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New Developments in T Cell Immunometabolism and Therapeutic Implications for Type 1 Diabetes

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Type 1 diabetes (T1D) is an autoimmune disease mediated by T cells and is becoming a serious public health threat. Despite the increasing incidence rate of T1D worldwide, our understanding of why T1D develops and how T cells lose their self-tolerance in this process remain limited. Recent advances in immunometabolism have shown that cellular metabolism plays a fundamental role in shaping T cell responses. T cell activation and proliferation are supported by metabolic reprogramming to meet the increased energy and biomass demand, and deregulation in immune metabolism can lead to autoimmune disorders. Specific metabolic pathways and factors have been investigated to rectify known deficiencies in several autoimmune diseases, including T1D. Most therapeutic strategies have concentrated on aerobic glycolysis to limit T cell responses, whereas glycolysis is the main metabolic pathway for T cell activation and proliferation. The use of metabolic inhibitors, especially glycolysis inhibitors may largely leave T cell function intact but primarily target those autoreactive T cells with hyperactivated metabolism. In this review, we provide an overview of metabolic reprogramming used by T cells, summarize the recent findings of key metabolic pathways and regulators modulating T cell homeostasis, differentiation, and function in the context of T1D, and discuss the opportunities for metabolic intervention to be employed to suppress autoreactive T cells and limit the progression of β-cell destruction.

Keywords: type 1 diabetes, T cell, T cell differentiation and function, T cell metabolism, autoimmunity

INTRODUCTION

T1D is a chronic immune-metabolic disease and is becoming a serious public health threat (1). Over the past three decades, the incidence of T1D has escalated worldwide, afflicting as many as 10 million people (2, 3). The pathogenesis of T1D is complicated, and available data suggest that T1D arises due to the combination of genetically determined susceptibility, environmental factors, and impairment of immunity, which eventually leads to the breakdown of immune tolerance to self (4, 5). It was demonstrated that autoreactive CD4+ and CD8+ T cells that infiltrate the islets of T1D

patients play a key role in the process of β-cell destruction (6, 7). Thus, those autoreactive T cells are regarded as a potential target for immune-based interventions aiming to combat T1D (8–11).

Recent advances in metabolomics, transgenic mice and immunometabolism have shown that metabolic adaptation plays a crucial role in shaping T cell responses (12–14). T cell activation is linked to metabolic reprogramming to meet the increased energy and biomass demand (15, 16). Binding of antigen to T cell receptor (TCR) initiates the activation of naïve T cells, which leads to a metabolic program shift from oxidative phosphorylation (OXPHOS) to robust aerobic glycolysis for rapid clonal proliferation and effector functions (17–19). In recent years, many exciting findings have uncovered novel metabolic pathways and key molecules that could be applied to improve the governance of autoimmunity and guide the treatment of autoimmune diseases (20). The use of metabolic inhibitors, especially glycolysis inhibitors, may largely leave T cell function intact but primarily target autoreactive T cells with hyperactivated metabolism (9, 20). This review aims to provide an overview of metabolic reprogramming used by T cells, summarize the recent findings of key metabolic pathways and regulators modulating T cell homeostasis, differentiation, and functions in the context of T1D, and discuss the opportunities for metabolic intervention to be employed to suppress autoreactive T cells and limit the progression of β-cell destruction.

METABOLIC REPROGRAMMING OF T CELLS IN T1D

The pathogenesis of T1D is mainly mediated by the activation of autoreactive CD4+ and CD8+ T cells, which are fueled by metabolic reprogramming (7, 21). Activated effector T cells are more metabolically active and engage mainly in aerobic glycolysis (22). The transition from naïve into effector T cells is driven by variations in anabolic and catabolic metabolism (23). Notably, researchers have reported that glycolysis is essential for cytotoxic T lymphocytes' function. Treatment of nonobese diabetic (NOD) mice with glycolysis inhibitors resulted in delayed T1D onset and protected β-cell mass (24). In addition, as part of the OXPHOS program, the movement of electrons generates a substantial amount of reactive oxygen species (ROS) (25). The role of ROS in controlling the differentiation of T cells by modulating metabolism has recently been described (21, 25–30). Investigators have shown that ROS can act as signaling molecules involved in the process of T cell activation, proliferation, and function (26). In T1D, ROS generation leads to the activation of autoreactive T cells and β-cell destruction (30). Regulatory T cells (Tregs) are key mediators of peripheral immune tolerance (31–33). Yet, in some autoimmune diseases, Tregs have been shown to have altered stability or function (32). Several researchers have confirmed that impaired Treg function, decreased Treg numbers, or the transition into Th1 (helper T cell 1)-like Treg, contributed to T1D development (33–38). Tregs have unique metabolic preferences that have not been characterized clearly (31, 39). It is generally recognized that Tregs preferentially use OXPHOS and fatty acid oxidation (FAO) for differentiation and function (35, 40, 41)(**Figure 1**).

METABOLIC INTERVENTIONS: A NEW OPPORTUNITY FOR T1D TREATMENT

Both mammalian target of rapamycin (mTOR) and AMP-activated protein kinase (AMPK) are metabolic sensors required for T cell proliferation and function (19, 42–44). Activation of AMPK inhibits

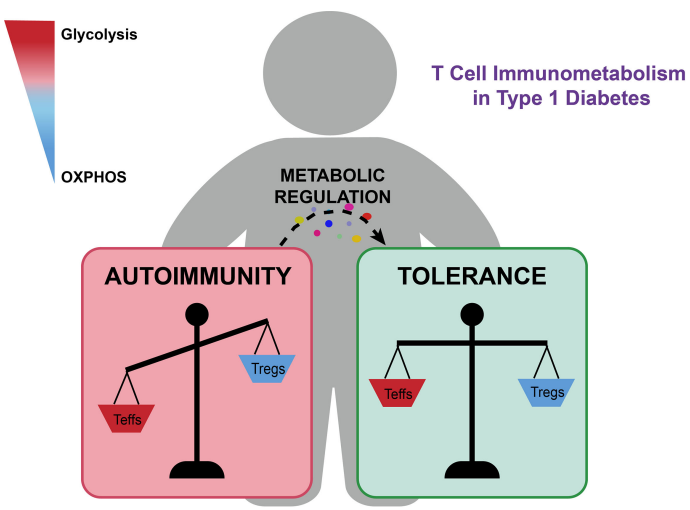

FIGURE 1 | The metabolic imbalance of autoreactive T cells and Tregs contributes to T1D development and progression. Glycolysis supports pro-inflammatory responses, while OXPHOS promotes anti-inflammatory responses and immune tolerance. Immunometabolism regulators of key metabolic pathways, such as metformin and PFK15, could suppress effector T cell responses and facilitate Treg expansion and function, which could provide a promising metabolic intervention strategy for limiting the progression of β-cell destruction and reversing pathologies of T1D.

anabolic metabolism, such as nucleic acid and lipid synthesis, but favors catabolic metabolism. In contrast, activation of mTOR signaling facilitates glycolysis, fatty acid production, and mitochondrial biogenesis (42, 45, 46). As mentioned above, autoreactive CD4+/CD8+ T cells exhibit a higher level of glycolysis and depend less on OXPHOS, thus suggesting that glycolysis could be used as an attractive therapeutic target (47). Inhibiting mTOR signaling with rapamycin or enhancing the AMPK signaling pathway with metformin are known to reduce glycolysis (19). Given the key role of AMPK in the activation of T cells, multiple studies have investigated the capacity of metformin to suppress autoimmune diseases, notably T1D. Metformin is now the first line of oral antidiabetic medicine and is used to regulate glucose metabolism (48). Mechanistically, metformin inhibits the mitochondrial electron transport chain (ETC) at Complex I and results in a reduction in intracellular ATP production (48–50). Furthermore, laboratory work demonstrated that metformin could reduce the expansion of activated T cells by inhibiting the expression of cellular myelocytomatosis oncogene (c-Myc) and hypoxia-inducible factor 1 alpha (HIF1-α) in an AMPK-independent way (51–53). Metformin exhibits a dose-dependent effect to control T cell proliferation and suppress the differentiation of Th1 and Th17 cells while enhancing Treg development *in vitro*. NOD mice treated with metformin showed alleviated autoimmune insulitis and reduced amounts of Th1 and Th17 cells in the spleens (50). Furthermore, the anti-inflammatory function of metformin has also been investigated in detail in mouse models of autoimmune arthritis, systemic lupus erythematosus and colitis, all of which portrayed a role of metformin as an anti-inflammatory coordinator and provided the rationale for possible islet protective properties (54–57). Currently, the REMOVAL study and some other smaller trials have proven the clinical advantage of metformin against diverse cardiovascular surrogate endpoints, while the long-term effect of metformin on islet autoimmunity still needs to be further investigated (58–61). As a master regulator of cell metabolism, mTOR has been shown to enhance helper T cell differentiation, especially Th1 and Th17, by modulating glucose metabolism through glucose transporter 1 (Glut1) (62). Therefore, targeting upstream or downstream of mTOR signaling is a potential therapeutic strategy. As a classic mTOR inhibitor, rapamycin decreases the proliferation of Th1 and Th17 cells (63). Furthermore, rapamycin was documented to facilitate Treg expansion and enhance their capability to suppress conventional T cells in a T1D mouse model (34, 64–66). Likewise, augmenting catabolic pathways in CD8+ T cells with metformin or rapamycin decreased the differentiation and proliferation of effector T cells instead of enhancing memory T cell expansion (67). In a phase 2, single-center, randomized, double-blind, placebo-controlled study, rapamycin was shown to decrease insulin requirement in patients with long-term T1D (68). Interestingly, ω-3 polyunsaturated fatty acids (ω-3 PUFAs) have been shown to inhibit CD4+ T cell differentiation *via* suppressing mTOR complex 1 (mTORC1). The pancreatic enrichment of ω-3 PUFAs could inhibit or avoid T1D progression in streptozotocin (STZ)-induced mice (69, 70).

Upon initial activation of lymphocytes, Glut1, one of the typical glucose transporters, is upregulated by the PI3K-Akt-mTOR signaling pathway to enhance glucose influx as well as concomitant with the increased production of key glycolytic enzymes (71, 72). The upregulation of Glut1 is critical for T cell activation, as deletion of Glut1 greatly suppresses proliferation and function of effector T cells (73, 74). Pharmacological blockade of Glut1 might be an efficient way to inhibit autoreactive T cells. The glycolysis inhibitor 2-deoxy-D-glucose (2-DG) is a glucose analog that selectively targets effector T cells with upregulated glycolytic activity (16, 24, 75, 76). NOD mice treated with 2-DG displayed a reduced frequency of activated T cells, decreased immune infiltration within pancreatic islets and increased β-cell granularity (24, 77, 78). Additionally, 2-DG facilitates the differentiation of naïve T cells into Tregs but represses their polarization to Th17 cells (36). Likewise, studies have demonstrated that the combination of 2-DG and metformin reduces CD4+/CD8+ effector T cell responses while inducing Tregs, probably by increasing FAO (79). However, in the light of translation from preclinical trials to clinical application for T1D patients, one of the most relevant side effects of 2-DG is central nervous system toxicity, which demands a prompt solution (80–82). In addition, various natural or synthetic molecules that function as Glut1 inhibitors have emerged in recent years, such as sodium meta-arsenite, STF-31, WZB117 and BAY876, which give us more therapeutic options (73, 83–89).

PFK15, a competitive inhibitor of the rate-limiting glycolysis enzyme, has been found to suppress glycolysis utilization of CD4+ T cells and decrease the response of CD4+ T cells to β-cell antigens. Additionally, treatment of PFK15 in NOD mouse models delayed T1D onset due to metabolic and functional exhaustion of T cells (47). In addition, peroxisome proliferator-activated receptors (PPARs) are transcription factors that control genes involved in glucose and lipid metabolism and FAO (90–92). PPARs are expressed in multiple immune cells including T cells, and modulation of FAO through PPARs provides the possibility to promote immunological intervention therapy (93, 94). Activation of PPARβ/δ inhibits Th1 and Th17 cell differentiation due to the transition from glycolysis to FAO and suppresses the proliferative burst of T cells upon activation (95, 96). Researchers have shown that the PPARα activator fenofibrate and the PPARγ activators troglitazone and rosiglitazone have the capability to decrease the incidence of T1D (95, 97, 98). With the treatment of troglitazone, STZ-induced T1D mice exhibited reduced hyperglycemia and insulitis (99, 100).

Another potential approach to improving T1D is to regulate ROS production. T1D is known to be highly actuated by oxidative stress, as CD4+ T cells require high levels of ROS for optimal activation (26, 101). Utilizing manganese metalloporphyrin (MnP), a ROS scavenger and potent antioxidant, delayed T1D progression through modulating aerobic glycolysis and the mTOR/AMPK axis (102–104). Given the critical role of ROS in autoimmune diseases, researchers have applied superoxide dismutase (SOD) mimetics in a T1D mouse model to promote the longevity and stability of antioxidants to delay β-cell damage (25, 105). T1D was significantly delayed or prevented in NOD mice treated with SOD mimic, partly owing to the decrease in proliferation of CD4+/CD8+ T cells as well as reduced production of pro-inflammatory factors (26, 53, 106, 107). Additionally, lymphocyte activation gene 3 (LAG-3) is an inhibitory receptor expressed on the CD4+ T cell

surface, whose deficiency would result in their homeostatic expansion. Studies have reported that the expression of LAG-3 in naïve CD4+ T cells contributes to the restriction of mitochondrial biogenesis and cellular metabolism to keep T cells quiescent. Loss of LAG-3 in NOD mice leads to accelerated T1D progression, potentially by enhancing OXPHOS and glycolytic metabolism and promoting mitochondrial biogenesis of CD4+ T cells (102, 108, 109).

Bacillus Calmette-Guérin (BCG) has been reported as a conducive environmental qualifier of the immune system that could reduce the incidence of autoimmune diseases such as T1D (110). Recent studies indicate that BCG vaccination in patients with long-term T1D showed promising antidiabetic effects, including death of autoimmune T cells as well as expansion of beneficial Tregs (111–113). In an 8-year human study with T1D, BCG vaccination was demonstrated to promote the transition from OXPHOS to aerobic glycolysis of immune cells, improving Treg generation and function, and conferring an immunotolerance effect (114–116). High-mobility group box 1 (HMGB1), an evolutionarily conserved chromosomal protein, was demonstrated to impair the stability and function of Tregs by enhancing PI3K-AKT-mTOR signaling. NOD mice with HMGB1 blockage could protect islet isografts from autoimmune attacks and delay or even reverse T1D development (117).

THERAPEUTIC APPLICATIONS OF IMMUNOMETABOLISM IN COMBINATION THERAPY

The complex etiology of T1D is the consequence of failures in controlling autoimmunity as well as perturbations of β cells (118). In addition to controlling autoimmune responses, ideal therapies would also aim to preserve β-cell function and promote β-cell regeneration (119, 120). To date, several immunometabolism-related interventions combined with other therapy regimens have been proven to be successful in NOD mouse models (63, 121–124). For example, the combination treatment regimen of rapamycin and a CD28 antagonist was reported to inhibit T cell activation and migration into pancreatic islets, hence suppressing the progression of T1D (122). Treatment of NOD mice with rapamycin and IL-2 limits T cell expansion and effectively protects islet β-cells from autoimmune attacks (125). Furthermore, combination therapy with rapamycin, islet autoantigen peptides, and IL-2/IL-2 monoclonal antibody complexes increases Treg numbers and protects against autoimmune diabetes in NOD mice (121). However, a phase 1 clinical trial of a rapamycin/IL-2 combination in 10 T1D patients led to transient dysfunction of β cells despite an enrichment of Treg cells (63). Laboratory evidence has demonstrated that IL-21 signaling plays a critical role in promoting lymphocyte infiltration into the pancreas and rewiring T cell metabolism to form long-lived memory CD8+ T cells, which are the predominantly presented T cell subsets in the pancreatic islets of T1D mouse model (126–128). Matthias von Herrath et al. evaluated the combination of immunotherapy (IL-21) and β-cell-directed treatment (liraglutide) in a randomized, double-blind and phase 2 trial in 308 adults with new-onset T1D (129). After fifty-four weeks of treatment and follow-up, C-peptide secretion was prominently improved in the combination therapy group compared with the placebo, but the effect disappeared after therapy cessation in the follow-up period. In conclusion, the effectiveness of combination therapies in animal models and the first large clinical trial provides a promising approach for the development of novel combination therapies (130).

CONCLUSION

Our understanding of immunometabolism has considerably advanced over the past few years. Multiple studies have demonstrated that key metabolic enzymes and regulators are involved in different processes of T cell responses by alternating the metabolic pathways and networks to match their specific functional requirements (18, 131, 132). Modulating T cell metabolism has the capability of selectively enhancing or inhibiting particular T cell subsets with distinct functions (133). Of note, although gene knockout mice have presented valuable information, an inescapable limitation is that there are differences between mouse and human immune systems as well as metabolic programs. Moreover, cellular metabolism *in vivo* is distinct from that *in vitro*, while a large number of studies have assessed the metabolism of immune cells during their differentiation, proliferation, and responses *in vitro*. Collectively, targeting T cell metabolism could be a promising strategy for the next wave of immunotherapies treating human diseases, including T1D.

AUTHOR CONTRIBUTIONS

JH and BZ: conceptualization and guidance. MZ and YZ wrote and edited the manuscript. All authors contributed to the article and approved the submitted version.

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