T cell-mediated adaptive immunity in type 2 diabetes mellitus

Zhimei Huang[1], Jiaqi Chen[1], and Jianping Wang[1]

[1]The Second Affiliated Hospital of the University of South China

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Abstract

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease characterized by hyperglycemia. T2DM is caused by various etiologies. The functional expansion of pancreatic β-cells is unable to compensate for the degree of insulin resistance (IR), resulting in a relative insulin deficiency. The onset and progression of T2DM are influenced by multiple variables, including genetics, lipid excess, oxidative stress, and inflammation. A growing body of research suggests that the components of the immune system are altered in T2DM. This suggests that T cell-mediated adaptive immunity stimulates inflammation and IR through the redistribution of cytokines, chemokines, and different T cell subsets. Metabolic inflammation is a central aspect of obesity, T2DM, and comorbidities. This review focuses on adaptive immune T cells, particularly CD4+ T cells, and examines the roles and effects of different helper T (Th) 1, Th2, Th17, Th22, and regulatory T cells (Tregs) in T2DM. Evidence for T cell activation and exhaustion in T2DM remains controversial and requires further investigation.

1 Introduction

Type 2 diabetes mellitus (T2DM) has become more common with the aging of the population and changing lifestyles, and in recent years, the worldwide incidence of T2DM has risen dramatically[1]. Many individuals with T2DM also have genetic variation, obesity, and decreased immune function, which increases the risk of infections, cardiovascular disorders, and cognitive disorders. These comorbidities are the main cause of death and disability in individuals with T2DM[2,3]. Firstly, genetics and environment are important factors in the high incidence of T2DM. According to a large cohort study, mutations in endocrine-related genes(such as Pax6, Hnf1A, PDX1) affect the regulation of β cell development and insulin secretion and are more likely to develop T2DM. In addition, factors such as smoking and a high-energy diet are also common risks for T2DM[4].

Overweight and obesity are positively associated with the risk of T2DM. In individuals with obesity, increased adipocytosis promotes the release of glycerol and free fatty acids as well as macrophage infiltration. Ongoing chronic inflammation stimulates T cell activation, which subsequently promotes the onset and development of insulin resistance (IR)[5], and IR and pancreatic β cell dysfunction frequently work together to cause T2DM[6]. There is an important link between chronic inflammation, poor immune response, and insulin resistance. These findings have prompted researchers to delve deeper into possible interactions between insulin and T cells. However, researchers have examined the immune system in T2DM because it is an inflammatory illness. Many people with T2DM have abnormally high levels of T-cell reactivity, which correlates adversely with the C-peptide index[7]. Further, the pro-inflammatory cytokine interleukin (IL)-1β promotes β cell apoptosis when released in response to high glucose induction[8], and tumor necrosis factor (TNF) has been found to exacerbate hyperglycemia in diabetic rats[9]. Further studies revealed that TNF-α activates c-Jun amino-terminal kinases (JNKs) and inhibitor of kappa B kinase beta(IKKβ)/nuclear factor kappa B (NF-ϰB) signaling[10], contributing to the inactivation of insulin receptor-associated pathways. This leads to IR upregulates inhibitor of matrix metalloproteinases in keratinocytes, and inhibits wound healing during diabetes[11]. Therefore, T cell response plays an important role in promoting T2DM.

The influence of adaptive immunity on T2DM has gained increasing attention in recent years, and recent studies have indicated that the number of B -lymphocytes and $CD8^+$ T cells are considerably higher in individuals with T2DM, whereas the numbers of total lymphocytes and $CD4^+$T cells are decreased[12]. T2DM is characterized by an increase in inflammatory cytokines such as IFN-γ and IL-6 and a decrease in anti-inflammatory cytokines such as IL-10[13]. T2DM and its complications are caused in part by chronic inflammation owing to $CD4^+$ T cell abnormalities. In this review, we discuss the role of different subpopulations of adaptive T cells in obesity and T2DM and explore the impact of T cell status on T2DM and the potential for immunotherapy.

2 T Cells in T2DM

Activation of the T cells is a characteristic of persistent inflammation. However, early studies on the immune system in T2DM focused on innate immunity, particularly macrophages. In individuals with T2DM and obesity, there is evidence of decreased NK cell activity[14], increased neutrophil apoptosis, decreased chemotaxis and phagocytosis, and predominance of M1-type macrophages with an inflammatory phenotype[15,16], which increases the risk of infection with tuberculosis and human immunodeficiency virus[17]. In addition, neutrophil and eosinophil levels were significantly decreased in T2DM patients[18], and obese mice lacking eosinophils exhibited impaired glucose tolerance and insulin resistance[19]. However, increasing attention has been focused on adaptive immunity, mainly on T cells. Adaptive immune cells mainly refer to T cells that mediate cellular immunity and B cells that mediate humoral immunity. Functional T cell subpopulations are required for B cell activation and development into plasma cells[20,21], suggesting that T cell components may change first in the early stage of antigen stimulation.

T-cell receptors are activated by recognizing complexes formed by CD8 with major histocompatibility complex (MHC) class I molecules, and CD4 with MHC class II molecules on antigen-presenting cells (APC)[21]. Depending on the cell surface differentiation antigens and their functions, $CD4^+$ T cells and $CD8^+$ T cells are the two primary subsets of T lymphocytes. Mice continuously fed an HFD had a higher proportion of $CD8^+$ T cells in the adipose tissue, whereas $CD4^+$ T cells and Tregs were consistently decreased, which began to reverse after 30 weeks[22]. Therefore, T cell activation during obesity may be mainly characterized by CD8 hypersecretion, after which T cells may enter a state of exhaustion. Different from T1DM, $CD8^+$T cells gradually accumulate in the metabolic tissues of T2DM during the progression of obesity and chronic inflammation. $CD8^+$T cells secrete monocyte chemoattractant protein-1 and interferon-inducible protein-10 and kill abnormal cells[22]. By contrast, T1DM-activated $CD8^+$ T cells are generated by autoimmune progenitor cells that target and attack insulin-producing pancreatic β cells[23]. $CD4^+$ T cells are an important regulatory factor subpopulation of T lymphocytes, and can generally be categorized into pro-inflammatory and anti-inflammatory Th cells based on their functional characteristics and secreted cytokines (Figure 1).

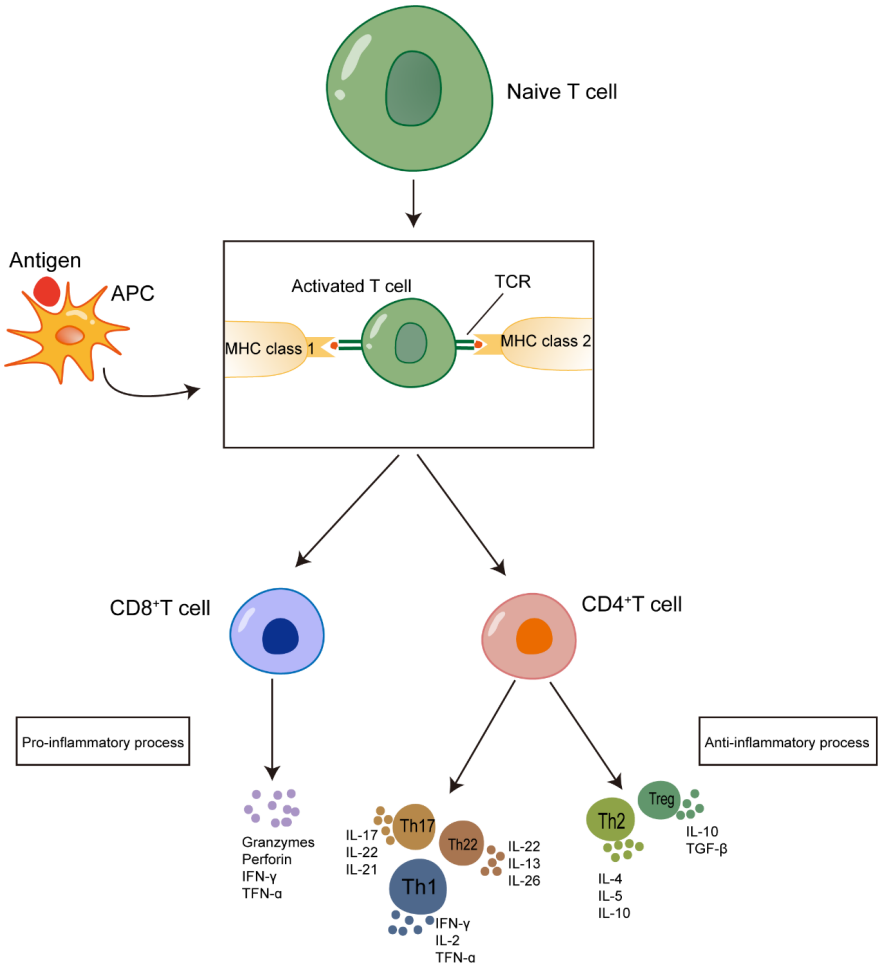

FIGURE 1 Adaptive T cell activation and subsets. Adaptive T-cell effects induce CD4 and CD8 expression through thymocyte expansion. The T cell receptor (TCR) is activated by the recognition of complexes formed by CD8 and major histocompatibility complex (MHC) class I and CD4 and MHC class II on antigen-presenting cells (APC). In CD4+T cells, help T (Th)1, Th17, Th22, Th2, and regulatory T cell (Treg) release respectively proinflammatory and anti-inflammatory cytokines to participate in the immune process.

3 Pro-inflammatory CD4$^+$ T Cells in T2DM

3.1 Th1 Cells

Th1 cells were first identified from mice in 1986[24]. They release mainly TNF-α and IL-2[25]. Their activation and repopulation are dependent on the co-stimulation of CD28 on the cell surface[26], and they participate in cellular immunity and mediate inflammatory responses. Early studies indicated increased IFN-γ secretion by Th1 cells in the visceral adipose tissue of obese mice, leading to disruption of glucose homeostasis and promoting IR in vivo[27]. Further studies have demonstrated that individuals with IR, hyperglycemia, and dyslipidemia have significantly higher levels of Th1 cells in their peripheral blood[28]. IFN-γ-related immune responses are involved in diabetic ketoacidosis, leading to a transient decline in β cell function and an increase in disease activity[29]. However, there is controversy as to whether IL-2 is elevated in individuals with T2DM[30–32], suggesting that IFN-γ is a key link in the Th1-mediated immune response to obesity and related metabolic syndromes.

Chronic IFN-γ expression mouse model (ARE-Del-/-) overlaps with upstream regulatory genes, such as

toll-like receptor (TLR) 4, when mice are fed a high-fat diet (HFD). These mice also induce both innate and adaptive immunity involved in hepatic inflammation[33], suggesting that IFN-γ-mediated inflammatory responses may crosstalk with TLR4-related inflammatory signaling. TLRs are an important class of receptors involved in innate immunity and an important bridge between adaptive and innate immunity. TLR4 expression is associated with elevated IFN-γ and promotes IR in individuals with T2DM[34]. IFN-γ inhibits the expression of insulin-related signaling genes, significantly reduces glucose transporter type 4 (GLUT4), insulin receptor, and insulin substrate (IRS)-1 levels, and decreases glucose uptake. Mechanistic studies revealed that IFN-γ activates the Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway to reduce insulin sensitivity and inhibit adipocyte differentiation[35](Table 1). In addition, IFN-γ promotion of adipocyte apoptosis and IR is dependent on stimulation of the T cell co-stimulatory factor CD80 by liver kinase B1 (LKB1)[36]. Direct substrates of LKB1, including AMP-activated protein kinase (AMPK), are key for maintaining metabolism and reducing oxidative stress[37]. Th1 activation relies on the regulation of metabolic stress, which in turn promotes pathological metabolic states. Th1 cells have important roles in adipose and insulin homeostasis, possibly through the secretion of IFN-γ. However, the mechanisms associated with other Th1 cytokines involved in lipid and glucose homeostasis have not yet been elucidated.

TABLE 1 Role of T cell subsets on T2DM proteins.

	Th1	Th17	Th2	Treg
GLUT4	— [34–36]	— [44]	— [69]	— [89]
IRS	— [26,34]	— [44]	— [67]	
PPAR-γ	— [32,34]	— [39,47]	— [69]	— [76,82,85]

GLUT4, glucose transporter type 4; IRS, insulin substrate; PPAR-γ, peroxisome proliferator-activated receptor gamma.

3.2 Th17 Cells

Th17 cells are a new class of $CD4^+$ T cell subpopulation involved in differentiation and development. This cell type is strongly reliant on differentiation factors such as transforming growth factor-beta (TGF-β) or IL-6, and transcription factors such as STAT and retinoic acid receptor-related orphan receptors (ROR)γt, and RORα. They are mainly characterized by the secretion of IL-17, IL-22, and IL-21[38]. Th17 cells are involved in intestinal inflammation in rodents[39]; they proliferate and worsen adipose inflammation in diet-induced obesity in mice[40], increase IL-17 and other Th17 factors in the liver[41], and promote hepatic inflammation and fibrosis[42]. In addition, patients with T2DM have elevated levels of IL-17 in the peripheral blood[43,44]. Tissue inflammation and IR brought on by Th17 cells are linked to the development of T2DM, suggesting that obesity-induced Th17 cell amplification plays an essential role in the crosstalk between immunity and metabolism.

IL-6 is involved in skeletal muscle[45] and adipocyte IR[46], and inhibition of the IL-6/JAK2/STAT3 pathway restores Th17 cell and regulatory T cell (Treg) homeostasis and attenuates inflammatory responses[47]. Further investigation of the mechanism revealed that IL-17 promotes the expression of inflammatory cytokines through activation of TANK-binding kinase 1 (TBK1) and I-kappa-B kinase epsilon (IKBKE)[48]. Activation of NF-ϰB/p53/Rb signaling triggers inflammation to promote endothelial cell senescence and injury[49]. Inhibition of NF-ϰB and STAT activation disrupts IKBKE-driven cytokine expression[50]. In addition, insulin and insulin-like receptor 1 act synergistically with the inflammatory factor IL-17, together promoting the phosphorylation of glycogen synthase kinase 3 alpha and beta[51]. Therefore, Th17 cells may induce a range of metabolic disorders through secreted factors and inflammatory cells that interfere with immune homeostasis in the fat, liver, and gut. In addition, Th17 cells inhibit the activity of kinases downstream of glycogen synthesis and promote the onset and progression of T2DM. However, the study of Th17 on pancreatic islet function remains unclear.

3.3 Th22 Cells

Th22 cells are a recently identified subset of $CD4^+$ T cells. They are named for their notable production of IL-22, along with IL-13, IL-26, TNF-α, and granzyme B[52]. However, other activated T cells can also secrete IL-22, including Th17 cells, Th1 cells, innate lymphocytes, and some non-lymphocytes[53]. The production and activation of Th22 cells are dependent on the aromatic hydrocarbon receptor and are positively regulated by IL-6 and TNF-α. IL-22 is expressed predominantly in epithelial cells and keratinocytes and is implicated in skin homeostasis and inflammation[54,55]. Th22 cells are involved in promoting endothelial cell disorders[56] and intestinal epithelial inflammation[57] and produce corresponding inflammatory factors. This suggests that Th22 cells exert their inflammatory effects mainly by disrupting the homeostasis of the internal and external surface barriers of various tissues, thus damaging tissues from the outside.

Th22 cells, like other pro-inflammatory cells, have been linked to obesity and IR in recent years, providing a foundation for the onset of T2DM. IL-22 is elevated to varying degrees in the liver, fat, and peripheral blood of individuals with obesity and T2DM[58]. The levels of IFN-γ, IL-17, and IL-22 are considerably higher in individuals with T2DM than in control individuals, with a positive connection between BMI and homeostasis model assessment (HOMA)-IR[59]. An overactivated Th22 phenotype adversely correlates with residual islet-cell function, and individuals with T2DM have higher aromatic hydrocarbon receptor gene expression, which promotes a synchronized increase in Th22 and Th1/Th17 cell frequencies[60]. The majority of naive T cells develop into Th22 cells as a result of IL-6 and TNF-α stimulation[55] and are negatively regulated by IL-10. IL-22 induces serum amyloid in a STAT-dependent manner and promotes Th17 activation to disrupt lipid metabolism in the intestinal epithelium[61,62]. Although several studies have provided evidence for the correlation between Th22 cells and inflammation, as well as IR, the role of IL-22 in the progression of obesity and its related metabolic consequences remains a subject of debate. Further research is required to gain a deeper understanding of this issue.

4 Anti-inflammatory CD4+ T Cells in T2DM

4.1 Th2 Cells

Unlike Th1 cells, Th2 cells mainly play an anti-inflammatory role. They were initially discovered for their importance in warding off parasitic illnesses[63]. GATA binding protein 3 is a major regulatory gene for Th2 cells, producing cytokines such as IL-5, IL-10, and IL-13, and IL-4 by activating STAT5 and STAT6[58,63]. Antigen dose and T cell receptor-mediated signaling intensity correlate with the generation of Th1 and Th2 cells during differentiation[64], with low or moderate doses of antigen promoting a dominant Th1 cell response and high doses of antigen favoring Th2 cell production[65]. IL-4 was the first stimulant identified to be produced by M2-type macrophages[66] and has an inhibitory effect on inflammation.

The proportion of IL-4 is significantly decreased in both the adipose tissue and peripheral blood of obese mice and the reduction in IL-4 is accompanied by IFN-γ-associated aggregation of Th1 cells[58,67,68]. Increased numbers of pro-inflammatory cells due to visceral adiposity and obesity are important drivers of IR and the development of T2DM. Th2 cells maintain adipose metabolic homeostasis by secreting IL-4 and IL-13, which induce an M2-like, anti-inflammatory state in macrophages associated with adipose tissue[69]. Furthermore, $CD4^+$ T cell transfer into lymphocyte-depleted Rag1 deleted mice with diet-induced obesity reduces weight gain and improves insulin sensitivity, mostly owing to an increase in the proportion of Th2 cells[27]; however, an equivalent effect can not be produced in mice with impaired Th2 cell development[70], indicating that Th2 cells play an essential role in mitigating obesity and IR.

Similarly, in humans, individuals with overweight or obesity have reduced Th2 cells, and Th2 cells in the visceral adiposity and peripheral blood are negatively associated with systemic IR and plasma high-sensitivity C-reactive protein[69]. Mechanistically, Th2 cells enhance glucose utilization by producing IL-4 polarized macrophages, increase peroxisome proliferator-activated receptor gamma (PPARγ) driven GLUT4 expression[71], and activate the mechanistic target of the rapamycin complex (mTORC)2 pathway[72]. In addition, IL-13 activation by JUN-STAT induces growth differentiation factor 15 expression to ameliorate poor glucose tolerance[73]. Therefore, an increase in Th2 cytokines is closely linked to the classical insulin signal-

ing pathway and macrophage polarization, which protect against disease progression by enhancing glucose sensitivity and anti-inflammatory properties.

4.2 Tregs

Tregs are a well-established subset of $CD4^+$ T cells that exhibit anti-inflammatory properties. They are characterized by the expression of CD4, CD25, and FOXP3. Tregs play a crucial role in modulating the immune response against autoimmune antigens and regulating T cell activation. They primarily secrete IL-10 and TGF-β to exert their immunomodulatory effects[58,74]. Tregs lack IL-6, and their differentiation is driven by TGF-β. Tregs deplete IL-2 via the high-affinity IL-2 receptor thereby inducing cytotoxic T-lymphocyte cadherin 4 (CTLA-4) expression, IL-10 production, and granzyme B secretion[74]. Tregs also decrease APC and effector T cells[74]. TGF-β serves as a shared developmental factor for both Th17 cells and Tregs, with IL-6 playing a crucial part in their differentiation process. IL-6 induces TGF-β to differentiate Th17 cells while inhibiting Tregs production under normal conditions, exacerbating the development of inflammatory and autoimmune diseases[75]. Several studies have shown that Tregs are abundant in healthy mouse adipose tissue but drastically diminished in obese animal models[76–78]. IL-10 secreted by Tregs maintains adipose tissue homeostasis by inhibiting the growth of white adipose tissue[79]. Tregs proliferation or over-transfer reduces adipose inflammation and ameliorates associated metabolic syndromes[80–82].

Clinical studies have found that individuals with T2DM have considerably lower levels of Tregs and associated cytokines than healthy individuals[83–85] and that the percentage of Tregs is negatively correlated with HOMA-IR in individuals with obesity[86]. Because Tregs play a role in regulating immune homeostasis and controlling the progression of metabolic syndromes, they have received increasing attention. Recently, exenatide has been shown to promote Treg proliferation by mediating the PI3K/AKT/FOXO1 pathway and reducing Th17 cells, thereby attenuating pancreatic islet inflammation[87]. The p38 AMPK/C/EBPβ pathway can also modulate granulocyte-macrophage colony-stimulating factor and the synthesis of IL-10[88]. In addition, Tregs express insulin receptors, and hyperinsulinemia inhibits IL-10 production through the activation of AKT/mTOR signaling[89], which may explain a decrease in Tregs in T2DM mouse models[87]. However, the AKT/mTOR signaling pathway appears to have a feedback effect on T cell differentiation, and stimulation of Treg differentiation activates this pathway and increases glucose transport[90]. These studies have guided us toward the treatment of T2DM.

5 $CD8^+$ T Cells in T2DM

$CD8^+$ T cells are a crucial type of adaptive immune cells that act as key mediators of immunological surveillance and clearance. Abnormal antigens are delivered through MHC class I molecules, where they are degraded to form peptides and delivered to $CD8^+$ T cells[91]. $CD8^+$ T cells kill cells carrying these abnormal antigens by releasing cytotoxic molecules, such as granzymes and perforins, and cytokines such as IFN-γ and TNF-α[92]. $CD8^+$ T cell differentiation is mainly determined by antigenic strength, co-stimulatory molecules, and inflammatory cytokines[93]. In animal models, the accumulation and polarization of macrophages, accompanied by increased numbers of $CD8^+$ T cells and corresponding cytokines, are observed in the AT of HFD-fed mice, promoting an inflammatory state[22,94,95]. Additionally, the infiltration of adipose $CD8^+$ T cells into adipose tissue precedes macrophage aggregation, and knocking $CD8^+$ T cells decreases adipose tissue inflammation and the number of macrophages, which improves systemic IR[22].

In human studies, increased $CD8^+$ T cells in the AT and peripheral blood are strongly associated with IR and hyperglycemia, and CD8+ T cells also increase with age and the onset of diabetes[96,97]. Furthermore, with the progression of obesity and T2DM, $CD8^+$ T cells expand to varying degrees in the skeletal muscle, liver, kidney, and intestine respectively, and negatively regulate vascular regeneration and function[98–102], suggesting a synergistic effect of $CD8^+$ T cells through the release of cytotoxic particles, and inflammatory factors leading to tissue immunopathology. Therefore, $CD8^+$ T cells that promote metabolic tissue infiltration may be a potential therapeutic target for obesity, aging, T2DM, and associated complications, which are important for treating and delaying related metabolic diseases.

6 T Cell Activation and Exhaustion in T2DM

6.1 T Cell Activation

Primary T cells enter the circulation after thymic development and maturation and are recognized by the MHC under initial and repeated antigenic stimulation. T cells interact with APC to induce the proliferation and differentiation of effector T cells and long-lived memory cells and the release of cytokines by effector T cells to kill specific antigens[103], a process known as T cell activation or cellular immunity. T2DM is a chronic, low-grade inflammatory disease caused by IR, hyperglycemia, and the persistent stimulation of immune cells, including macrophages, mast cells, and T cells. During obesity, excessive levels of free fatty acids and glucose stimulate an increase in the number and activity of T cells in islet-sensitive tissues (especially adipose, liver, and muscle tissues), accompanied by the accumulation and polarization of macrophages[104]. Reduced insulin sensitivity results from the accumulation of activated immune cells in tissues and the production of pro-inflammatory cytokines that then interact with nearby insulin target cells[9]. In general, Th1 cells, and Th17 cells increase inflammation and IR, whereas Th2 and Treg have a suppressive role[104], based on the context and level of disease development.

The bidirectional interaction between T2DM and inflammation is achieved through immune cell regulation (Figure 2). In diabetes, high levels of blood glucose react with proteins to form advanced glycosylation end-products (AGEs), which AGEs upregulate electrogenic $Ca2^{+}$-activated K^{+} channels to promote peripheral blood mononuclear cell (PBMC) migration, participate in T and B cell activation, and are positively correlated with glycated hemoglobin (HbA1c) levels[105]. In addition, AGEs promote the emission of inflammation-related mediators via the control of pathways such as PI3K/AKT, and prolonged exposure to inflammatory factors ultimately leads to blockage of insulin signaling receptors and exacerbates hyperglycemia[105,106]. In addition, HFD-induced obesity leads to dysregulation of Th17/Treg homeostasis through the TGFβ1/IRF3/STAT3 pathway, which promotes the release of Th1 cytokines, facilitates macrophage conversion to the M1 type, and exacerbates inflammation and IR[107] (Figure 3). Obesity and diabetes disrupt adaptive immune homeostasis, activate T cells to proliferate toward pro-inflammatory phenotypes, and release inflammatory factors and chemokines to exacerbate the course of the disease. However, T cell activation is dependent on lactate production from aerobic glycolysis, and the addition of lactate during T cell differentiation can activate the AKT/mTOR signaling, promote T cell differentiation toward Tregs, and inhibit Th1 cell differentiation[90]. Therefore, the full utilization of glucose to promote increased lactate production during hyperglycemia may serve as a feedback mechanism to limit inflammatory diseases. Conversely, it has been suggested that hyperglycemia interferes with calcium transduction signaling and prevents T cell activation[108]. Therefore, T cell activation and T cell immunity in T2DM are unclear, and how T cell subsets and pro-inflammatory or anti-inflammatory factors are distributed during T cell activation needs to be explored.

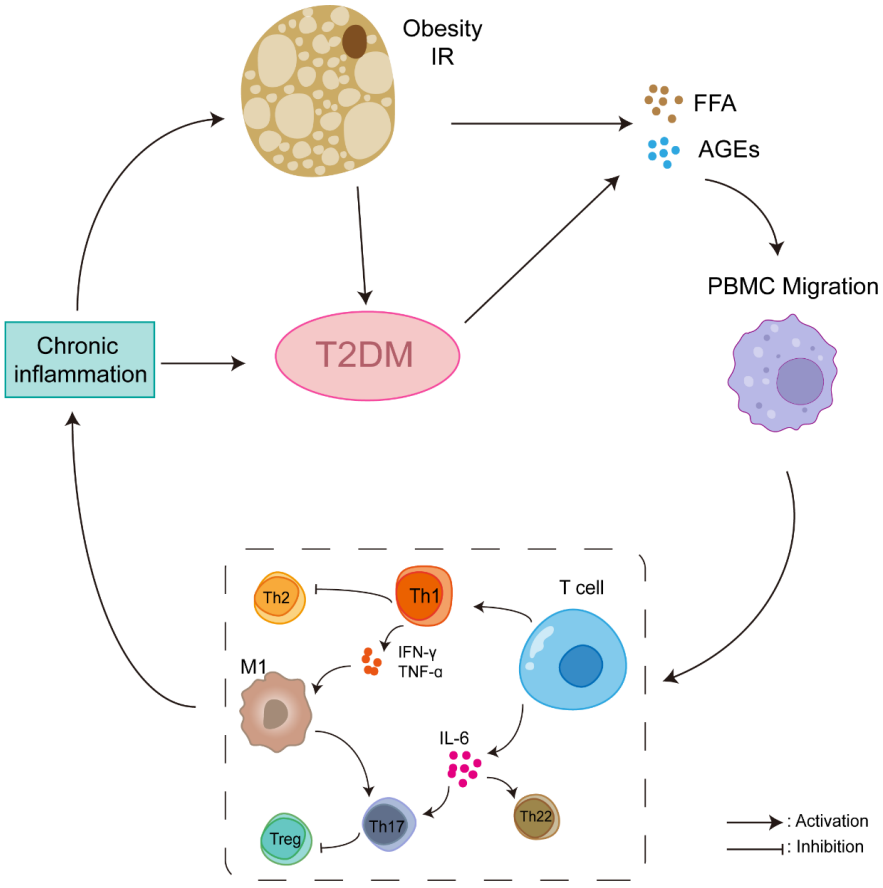

FIGURE 2 The interaction between T2DM and inflammation is bidirectional through the regulation of immune cells. IR, insulin resistance; FFA, Free fatty acids; AGEs, advanced glycated end-products; PBMC, peripheral blood mononuclear cell; IFN-γ, interferon gamma; TNF-α, necrosis factor alpha; IL-6, interleukin-6.

6.2 T Cell Exhaustion

T cell exhaustion refers to the impaired T cell activity seen in persistent infections and malignancies. This condition is marked by a gradual decline in T cell function, eventually resulting in a total lack of cascade effects[109]. New research has shown elevated levels of cytotoxic and T helper cell exhaustion in individuals diagnosed with T2DM[110]. A study examining the association between programmed cell death 1 and its ligand (PD-1/PD-L1) in T2DM and macrovascular lesions, demonstrated that PD-1 levels were higher in individuals diagnosed with T2DM than the control group[111]. The first phase of T cell exhaustion is characterized by a decrease in IL-2 production and PD-1 expression, followed by defective TNF production. Some cytotoxic effector function is regained in the middle stage, and cells eventually have high PD-1 expression[112]. The combination of T cell activation and exhaustion may seem to be contradictory, but they can co-exist in a certain disease state, suggesting that at least partial T cell exhaustion is present in patients with T2DM.

T-cell exhaustion occurs primarily in cancer, chronic infections, and autoimmune diseases. As a result of prolonged exposure to persistent antigens and inflammation, T cells are activated to form early exhausted T cells, which maintain some degree of effector capacity and proliferation. As activation continues, early exhausted T cells gradually lose their effector function, are unable to differentiate into memory cells, and ultimately lose their proliferative and effector capacities altogether[113]. Studies on the PD-1/PD-L1 pathway in T2DM have found that PD-1 expression is downregulated in individuals with T2DM and that it is

positively correlated with insulin and diabetes duration and negatively correlated with BMI[114]. With aging and disease progression, individuals with T2DM show a decreasing total number of $CD4^+$ and $CD8^+$ T cells, reduced differentiation of naïve T cells, and immune senescence and depletion. Therefore, the stimulation and subsequent exhaustion of T cells are significant factors in the pathogenesis of T2DM, ultimately leading to full T-cell depletion as the illness progresses.

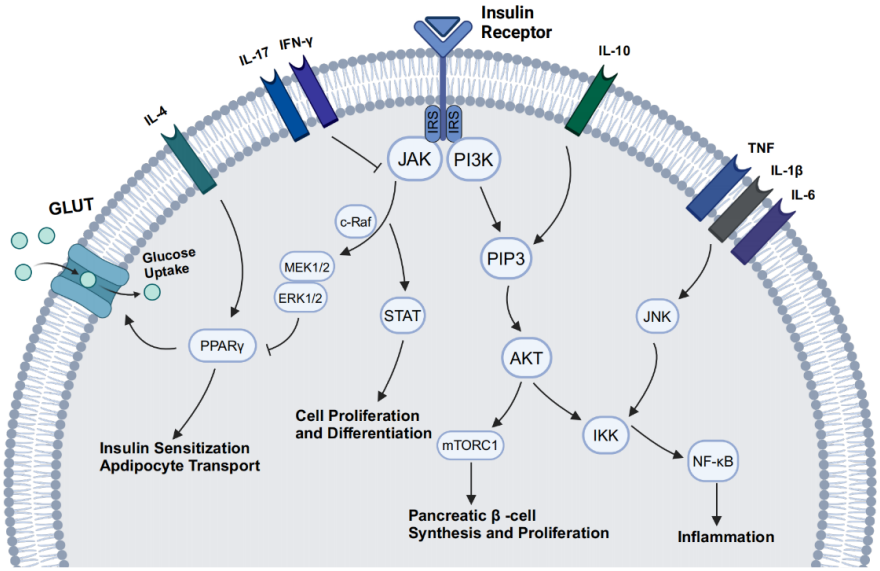

FIGURE 3 Role of T cells on the T2DM pathway. The activation of intracellular signals by cytokines secreted by T cells helps to promote or inhibit the pathogenesis of T2DM. GLUT, glucose transporter type; IL-4, interleukin-4; IL-17, interleukin-17; IFN-γ, interferon gamma; IL-10, interleukin-10; TNF, necrosis factor; IL-1β, interleukin-1 beta; IL-6, interleukin-6; IRS, insulin substrate; JAK, Janus kinase; PI3K, phosphatidylinositol 3-kinase; c-Raf, Raf proto-oncogene, serine/threonine kinase; MEK1/2, mitogen-activated protein kinase kinases 1 and 2; ERK1/2, extracellular signal-regulated protein kinases 1 and 2; PPARγ, peroxisome proliferator-activated receptor gamma; STAT, signal transducer and activators of transcription; PIP3, phosphatidylinositol triphosphate 3; AKT, protein kinase B; mTORC1, mechanistic target of rapamycin complex 1; JNK, Jun amino-terminal kinase; IKK, inhibitor of kappa B kinase; NF-ϰB, nuclear factor kappa B.

6.3 Complications and Treatment

Dysregulation of T-cell homeostasis resulting from the progression of diabetes mellitus can affect all vital organs in the body, resulting in a variety of chronic complications. The adipose tissue is an endocrine organ that plays an important role in regulating glucose metabolism and fatty acid oxidation. Under physiological conditions, adipokines (such as leptin) continually activate effector T cells, which leads to the generation of cytokines that suppress inflammation; the liver first undergoes steatosis, and the secretion of chemokines by hepatocytes and Kupffer cells eventually leads to inflammation and fibrosis[58,115]. A study on T2DM and cardiovascular risk found increased immune activation in individuals with T2DM and cardiovascular disease[116] and that signaling by inducible T cell costimulator and its ligand (ICOS/ICOSL), a co-stimulatory immune checkpoint, induces cytotoxic effects, such as activation of cytotoxic T lymphocytes, and inhibits Treg activity[117]. High glucose levels and AGEs may cause T-cell inflammatory responses and vascular endothelial dysfunction by upregulating ICOS signaling[118]. In addition, diabetic nephropathy[100] and retinopathy[119]exhibit varying degrees of T cell homeostasis disruption, exacerbating inflammation and dysfunction.

A growing body of research is exploring immunotherapies for T2DM to reduce disease progression and

complications. Conventional oral hypoglycemic agents such as glucagon-like peptide (GLP)-1 agonists have been shown to help inhibit T cell proliferation, promote Th2 transition, and reduce the IL-1/IFN-γ ratio to reduce renal and cardiovascular deterioration[120,121]. Patients with newly diagnosed T2DM who have a short course of rigorous insulin treatment have substantial reductions in inflammatory markers such as IL-6, TNF-α, and chemokines and increases in activating factors that govern proper T cell production and secreted chemokines[122], further suggesting that insulin regulates T cell immune homeostasis in addition to its glucose-lowering effects. However, the effects of these factors on the inflammatory signaling pathway in blood glucose levels are understudied. Additionally, the role of immunomodulation in the treatment of T2DM goes far beyond that. Adult stem cells from individuals with obesity and T2DM inhibit $CD4^+$ T cell proliferation, modulate T cell activation markers (CD69 and CD25), and increase Treg frequency[123] thereby facilitating immunotherapy.

Researchers are currently exploring the development of a diabetes vaccine that modulates immune cell subsets in T2DM. A vaccine targeting IL-1β with polylactic acid particles as an adjuvant targets and inhibits IL-1β and blocks NF-κB activation by decreasing the levels of IKKβ and phosphorylated RelA[124] and blocking the release of pro-inflammatory factors. The PD-1 pathway is important for regulating T-cell activation, tolerance, and exhaustion. There have been opposing findings regarding whether PD-1 is upregulated[110,111]or downregulated[114] in T2DM, but it has been suggested that PD-1-deficient Tregs may protect non-obese diabetic mice from diabetes by inhibiting the PI3K/AKT pathway[125]. Therefore, the use of PD-1 as an immune checkpoint inhibitor may be beneficial in restoring immune function in patients with T2DM.

7 Conclusion and Perspectives

In summary, T cell-mediated adaptive immunity is closely associated with T2DM, which is a chronic metabolic inflammatory illness. With the progression of obesity, IR, and gradual elevation of blood glucose levels, innate immunity is activated first, and there is an increase in the number of T cells under macrophage infiltration, differentiation of $CD4^+$ T cells into pro-inflammatory cells, and a decline in the expression of inflammation-suppressing factors. Among the unconventional T cells that play a bridging role between innate and adaptive immunity are natural killer T cells, mucosal constant T cells (MAIT), and γ-δ-T cells[126]. These cells recognize lipids, small molecule metabolites, specifically modified peptides, and peptide antigens presented on the cell surface through the classical MHC family and are characterized by broad recognition and rapid response[127]. Both MAIT and adaptive T cells are activated in pre-diabetes, and the inflammatory balance is tipped toward a pro-inflammatory state. A self-amplified chronic pro-inflammatory milieu and the presence of amyloid peptides contribute to the decline in β cell mass and function, ultimately culminating in the development of T2DM. However, the demarcation between T-cell immune activation and exhaustion in the pathogenesis of T2DM remains unclear, as does when T-cell exhaustion begins. These questions need to be addressed in the future to lay the foundation for the development of new immunotherapies.

Author Contributions

Zhimei Huang: Formal analysis; wrote the manuscript. Jiaqi Chen: Formal analysis. All authors contributed to the article and approved the submitted version.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data Availability Statement

The data in this article are all included in the content. The data that support the findings of this article are included within this article (Figure1-3 and Table 1).

Reference

1. Tinajero, M. G.; Malik, V. S. An Update on the Epidemiology of Type 2 Diabetes: A Global Perspective. *Endocrinol Metab Clin North Am***2021** , *50* (3), 337–355.

2. Ma CX, Ma XN, Guan CH, Li YD, Mauricio D, Fu SB. Cardiovascular disease in type 2 diabetes mellitus: progress toward personalized management. *Cardiovasc Diabetol* . 2022;21(1):74.

3. Tomic D, Shaw JE, Magliano DJ. The burden and risks of emerging complications of diabetes mellitus. *Nat Rev Endocrinol* . 2022;18(9):525-539.

4. Hur HJ, Yang HJ, Kim MJ, Lee KH, Kim MS, Park S. Association of Polygenic Variants with Type 2 Diabetes Risk and Their Interaction with Lifestyles in Asians. *Nutrients* . 2022;14(15):3222.

5. Sell H, Habich C, Eckel J. Adaptive immunity in obesity and insulin resistance. *Nat Rev Endocrinol* . 2012;8(12):709-716.

6. Galicia-Garcia U, Benito-Vicente A, Jebari S, et al. Pathophysiology of Type 2 Diabetes Mellitus. *Int J Mol Sci* . 2020;21(17):6275.

7. Brooks-Worrell B, Hampe CS, Hattery EG, et al. Islet Autoimmunity is Highly Prevalent and Associated With Diminished β-Cell Function in Patients With Type 2 Diabetes in the Grade Study. *Diabetes* . 2022;71(6):1261-1271.

8. Maedler K, Sergeev P, Ris F, et al. Glucose-induced beta cell production of IL-1beta contributes to glucotoxicity in human pancreatic islets. *J Clin Invest* . 2002;110(6):851-860.

9. Feingold KR, Soued M, Staprans I, et al. Effect of tumor necrosis factor (TNF) on lipid metabolism in the diabetic rat. Evidence that inhibition of adipose tissue lipoprotein lipase activity is not required for TNF-induced hyperlipidemia. *J Clin Invest* . 1989;83(4):1116-1121.

10. Park JE, Kang E, Han JS. HM-chromanone attenuates TNF-α-mediated inflammation and insulin resistance by controlling JNK activation and NF-ϰB pathway in 3T3-L1 adipocytes. *Eur J Pharmacol* . 2022;921:174884.

11. Huang SM, Wu CS, Chiu MH, et al. High glucose environment induces M1 macrophage polarization that impairs keratinocyte migration via TNF-α: An important mechanism to delay the diabetic wound healing. *J Dermatol Sci* . 2019;96(3):159-167.

12. Allahyani M, Alshalawi AM, Alshalawii MR, et al. Phenotypical evaluation of lymphocytes and monocytes in patients with type 2 diabetes mellitus in Saudi Arabia. *Saudi Med J* . 2023;44(3):296-305.

13. Mahmoud FF, Haines D, Dashti AA, El-Shazly S, Al-Najjar F. Correlation between heat shock proteins, adiponectin, and T lymphocyte cytokine expression in type 2 diabetics. *Cell Stress Chaperones* . 2018;23(5):955-965.

14. Wang H, Cao K, Liu S, Xu Y, Tang L. Tim-3 Expression Causes NK Cell Dysfunction in Type 2 Diabetes Patients. *Front Immunol* . 2022;13:852436.

15. Delamaire M, Maugendre D, Moreno M, Le Goff MC, Allannic H, Genetet B. Impaired leucocyte functions in diabetic patients. *Diabet Med* . 1997;14(1):29-34.

16. 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(12):3239-3246.

17. Ronacher K, Joosten SA, van Crevel R, Dockrell HM, Walzl G, Ottenhoff THM. Acquired immunodeficiencies and tuberculosis: focus on HIV/AIDS and diabetes mellitus. *Immunol Rev* . 2015;264(1):121-137.

18. Ashraf T, Sarker PK, Hosen MI, Rahman A, Hasan AKMM, Rahman T. Association of Chronic Toxoplasma gondii Infection with Pro-Inflamatory Cytokine Interleukin (IL)-12 Responses in Type-2 Diabetes Mellitus Patients of Bangladesh. *J Parasitol Res* . 2023;2023:3885160.

19. Wu D, Molofsky AB, Liang HE, et al. Eosinophils sustain adipose alternatively activated macrophages associated with glucose homeostasis.*Science* . 2011;332(6026):243-247.

20. Crotty S. T Follicular Helper Cell Biology: A Decade of Discovery and Diseases. *Immunity* . 2019;50(5):1132-1148.

21. Bonilla FA, Oettgen HC. Adaptive immunity. *J Allergy Clin Immunol* . 2010;125(2 Suppl 2):S33-40.

22. Nishimura S, Manabe I, Nagasaki M, et al. CD8+ effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity. *Nat Med* . 2009;15(8):914-920.

23. Gearty SV, Dündar F, Zumbo P, et al. An autoimmune stem-like CD8 T cell population drives type 1 diabetes. *Nature* . 2022;602(7895):156-161.

24. Mosmann TR, Cherwinski H, Bond MW, Giedlin MA, Coffman RL. Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. *J Immunol* . 1986;136(7):2348-2357.

25. O'Garra A, Robinson D. Development and function of T helper 1 cells.*Adv Immunol* . 2004;83:133-162.

26. Langenhorst D, Haack S, Göb S, et al. CD28 Costimulation of T Helper 1 Cells Enhances Cytokine Release In Vivo. *Front Immunol* . 2018;9:1060.

27. Winer S, Chan Y, Paltser G, et al. Normalization of obesity-associated insulin resistance through immunotherapy. *Nat Med* . 2009;15(8):921-929.

28. Matia-Garcia I, Vadillo E, Pelayo R, et al. Th1/Th2 Balance in Young Subjects: Relationship with Cytokine Levels and Metabolic Profile.*J Inflamm Res* . 2021;14:6587-6600.

29. Satomura A, Oikawa Y, Haisa A, et al. Clinical Significance of Insulin Peptide-specific Interferon-γ-related Immune Responses in Ketosis-prone Type 2 Diabetes. *J Clin Endocrinol Metab* . 2022;107(5):e2124-e2132.

30. AlAfaleq NO, Hussein TM, Al-Shouli ST, et al. Proinflammatory cytokine profiles in prediabetic Saudi patients. *Saudi J Biol Sci* . 2023;30(8):103714.

31. Sheikh V, Zamani A, Mahabadi-Ashtiyani E, Tarokhian H, Borzouei S, Alahgholi-Hajibehzad M. Decreased regulatory function of CD4+CD25+CD45RA+ T cells and impaired IL-2 signalling pathway in patients with type 2 diabetes mellitus. *Scand J Immunol* . 2018;88(4):e12711.

32. Suri S, Mitra P, Abhilasha A, et al. Role of interleukin-2 and interleukin-18 in newly diagnosed type 2 diabetes mellitus. *J Basic Clin Physiol Pharmacol* . 2021;33(2):185-190.

33. Bae HR, Choi MS, Kim S, et al. IFNγ is a Key Link between Obesity and Th1-Mediated AutoImmune Diseases. *Int J Mol Sci* . 2020;22(1):208.

34. Aly RH, Ahmed AE, Hozayen WG, et al. Patterns of Toll-Like Receptor Expressions and Inflammatory Cytokine Levels and Their Implications in the Progress of Insulin Resistance and Diabetic Nephropathy in Type 2 Diabetic Patients. *Front Physiol* . 2020;11:609223.

35. 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(46):31936-31944.

36. Sun Y, Wang B, Hu Q, et al. Loss of Lkb1 in CD11c+ myeloid cells protects mice from diet-induced obesity while enhancing glucose intolerance and IL-17/IFN-γ imbalance. *Cell Mol Life Sci* . 2023;80(3):63.

37. Bi L, Ren Y, Feng M, et al. HDAC11 Regulates Glycolysis through the LKB1/AMPK Signaling Pathway to Maintain Hepatocellular Carcinoma Stemness. *Cancer Res* . 2021;81(8):2015-2028.

38. Korn T, Bettelli E, Oukka M, Kuchroo VK. IL-17 and Th17 Cells.*Annu Rev Immunol* . 2009;27:485-517.

39. Xiao QP, Zhong YB, Kang ZP, et al. Curcumin regulates the homeostasis of Th17/Treg and improves the composition of gut microbiota in type 2 diabetic mice with colitis. *Phytother Res* . 2022;36(4):1708-1723.

40. Bapat SP, Whitty C, Mowery CT, et al. Obesity alters pathology and treatment response in inflammatory disease. *Nature* . 2022;604(7905):337-342.

41. Cavallari JF, Denou E, Foley KP, Khan WI, Schertzer JD. Different Th17 immunity in gut, liver, and adipose tissues during obesity: the role of diet, genetics, and microbes. *Gut Microbes* . 2016;7(1):82-89.

42. Van Herck MA, Vonghia L, Kwanten WJ, et al. Diet Reversal and Immune Modulation Show Key Role for Liver and Adipose Tissue T Cells in Murine Nonalcoholic Steatohepatitis. *Cell Mol Gastroenterol Hepatol* . 2020;10(3):467-490.

43. Zhu L, Song H, Zhang L, Meng H. Characterization of IL-17-producing Treg cells in type 2 diabetes patients. *Immunol Res* . 2019;67(4-5):443-449.

44. Li Y, Chen S, Zhao T, Li M. Serum IL-36 cytokines levels in type 2 diabetes mellitus patients and their association with obesity, insulin resistance, and inflammation. *J Clin Lab Anal* . 2021;35(2):e23611.

45. Lin W, Song H, Shen J, et al. Functional role of skeletal muscle-derived interleukin-6 and its effects on lipid metabolism.*Front Physiol* . 2023;14:1110926.

46. Huang T, Song J, Gao J, et al. Adipocyte-derived kynurenine promotes obesity and insulin resistance by activating the AhR/STAT3/IL-6 signaling. *Nat Commun* . 2022;13(1):3489.

47. Zhao Y, Luan H, Jiang H, et al. Gegen Qinlian decoction relieved DSS-induced ulcerative colitis in mice by modulating Th17/Treg cell homeostasis via suppressing IL-6/JAK2/STAT3 signaling.*Phytomedicine* . 2021;84:153519.

48. 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.

49. Zhang L, Liu M, Liu W, et al. Th17/IL-17 induces endothelial cell senescence via activation of NF-ϰB/p53/Rb signaling pathway. *Lab Invest* . 2021;101(11):1418-1426.

50. Barbie TU, Alexe G, Aref AR, et al. Targeting an IKBKE cytokine network impairs triple-negative breast cancer growth. *J Clin Invest* . 2014;124(12):5411-5423.

51. Chen C, Zhang Q, Liu S, Lambrechts M, Qu Y, You Z. AZD5363 Inhibits Inflammatory Synergy between Interleukin-17 and Insulin/Insulin-Like Growth Factor 1. *Front Oncol* . 2014;4:343.

52. Eyerich S, Eyerich K, Pennino D, et al. Th22 cells represent a distinct human T cell subset involved in epidermal immunity and remodeling. *J Clin Invest* . 2009;119(12):3573-3585.

53. Jia L, Wu C. The biology and functions of Th22 cells. *Adv Exp Med Biol* . 2014;841:209-230.

54. Pavel AB, Zhou L, Diaz A, et al. The proteomic skin profile of moderate-to-severe atopic dermatitis patients shows an inflammatory signature. *J Am Acad Dermatol* . 2020;82(3):690-699.

55. Jiang Q, Yang G, Xiao F, et al. Role of Th22 Cells in the Pathogenesis of Autoimmune Diseases. *Front Immunol* . 2021;12:688066.

56. Ye J, Ji Q, Liu J, et al. Interleukin 22 Promotes Blood Pressure Elevation and Endothelial Dysfunction in Angiotensin II-Treated Mice.*J Am Heart Assoc* . 2017;6(10):e005875.

57. Ratsimandresey RA, Indramohan M, Dorfleutner A, Stehlik C. The AIM2 inflammasome is a central regulator of intestinal homeostasis through the IL-18/IL-22/STAT3 pathway. *Cell Mol Immunol* . 2017;14(1):127-142.

58. Van Herck MA, Weyler J, Kwanten WJ, et al. The Differential Roles of T Cells in Non-alcoholic Fatty Liver Disease and Obesity. *Front Immunol* . 2019;10:82.

59. Guo H, Xu BC, Yang XG, et al. A High Frequency of Peripheral Blood IL-22(+) CD4(+) T Cells in Patients With New Onset Type 2 Diabetes Mellitus. *J Clin Lab Anal* . 2016;30(2):95-102.

60. Zhao RX, He Q, Sha S, et al. Increased AHR Transcripts Correlate With Pro-inflammatory T-Helper Lymphocytes Polarization in Both Metabolically Healthy Obesity and Type 2 Diabetic Patients. *Front Immunol* . 2020;11:1644.

61. Ouyang W, O'Garra A. IL-10 Family Cytokines IL-10 and IL-22: from Basic Science to Clinical Translation. *Immunity* . 2019;50(4):871-891.

62. Sano T, Huang W, Hall JA, et al. An IL-23R/IL-22 Circuit Regulates Epithelial Serum Amyloid A to Promote Local Effector Th17 Responses. *Cell* . 2015;163(2):381-393.

63. Zhu J, Paul WE. CD4 T cells: fates, functions, and faults. *Blood* . 2008;112(5):1557-1569.

64. Nakayama T, Hirahara K, Onodera A, et al. Th2 Cells in Health and Disease. *Annu Rev Immunol* . 2017;35:53-84.

65. Nj T, Mk J. TCR signal quantity and quality in CD4+ T cell differentiation. *Trends Immunol* . 2014;35(12):591-596.

66. Cutolo M, Campitiello R, Gotelli E, Soldano S. The Role of M1/M2 Macrophage Polarization in Rheumatoid Arthritis Synovitis. *Front Immunol* . 2022;13:867260.

67. O'Connor JC, Sherry CL, Guest CB, Freund GG. Type 2 diabetes impairs insulin receptor substrate-2-mediated phosphatidylinositol 3-kinase activity in primary macrophages to induce a state of cytokine resistance to IL-4 in association with overexpression of suppressor of cytokine signaling-3. *J Immunol* . 2007;178(11):6886-6893.

68. Jung C, Lichtenauer M, Strodthoff D, et al. Alterations in systemic levels of Th1, Th2, and Th17 cytokines in overweight adolescents and obese mice. *Pediatr Diabetes* . 2017;18(8):714-721.

69. Wensveen FM, Valentić S, Šestan M, Turk Wensveen T, Polić B. The "Big Bang" in obese fat: Events initiating obesity-induced adipose tissue inflammation. *Eur J Immunol* . 2015;45(9):2446-2456.

70. 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(5):467-476.

71. Phu TA, Ng M, Vu NK, Bouchareychas L, Raffai RL. IL-4 polarized human macrophage exosomes control cardiometabolic inflammation and diabetes in obesity. *Mol Ther* . 2022;30(6):2274-2297.

72. Huang SCC, Smith AM, Everts B, et al. Metabolic Reprogramming Mediated by the mTORC2-IRF4 Signaling Axis Is Essential for Macrophage Alternative Activation. *Immunity* . 2016;45(4):817-830.

73. Lee SE, Kang SG, Choi MJ, et al. Growth Differentiation Factor 15 Mediates Systemic Glucose Regulatory Action of T-Helper Type 2 Cytokines. 2017;66(11):2774-2788.

74. Togashi Y, Nishikawa H. Regulatory T Cells: Molecular and Cellular Basis for Immunoregulation. *Curr Top Microbiol Immunol* . 2017;410:3-27.

75. Kimura A, Kishimoto T. IL-6: regulator of Treg/Th17 balance. *Eur J Immunol* . 2010;40(7):1830-1835.

76. Ishikawa A, Wada T, Nishimura S, et al. Estrogen regulates sex-specific localization of regulatory T cells in adipose tissue of obese female mice. *PLoS One* . 2020;15(4):e0230885.

77. He B, Wu L, Xie W, et al. The imbalance of Th17/Treg cells is involved in the progression of nonalcoholic fatty liver disease in mice.*BMC Immunol* . 2017;18(1):33.

78. Gajic D, Koprivica I, Stojanovic I, Saksida T. Defective immunosuppressive function of Treg cells in visceral adipose tissue in MIF deficient mice. *Cytokine* . 2021;138:155372.

79. Beppu LY, Mooli RGR, Qu X, et al. Tregs facilitate obesity and insulin resistance via a Blimp-1/IL-10 axis. *JCI Insight* . 2021;6(3):e140644, 140644.

80. Sabapathy V, Stremska ME, Mohammad S, Corey RL, Sharma PR, Sharma R. Novel Immunomodulatory Cytokine Regulates Inflammation, Diabetes, and Obesity to Protect From Diabetic Nephropathy. *Front Pharmacol* . 2019;10:572.

81. Wara AK, Wang S, Wu C, et al. KLF10 Deficiency in CD4+ T Cells Triggers Obesity, Insulin Resistance, and Fatty Liver. *Cell Rep* . 2020;33(13):108550.

82. Cipolletta D, Feuerer M, Li A, et al. PPAR-γ is a major driver of the accumulation and phenotype of adipose tissue Treg cells.*Nature* . 2012;486(7404):549-553.

83. Guzmán-Flores JM, Ramírez-Emiliano J, Pérez-Vázquez V, López-Briones S. Th17 and regulatory T cells in patients with different time of progression of type 2 diabetes mellitus. *Cent Eur J Immunol* . 2020;45(1):29-36.

84. Fagninou A, Nekoua MP, Sossou D, Moutairou K, Fievet N, Yessoufou A. Th2-Immune Polarizing and Anti-Inflammatory Properties of Insulin Are Not Effective in Type 2 Diabetic Pregnancy. *J Immunol Res* . 2020;2020:2038746.

85. Wang C, Wang H, Dai L, et al. T-Helper 17 Cell/Regulatory T-Cell Imbalance in COPD Combined with T2DM Patients. *Int J Chron Obstruct Pulmon Dis* . 2021;16:1425-1435.

86. Yuan N, Zhang HF, Wei Q, Wang P, Guo WY. Expression of CD4+CD25+Foxp3+ Regulatory T Cells, Interleukin 10 and Transforming Growth Factor β in Newly Diagnosed Type 2 Diabetic Patients. *Exp Clin Endocrinol Diabetes* . 2018;126(2):96-101.

87. Xu Q, Zhang X, Li T, Shao S. Exenatide regulates Th17/Treg balance via PI3K/Akt/FoxO1 pathway in db/db mice. *Mol Med* . 2022;28(1):144.

88. Guindi C, Khan FU, Cloutier A, et al. Inhibition of PI3K/C/EBPβ axis in tolerogenic bone marrow-derived dendritic cells of NOD mice promotes Th17 differentiation and diabetes development. *Transl Res* . 2023;255:37-49.

89. Han JM, Patterson SJ, Speck M, Ehses JA, Levings MK. Insulin inhibits IL-10-mediated regulatory T cell function: implications for obesity. *J Immunol* . 2014;192(2):623-629.

90. Pitmon E, Meehan EV, Ahmadi E, Adler AJ, Wang K. High glucose promotes regulatory T cell differentiation. *PLoS One* . 2023;18(2):e0280916.

91. Andersen MH, Schrama D, Thor Straten P, Becker JC. Cytotoxic T cells. *J Invest Dermatol* . 2006;126(1):32-41.

92. Kaech SM, Cui W. Transcriptional control of effector and memory CD8+ T cell differentiation. *Nat Rev Immunol* . 2012;12(11):749-761.

93. Henning AN, Roychoudhuri R, Restifo NP. Epigenetic control of CD8+ T cell differentiation. *Nat Rev Immunol* . 2018;18(5):340-356.

94. Majdoubi A, Lee JS, Kishta OA, et al. Lack of the E3 Ubiquitin Ligase March1 Affects CD8 T Cell Fate and Exacerbates Insulin Resistance in Obese Mice. *Front Immunol* . 2020;11:1953.

95. Kiran S, Kumar V, Murphy EA, Enos RT, Singh UP. High Fat Diet-Induced CD8+ T Cells in Adipose Tissue Mediate Macrophages to Sustain Low-Grade Chronic Inflammation. *Front Immunol* . 2021;12:680944.

96. Yi HS, Kim SY, Kim JT, et al. T-cell senescence contributes to abnormal glucose homeostasis in humans and mice. *Cell Death Dis* . 2019;10(3):249.

97. Lee YH, Kim SR, Han DH, et al. Senescent T Cells Predict the Development of Hyperglycemia in Humans. *Diabetes* . 2019;68(1):156-162.

98. 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 (Lond)* . 2015;39(11):1607-1618.

99. Ghazarian M, Revelo XS, Nøhr MK, et al. Type I Interferon Responses Drive Intrahepatic T cells to Promote Metabolic Syndrome. *Sci Immunol* . 2017;2(10):eaai7616.

100. Zhang F, Wang C, Wen X, et al. Mesenchymal stem cells alleviate rat diabetic nephropathy by suppressing CD103+ DCs-mediated CD8+ T cell responses. *J Cell Mol Med* . 2020;24(10):5817-5831.

101. Monteiro-Sepulveda M, Touch S, Mendes-Sá C, et al. Jejunal T Cell Inflammation in Human Obesity Correlates with Decreased Enterocyte Insulin Signaling. *Cell Metab* . 2015;22(1):113-124.

102. Wang L, Sun P, Wu Y, Wang L. Metabolic tissue-resident CD8+ T cells: A key player in obesity-related diseases. *Obes Rev* . 2021;22(3):e13133.

103. Chapman NM, Boothby MR, Chi H. Metabolic coordination of T cell quiescence and activation. *Nat Rev Immunol* . 2020;20(1):55-70.

104. Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease.*Nat Rev Immunol* . 2011;11(2):98-107.

105. Zhang Y, Ma XZ, Zhao XY, et al. AGEs-RAGE-KCa3.1 pathway mediates palmitic acid-induced migration of PBMCs from patients with type 2 diabetes. *Heliyon* . 2023;9(4):e14823.

106. Nyambuya TM, Dludla PV, Nkambule BB. T cell activation and cardiovascular risk in type 2 diabetes mellitus: a protocol for a systematic review and meta-analysis. *Syst Rev* . 2018;7(1):167.

107. Kiran S, Rakib A, Kodidela S, Kumar S, Singh UP. High-Fat Diet-Induced Dysregulation of Immune Cells Correlates with Macrophage Phenotypes and Chronic Inflammation in Adipose Tissue. *Cells* . 2022;11(8):1327.

108. Boldizsár F, Berki T, Miseta A, Németh P. Effect of hyperglycemia on the basal cytosolic free calcium level, calcium signal and tyrosine-phosphorylation in human T-cells. *Immunol Lett* . 2002;82(1-2):159-164.

109. Pauken KE, Wherry EJ. SnapShot: T Cell Exhaustion. *Cell* . 2015;163(4):1038-1038.e1.

110. Nyambuya TM, Dludla PV, Mxinwa V, Nkambule BB. A systematic review and meta-analysis on the regulation of programmed cell death-1 on T-cells in type 2 diabetes. *Medicine (Baltimore)* . 2021;100(15):e25488.

111. Shi B, Du X, Wang Q, Chen Y, Zhang X. Increased PD-1 on CD4(+)CD28(-) T cell and soluble PD-1 ligand-1 in patients with T2DM: association with atherosclerotic macrovascular diseases.*Metabolism* . 2013;62(6):778-785.

112. Beltra JC, Manne S, Abdel-Hakeem MS, et al. Developmental Relationships of Four Exhausted CD8+ T Cell Subsets Reveals Underlying Transcriptional and Epigenetic Landscape Control Mechanisms.*Immunity* . 2020;52(5):825-841.e8.

113. McLane LM, Abdel-Hakeem MS, Wherry EJ. CD8 T Cell Exhaustion During Chronic Viral Infection and Cancer. *Annu Rev Immunol* . 2019;37:457-495.

114. Sun P, Jin Q, Nie S, et al. Unlike PD-L1, PD-1 Is Downregulated on Partial Immune Cells in Type 2 Diabetes. *J Diabetes Res* . 2019;2019:5035261.

115. Zhou Y, Zhang H, Yao Y, Zhang X, Guan Y, Zheng F. CD4+ T cell activation and inflammation in NASH-related fibrosis. *Front Immunol* . 2022;13:967410.

116. Rattik S, Engelbertsen D, Wigren M, et al. Elevated circulating effector memory T cells but similar levels of regulatory T cells in patients with type 2 diabetes mellitus and cardiovascular disease.*Diab Vasc Dis Res* . 2019;16(3):270-280.

117. Solinas C, Gu-Trantien C, Willard-Gallo K. The rationale behind targeting the ICOS-ICOS ligand costimulatory pathway in cancer immunotherapy. *ESMO Open* . 2020;5(1):e000544.

118. Zhang HY, Ruan LB, Li Y, et al. ICOS/ICOSL upregulation mediates inflammatory response and endothelial dysfunction in type 2 diabetes mellitus. *Eur Rev Med Pharmacol Sci* . 2018;22(24):8898-8908.

119. Yang TT, Song SJ, Xue HB, Shi DF, Liu CM, Liu H. Regulatory T cells in the pathogenesis of type 2 diabetes mellitus retinopathy by miR-155.*Eur Rev Med Pharmacol Sci* . 2015;19(11):2010-2015.

120. Moschovaki Filippidou F, Kirsch AH, Thelen M, et al. Glucagon-Like Peptide-1 Receptor Agonism Improves Nephrotoxic Serum Nephritis by Inhibiting T-Cell Proliferation. *Am J Pathol* . 2020;190(2):400-411.

121. Ntika S, Jois H, Lång K, et al. Elevated Glucagon-like Peptide-1 and a Th2 Shift May Support Reduced Prevalence of Thoracic Aortic Aneurysm in Patients with Diabetes. *J Cardiovasc Dev Dis* . 2021;8(11):143.

122. He J, Dai P, Liu L, et al. The effect of short-term intensive insulin therapy on inflammatory cytokines in patients with newly diagnosed type 2 diabetes. *J Diabetes* . 2022;14(3):192-204.

123. Mahmoud M, Juntunen M, Adnan A, et al. Immunomodulatory Functions of Adipose Mesenchymal Stromal/Stem Cell Derived from Donors with Type 2 Diabetes and Obesity on CD4 T cells. *Stem Cells* . 2023;41(5):505-519.

124. Zha J, Chi XW, Yu XL, et al. Interleukin-1β-Targeted Vaccine Improves Glucose Control and β-Cell Function in a Diabetic KK-Ay Mouse Model. *PLoS One* . 2016;11(5):e0154298.

125. Tan CL, Kuchroo JR, Sage PT, et al. PD-1 restraint of regulatory T cell suppressive activity is critical for immune tolerance. *J Exp Med* . 2021;218(1):e20182232.

126. Touch S, Clément K, André S. T Cell Populations and Functions Are Altered in Human Obesity and Type 2 Diabetes. *Curr Diab Rep* . 2017;17(9):81.

127. Godfrey DI, Uldrich AP, McCluskey J, Rossjohn J, Moody DB. The burgeoning family of unconventional T cells. *Nat Immunol* . 2015;16(11):1114-1123.