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Review

Metabolic hallmarks of type 2 diabetes compromise T cell function

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Type 2 diabetes (T2D) manifests as profound systemic metabolic dysregulation. Mounting evidence indicates T2D significantly impairs T cell immunity, compromising both protective immune responses and immune homeostasis. This dysfunction stems from the multitude roles of metabolites in T cell biology: energy substrates, signaling molecules, and epigenetic regulators. In this review, we synthesize current evidence on how the metabolic hallmarks of T2D (hyperglycemia, hyperinsulinemia, and dyslipidemia) reprogram T cell metabolism and their functionalities. Notably, most patients with T2D receive combination antidiabetic therapies which not only correct systemic metabolism but also exert direct immunomodulatory effects on T cells. Unraveling the interplay between disease-driven metabolic perturbations and pharmacologically induced immunomodulation is essential to advance therapeutic strategies that restore immune competence while preserving immunoregulatory balance.

Highlights

Type 2 diabetes (T2D) metabolically impairs T cell protective immunity and immune homeostasis.

The response of T cells to metabolic stress varies depending on their subsets and differentiation stages.

Hyperglycemia, hyperinsulinemia, and dyslipidemia precondition T cells to exhibit proinflammatory traits. Yet, during immune challenges, T2D-conditioned T cells display significant functional impairment.

Antidiabetic drugs can directly impact T cell metabolic rewiring and function.

T2D metabolically impairs T cell function

T2D is a chronic inflammatory disease characterized by systemic metabolic dysregulation, including hyperglycemia, hyperlipidemia, hyperinsulinemia, and bile acid alterations [1,2]. While chronic metabolic stress and inflammatory environment (Box 1) lead to well-documented complications including diabetic retinopathy, nephropathy, neuropathy, and cardiovascular diseases, their impact on the immune system, particularly T cells, remains less thoroughly characterized. Patients with T2D, especially those with poor glycemic control, exhibit increased susceptibility and severity during bacterial and viral infections, along with impaired vaccine responses [3–6]. Similarly, these patients demonstrate higher incidence of various malignancies and diminished responses to **immune checkpoint blockade (ICB)** (see Glossary) therapy [7,8]. At the cellular level, patients with T2D show increased circulating **senescent T cells**, elevated Th17/Treg ratios, impaired Th1 polarization during viral infection, and exacerbated **T cell exhaustion** in the **tumor microenvironment (TME)** [9–13]. These clinical observations collectively suggest underlying T cell defects in patients with diabetes.

T cells are highly sensitive to their metabolic environment, with nutrients increasingly recognized as the fourth signal determining T cell differentiation and function, complementing the established roles of T cell receptor (TCR) signaling, co-stimulation, and cytokines [9–12]. Beyond providing energy for activation and memory formation, metabolites also function as signaling propagators, signaling intermediates, and epigenetic modifiers, closely regulating T cell function.

Notably, one of the key characteristics of T cells is their metabolic diversity (Box 2), with different subsets and differentiation states exhibiting distinct metabolic adaptations. This diversity explains why seemingly contradictory patterns on different T cell subsets may emerge throughout this review, which reflects the intrinsically heterogeneous responses to the complex metabolic

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Box 1. Chronic inflammatory cytokines and T cells

Persistent hyperglycemia, free fatty acid (FFA) accumulation, and other metabolic abnormalities stimulate pro-inflammatory factor elevation in T2D. Among these, TNF-α and IL-6 stand out as well-recognized cytokines upregulated in T2D that are abundantly produced in adipose tissue and contribute significantly to insulin resistance [2,102]. IL-6 functions as a key regulator of $CD4^+$ T cell differentiation, with context-dependent effects[103] (Figure I). In TGF-β-deficient environments, IL-6 influences Th1/Th2 differentiation by favoring Th2 development [103]. While in TGF-β-rich settings, it promotes Th17 lineage commitment through JAK–STAT3 signaling – potentially explaining the elevated Th17 populations observed in patients with T2D [103,104]. IL-6 also regulates $CD8^+$ T cell function, which was shown to activate JAK–STAT3 signaling and impair effector differentiation $CD8^+$ T cells within the TME [105]. Whether similar immunosuppressive mechanisms can be observed within the IL-6-enriched diabetic milieu remains an important question awaiting further investigation.

Alongside IL-6, TNF-α represents another critical inflammatory mediator in the diabetic microenvironment with significant implications for T cell function [106] (Figure I). While T cells represent major sources of TNF-α production, they simultaneously respond to this cytokine in temporally and subset-specific manners. Early during T cell priming, TNF-α reinforces survival and clonal expansion via NF-κB-dependent mechanisms [106]. However, this supportive effect reverses during terminal differentiation stages, when TNF-α triggers apoptotic machinery through caspase activation [106]. The effects of TNF-α further diverge across T cell subpopulations, generally reinforcing proinflammatory subset development while suppressing regulatory T cell function [106]. Recent study in the context of rheumatoid arthritis reveals that beyond two conventional signaling mentioned above, TNF-α also activates mTORC signaling in activated T cells, which enhances glycolytic metabolism [107]. This metabolic shift disadvantages Treg cell development while facilitating Th1/Th17 polarization (Box 2), further exacerbating chronic inflammation.

Collectively, these findings underscore the pleiotropic nature of both IL-6 and TNF-α in T cell regulation. Future research aimed specifically at deciphering their multifaceted roles within the complex inflammatory and metabolic landscape of T2D is required to develop cytokine-based therapies to modulate T cell function in different contexts.

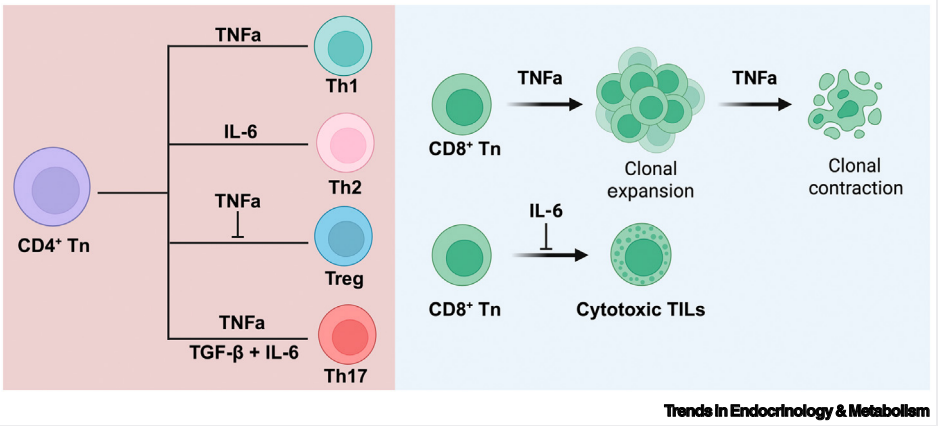

Figure I. Modulation of T cell function by two major chronic inflammatory cytokines. Abbreviations: IL-6, interleukin 6; TGF-β, transforming growth factor beta; Th1, T helper 1 cell; Th2, T helper 2 cell; Th17, T helper 17 cell; TILs, tumor-infiltrating lymphocytes; Tn, naïve T cell; TNFa, tumor necrosis factor α; Treg, regulatory T cell.

perturbations in T2D. Such heterogeneity may also limit the efficacy of many antidiabetic medications to restore T cell immunity in patients with T2D, since they function as effective metabolic rewirers but lack subset-specific targeting precision. Understanding subset-specific responses to altered metabolic environment and to antidiabetic drugs carries significant clinical implications. This knowledge will enable more refined interventions, either through developing new drugs or optimizing dosage regimens of current medications, to restore T cell immunity while maintaining immune homeostasis in patients.

In this review, we first examine how four metabolic hallmarks of T2D influence the differentiation and function of various T cell subsets. Subsequently, we analyze the direct effects of five major classes of antidiabetic medications on T cell function and assess their potential repurposing to

Glossary

Glycated hemoglobin (HbA1c): form of hemoglobin that becomes chemically linked to glucose over time, with higher levels indicating poorer blood sugar management. It is a key diagnostic and monitoring tool for diabetes and prediabetes.
Immune checkpoint blockade (ICB): therapeutic strategy that uses antibodies to inhibit immune checkpoint proteins (such as PD-1, PD-L1, or CTLA-4) that normally suppress T cell activation.
Lipid peroxidation (LPO): chain reaction process in which reactive oxygen species attack polyunsaturated fatty acids in cell membranes, generating toxic aldehydes and other oxidative products.
Myeloid-derived suppressor cells (MDSCs): diverse group of immature myeloid cells that expand in cancer. They suppress T cell- and NK cell-mediated antitumor immunity and are categorized into two main subsets: polymorphonuclear and monocytic.
Receptor for advanced glycation end-products (RAGE): multiligand receptor that binds to advanced glycation end-products formed by nonenzymatic glycation of proteins and lipids under hyperglycemic conditions.
Regulatory T cells: defined by the expression of the lineage-specifying transcription factor Foxp3. These cells play a crucial role in preserving immune tolerance and ensuring immune homeostasis.
Senescent T cells: aged or functionally impaired T cells that are characterized by telomere shortening and altered DNA methylation. These cells lost the ability to proliferate but remain cytotoxic.
T cell exhaustion: state of T cell dysfunction that occurs due to persistent antigenic exposures in chronic infections, cancer, and other chronic inflammatory diseases.
T helper 1 (Th1): defined by the expression of the lineage-specifying transcription factor T-bet and characterized by the production of IFNγ. These cells play a crucial role in cellular response against intracellular pathogens, like viruses.
T helper 17 (Th17): defined by the expression of the lineage-specifying transcription factor RORγT and characterized by their production of IL-17. These cells play a crucial role in the immune response to extracellular bacteria and fungi, as well as in the development of autoimmune diseases.

restore T cell immunity in T2D patients and broader populations. This comprehensive analysis represents the first systematic review of this timely intersection, driven by two converging clinical trends: the rapidly escalating global prevalence of T2D, now affecting >500 million individuals worldwide, and the concurrent expansion of T cell-based immunotherapy applications across diverse cancer types and autoimmune conditions [13–15]. As immunotherapeutic interventions become standard care for an increasing number of patients, understanding how T2D-associated metabolic dysfunction compromises immune responses has become critically important for optimizing treatment outcomes in this substantial and growing patient population.

Tumor microenvironment (TME): complex, dynamic ecosystem within tumors, comprising both cellular and noncellular elements that interact with cancer cells.

Hyperglycemia disrupts multiple T cell subsets

Naïve $CD4^+$ T cells in diabetic individuals exhibit an exaggerated response to initial TCR stimulation. Mechanistically, hyperglycemia promotes **receptor for advanced glycation end-products (RAGE)**-mediated chromatin decondensation, thereby enhancing transcription factor accessibility to DNA and amplifying proliferation following TCR engagement [16]. However, this heightened initial activation does not always translate into optimized effective protective immunity.

Hyperglycemia directly impacts $CD4^+$ T cells functionality (Figure 1). By stratifying patients by glycemic control [17], it emerged that $CD4^+$ T cells from poorly controlled patients (**hemoglobin A1c; HbA1c** ≥8) fail to differentiate into functional Th1 cells despite robust initial TCR signaling. In contrast, Th1 differentiation capacity remains comparable between healthy controls and patients with well-controlled T2D (HbA1c <8). This defect is linked to hyperglycemia-induced **lipid peroxidation (LPO)**, which triggers carbonylation of STAT4 – a transcription factor critical for Th1 lineage commitment. Such irreversible protein modification accelerates STAT4 degradation,

Box 2. Metabolic diversity of T cell subsets

The metabolic diversity of T cells stems from two fundamental dimensions: their lineage diversity and differentiation stage [9–12]. Lineage diversity encompasses both $CD8^+$ and $CD4^+$T cells, with the latter further diversifying into specialized subsets including **T helper 1 (Th1)**, T helper 2 (Th2), **T helper 17 (Th17)**, **regulatory T cells** (Tregs), and T follicular helper (Tfh) cells. Simultaneously, each lineage progresses through distinct differentiation phases – from naïve to effector to memory states – with each transition requiring unique metabolic reconfiguration to support stage-specific immunological functions (Figure I).

Naïve T cells exist in a relatively metabolic-quiescent state [11]. Upon TCR activation, $CD8^+$ T cells undergo active metabolic rewiring through PI3K/Akt/mTORC pathways and cMyc upregulation. This accelerates glucose uptake and prioritizes aerobic glycolysis along with glutamine utilization, fueling the robust proliferative burst essential for immune defense. During this expansion, asymmetric division occurs, where daughter cells with attenuated mTORC signaling differentiate toward memory phenotypes. These memory precursors subsequently downregulate glycolysis and primarily rely on mitochondrial respiration for long-term persistence. Enhanced mitochondrial biogenesis and fusion increase spare respiratory capacity and cristae area of memory cells, preparing them for rapid energy generation during recall responses.

While inflammatory $CD4^+$ T cell subsets (Th1, Th2, and Th17) generally follow similar metabolic trajectories, noteworthy distinctions exist between T cell populations [11]. For instance, glucose uptake in $CD4^+$ T cells predominantly depends on GLUT1, while $CD8^+$ T cells demonstrate greater flexibility in glucose transporter utilization, with GLUT2 playing a significant role in $CD8^+$ but not $CD4^+$ T cells [108]. Within $CD4^+$ T cells, Th17 cells also exhibit a unique metabolic profile, preferentially engaging in *de novo* fatty acid synthesis mediated by ACC1 – a process indispensable for RORγt-mediated transcriptional programming [11].

In contrast with the proinflammatory populations, Treg cells pursue a distinctly different metabolic trajectory [11]. When activated, Treg cells actively restrain PI3K/mTORC pathways by PTEN and AMPK activation to preserve Foxp3 expression and suppressive capabilities. The activation of AMPK further promotes FAO while suppressing ACC1-mediated FAS that would otherwise favor Th17 development. This metabolic divergence represents an intricate evolutionary solution, where distinct metabolic programs effectively segregate proinflammatory from anti-inflammatory responses.

In summary, T cell metabolism demonstrates remarkable diversity across subsets and differentiation states. This complexity necessitates careful consideration when investigating how metabolic perturbations in T2D affect different T cell populations, as each subset may respond uniquely to the metabolic microenvironment.

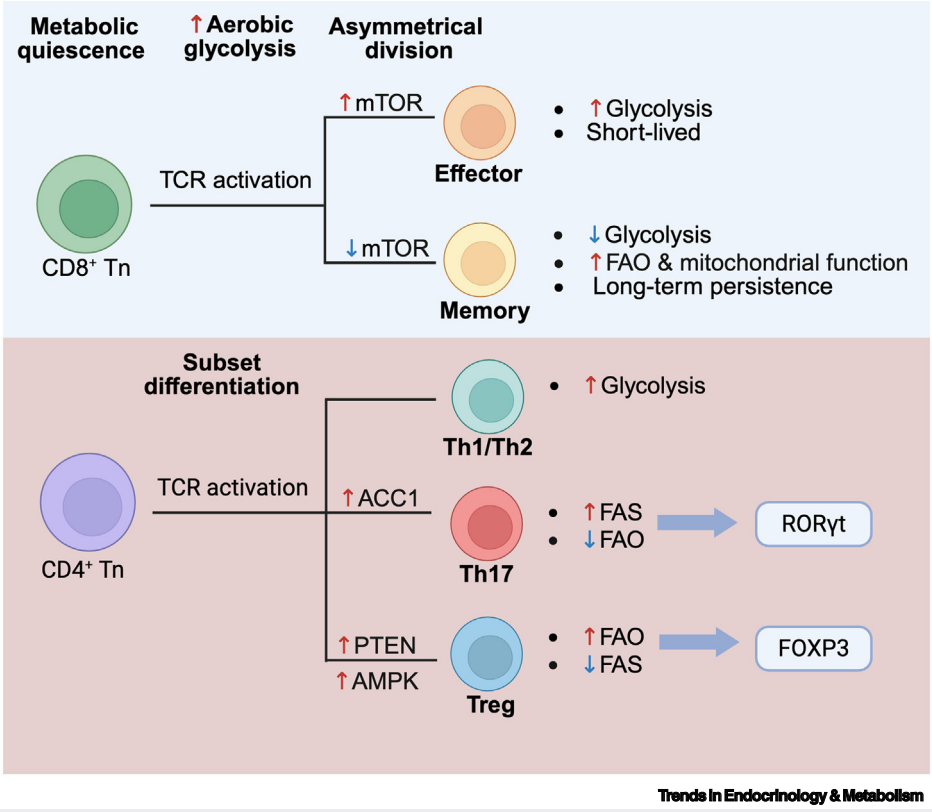

Figure I. Metabolic diversity of T cell subsets. Abbreviations: ACC1, acetyl-CoA carboxylase 1; AMPK, AMP-activated protein kinase; FAO, fatty acid oxidation; FAS, fatty acid synthesis; FOXP3, forkhead box P3; mTOR, mechanistic target of rapamycin; PTEN, phosphatase and tensin homolog; RORγt, retinoic acid-related orphan receptor γt; TCR, T cell receptor; Th1, T helper 1 cell; Th2, T helper 2 cell; Th17, T helper 17 cell; Tn, naïve T cell; Treg, regulatory T cell.

leading to diminished Th1 differentiation. Consequently, this hyperglycemia-mediated metabolic disruption in $CD4^+$ T cells compromises antiviral immunity, rendering patients with T2D more susceptible to severe viral infections.

Hyperglycemia not only suppresses protective antiviral $CD4^+$ T cell immunity but also promotes detrimental Th17 polarization (Figure 1) [18]. In mouse models of colitis and experimental autoimmune encephalomyelitis (EAE), elevated glucose uptake by $CD4^+$ T cells increases mitochondrial reactive oxygen species (mROS) production. This surge in mROS facilitates the cleavage of latent transforming growth factor (TGF)-β, leading to higher levels of active TGF-β in the microenvironment. The increased availability of active TGF-β, in combination with IL-6, enhances Th17 cell differentiation and exacerbates inflammation [18]. While this mechanism has been implicated in autoimmune models, whether it contributes to the observed elevation of Th17 cells in humans remains to be demonstrated.

Accompanied by increased Th17 polarization, hyperglycemia also impairs Treg cell differentiation and suppressive function, further disrupting immune homeostasis (Figure 1). Unlike conventional T cells, activated Treg cells actively suppress PI3K/Akt/mTOR pathways and cMyc expression to downregulate glycolysis while extensively utilizing fatty acid oxidation (FAO), which is essential for maintaining their phenotypic stability (Box 2). Forced enhancement of glucose uptake, such as

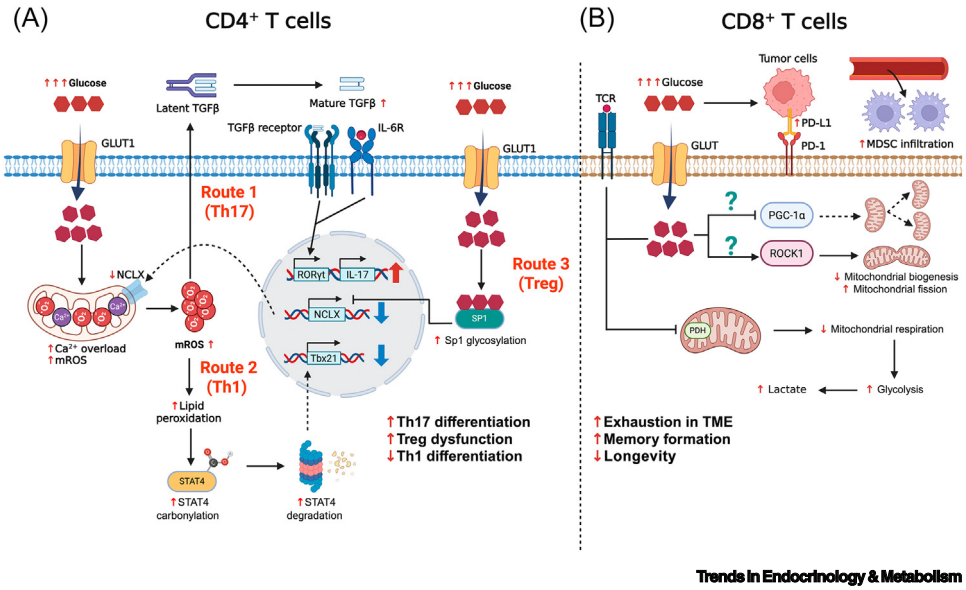

Figure 1. Hyperglycemia and T cell function. (A) In CD4$^+$ T cells, type 2 diabetes induces subset-specific dysregulation through distinct metabolic pathways. Route 1: hyperglycemia stimulates mROS generation, which facilitates cleavage of latent TGF-β into its mature form. This process, combined with elevated IL-6, enhances Th17 polarization. Route 2: hyperglycemia-induced mROS production increases lipid peroxidation, resulting in STAT4 carbonylation and subsequent proteasomal degradation. Diminished STAT4 levels reduce T-bet expression, thereby impairing Th1 differentiation. Route 3: hyperglycemia promotes Sp1 glycosylation, inhibiting NCLX expression. Reduced NCLX at the mitochondrial membrane causes mitochondrial calcium overload, compromising Treg cell fitness and function. (B) In CD8$^+$ T cells, hyperglycemia creates a hostile microenvironment that accelerates exhaustion, characterized by enhanced MDSC recruitment and PD-L1 overexpression on tumor cells. Additionally, hyperglycemia promotes mitochondrial fission while inhibiting mitochondrial fusion and respiration, significantly impairing T cell longevity and increasing susceptibility to exhaustion. Abbreviations: GLUT1, glucose transporter 1; IL-17, interleukin 17; IL-6R, interleukin-6 receptor; MDSC, myeloid-derived suppressor cell; mROS, mitochondrial reactive oxygen species; NCLX, mitochondrial Na^+/Ca^{2+} exchanger; PD-L1, programmed death-ligand 1; PDH, pyruvate dehydrogenase; PGC1α, peroxisome proliferator-activated receptor γ coactivator 1-α; RORγt, RAR-related orphan receptor γ t; ROCK1, rho-associated coiled-coil containing protein kinase 1; SP1, specificity protein 1; STAT4, signal transducer and activator of transcription 4; Tbx21 (T-bet), T-box transcription factor TBX21; TCR, T cell receptor; TGFβ, transforming growth factor β; Th1, T helper 1 cell; Th17, T helper 17 cell; TME, tumor microenvironment; Treg, regulatory T cell. Figure created with BioRender.

through GLUT1 overexpression, skews CD4$^+$ T cell differentiation toward effector phenotypes [19]. In the context of neuroinflammation, elevated glucose levels trigger mitochondrial calcium overload in Treg cells that compromises their suppressive function [20]. This subsequently promotes proinflammatory polarization of microglia, exacerbating neuroinflammation and contributing to cognitive impairment in patients with T2D. Mechanistically, hyperglycemia enhances O-GlcNAcylation of transcription factor Sp1, which recruits histone deacetylase (HDAC)2 to the promoter region of the sodium/lithium/calcium exchanger (NCLX) gene to suppress its expression. NCLX functions as a calcium efflux pump on the mitochondrial membrane; its reduced expression results in calcium accumulation and consequent mitochondrial dysfunction in Treg cells. The suppressive effect of glucose on Treg cells is dose dependent [21]. Moderate glucose supplementation (6% w/v) in murine diets induces intestinal Treg cell differentiation and alleviates intestinal inflammation, whereas high glucose concentrations (20% w/v) exacerbate autoimmune colitis. This underscores the importance of stratifying patients by glycemic control status in T2D research.

Additionally, hyperglycemia also impairs CD8$^+$T cell responses (Figure 1), manifested as diminished memory recall against viral infection and heightened exhaustion within the TME [22,23]. Functional memory CD8$^+$ T cells require a tightly regulated shift from aerobic glycolysis to FAO

and enhanced mitochondrial oxidative phosphorylation (Box 2). Hyperglycemia enforces excessive glycolytic activity in chimeric antigen receptor (CAR)-T and TCR-T cells and prevents the glycolysis to FAO shift, reducing their persistence in tumors [24]. Memory T cells rely on mitochondrial remodeling – including increased biogenesis, fusion, and cristae expansion – to stabilize the electron transport chain (ETC) and enable rapid ATP production upon reactivation [11]. While the direct effects of hyperglycemia on mitochondrial homeostasis in $CD8^+$T cells remain unclear, parallels can be drawn from its impact on other cell types: hyperglycemia reduces PGC-1α (a master regulator of mitochondrial biogenesis) in $CD4^+$ T cells, and induces ROCK1-dependent mitochondrial fission in podocytes [17,25].

Dysregulated metabolic rewiring and aberrant mitochondrial remodeling are hallmarks of exhausted $CD8^+$ T cells [26–28]. Hence, while hyperglycemia disrupts $CD8^+$ T cell memory formation in infections via metabolic dysregulation, it potentially promotes exhaustion in the TME through similar dysfunction. In addition, hyperglycemia also acts as a potent remodeler of the TME. As detailed elsewhere [29], elevated glucose increases tumor cell PD-L1 expression, intensifies hypoxia, and recruits immunosuppressive cells [e.g., Treg cells, **myeloid-derived suppressor cells (MDSCs)**], creating a hostile niche that accelerates $CD8^+$ T cell dysfunction. Thus, hyperglycemia impact tumor-infiltrating $CD8^+$ T cells through both intrinsic metabolic disruption and extrinsic TME remodeling. Delineating these mechanistic details in the future will be critical for developing therapeutic strategies to restore $CD8^+$ T cell function against cancers in patients with T2D.

Hyperinsulinemia shapes T cell responses

Chronic hyperinsulinemia represents a feedback mechanism triggered by peripheral insulin resistance and stands as a hallmark of T2D [2]. Notably, insulin receptors (INSRs) are upregulated on activated T cells, which primarily engage the PI3K/AKT/mTORC signaling cascades – largely overlapping with the CD28-driven co-stimulatory signals [30,31]. Thus, it is not surprising that insulin may enhance T cell activation and subsequent effector responses. Indeed, several studies have consistently demonstrated that T cell-specific insulin receptor knockout directly impairs antigen-specific $CD4^+$ and $CD8^+$ T cell formation and subsequent viral clearance in acute infection [30,31]. Virus-induced IFN-γ secretion promotes skeletal muscle insulin resistance and feedback hyperinsulinemia, serving as a natural defensive response to increase T cell antiviral immunity [31]. However, how chronic hyperinsulinemia affects T cell responses remains largely unexplored.

Downstream insulin signaling potently suppresses FOXO1 activity to inhibit gluconeogenesis and glycogenolysis to decrease blood glucose levels [32]. Beyond this metabolic role, FOXO1 orchestrates T cell self-renewal and persistence by controlling the expression of stemness genes, particularly *TCF1* [33]. Two recent independent studies have demonstrated that FOXO1 overexpression in CAR-T cells enhances their memory formation and metabolic fitness, ultimately strengthening tumor control [34,35]. This suggests that chronic hyperinsulinemia-induced FOXO1 suppression might compromise memory T cell generation and persistence in patients with T2D. However, this proposition conflicts with findings in high-fat diet mice infected with mCMV-N4, where hyperinsulinemia minimally affected T cell memory formation [22]. Notably, activated T cells from patients with T2D exhibit insulin resistance [36]. This raises a critical paradox: while systemic hyperinsulinemia may suppress FOXO1, T cell insulin resistance may blunt the INSR signaling efficacy. Thus, determining how chronic hyperinsulinemia – amidst T cell insulin resistance – shapes T cell responses in patients remains essential.

Notably, insulin also regulates Treg cell function, specifically adipose-residing Treg cells [37]. Obesity or age-associated hyperinsulinemia drives the differentiation of $CD73^{hi}ST2^{lo}$ Treg cells

to CD73^{lo}ST2^{hi} Tregs in adipose tissues – a phenotypic shift that is completely abolished in Foxp3^{cre}Insr$^{flox/flox}$ mice, demonstrating the importance of insulin in regulating Treg cell differentiation. Mechanistically, INSR signaling promotes HIF1α activation, which forms a transcription complex with Med23 to mediate PPARγ expression. The upregulated PPARγ suppresses CD73 and promotes the transition into

CD73^{lo}ST2^{hi} adipose-residing Treg cells. Compared to CD73^{lo}ST2^{hi} Treg cells, the CD73^{hi}ST2^{lo} population more effectively suppresses the proliferation and effector function of T effector (Teff) cells by secreting higher levels of immunosuppressive adenosine. Additionally, CD73^{hi}ST2^{lo} Treg cells also promote beige fat thermogenesis by maintaining high IL-33 signaling in fat tissues. Thus, depletion of this CD73^{hi}ST2^{lo} population under hyperinsulinemia conditions further intensifies insulin resistance by exacerbating adipose inflammation and impairing beige thermogenesis. This subsequently promotes more insulin secretion, highlighting the underlying vicious cycle.

Dyslipidemia skews T cell responses via high-density lipoprotein (HDL) loss and oxidized lipid accumulation

Although many diabetes patients are obese, which can independently impair T cell function (Box 3), diabetes itself can also cause dyslipidemia - a metabolic complication that arises from prolonged hyperglycemia and insulin resistance. Diabetic dyslipidemia is characterized by elevated level of triglycerides and reduced HDL [38]. Additionally, although low-density lipoprotein (LDL) level is not significantly altered in patients with T2D, a qualitative shift towards small dense LDLs that are more susceptible to oxidation is observed, resulting in a higher oxidized LDL (oxLDL) level in patients [39].

The anti-inflammatory role of HDL on CD4$^+$ T cells are well characterized and has been reviewed [40]. Apolipoprotein (APO)A and APOE on HDL particles directly bind to CD4$^+$ T cells, inhibiting downstream proinflammatory signaling cascades that regulate activation, proliferation, and Th1/Th17 differentiation [41–43] (Figure 2). APOE could facilitate cholesterol efflux from dendritic cells, subsequently reducing their secretion of IL-1β and IL-18, creating an additional barrier to CD4$^+$ T cell activation [44,45]. Thus, in patients with T2D, significant reduction of HDL may promote a proinflammatory shift in CD4$^+$T cell polarization beyond hyperglycemia-induced effects, contributing to chronic inflammation. Notably, the impact of HDL on CD8$^+$ T cells remains largely unexplored, and further investigations are needed to elucidate how low HDL levels shape T cell behavior in T2D.

Elevated levels of oxLDLs in T2D may suppress adaptive T cell immunity, potentially through CD36-mediated mechanisms (Figure 2). As the major receptor for lipid uptake in CD8$^+$ T cells, CD36 has been implicated in divergent metabolic reprogramming in different T cell subsets. In CD8$^+$ T cells, CD36-mediated uptake of oxLDLs and free fatty acids trigger ferroptosis and accelerates T cell exhaustion [46,47]. In contrast, CD36 upregulation on Treg cells enhances their mitochondrial fitness and sustains their survival in the lactate-rich TME [48]. Although these findings were made in the context of cancers, their implications could extend to T2D. As the elevated levels of free fatty acids and oxLDL may similarly drive a dichotomous metabolic response, resulting in an increase in Treg/CD8$^+$ T cell ratio which contributes to impaired pathogen clearance and elevated cancer prevalence seen in patients with T2D.

Beyond exogenous lipid alterations, aberrant intrinsic lipid metabolism, including *de novo* cholesterol synthesis, FA synthesis and beta-oxidation, profoundly impacts T cell differentiation and functions [49–51]. For example, CD4$^+$ T cells in patients with T2D exhibit upregulated carnitine palmitoyltransferase (CPT)1, which shuttles FAs from the cytosol to the mitochondrial intermembrane space, while simultaneously downregulating expression of carnitine–acylcarnitine

Box 3. Obesity and T cell function

Obesity represents a well-established risk factor and comorbidity for T2D, with the underlying pathophysiological mechanisms comprehensively reviewed elsewhere[109]. Obesity and T2D exhibit numerous overlapping systemic dysregulations, encompassing dyslipidemia, chronic inflammation, insulin resistance, and gut microbiota dysbiosis. In agreement with the pivotal role of dyslipidemia and inflammatory cytokines in promoting proinflammatory differentiation of $CD4^+$ T cells, patients with obesity demonstrate elevated susceptibility to inflammatory diseases, particularly dermatological conditions such as atopic dermatitis and psoriasis[92,93]. Mechanistically, dysregulated PPARγ orchestrates compromised immune homeostasis in obesity. On the inflammatory arm, PPARγ activity becomes markedly suppressed in Th2 cells of HFD mice, thereby favoring more severe Th17-mediated immunopathology[93]. Concurrently, HFD selectively eliminates $PPAR\gamma^+$ skin resident Treg cells, which display enhanced CD36 expression and exhibit greater susceptibility to lipotoxic damage[92].

Nevertheless, obesity and T2D may exert differential effects on T cell-mediated antitumor immunity [8,110]. While patients with T2D exhibit diminished ICB responses, obesity correlates with enhanced ICB responses – a phenomenon termed the obesity paradox[110,111]. This highlights the critical role of hyperglycemia in mediating ICB resistance among patients with T2D and emphasizes the necessity of distinguishing the impacts of obesity and T2D on antitumor immunity. Vigilance must be maintained when utilizing HFD mouse models that simultaneously develop hyperglycemia[17]. To dissect the individual roles of obesity and hyperglycemia, administration of SGLT2i in HFD mice presents a suitable approach, since this intervention specifically ameliorates hyperglycemia while maintaining other metabolic features of obesity [112].

Hyperglycemia serves as the defining characteristic distinguishing obese patients with T2D from other obese individuals, whereas adipose-derived adipokines isolate the specific impact of obesity from other shared systemic influences in T2D patients [113]. Compared with healthy controls, nonobese patients with T2D exhibit unchanged levels of leptin, adiponectin, resistin, and visfatin [113]. Indeed, these adipokines critically modulate T cell function [114]. Among them, leptin and its downstream STAT3 signaling assumes a predominant function in orchestrating obesity-mediated inflammation and impaired tumor evasion [115–117]. In inflammatory disease contexts, leptin inhibits Treg cell proliferation while facilitating Th17 differentiation [116,117]. In breast tumor models, leptin promotes FAO and inhibits glycolysis in $CD8^+$ T cells, impairing their antitumor functions [115].

These observations underscore the intricate relationship between metabolic perturbations and T cell dysfunction across obesity and T2D. Future investigations should clarify these mechanistic differences and develop targeted therapeutic interventions recognizing their divergent T cell consequences.

translocase (CACT), which facilitates fatty acid transport into the mitochondrial matrix [51]. This metabolic imbalance culminates in fatty acid accumulation within the intermembrane space, ultimately driving preferential Th17 differentiation.

However, the intrinsic rewiring of lipid metabolism in other T cell subsets remains a critical knowledge gap with high clinical significance. For example, pharmacological ACC inhibition (ACCi) metabolically rejuvenates antitumoral response of $CD8^+$ T cells by enhancing FA utilization [52]; since insulin is a well-characterized ACC1 activator [53], insulin resistance induced by chronic hyperinsulinemia exposure may result in reduced ACC1 activity in $CD8^+$ T cells, potentially altering the pharmacodynamic profile of ACCi in patients with T2D. This highlights the importance of comprehensive studies coupling lipidomics, metabolic flux analysis, and functional assays to characterize T cell-specific lipid metabolism rewiring in T2D. Such investigations will enable novel actionable targets identification and personalized therapeutic approaches for patients with T2D.

Bile acid alterations modulate T cell function and differentiation

Bile acids (BAs), as lipid derivatives, also undergo significant alterations in T2D [54]. Hyperglycemia and dysregulated insulin signaling enhance the expression of two key hepatic enzymes: CYP7A1, the rate-limiting enzyme initiating BA synthesis, and CYP8B1, the 12a-hydroxylase which favors cholic acid synthesis over chenodeoxycholic acid [54]. These metabolic dysregulations contribute to elevated concentrations and a compositional shift of primary BAs pool among people with T2D. Additionally, recent large-scale shotgun metagenomic sequencing has revealed significantly altered gut microbiome in T2D [55]. These altered microbiota significantly modulated T cell function (Box 4), with one of the potential pathways being the modification

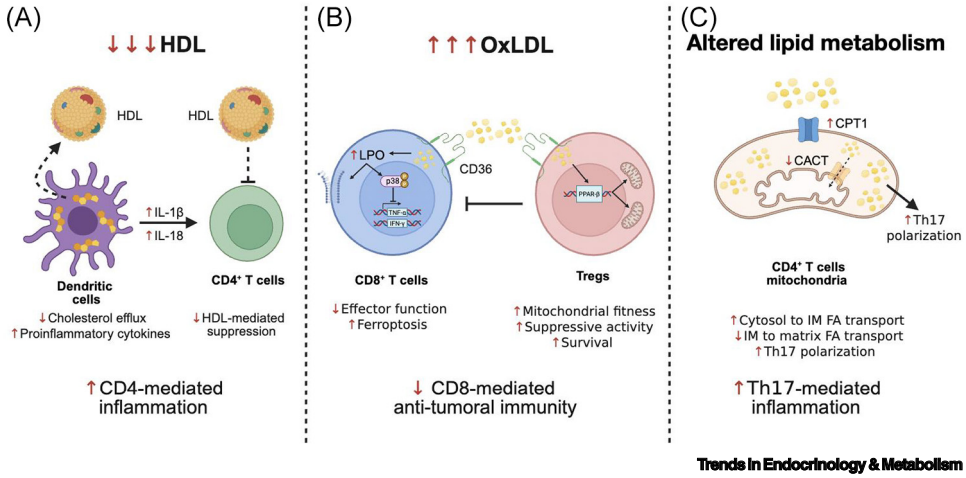

Figure 2. Type-2-diabetes-associated dyslipidemia and T cell functions. (A) Reduced HDL impairs APOA/E-mediated inhibition of $CD4^+$ T cell activation and diminishes cholesterol efflux from dendritic cells. The latter leads to increased IL-1β and IL-18 secretion and skewing $CD4^+$ T cells toward proinflammatory Th1/Th17 differentiation. (B) In the TME, uptake of oxLDL via CD36 in $CD8^+$ T cells triggers lipid peroxidation, leading to p38-driven effector function impairment and ferroptosis. However, for Tregs, CD36 upregulation enhances PPAR-β-driven mitochondrial fitness, promoting their suppressive activity and survival. (C) Intrinsic rewiring of $CD4^+$ T cell lipid metabolism also occurs – with upregulated carnitine palmitoyltransferase I (CPT1) and downregulated carnitineacyl carnitine translocase (CACT) – causing FA accumulation in the mitochondrial intermembrane space and drives Th17 polarization. Abbreviations: APOA/E, apolipoprotein A/E; CACT, carnitine–acylcarnitine translocase; CPT1, carnitine palmitoyltransferase I; FA, fatty acid; HDL, high-density lipoprotein; IFN, interferon; IL, interleukin; LDL, low-density lipoprotein; LPO, lipid peroxidation; oxLDL, oxidized low-density lipoprotein; p38, p38 mitogen-activated protein kinase; PPAR-β, peroxisome proliferator-activated receptor beta; TAG, triglycerides; TME, tumor microenvironment; TNF, tumor necrosis factor. Figure created with BioRender.

of the secondary BAs pool. For example, *Bacteroides fragilis*, whose bile salt hydrolase initiates secondary BAs synthesis, is more enriched in patients with T2D. This suggests concurrent elevation of secondary BAs production among patients, which closely aligns with recent metabolomic analyses and a previous clinical study demonstrating increased plasma levels of deoxycholic acid (DCA), a major secondary BA, in T2D [56,57].

Mounting evidence suggests BAs significantly but differentially modulate T cell functions, with effects varying by both bile acid species and T cell subsets. A recent study demonstrates that a primary BA, taurochenodeoxycholic acid (TCDCA), compromises $CD8^+$ T cell survival by inducing oxidative stress, while secondary BAs such as lithocholic acid promote T cell exhaustion through elevated endoplasmic reticulum stress in hepatocellular carcinoma [58]. DCA directly facilitates calcium efflux and undermines Ca^{2+}-NFAT signaling in $CD8^+$T cells, further corroborating the role of secondary BAs in T cells dysfunction [59]. Given that metabolomic profiling reveals elevated TCDCA and DCA levels in T2D [56,57,59], these alterations likely contribute to the observed $CD8^+$ T cell immunity defects.

Additionally, BAs play an important role in regulating colonic Treg/Th17 differentiation, specifically promoting the differentiation of $ROR\gamma^+$ Treg cells [60–62]. Considering the elevation of secondary BA pools, patients with T2D may harbor increased numbers of $ROR\gamma^+$ Treg cells in the gut. Under the steady state, $ROR\gamma^+$ Treg cells execute a beneficial immunomodulatory role in maintaining immune tolerance towards the mucosal barrier, consistent with recent bidirectional Mendelian randomization study showing patients with T2D possess a lower risk of ulcerative colitis [63]. However, under pathological conditions, such as in tumors, $ROR\gamma^+$ Treg cells more readily undergo Th17 polarization, paradoxically promoting inflammation and

Box 4. Gut microbiome alteration and T cell function in patients with T2D

The gut microbiome governs T cell differentiation and function through diverse mechanisms. Through local interactions, microbial polysaccharides direct the development of gut-resident Treg/Th17 cells, establishing peripheral tolerance to microbial communities and food antigens [67]. Systemically, microbes produce metabolites like short-chain fatty acids (SCFAs) – such as butyrate – that modulate distal T cell responses.

While mechanistic understanding of T2D-induced microbiome changes remains limited, advanced shotgun metagenomic sequencing has identified specific species alterations in patients [55] (Table I). The species with known T cell immunoregulatory role are summarized in Table I. In terms of local T cell differentiation, patients with T2D display increased levels of Treg cell-inducing species, including *Bifidobacterium bifidum* and *Bacteroides fragilis*, yet simultaneously exhibit elevated proinflammatory *Collinsella aerofaciens* and reduced anti-inflammatory *Faecalibacterium prausnitzii* [118–121]. For microbial metabolites, patients with T2D show diminished butyrate-producing species that promote T cell antitumoral response, yet also enriched in *Flavonifractor plautii* whose desaminotyrosine produced enhances anti-CTLA-4-mediated T cell activation[122,123]. This mosaicism underscores the necessity for functional studies to decipher the net impact of these microbial shifts on T cells in T2D.

While microbes actively regulate T cell peripheral tolerance, T cells reciprocally curate microbial communities to maintain homeostasis. Rather than following a linear causative pathway, T2D directly influences the T cell–microbiome coevolution. When T2D disrupts either gut-resident T cells (e.g., through aberrant bile acid production) or microbial communities, these effects self-amplify, culminating in dramatic shifts in the gut immunological landscape. Altered T cell differentiation, like elevated level of IL-10 producing Treg cells, may exacerbate insulin resistance [68], while dysbiosis can modulate diabetic status by altering SCFAs production or upregulating CD36 on intestinal epithelium to increase lipid absorption [124,125]. This interlocking triangle suggests a potential T2D–T–microbiome vicious cycle in T2D pathogenesis while also illuminating promising therapeutic feedback loop targeting the gut ecosystem. For example, microbiome-derived metabolites like butyrate simultaneously enhance $CD8^+$ T cell antitumor functions while improving insulin homeostasis [122,126,127]. The relief of T2D disease burden further contributes to improved T cell functions. This represents a promising synergy to restore T cell immunity and highlight the importance of relevant research on T2D–T–microbiome axis in patients with T2D.

Table I. Documented functions of gut microbiota species altered in T2D

T2D-enriched species	Direct impact on T cells
Bifidobacterium bifidum	Polysaccharides bind to TLR2 on dendritic cells (DCs), inducing the formation of regulatory DCs and subsequent $Foxp3^+$ Treg cells [119].
Bacteroides fragilis	Induce $Foxp3^+$ Treg cells through TLR2-dependent pathway [120].
Bacteroides thetaiotaomicron	Induce self-regulatory Teff and Treg cells to prevent colitis [128].
Flavonifractor plautii	Strongly suppresses Th2 immune responses in mice [129].
	Produce desaminotyrosine to enhance anti-CTLA-4-mediated T cell activation [123].
Streptococcus anginosus	*S. anginosus* infected gastric tumor shows an increased Th17/Treg ratio and elevated T cell exhaustion [130].
Ruminococcus gnavus	Capsular-negative *R. gnavus* promotes lamina propria $CD4^+$T cell activation and proinflammatory differentiation, while capsular-positive *R. gnavus* induces Treg cell differentiation [131].
Collinsella aerofaciens	Promotes Th17 differentiation and aggravate the condition of rheumatoid arthritis [121].
T2D-depleted species	
Barnesiella intestinihominis	Induces antitumoral $CD4^+$ Th1, $CD8^+$ Tc1 cells, and IFN-γ-producing γδ T cells to enhance the antitumoral efficacy of cyclophosphamide [132].
Roseburia intestinalis	Generates butyrate and directly binds to TLR5 receptor on $CD8^+$T cells to induce their effector differentiation and improve antitumoral response [122].
Bacteroides plebeius	Hinders T cell proliferation and effector cytokine secretion to impair antitumoral immunity [133].
Eubacterium rectale	Suppresses $TNFα^+$ $CD4^+$ and $CD8^+$ T cells to prevent TNFα-mediated B cell lymphomagenesis [134].
Faecalibacterium prausnitzii	Induces IL-10 secreting $Foxp3^-CD8^+CD4^+$ Treg cells to prevent inflammatory bowel diseases [118].
Odoribacter splanchnicus	Induces anti-inflammatory Th17 population to confer resistance against colitis and colorectal cancer [135].

tumorigenesis [64]. This may partially explain the higher risk and poorer prognosis of colon cancer observed in patients with T2D [65,66]. Furthermore, RORγ$^+$ Treg cells exhibit IL-10 secreting capability [67]. In adipose tissue, IL-10 secreted by Treg cells promotes insulin resistance and obesity [68]. Combined with recent research demonstrating that RORγ$^+$ Treg cells can translocate beyond the gut [69], a vicious cycle may emerge: intestinal RORγ$^+$ Treg cells translocate to adipose tissues, exacerbating insulin resistance, which subsequently stimulates bile acid secretion and promotes further RORγ$^+$ Treg cell differentiation. Collectively, these findings suggest the plasticity of Treg cell differentiation, function, and tissue distribution in response to BAs in patients with T2D and emphasize the critical need for future research in this domain.

Antidiabetic drugs and their impact on T cell immunity

Beyond metabolic dysregulation, T cell immunity in patients with T2D is significantly influenced by glucose-lowering medications. While normalization of the metabolic milieu inherently benefits T cell function, many of these medications directly regulate T cell signaling, differentiation, and effector functions (Table 1). Deciphering their direct T cell immunomodulatory effects is crucial to distinguish drug-induced from disease-related metabolic alterations and for comprehensively assessing treatment outcomes. This understanding also reveals promising opportunities to strategically repurpose antidiabetic drugs as targeted immuno-metabolic therapies and carries substantial clinical significance for optimizing dosage regimen in patients with T2D confronting concurrent immune challenges.

Metformin

Metformin, as the most commonly used glucose-lowering mediation in patients with T2D, alter cellular energetic status by inhibiting OXPHOS and subsequent activation of AMPK. The impact of metformin on T cell subsets was extensively studied and its beneficial T cell immunomodulatory roles have been found in the context of autoimmune diseases [70–72], infection [73–75], and malignancies [76–85].

Metformin mediates tumor shrinkage in a T cell-dependent manner, functioning as both a TME remodeler and an intrinsic modulator of T cell metabolism and signaling pathways to enhance antitumor responses [81]. T2D creates an immunosuppressive TME that promotes T cell exhaustion by elevating PD-L1 expression on tumor cells, establishing hypoxic conditions, and recruiting immunosuppressive MDSCs [29]. To counter these effects, metformin diminishes

Table 1. Summary of antidiabetic drug classes, their mechanism of action (MOA), and immunomodulatory effects on CD8$^+$ and CD4$^+$ T cells

Class	Antidiabetic MOA	Impact on CD8$^+$ T cells	Impact on CD4$^+$ T cells
Metformin	• ↓OXPHOS • ↓AMPK	• ↓Hostile TME (↓PD-L1, ↓hypoxia, ↓MDSCs) • ↓T cell exhaustion	• ↓Th17 polarization • ↓CD4 hyperactivation • ↓CD4 hyperactivation
SGLT2 inhibitors	• ↓proximal tubule glucose absorption	• ↑Ketogenesis • ↓Effector function in MASH • ↓PD-L1 in TME	• ↓TCR proximal signaling • ↓activation and effector function
TZD	• PPARγ agonist -> insulin sensitizer	• ↓Ferroptosis (?)	• ↑PPARγ$^+$ Treg cells and ↓adipose inflammation • ↓ LPO-mediated Th1 defect (?)
Incretin modulators	• ↑GLP-1/GIP -> ↑insulin secretion	• ↓TCR signaling of IELs and ↑gut mucosa homeostasis • ↑Negative co-stimulatory -> ↓Alloimmunity and ↓antitumoral immunity • ↓PMN-MDSCs recruitment in TME	• ↑Negative co-stimulatory • ↓Alloimmunity • ↓Antitumoral immunity
Sulfonylureas	• ↑Insulin secretion	Largely unknown	

tumor cell PD-L1 expression by accelerating endoplasmic reticulum-associated protein degradation and inhibiting cMyc/STAT3 signaling cascades while strategically reengineering the metabolic environment [76,78]. By inhibiting OXPHOS of tumor cells and normalizing the blood vasculature, metformin effectively mitigates intratumoral hypoxia [79,84]. The normalization of oxygen level and direct inhibition on HIF1α pathway further reduce the immunosuppressive CD39/CD73 expression on MDSCs, preventing T cell exhaustion [85]. Intrinsically, metformin enhances $CD8^+$ T cell function through dual mechanisms. At the transcriptional level, metformin suppresses miR-107 expression, consequently upregulating EOMES and reducing PD-1 expression on $CD8^+$ T cell surfaces [82]. Metabolically, metformin preserves $CD8^+$ T cell fitness by maintaining mitochondrial integrity, preventing ETC leakage, and limiting ROS accumulation – collectively protecting T cells from hypoxia-induced apoptosis and terminal exhaustion [77,83]. Conversely, metformin inhibits Treg cell differentiation and immunosuppressive function [80]. This dichotomous impact on $CD8^+$ T cells versus Treg cells likely stems from their different metabolic dependencies, where Treg cells predominantly rely on OXPHOS, while $CD8^+$ T cells preferentially engage glycoses upon activation [86].

Metformin promotes immune tolerance rather than immune activation in autoimmune diseases [70–72]. The anti-inflammatory role of metformin is through three distinct mechanisms: inhibiting proinflammatory Th17 differentiation via STAT3 suppression [71], metabolically constraining $CD4^+$ T cell hyperactivation by limiting OXPHOS [72], and suppressing IFN-stimulated gene transcription through STAT1 inhibition [70].

This context-dependent modulation suggests that metformin plays a critical role in maintaining T cell homeostasis in a disease-specific manner. However, significant questions remain regarding whether physiological doses of metformin can achieve optimal immunomodulation and whether dosage optimization could enhance therapeutic outcomes in different pathological contexts. For example, physiological metformin concentrations, rather than suppressing mitochondrial ROS production, facilitate mROS generation and activate downstream ROS-sensing pathways to boost T cell proliferation and IFN-γ secretion [87].

SGLT2 inhibitors

While SGLT2 inhibitors are known for their glucose-lowering effects via proximal tubule glucose reabsorption blockade, emerging evidence reveals direct immunomodulatory properties. For instance, empagliflozin binds to SGLT2, which is indeed moderately expressed on $CD8^+$T cells, and suppress their effector function in metabolic-associated steatohepatitis (MASH) [88]. Empagliflozin enhances 3-hydroxybutyrate dehydrogenase 1 expression within $CD8^+$ T cells, promoting T cell ketogenesis [88]. The resulting β-hydroxybutyric acid production interferes with nuclear translocation of IRF4, thereby attenuating $CD8^+$ T effector functions and alleviating MASH progression. Additionally, canagliflozin, through off-target inhibition on glutamine dehydrogenase and complex I, impairs TCR proximal signaling in both $CD8^+$ and $CD4^+$ T cells to ameliorate autoimmune pathology [89]. These findings collectively suggest an anti-inflammatory role for SGLT2 inhibitors in different disease settings.

Within the TME, canagliflozin blocks the interaction between PD-L1 and SGLT2, exposing E3-ligase targeting sites on PD-L1. This triggers the proteasomal degradation of PD-L1, thereby improving T cell-mediated antitumoral response [90]. However, the direct impact of SGLT2 inhibitors on T cell function within the TME remains largely unexplored, particularly whether these SGLT2i might directly impair T cell effector function similar to MASH and autoimmune contexts [88,89]. This understanding is crucial for optimizing therapeutic approaches in diabetic patients with cancer.

Thiazolidinedione

Thiazolidinedione (TZD) is a PPARγ agonist and a commonly used insulin sensitizer in patients with T2D. The role of PPARγ is best characterized in tissue-resident Treg cells, specifically adipose tissue and skin resident Treg cells [91,92]. In visceral adipose tissue, TZD promotes the accumulation and enhance the immunosuppressive function of PPARγ$^+$ Treg cells, thereby ameliorating inflammation-induced insulin resistance [91]. In skin, TZD restores PPARγ$^+$ Treg cell homeostasis in HFD mice models, directly counteracting IL17A$^+$γδ T cell-mediated inflammation and attenuating psoriasis [92]. Synergistically, TZDs can also promote Th2 differentiation in skin and suppress aberrant Th17 differentiation, thereby preventing the subsequent severe immunopathology [93].

Notably, in addition to their roles as PPARγ agonists, rosiglitazone and pioglitazone are also effective ACSL4 inhibitors [94]. ACSL4 converts polyunsaturated fatty acids (PUFAs) to PUFA-CoA species, served as the most important initiator for LPO [95]. By suppressing this pathway, TZDs potentially counteract LPO-driven suppression of Th1 polarization and prevent ferroptotic cell death in tumor-infiltrating CD8$^+$ T cells [17,47]. This dual mechanism positions TZDs as synergistic agents to augment both CD4$^+$ and CD8$^+$ T cell-mediated immunity. Future research is required to elucidate the immunoprotective effects of TZDs beyond their established metabolic benefits.

Incretin modulators

Incretins, including glucagon-like peptide (GLP)-1 and glucose-dependent insulinotropic peptide (GIP), enhance insulin secretion and inhibit glucagon release by binding directly to pancreatic beta cells, effectively lowering blood glucose. This physiological mechanism has been harnessed therapeutically through DPP4 inhibitors that prevent incretin breakdown and GLP-1/GIP receptor agonists – both representing potent glucose-lowering medication classes.

GLP-1 receptor (GLP-1R) expression extends beyond pancreatic tissue to T cells, with its function first characterized in natural gut intraepithelial lymphocytes (natural IELs) [96]. Studies involving IEL-depleted mice and those reconstituted with Glp1r-KO bone marrow chimeras demonstrated significantly elevated plasma GLP-1 levels and resistance to various metabolic disorders [96]. However, more precise investigations using Glp1r T cell conditional knockout mice revealed that rather than maintaining glucose homeostasis, GLP-1R on IELs primarily suppresses TCR signaling through PKA activation to help maintain immune homeostasis in gut mucosa [97].

Beyond intestinal tissues, GLP-1R expression has been detected on ~6% of CD4$^+$ T cells and 28% of CD8$^+$ T cells in human peripheral blood mononuclear cells (PBMCs) [98]. Functionally, GLP-1R acts as a negative co-stimulatory molecule that attenuates alloimmunity and impairs antitumor immunity. This immunosuppressive effect parallels recent observations that PGE2 signaling, whose pathways largely overlap with GLP-1R signaling, impairs Teff cell function in the TME, raising concerns about potential negative impacts of incretin-based therapies on antitumor immunity[99,100]. Conversely, some evidence indicates that GLP-1R can inhibit LCN2 secreted by tumor-infiltrating T cells. LCN2 is a chemoattractant for polymorphonuclear MDSCs (PMN-MDSCs). Thus, GLP-1R can reduce the infiltration of PMN-MDSCs, thereby enhancing antitumor immunity [101]. Given these conflicting effects, further investigation is essential to determine the overall impact of GLP-1R agonists and DPP4 inhibitors on T cell responses.

Concluding remarks

T2D presents a distinctive immunological paradox. The meta-inflammatory milieu of the disease (characterized by nutrient excess, lipotoxic metabolites, and chronic cytokines stimulation) drives

Outstanding questions

How do circulating T cells metabolically adapt to sustained high glucose exposure, and how do these pre-existing metabolic alterations compromise their activation potential and effector functions upon disease challenge?

Do metabolic microenvironments differ significantly across tissues in T2D? To what extent do these tissue metabolic niches differ from the circulatory metabolic environment? How do these tissue-specific metabolic alterations modulate the phenotype and function of tissue-resident and newly infiltrating T lymphocytes?

What are the molecular mechanisms leading to insulin resistance in T cells? Do these mechanisms diverge from the canonical insulin resistance pathways characterized in metabolic tissues such as skeletal muscle, liver, and adipose tissue? How does chronic hyperinsulinemia reprogram the intrinsic metabolic machinery and modulate the function of T cells?

What are the immunomodulatory effects of various T2D drug combinations on distinct T cell subpopulations, and do these effects synergize or antagonize to create unique immunometabolic signatures? Can the pharmacological properties of T2D therapeutics be leveraged or modified to selectively target specific T cell subsets, potentially offering precision immunotherapy options for patients with T2D?

T cell lineage skewing toward pathogenic Th17 polarization, while impairing the immunoregulatory capacity of adipose-resident Treg cells. This imbalance fuels a vicious cycle of tissue inflammation and systemic insulin resistance. Conversely, under immunogenic challenges (e.g., viral infections and malignancies), diabetic T cells exhibit profound functional impairments marked by defective Th1 differentiation and exacerbated T cell exhaustion. This dichotomy underscores the delicate challenge of balancing T cell activation and tolerance in patients with T2D.

However, several critical gaps remain in our understanding of T cell immunometabolism in T2D (see Outstanding questions). First, the molecular mechanisms underlying how circulating T cells metabolically adapt to sustained hyperglycemia, and how these adaptations subsequently compromise their responsiveness to immune challenges, require deeper investigation. Additionally, it remains unclear whether tissue-specific metabolic microenvironments in T2D create distinct immunometabolic niches that differentially program resident versus infiltrating T lymphocytes compared to the systemic circulation. Furthermore, while T cells develop insulin resistance in T2D, whether this occurs through canonical pathways identified in metabolic tissues or via T cell-specific mechanisms remains poorly understood.

The therapeutic implications of these knowledge gaps are particularly evident when considering antidiabetic medications. Certain drugs, such as metformin, demonstrate a unique ability to navigate the T cell activation–tolerance balance effectively, curbing excessive activation in autoimmune settings while enhancing functionality against cancer and mycobacterial infections. In contrast, incretin-based therapies present a dual-edged effect: while they excel in suppressing alloimmunity and autoimmunity, they may simultaneously compromise antitumor immune responses. However, our understanding of how various T2D drug combinations affect distinct T cell subpopulations, and whether these effects synergize or antagonize to create unique immunometabolic signatures, remains limited.

We envision the field evolving toward precision immunometabolic medicine, tailoring T2D treatment to individual immune profiles and disease susceptibilities. Critically, leveraging pharmacological properties of T2D therapeutics for subset-specific T cell targeting could offer precision immunotherapy options. Next-generation antidiabetic drugs with programmable immunomodulatory effects through targeted delivery or combination therapies represent an exciting frontier.

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Declaration of interests

All authors declare no competing interests.

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