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Metabolism of T_H17 Cells: New Insights and Therapeutic Opportunities

Ran Wang and **Laura A. Solt**

Department of Molecular Therapeutics, The Scripps Research Institute, Jupiter, FL, USA

Abstract

An effective adaptive immune response relies on the ability of lymphocytes to rapidly act upon a variety of infectious insults. In T lymphocytes, this response includes cell growth, clonal expansion, differentiation, and cytokine production, all of which places a significant energy burden on the cell. As a result, T cells engage specific metabolic pathways to carry out their effector functions. Recent insights have demonstrated that T-cell metabolic reprogramming is an essential component of the adaptive immune response and specific metabolic pathways dictate T-cell fate decisions, including the development of T_H17 versus T regulatory (Treg) cells. T_H17 cells have garnered significant attention since their discovery nearly a decade ago due to their roles in the pathology of several immune-mediated inflammatory diseases. Attempts to fully characterize T_H17 cells have demonstrated that they are highly dynamic, adjusting their function to environmental cues which dictates the metabolic program of the cell. In this short review, we will highlight recent data demonstrating the impact of cellular metabolism on the T_H17/Treg balance and present factors that mediate T_H17 cell metabolism. Finally, we discuss the potential therapeutic options and the implications of modulating T_H17 cell metabolism for the treatment of T_H17-mediated diseases.

Keywords

autoimmunity; metabolic regulation; regulatory and helper T cells; RORγt; T_H17/Treg balance; glucose metabolism; glycolysis; immunometabolism

Introduction

The ability of an organism to respond to environmental changes is essential for survival. An effective immune response abides by this same rule, with engagement of cellular metabolic pathways an essential component. In mammals, coordination and communication between multiple organs mediates homeostasis and dysregulation of this process leads to disease states. A similar parallel can be drawn between cells of the immune system and an effective immune response. Coordinate changes in cellular metabolism upon pathogenic insult is

Full correspondence: Dr. Laura A. Solt, Department of Molecular Therapeutics, The Scripps Research Institute, 130 Scripps Way, 1B2, Jupiter, FL 33458 USA, Fax: +1-561-228-3088, lsolt@scripps.edu.

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essential for immune cell proliferation and function, dysregulation of which can result in autoimmunity or cancer.

An effective adaptive immune response requires T cells to adapt and function in various microenvironments[1-5]. Since quiescent T-cell energy demands are low, they primarily oxidize glucose-derived pyruvate in their mitochondria via oxidative phosphorylation (OXPHOS), which ensures maximal ATP production (32 ATP) per molecule of glucose[1, 5, 6]. However, upon antigen stimulation, T cells undergo metabolic reprogramming in order to provide energy and building blocks for clonal expansion and effector function[1, 3, 4]. These events require significant amounts of ATP in a short period of time and thus rely primarily on glycolysis, a process which catabolizes six-carbon sugars to produce two molecules of ATP and pyruvate (each), for their energy demands[1, 5]. Glycolysis is an essential metabolic pathway for T-cell development as it yields energy and molecules required for cellular growth and proliferation[2, 3]. This process occurs in the presence of oxygen (aerobic glycolysis) and is reminiscent of the Warburg effect observed in most cancer cells[5, 6]. The observation that removal of glucose inhibits T-cell proliferation and cytokine production led to the discovery that upregulation of glucose transporter 1 (Glut1) is another essential component of T-cell metabolic reprogramming[7-9]. Therefore, the upregulation of glucose metabolism is required to generate metabolic intermediates for the synthesis of proteins, nucleic acids, and lipids[2]. Several recent review articles have been published providing an extensive overview of T-cell metabolism in immune regulation[3, 4, 10-12], anti-tumor immunity[13], mTOR and metabolic control of T regulatory (Treg) cells[14-16], and targeting T-cell metabolism for therapeutic purposes[17], therefore we will not belabor these points. In this review, we focus on T_H17 cells, providing an overview of recent insights into metabolic pathways that regulate T_H17 cell development and function, dictate T_H17/Treg cell fate decisions, and ultimately affect immune homeostasis. We conclude with a brief discussion about the therapeutic implications of the research and the potential for targeting T_H17 cell metabolism to treat autoimmune diseases.

The T_H17 and T regulatory cell balance

Naïve $CD4^+$ T cells differentiate into distinct effector lineages as a consequence of antigen engagement coupled with specific cytokine signals. T_H17 cells differentiate in response to the STAT3-activating cytokines IL-6 and IL-21 in combination with transforming growth factor β (TGF-β) and IL-1β[18]. This combination leads to the induction of the T_H17-specific nuclear receptor, RORγt, also known as the “master” transcription factor. Interestingly, T_H17 cells are only reduced, not absent in RORγt-deficient mice. This observation led to the discovery that the close family member of RORγt, RORα, is also induced in T_H17 cells and while endogenous expression of RORα can not completely fulfill the role of RORγt, both receptors are required for full T_H17 cell development[19]. In combination with several other general transcription factors, STAT3 and RORγt synergize to regulate transcription of the T_H17-signature cytokines, IL-17A, IL-17F, IL-21, and IL-22[20].

Significant interest in T_H17 cells was garnered when they were implicated as pathogenic mediators of several autoimmune diseases in mice and humans, including experimental

autoimmune encephalomyelitis (EAE, a mouse model of multiple sclerosis), collagen induced arthritis (a mouse model of rheumatoid arthritis), psoriasis, and some forms of colitis[21]. T_H17 cells exist in both mice and humans and while there are a significant number of similarities between the two species, a few differences have been observed, some of which pertain to T-cell metabolism and are discussed in this review article [22].

Despite their opposing functions, T_H17 cells and inducible T regulatory (iTreg) cells share a common requirement for the pleiotropic cytokine TGF-β for development; T_H17 cells are pro-inflammatory and iTregs are anti-inflammatory[21]. Unlike thymus-derived natural Tregs (nTregs), iTregs can be induced from naïve $CD4^+$ T cells in the periphery upon antigen stimulation and exposure to TGF-β[23-25]. In addition to RORγt, TGF-β also induces the expression of the transcription factor forkhead box protein 3 (Foxp3), the core subset-specific transcription factor for both nTregs and iTregs [24, 26, 27]. Therefore, when activated in the presence of TGF-β or TGF-β + IL-6, naïve $CD4^+$ T cells simultaneously upregulate both Foxp3 and RORγt to generate an intermediate $Foxp3^+ROR\gamma t^+$ cell type that can either differentiate into $Foxp3^+$ iTregs or $ROR\gamma t^+$ T_H17 cells *in vitro* and *in vivo*[26-28]. During the intermediate stage, RORγt and Foxp3 can interact with each other, but Foxp3 is dominant and antagonizes RORγt function unless IL-6 or IL-21 is present in the milieu[26, 27]. Full T_H17 cell differentiation is then associated with downregulation of Foxp3 and sustained RORγt transcription. Finally, T_H17 cells and iTregs have been shown to have unstable phenotypes *in vivo*. For instance, under certain pro-inflammatory conditions, T_H17 cells have been demonstrated to acquire a T_H1-like phenotype, whereas iTregs can convert into T_H1 and T_H17 cells[27, 29].

An imbalance between T_H17 and Treg cell number and function has been suggested to be a key mediator of T_H17-mediated autoimmune diseases[30]. Therefore, it is not surprising that a considerable amount of research is focused on understanding the factors that mediate the T_H17/iTreg balance. What is surprising is that a number of recent studies have implicated various metabolic pathways in the regulation of T_H17/iTreg cell fate[31-36]. While most work on T-cell metabolism has primarily occurred using murine systems, due to the growing interest in immunometabolism more studies characterizing the link between human cellular metabolism and function are being performed. Therefore, where applicable, we will describe work that has been performed using human T cells and compare the data to mouse studies.

mTOR signaling and $CD4^+$T-cell fate

An activated T cell depends on cell intrinsic and external cues from the environment to fully develop. These cues are assimilated by the evolutionarily conserved serine/threonine kinase mTOR (mammalian target of rapamycin), which regulates cell growth, proliferation, and survival[37]. mTOR signaling occurs via two complexes, mTORC1 and mTORC2, each with their own unique function, and is activated by amino acids, cellular stress, and nutrient availability in the environment[37]. Activation of mTOR leads to the upregulation of glycolysis to support effector T-cell development and function[7, 38]. The activity of the different mTORC complexes is critical for T-cell fate decisions[14, 15]. In the absence of mTORC1 signaling, murine T_H1 and T_H17 cells failed to differentiate *in vitro* and *in vivo* whereas the ability of $CD4^+$ T cells to differentiation into a T_H2 lineage was intact[34].

Conversely, in the absence of mTORC2 signaling, naïve mouse $CD4^+$ T cells failed to develop into T_H2 cells *in vitro* and *in vivo*, whereas they retained their ability to differentiate into T_H1 and T_H7 cells[34]. Mouse naïve $CD4^+$ T cells lacking both mTORC1 and mTORC2 failed to develop into any T helper (Th) lineage, instead differentiating into iTregs[39]. Treatment of naïve mouse $CD4^+$ T cells with the mTOR inhibitor rapamycin yielded a similar phenotype[40]. Interestingly, dysregulation of mTOR signaling has been documented in various human autoimmune diseases. Increased mTORC1 has been observed in T cells from patients with multiple sclerosis (MS), possibly underlying the decreased Tregs observed in these patients[41]. In patients with systemic lupus erythematosus (SLE), mTORC1 is activated whereas mTORC2 is reduced leading to increased production of IL-4 and decreased numbers of Tregs[42]. *In vitro*, rapamycin inhibited IL-17 expression from human $CD4^+$ T cells and expanded Tregs from SLE patients [43]. When administered *in vivo*, rapamycin corrected the T cell abnormalities and increased the expression of Tregs in SLE patients [44]. Treatment of peripheral blood mononuclear cells (PBMCs) from kidney transplant recipients with sirolimus, the pharmaceutical designation for rapamycin, also inhibited T_H17 cells and expanded Tregs *in vitro* and *in vivo*[45].

At the molecular level, the ability of mTORC1 to regulate the development of T_H17 cells appears to be dependent on suppression of *Gfi1*, a zinc finger protein that functions as a transcriptional repressor[35]. mTORC1 mediated repression of *Gfi1* enhanced nuclear translocation of RORγt and the subsequent development of murine T_H17 cells[35]. In addition to glucose, the non-essential amino acid is also critical for T-cell activation as it is thought to provide fuel for rapidly dividing cells, but the exact mechanisms for glutamine uptake and T-cell activation are not completely understood[1, 46]. Importantly, amino acids have been shown to activate mTORC1 by targeting it to lyososmal-membranes for activation[47]. To better understand how glutamine regulates immune responses, one group recently used a gene targeting approach and demonstrated that the glutamine transporter ASCT2 is required for TCR-stimulated activation of mTORC1[33]. Murine T_H1 and T_H17 cell development was impaired in ASCT2-deficient T cells and the symptoms of MOG induced EAE were delayed and reduced[33]. This study also demonstrated that ASCT2 is required for the uptake of glutamine and leucine in murine T cells, the later of which appears to mediate T_H17 cell development over T_H1[34]. Interestingly, the absence of ASCT2 also attenuated the expression of Glut1, significantly inhibiting glucose uptake and reducing the rate of glycolysis in murine T cells[33]. Since mTORC1 is known to mediate induction of Glut1 expression[48, 49] and elevated levels of glutamine and glutamate have been reported in clinical cases MS[50], this study correlates TCR/CD28 signaling, glutamine uptake, and mTORC1-mediated regulation of T_H17 cell differentiation with immune pathogenesis[33]. Collectively, these studies highlight the important role for mTOR in $CD4^+$ T cell differentiation, the T_H17/iTreg balance, and its promise for the treatment of autoimmune diseases.

HIF1α and the regulation of glycolysis

Much like mTOR, hypoxia inducible factor 1 alpha (HIF1α) is another well-known integrator of metabolic cues important for T-cell activation and development[4, 38]. In fact, mTORC1 enhances HIF1α expression at both the transcriptional and translational level to

drive glucose uptake and glycolysis[38]. Glut1 is upregulated in both mouse and human T cells upon activation and is critical for metabolic reprogramming, growth, and effector function[51]. HIF1α promotes increased glucose uptake via upregulation of Glut1 and reinforces glycolysis through upregulation of pyruvate dehydrogenase kinase 1 (PDK1). Increased PDK1 activity, in turn, prevents entry of pyruvate into the TCA cycle and redirects it to be metabolized into lactate[10]. HIF1α has been demonstrated to be a critical factor in the development of T_H17 cells versus Tregs. HIF1α is highly expressed at the mRNA and protein level in mouse T_H17 cells relative to other T helper lineages[36, 52]. Human T_H17 cells also express HIF1α and require it along with mTOR activity to produce IL-17[53]. Deletion of HIF1α in murine T cells reduces the expression of several genes involved in glycolysis, including Glut1, *Hexokinase 2* (*Hk2*), *Pyruvate kinase muscle* (*Pkm*), and *Lactate dehydrogenase* (*Ldha*), most of which represent rate limiting steps in glycolysis[36]. Mouse T cells lacking HIF1α also have diminished T_H17 cell development and enhanced iTreg development, a consequence of decreased glycolysis[36, 52]. One group found that pharmacological inhibition of glycolysis with rapamycin or 2-deoxyglucose (2-DG), an inhibitor of HK2 activity, also suppressed glycolysis in murine cells, shifting the T_H17/iTreg balance in favor of iTregs.[36]. While 2-DG inhibited glycolysis and affected the T_H17/iTreg balance, it is likely not specific to T_H17 cells since glycolysis, and HK2, is upregulated in all T effector lineages which is consistent with data demonstrating that 2-DG treatment of human T cells inhibited their growth, activation, and proliferation[51]. Interestingly, a separate study demonstrated that HIF1α drives murine T_H17 cell development through dual mechanisms involving RORγt; HIF1α not only transactivates RORγt but also forms a transcriptional complex with p300 and RORγt to drive T_H17 cytokine gene expression[52]. This group also demonstrated that HIF1α attenuates Foxp3 expression by binding to Foxp3 and targeting it for proteasomal degradation[52]. Precisely how HIF1α interacts with RORγt to drive IL-17 transcription while also interacting with Foxp3 and targeting it for degradation have yet to be determined. However, in both studies, mice with HIF1α-deficient T cells had delayed and reduced symptoms of EAE[36, 52]. While these studies describe very different and unique mechanisms for HIF1α-mediated regulation of T_H17 cells, it is likely a combination of all mechanisms that affects the T_H17/iTreg balance.

AMPK and the T_H17/iTreg balance

In contrast to mTOR and HIF1α, AMP-activated protein kinase (AMPK), a heterotrimeric kinase complex, is activated in response to low energy levels (low AMP:ATP ratio) and induces catabolic pathways such as fatty acid oxidation or autophagy under times of cellular stress or a decline in cellular energy stores[10]. In T cells, AMPK is directly activated through TCR-dependent Ca^{2+} signaling or by phosphorylation of liver kinase B1 (LKB1) [54, 55]. Activation of AMPK leads to energy-yielding processes while inhibiting glucose and fatty acid synthesis through AMPK-dependent phosphorylation of acetyl-coA carboxylases 1 and 2 (ACC1, ACC2)[10, 56]. ACC1 is present in the cytosol and is crucial for *de novo* fatty acid synthesis whereas ACC2 is associated with the outer mitochondrial membrane[56]. Inhibition of ACC2 leads to increased expression of carnitine palmitoyl transferase (CPT-1) which mediates the influx of fatty acids into the mitochondria[3, 56].

Further discussion of the roles for the ACCs and lipid metabolism are described in the next section.

Unlike T effector cells, murine iTregs have been demonstrated to primarily rely on fatty acid oxidation (FAO) for their energy needs in lieu of glycolysis[57]. iTregs display increased AMPK activity and activation of AMPK *in vitro* promotes lipid oxidation in T cells[57]. Importantly, activation of AMPK with metformin, a commonly used anti-diabetic drug, increased the frequency of Tregs *in vivo* when assessed in a murine model of allergic asthma[57, 58]. When administered to newly diagnosed type 2 diabetes patients, metformin treatment lead to a significant reduction in the serum concentration of IL-17 but not IFNγ indicating a conserved effect on T_H17 cells[59]. Given that AMPK is a negative regulator of mTOR activity, these data suggest that activation of AMPK should suppress T_H17 cell development and promote iTregs in *vitro* and *in vivo*[32, 60]. Alternatively, loss of AMPK should increase mTOR activity and lead to the generation of T_H17 cells over iTregs. To address this question, one group generated mice in which the AMPKa1 subunit was deleted in $CD4^+$ and $CD8^+$ T cells[61]. While *AMPKa1*$^{-/-}$ $CD8^+$ T cells had increased glycolytic activity and produced more inflammatory cytokines than wild type cells *in vitro*, there was no observable difference in $CD4^+$ T cells deficient in *AMPKa1* despite having increased glycolytic rates[61]. However, in a separate study, this same group demonstrated that *AMPKa1*$^{-/-}$ T cells display reduced T_H1 and T_H17 responses to bacterial and viral infections *in vivo*[62]. Furthermore, loss of AMPKα1 led to reduced mitochondrial bioenergetics and cellular ATP in response to glucose limitation *in vitro*[62]. While these data are perplexing, it is clear that AMPK plays an important role in T-cell metabolism, but may not be specific to T_H17 cells. These studies also demonstrate the disconnect that sometimes occurs between genetic and pharmacological approaches. While gene disruption in mice has been the gold-standard for elucidating mechanism, several caveats may ensue, including compensation among factors that may not be present with pharmacological approaches. Thus, use of genetic and pharmacological approaches will likely yield the greatest insight into complex biological systems, including T-cell metabolism.

Fatty Acid synthesis and Lipid Metabolism

Much like glucose metabolism, lipid metabolism is also an essential component of T-cell activation[4, 10, 11]. Lipids are vital components of cell membranes, can serve as energy sources, and supply substrates for cell signaling[11]. Induction of *de novo* fatty acid (FA) synthesis is necessary for effector T-cell proliferation and differentiation with ACC1, ACC2, and fatty acid synthase (FASN) recognized as key rate limiting steps in this process[39]. Conversely, T cells can utilize FAs as an energy source, in a process called β-oxidation (fatty acid oxidation; FAO)[4, 13]. However, recent insights suggest that lipids are more than just structural components and may represent key metabolic checkpoints in T-cell activation[1, 11, 31]. Using a mass-spectrometry based approach, one group found that following initial T-cell activation, murine T cells accumulate metabolites involved in anabolic processes and FA synthesis[1]. Increased FA synthesis correlated with decreased FAO, suggesting a reciprocal relationship between these two processes[1]. Further characterization of T-cell lipid metabolism has found that the preferential usage of FAO or FA synthesis can dictate cellular fate and functions, including the T_H17/iTreg balance[31].

Given that AMPK is an important regulator of FAO and promotes iTregs, one group set out to try and better understand how lipid metabolism may affect the T_H17/iTreg balance. Berod *et al.* demonstrated that murine T_H17 cells were highly dependent on *de novo* FA synthesis and did not utilize externally derived FAs for proliferation or differentiation[31]. By blocking FASN activity through use of an ACC-specific inhibitor, Soraphen A, or ACC1-deficient T cells, this group showed that murine T_H17 cell differentiation, as well as T_H1 and T_H2, was significantly decreased, suggesting that $CD4^+$ T effector cells share a common requirement for FA synthesis[31]. These effects were ACC1-dependent because deletion of ACC2 did not yield a similar phenotype. iTregs were not affected in either experimental scenario. In an autoimmune setting, mice with T cells lacking ACC1 or treatment of mice with a derivative of Soraphen A demonstrated delayed onset and severity of symptoms of EAE[31]. Finally, the addition of exogenous FAs rescued the T_H17 phenotype in ACC1-deficient T cells. While these data are interesting, one must wonder why T_H17 cells need to make their own FAs rather than just acquire them from the milieu? Finally, it is clear that targeting a factor shared among effector cells is not ideal if the goal is to specifically target the T_H17/Treg balance. Identification and targeting a factor specific to both T_H17 cells and a metabolic pathway may be the better therapeutic option.

Nuclear Receptors in T-cell metabolism and T_H17 development

Nuclear receptors (NRs) are highly conserved ligand-regulated transcription factors that have been demonstrated to play significant roles in many diverse physiological processes, including development, cell growth, regulation of the circadian rhythm, metabolism, and immune functions[63]. NRs are attractive therapeutic targets since their activity can be modulated by small lipophilic molecules and approximately 10-15% of FDA approved drugs target NRs, highlighting their tractability for therapeutic intervention[64]. Several NRs have been demonstrated to regulate T-cell metabolic processes and T_H17 cell development, including estrogen related receptor alpha (ERRα), liver x receptors alpha and beta (LXRα and LXRβ), peroxisome proliferator-activated receptors (PPARα, PPARβ/δ, PPARγ), and probably the best known, the retinoic acid-related receptors alpha and gamma (RORα and RORγt)[3, 4, 21, 65]. Interestingly, many of these NRs have been described as key metabolic regulators controlling a number of metabolic processes, including FAO, OXPHOS, FA uptake, and glucose metabolism[66-68].

While expressed at very low levels in naïve $CD4^+$ T cells, ERRα is upregulated upon T-cell activation[69]. Deficiency in ERRα or pharmacological modulation of ERRα activity with XCT790 reduced murine T-cell activation, glucose and mitochondrial metabolism, affecting the development of all T helper subsets[69]. While addition of exogenous FAs rescued proliferation in all subsets, it could not rescue T effector function, only iTregs[69]. In MOG induced EAE, defective ERRα signaling led to a significant decrease in T_H17 cells whereas iTreg numbers remained unchanged suggesting ERRα plays a role in T effector cell generation *in vivo*, but not iTregs[69].

The LXRs have also been demonstrated to influence T-cell differentiation and fate decisions through regulation of cholesterol metabolism[65, 70]. The LXRs control intracellular cholesterol homeostasis through regulation of the cholesterol efflux transporters, *Abca1* and

Abcg1, and fatty acid synthesis, through control of the transcription factor sterol regulatory element binding protein-1c (*SREBP-1c*), and *FASN*[65, 70]. Pharmacological activation of LXR inhibited murine T_H17 cell development *in vitro* and decreased severity of symptoms of EAE[71, 72]. Activation of LXR also impairs murine T-cell proliferation, which can be overcome by the addition of mevalonate, a cholesterol precursor[70]. Interestingly, SLE is associated with abnormal lipid metabolism and T cells from SLE patients present with elevated expression of LXR[73]. While the exact molecular mechanisms driving dyregulated lipid metabolic function in SLE are unknown, these data identify LXR as a potential therapeutic target for the treatment of SLE and link metabolic dysregulation and autoimmunity. Other NRs, the PPARs, particularly PPARγ has been shown to inhibit murine T_H17 cells through suppression of STAT3 transcriptional activity, which led to decreased RORγt induction[74]. Ligand regulation of PPARγ activity has yielded conflicting results, with some agonists affecting all T helper subsets while other ligands did not[75, 76]. These data suggest that ligand mediated regulation may have differential effects on PPARγ activity and development of ligands to modify specific immune pathologies may yield novel therapies. While the T_H17/iTreg balance was not addressed in these studies[76], given PPARγ's role in the regulation of lipid metabolism, it is conceivable that certain ligands may have effects on the T_H17/iTreg balance[75].

RORs, particularly RORγt, have garnered significant attention given their essential roles in T_H17 cell development[21]. Outside of the immune system, the RORs have been extensively studied due to their key roles in the regulation of the circadian rhythm, lipid, and glucose metabolism[66, 68, 77, 78]. A significant number of RORγ-selective ligands have been identified and while these ligands led to the suppression of T_H17 cell development and function, many have been demonstrated to affect the T_H17/iTreg balance as well[79-82]. These effects have been attributed to decreased RORγt activity and stabilization of Foxp3 expression. Furthermore, RORα is also expressed in T_H17 cells, yet it is thought to be redundant to RORγt[19, 21, 27]. Given the ROR's roles in the regulation of metabolism in other cell types, and that changes in metabolic state can influence T-cell fate decisions, it is possible that in addition to cytokine regulation, the RORs may help drive T_H17-cell metabolism. Given the transcriptional targets for murine RORγt has been extensively evaluated and RORγt appears to regulate a small number of core target genes, very few of which are metabolism-related, perhaps RORα's role is to aid in driving the increased glucose and lipid metabolism observed in T_H17 cells relative to iTregs[20]? While this is an intriguing notion, more work needs to be performed exploring RORα's role in T_H17 cell development to address this question.

Targeting T_H17 cell metabolism for therapeutic purposes

Typical treatment options for many autoimmune diseases include corticosteroid use, though long-term treatment is not practical due to negative side effects, including global immunosuppression[83]. Therefore, an overarching goal is to develop novel therapeutics that specifically target pathological immune cells. Given that an imbalance between T_H17 and iTreg cell number and function has been suggested to be a key regulator of T_H17-mediated autoimmune diseases[30], and T-cell metabolism has been demonstrated to be a key factor

dictating this balance, exploiting these pathways represent novel therapeutic options[4, 10-12, 15-17].

While T_H17 cells primarily utilize glycolysis relative to iTregs, exploiting factors that dictate this pathway, including mTOR and HIF1α, may initially appear to be an obvious choice for therapeutic treatment[36]. However, in contrast to murine iTregs, a recent report has demonstrated that glycolysis is actually required for the generation of human iTregs from $CD4^+CD25^-$ conventional T cells (T_{conv})[84]. The suppressive function of iTregs was dependent on glycolysis and 2-DG treatment inhibited the development of iTregs from T_{conv} [84]. Increased iTreg glycolysis and metabolism was dependent on the expression of the Foxp3 splice variant containing exon 2 (Foxp3-E2)[84]. Human Tregs, unlike mouse Tregs, express multiple Foxp3 splice variants, but their individual functions are poorly defined[85]. This study highlights one of the differences between mouse and human studies and needs to be considered when determining the therapeutic potential of targeting specific pathways or cell types for immune-mediated diseases. Moreover, glycolysis is upregulated in all effector T cell populations, including $CD8^+$ T cells, therefore targeting glycolysis in general may lead to non-specific immunosuppression[17]. Indeed, while rapamycin and other inhibitors of mTOR have demonstrated effects on the T_H17/iTreg balance in human patients, rapamycin is a potent immunosuppressant with anti-proliferative properties. Thus, mTOR inhibition may be ideal under certain conditions, including transplant rejection and treatment of patients with SLE, but inhibition of mTOR or glycolysis may not be ideal for all autoimmune therapies [41][43, 45]. For instance, naïve $CD4^+$ T cells from patients with Rheumatoid arthritis (RA) fail to significantly upregulate glycolysis, yet vigorously proliferate upon activation due to insufficient induction of a key regulatory enzyme in the glycolytic pathway[86]. However, sera from RA patients present with autoantibodies against several glycolytic enzymes[86]. Based on this information, targeting glycolysis or factors that regulate glycolysis may have little impact on T-cell mediated effects in RA, but may have other beneficial consequences outside of T cell activity. Therefore, a better understanding of immune and T-cell dysfunctions associated with metabolic alterations in human autoimmune diseases is imperative. Importantly, these data suggest that personalized medicine may be a therapeutic avenue to pursue in the future for autoimmune diseases.

Targeting AMPK to modulate immune responses is another option for targeting the T_H17/iTreg balance in autoimmunity. Metformin treatment could enhance the iTreg population at the expense of T_H17 cells and one preliminary study in human patients suggests this may occur[59]. However, more work evaluating AMPK activation in humans for immune-modulating therapies needs to be performed since targeting AMPK will likely affect other immune cell populations and may not specifically affect the T_H17/iTreg balance.. In fact, many of the targets described in this review, while having a profound role on the T_H17/iTreg balance, also affect other immune cell subsets[17]. So the question remains, how do we specifically target the T_H17/iTreg balance and leave other immune populations functional? The key may lie in exploiting factors that are specific to T_H17 cells, like the RORs[21]. While little is known about the roles for these NRs in regulating T_H17 cell metabolism, given their roles outside of the immune system it is plausible that they might also regulate metabolic processes[66, 68]. Furthermore, the RORs are ligand-regulated transcription factors, so targeting the RORs may be an ideal way to specifically target T_H17 cells without

compromising the immune system as a whole[77]. There has been a significant effort by many pharmaceutical companies to identify RORγ ligands and synthetic ligands targeting RORα have been described[79, 87]. Therefore, specifically targeting "select" immune cell populations regulated by the RORs versus targeting a pathway or factor that is present in most immune cell populations (i.e. mTOR, AMPK, etc.) may provide more specific treatment options with fewer side effects.

Concluding remarks and Future Perspectives

While immunometabolism is still in its infancy, it is clear that metabolic reprogramming is an essential component of an effective immune response. Recent advances have led to an increased understanding of how metabolism dictates T-cell fate decisions and this review has highlighted several of which appear to specifically affect the T_H17/iTreg balance. However, there is still much work and many challenges ahead to definitively determine whether targeting T_H17-cell metabolism is a viable therapeutic option. More work exploring human versus mouse T_H17 cell metabolism needs to be performed to determine whether the metabolic reprogramming that occurs is conserved and if not, where the differences may lie. This understanding is critical for successful therapeutic targeting of the T_H17/iTreg balance in human autoimmune disease. A more comprehensive assessment of the dysregulated metabolic programs occurring in various autoimmune diseases is also warranted. Evidence from SLE and RA patients indicate that a "one-size-fits-all" therapeutic approach may not work and more personalized therapeutic strategies may be warranted. Other aspects, including whether the T-cell metabolic imbalances observed in various autoimmune diseases is a cause or consequence of T-cell alterations needs to be explored and may also lend significant insight into therapeutic design. In line with this, identifying factors that are specific to T_H17 cells is also critical to specifically target this cell type therapeutically. Finally, no cell stands alone during an immune response, meaning that signals from the microenvironment also help dictate the immune response. Understanding the cross-talk between the intracellular and extracellular signals driving immune responses will reveal fundamental insights in T_H17-cell biology and autoimmunity. Thus, the challenge for successfully targeting T_H17-cell metabolism and the T_H17/iTreg balance lies in a detailed understanding of T cell intrinsic and extrinsic mechanisms which will likely lead to novel therapeutic strategies for the treatment of T_H17-mediated autoimmune disorders.

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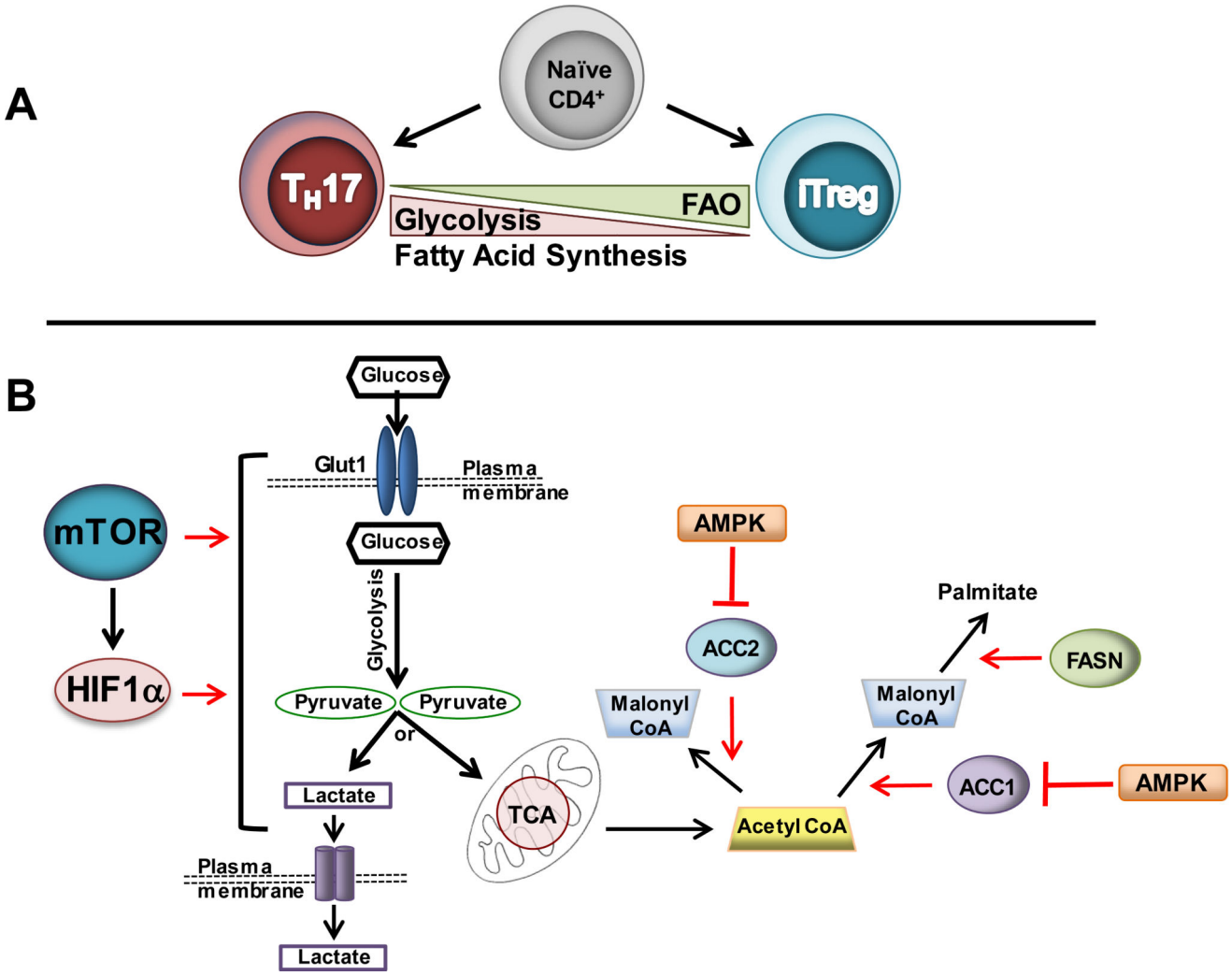

Figure 1. Metabolic regulation of the T_H17/Treg balance

(A) Glycolysis and fatty acid (FA) synthesis provide energy and promote T_H17 cell differentiation whereas Tregs rely on fatty acid oxidation (FAO) for their energy needs. **(B)** Schematic of key components and regulators of metabolic processes that drive T_H17 cell metabolism. mTOR is a central activator of cellular metabolism and can also promote HIF1α, which drives several genes important for glycolysis. Glycolysis generates 2 pyruvate molecules, which can be converted to lactate or shuttled into the TCA cycle where it gets converted to Acetyl-CoA. Acetyl-CoA is a precursor to fatty acid synthesis, which is driven by the enzymes ACC1, ACC2, and FASN. Activation of AMPK inhibits ACC1 and ACC2 leading to decreased fatty acid synthesis and increased FAO.