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...
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 naive 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-arsenate, 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 acted upon by oxidative stress, as CD4+ T cells require high levels of ROS for optimal activation (26, 101). Utilizing manganese metallocorphyrin (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 β-cells. Researchers have applied superoxide dismutase (SOD) mimetics in a T1D mouse model to promote the longevity and stability of β-cells. 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
naive 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 blockade 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.

FUNDING

This study was supported by the National Natural Science
Foundation of China (grant numbers 82107985 and
82100949), and the Outstanding Young Investigator of Hunan
Province (2022JJ10094).

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