory genes in WAT (19), while upregulation of inflammatory genes in WAT of obese mice precedes an increase of circulating insulin level (20). Overall, these results indicate that obesity-induced inflammation is considered as a causative event leading to metabolic syndrome such as insulin resistance.

AT RESIDENT IMMUNE CELLS AND INFLAMMATION IN OBESITY

In conditions of obesity, the AT shows a marked accumulation of immune cells, and numerous studies have linked this increase in AT resident immune cells to obesity-induced inflammation (5,21). Here, we will focus on macrophage and T cell populations that have been studied most intensively in the context of AT in obesity.

Macrophages

Macrophages are mononuclear tissue-resident phagocytes that have crucial roles in tissue homeostasis and immunity by engulfing target pathogens (22,23). Macrophages undergo dramatic change during obesity. AT macrophages (ATMs) are key mediators of inflammation and are the most abundant immune cell in AT in obesity. While they comprise fewer than 10% of immune cells in lean AT, this fraction rises to over 50% in obese AT (20,24). MCP-1 in the plasma is elevated in obesity and induces monocyte/macrophage infiltration from the blood into AT (25-27). MCP-1 is produced directly by adipocytes along with monocytes, macrophages, dendritic cells, and endothelial cells (28). Overexpression of MCP-1 in mice increases ATM infiltration, insulin resistance, and hepatic triglyceride content (26,29), whereas MCP-1 deficient mice have lower ATM infiltration with decreased insulin resistance and hepatic steatosis (26).

During obesity, adipocytes increase in size and the frequency of adipocyte death increases progressively. This induces the engulfment of dead adipocytes by phagocytic cells such as ATMs. Thus, it is common to observe “crown-like structure” of ATMs surrounding dead adipocytes in histology analysis (24,30). ATMs switch their phenotype from alternatively activated (M2) into the classically activated (M1) states with proinflammatory phenotype. They secrete numerous proinflammatory cytokines, such as TNF- α , IL-6, IL-1 β , and inducible nitric oxide synthase, in response to obesity (31,32). The signals that regulate ATM polarization are not fully elucidated, but several factors are suggested to trigger an increase of inflammatory ATMs as obesity progresses (33). First, adipocyte death driven by hypertrophy is a stimulus for polarization to proinflammatory ATMs and production of MCP-1 (30,34,35). Second, AT hypoxia induced by rapidly proliferating adipocyte cells creates a low-oxygen microenvironment and promotes stabilization of hypoxia-inducible factor 1 alpha (36,37). Third, endothelial reticulum stress can influence macrophage polarization (38,39). Finally, free fatty acids released from adipocytes such as palmitate can trigger macrophage activation by signaling via TLR2/TLR4 (40). Additional mechanisms yet to be discovered likely also contribute. Overall, the infiltrating proinflammatory classical activated ATMs (M1 ATMs) result in inflammation in the AT, insulin resistance, and hepatic steatosis in mice and human.

T cells

In obese AT, T cells constitute the second largest population of immune cells after ATMs. High fat diet (HFD)-induced obesity triggers the accumulation of T cells in AT compared with lean mice (41). The CCL5, which is also known as RANTES (regulated on activation, normal T cells expressed and secreted), is dramatically increased in obese AT and promotes T cell infiltration. As obesity progresses, the proportions of different T cell subsets are significantly altered. Obesity dramatically increases the frequency of Th1, Th17, and CD8⁺ T cells in WAT, whereas the frequency of Th2 and Treg cells is decreased in WAT (42). The contributions and mechanisms of different T cell subsets in obesity-related inflammation are poorly understood.

CD4⁺ T cells

CD4⁺ T cells (also known as T helper cells or Th) can be further categorized according to their cytokine expression profiles; Th1 (IFN- γ), Th2 (IL-4, IL-5, and IL-13), Th17 (IL-17, IL-21, and IL-22), and Treg (IL-10, TGF β) (43). The cytokines produced by these T cells subsets determine their unique function and roles in disease. IFN- γ produced by Th1 cells promotes the polarization of classically activated M1 macrophage against intracellular pathogens (44). IL-4 and IL-13 produced from Th2 cells promotes the polarization of alternatively activated M2 macrophage against helminthic infections to promote tissue repair and help B cell responses (44). IL-17 produced by Th17 cells induces neutrophil inflammation and is important in several autoimmune diseases (45). IL-10 and TGF β , produced by Tregs, are potent anti-inflammatory cytokines that play crucial roles in preventing inflammatory and autoimmune pathologies (46).

CD4⁺ T cell infiltration increases in obese VAT and shows significant correlation with the body mass index (47). CD4⁺ T cells in obese VAT produce higher levels of IFN- γ than CD4⁺ T cells in lean VAT, demonstrating their polarization into an active Th1 phenotype in obese ATs (48-50). Indeed, the Th1 phenotype contributes to metabolic dysfunction, as obese mice that are IFN- γ deficient have lower AT inflammation, reduced ATM accumulation in WAT, and improved insulin resistance compared to obese control mice (51). Adoptive transfer of Th1 cells into HFD-fed obese mice deficient in T cells increases inflammation in skeletal muscles and adipocytes (52), suggesting a substantial contribution of Th1 cells to adipose inflammation and metabolic disorder in obesity (51,53). In addition, α CD3 treatment to obese mice reduces the predominance of Th1 cells over Treg cells and reverses insulin resistance (53).

The frequency of Th2 cells in WAT is negatively correlated with systemic inflammation and insulin resistance in mice and humans, indicating that Th2 cells have a protective function (53,54). HFD-fed obese Rag-1 deficient mice, which lack mature B and T lymphocytes, gain more body weight and have worse associated adipocyte hypertrophy, more insulin resistance, and higher glucose levels than WT mice (53). This negative metabolic state is reversed by the adoptive transfer of CD4⁺ T cells (but not CD8⁺ T cells) into HFD-fed Rag-1 deficient obese mice (53). This result was dependent on Th2 cells as the improvement of metabolic parameters was not observed when using Stat6^{-/-}CD4 T cells, which have impaired Th2 development but normal Th1 development (53). This suggest Th2 cells have suppressive roles on obesity-induced inflammation and insulin resistance.

T cells in obese VAT show a limited TCR repertoire, suggesting that VAT T cells undergo clonal expansion (53,55). The specific Ags driving this expansion in obese states remain unknown. This local stimulation, however, is likely to contribute to metabolic dysfunction. For example, obese mice with macrophage-specific MHC II expression deficiency have a reduced accumulation of effector/memory phenotype CD4⁺ T cells and ATMs, but not CD8⁺ T cells in WAT (49). These mice also have less inflammation in WAT and improved insulin resistance, highlighting that Ag presentation by ATMs via MHC II to CD4 T cells plays an essential role in obesity-induced adipose inflammation and insulin resistance.

Tregs

Tregs are enriched in VAT from lean mice, but Treg are markedly reduced in VAT of obese mice (56). Depletion of Treg in lean mice increases the expression of inflammatory genes in VAT (such as TNF- α , IL-6, MMP-3, and RANTES) and impairs insulin signaling in VAT and liver. In contrast, expanding Treg with IL-2 treatment in obese mice improves glucose

sensitivity and insulin resistance (57). These observations suggest that Treg are important for the maintenance of immunity and metabolic homeostasis in AT and have beneficial effects that help inhibit development of insulin resistance.

CD8⁺ T cells

Obesity increases infiltrating CD8⁺ T cells in AT, which stimulates M1 ATMs polarization (58). In fact, the infiltration by CD8⁺ T cells into obese AT precedes ATM accumulation and likely directly contributes to it. For example, CD8⁺ T cell depletion using neutralizing Ab treatment decreases ATM infiltration, AT inflammation, and insulin resistance. Adoptive transfer of CD8⁺ T cells into CD8-deficient obese mice increases M1 ATM accumulation and AT inflammation, including expression of TNF- α and IL-6 (59). In fact, co-cultured adipocyte and HFD-induced CD8⁺ T cells with circulating peripheral monocytes induced a secretion of MCP-1 and CXCL10 chemokines (60). MCP-1 is a chemokine for monocyte and macrophage, and CXCL10 is a chemoattractant for CXCL3⁺ cells, such as activated CD4⁺ Th1, CD8 T cells, and NK cells (61). However, the mechanism by which CD8⁺ T cells lead to recruitment of macrophages is unclear.

iNKT cells

iNKT cells, also known as type I or classical NKT cells, are a unique subset of T cell cells that express both NK cell markers and an invariant $\alpha\beta$ TCR (V α 14J α 18 in mice and V α 24J α 18 in humans). This specific invariant TCR recognizes a glycolipid Ag, α -galactosylceramide (α -GalCer), presented by the MHC class I like molecule CD1d (62). iNKT cells are highly enriched in lean AT (\leq 20% of total T cells), but decrease in prevalence during obesity (63). Mice lacking iNKT cells show enhanced weight gain, increased fatty liver deposition, and elevated insulin resistance after HFD feeding compared to WT mice. Adoptive transfer of iNKT cells or *in vivo* activation of iNKT cells with α -GalCer treatment substantially decreases metabolic dysfunction in obese mice. These improvements are associated with Th2 cell-type cytokine production by adipose-derived iNKT cells (63). Further studies have shown that iNKT cell activation also induces fibroblast growth factor 21 production and thermogenic browning of WAT, which leads to weight loss in mice (64).

$\gamma\delta$ T cells

$\gamma\delta$ T cells play a critical role as guardians against pathogens at barrier sites, including the epidermis and intestinal epithelium. They can have either pro- or anti-inflammatory function depending on the distinct cytokine milieu exposure (65). $\gamma\delta$ T cells, mostly expressing V γ 4⁺ TCRs, are enriched in lean AT (\leq 20% of total T cells) and increase further during obesity (66). The increase of infiltrating AT $\gamma\delta$ T cells promotes the accumulation of ATM, inflammation, and insulin resistance in obese mice (66), suggesting a pro-inflammatory function of $\gamma\delta$ T cells. However, IL-17A-producing adipose resident $\gamma\delta$ T cells are also necessary for IL-33 production by AT stromal cells, which promotes the maintenance of Treg homeostasis in WAT and thermogenesis in BAT and WAT (67,68). Together these experiments demonstrate that $\gamma\delta$ T cells play a role in shaping both pro- and anti-inflammatory responses in ATs.

GUT INFLAMMATION IN THE DEVELOPMENT OF OBESITY

Dysbiosis

In addition to AT, growing evidence suggests that intestine is also a key site that contributes to obesity-related metabolic diseases. The intestine is home to over a trillion symbiotic

microbial cells that can be both helpful and potentially harmful. The link between the microbiome and obesity-related metabolic disorders stems from the initial observation that germ-free (GF) mice have reduced body fat and do not develop insulin resistance during HFD feeding, unlike conventionally raised mice (69,70). However, the introduction of conventional gut microbiota into GF mice produces an increase in body fat content and insulin resistance (69). Gut microbial imbalance (dysbiosis) can impact energy metabolism, body fat, systemic inflammation, and insulin resistance (71,72). Dysbiosis is known to cause systemically low-grade inflammation through enhanced leakage of bacterial products such as LPS (73-75). Binding of LPS to TLR4 induces the release of critical proinflammatory cytokines such as IL-6 and TNF- α , and is thought to augment inflammation in VAT (76,77). Mice lacking the TLR4 adapter protein, CD14, resist the accumulation of ATMs and adipocyte hypertrophy during HFD feeding (73).

Intestinal T cells and inflammation

Obesity has been shown to impact the intestinal immune population and contribute to gut inflammation. In intestinal epithelium, both $\alpha\beta$ T cells and $\gamma\delta$ T cells decrease in number and downregulate the expression of CD103 (α subunit of $\alpha\text{E}\beta 7$ integrin) and CCR9 during HFD feeding (78). Intraepithelial T cells (IELs T cells) homing and retention are regulated by CD103 and CCR9 (79,80). HFD-fed obese CCR9-deficient mice exhibited a comparable weight gain, but glucose tolerance and insulin resistance were significantly improved than WT mice (81). Accumulation of IFN- γ producing Th1 cells and increased intestinal permeability in the small intestine was observed in obese WT mice, but these changes were suppressed in obese CCR9-deficient mice (81). Adoptive transfer of CCR9-expressing lamina propria T cells into obese CCR9-deficient mice exacerbates glucose tolerance, suggesting a pathogenic role of CCR9-dependent homing of pathogenic IFN- γ producing Th1 cells (81). In the intestinal lamina propria, the number of pathogenic IFN- γ producing Th1, CD8⁺ T cells, and IL-17 producing TCR $\gamma\delta$ ⁺ T cells is increased, whereas the number of protective Th17 cells, and IL-10 producing Treg is decreased during HFD feeding (82-84). Treatment with the local gut anti-inflammatory compound, 5-aminosalicylic, reverses gut and VAT inflammation and improves metabolic parameters in obese mice (82). Reduction of homing of immune cells into the gut in integrin $\beta 7$ -deficient mice improves HFD-induced insulin resistance by decreasing VAT inflammation (82). These results indicate that the intestinal immune system is an important regulator of obesity-related gut inflammation and insulin resistance.

Two functionally distinct subsets of Th17 cells are present in the intestine (85). a) homeostatic Th17 cells that show mutated metabolism and are non-inflammatory, and b) pathogenic-elicited inflammatory Th17 cells that show extensive plasticity with production of pro-inflammatory cytokines such as IFN- γ (85). Intestinal Th17 cells overall are reduced in obese mice (84). Adoptive transfer of *ex-vivo* expanded gut-homing Th17 cells into obese integrin $\beta 7$ -deficient mice promotes the expansion of commensal microbes associated with metabolic homeostasis and improves HFD-induced insulin resistance (84). These observations suggest that intestinal Th17 cells contribute to development of microbiota associated metabolic homeostasis and have beneficial effects in inhibiting obesity-induced insulin resistance.

Mucosal-associated invariant T cells (MAIT cells) are innate-like T cells expressing a semi-invariant $\alpha\beta$ TCR that recognizes biosynthetic derivatives of riboflavin synthesis presented by the non-classical MHC class I molecule MR1 (86). The number of MAIT cells is reduced in AT and intestine during obesity. However, the remaining MAIT cells show an activated phenotype and produce inflammatory cytokines, which promotes HFD-

induced inflammation and insulin resistance (87). How to regulate the responses of these inflammatory MAIT cells in obesity requires further studies.

Bioavailability of gastric hormones

IELs T cells can regulate bioavailability of gastrointestinal hormones, such as incretin glucagon-like peptide 1 (GLP-1) hormone (88). Integrin β 7-deficient mice are metabolically hyperactive and resistant to HFD-induced obesity, diabetes, hypertension, and atherosclerosis (88). These beneficial effects depend on enteroendocrine-derived GLP-1, which is negatively controlled by gut intraepithelial T cells, such as TCR $\gamma\delta^+$ IELs T cells and CD8 $\alpha\alpha^+$ TCR $\alpha\beta^+$ IELs T cells, through expression of GLP-1 receptor (88). GLP-1 induces postprandial pancreatic insulin secretion, exerts glucose control, and mediates various beneficial effects on metabolism (89). These studies suggest that obese-related metabolic disorders and gut hormone production are associated with IEL T cells and highlight the need for additional research in the area.

Conclusion and perspectives

T cells in ATs and intestine function as critical players in regulating obesity-induced systemic inflammation. However, the precise pathological and regulatory mechanisms of T cell subsets in AT and intestine needed to be explored further. Additional T cells subsets may function during obesity. It remains unknown whether newly identified T cells subsets, such as Th9 and Th22 cells, play a role in the development of obesity-induced inflammation. Given the role of iNKT cells and $\gamma\delta$ T cells in thermogenesis (64,67), precise elucidation of T cells function on thermogenesis may provide new insight to treat obesity. It would be intriguing to investigate the interaction of gut T cells with microbiota or diet components that may all contribute to initiation and maintenance of gut inflammation. Further studies will also need to explore the crosstalk between enteroendocrine cells and gut immune cells. In the HFD-induced gut inflammatory environment, activated IEL T cells might modulate levels of other gut hormones in addition to GLP-1.

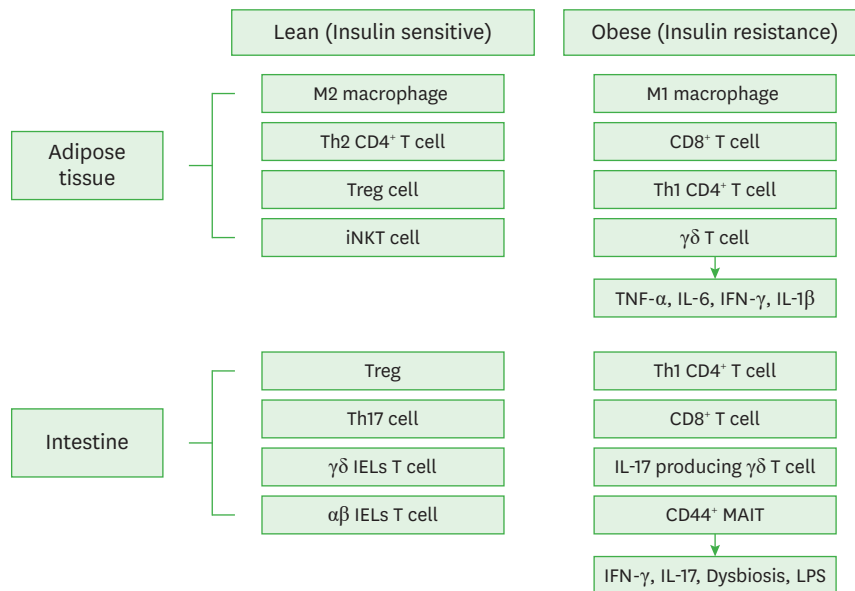
It has become apparent that obesity is associated with systemic low-grade inflammation leading to obesity-related metabolic disorders. Immune cells in ATs function as critical players in regulating systemic inflammation and obesity-related metabolic disorders (Table 1). When obesity develops, proinflammatory M1 ATMs, Th1 T cells, CD8 $^+$ T cells, and $\gamma\delta$ T cells accumulate in AT, while the frequency of alternative activated ATMs, Th2 T cells, Treg cells, and iNKT cells is decreased, causing systemic low-grade inflammation and metabolic disorders (Figure 1). Obesity-induced inflammation and dysregulation also occurs in other tissues, such as the intestine, liver, and pancreatic islets. These inflammatory changes are important because they represent potential therapeutic targets in obesity-induced metabolic disorder. Thus, much work is required to understand systemic impact of metabolic inflammation and dynamic changes of the role of immune cells on the development of obesity-related metabolic disorders. Future studies will be required to explore the potential of targeting inflammation in specific organs to treat obesity-related metabolic disease in mice and humans.

ACKNOWLEDGEMENTS

We thank Scheherazade Sadegh-Nasseri for suggestions and guidance on the manuscript and J David Peske and Jesus Contreras Rodriguez for editorial comments. This work was supported by NIH grant (R01AI130210, R01AI121174, R37AI060040).

Table 1. Role of macrophage and T cell subsets in obesity-associated inflammation and insulin resistance

Role of immune system seen in obesity	Reference
Macrophage	
Engulfment of dead adipocytes by phagocytic cells such as ATMs	(24,30)
Polarization from M2 to M1 with proinflammatory phenotype	(31,32,34)
Proinflammatory macrophages are associated with insulin resistance	(26,29)
CD4 T cells	
Obese Interferon- γ -KO mice have significantly reduced adipose inflammation	(51)
α CD3 treatment to obese mice reduces the predominance of Th1 cells over Treg cells, and reverses insulin resistance	(53)
Th2 frequency is negatively correlated with systemic inflammation and insulin resistance	(53,54)
MHC II dependent interaction between macrophage and CD4 T cells contributes to adipose tissue inflammation	(49)
Treg	
Expanding Treg with IL-2 treatment improves insulin resistance	(57)
CD8 T cells	
CD8 T cells contribute to macrophage recruitment and adipose tissue inflammation	(58,59)
CXCR3-expressing CD8 T cells may promote the recruitment and M1 polarization of macrophage	(60)
iNKT	
Adoptive transfer of iNKT cells or <i>in vivo</i> activation of iNKT cells improves insulin resistance	(63)
iNKT cells activation induces thermogenic browning in WAT	(64)
$\gamma\delta$ T	
$\gamma\delta$ T cells promote macrophage infiltration, systemic inflammation, and insulin resistance	(66)
$\gamma\delta$ T cells producing IL-17A regulates Treg homeostasis and thermogenesis	(67,68)
Gut T cells	
Obesity induces a chronic phenotypic pro-inflammatory shift in bowel lamina propria immune cell populations	(81,82)
Adoptive transfer of ex-vivo expanded gut-homing Th17 cells into obese integrin β 7-KO mice improves insulin resistance	(84)
MAIT cells promote inflammation and insulin resistance	(87)
Intraepithelial T cells regulate bioavailability of GLP-1 hormone	(88)


Figure 1. Changes in T cell subsets in adipose tissue and intestine during high-fat diet feeding.

Adipose tissue: In lean AT, resident immune cells, such as M2 ATMs, Th2 cells, Treg, and iNKT cells support adipocytes physiology. Together these cells secrete anti-inflammatory cytokines such as IL-4 and IL-10, which inhibit inflammation. During obesity, accumulation of M1 ATMs, CD8⁺ T cells, Th1 cells, and $\gamma\delta$ T cells results in excess production of pro-inflammatory cytokines such as TNF- α , IL-6, IFN- γ , and IL-1 β . These cytokines contribute to systemic inflammation and insulin resistance.

Intestine: In health, the intestinal immune environment is dominated by anti-inflammatory immune cells. These cells include IL-10 producing Treg, protective IL-17 producing Th17 cells, $\alpha\beta$ IELs T cells, and $\gamma\delta$ IELs T cells. During obesity, the number of pathogenic IFN- γ producing Th1 cells, CD8⁺ T cells, IL-17 producing $\gamma\delta$ IELs T cells, and CD44⁺ MAIT cells is increased. These proinflammatory changes contribute to intestinal dysfunction, dysbiosis, and systemic inflammation through enhanced leakage of LPS.

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