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Metabolic regulation of T_H17 cells

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ABSTRACT

IL-17-producing T_H17 cells have been associated with autoimmune diseases such as multiple sclerosis (MS), psoriasis, Crohn's disease, and ulcerative colitis (Han et al., 2015), many of which lack effective therapies. Identifying effective approaches to selectively suppress T_H17 cell development and function represents a legitimate strategy to cure these autoimmune disorders. T_H17 cell differentiation requires rewiring of their metabolic program, transition from the oxidative phosphorylation-dominant catabolic phenotype in quiescent naïve T cells to glucose metabolism-orchestrated anabolic phenotype including lipogenesis. Here, we provide a focused review on the glycolytic-lipogenic pathway in T_H17 development and pathogenicity. These studies reveal several metabolic checkpoints with specific regulation of T_H17 cells (but not other T cell lineages), manifesting potential therapeutic opportunities to T_H17 cell-mediated autoimmune diseases.

1. Introduction

T cells are the circulating soldiers of our adaptive immune system. Each human being has about 100 million T cells with different receptors that are capable of responding to a wide array of exogenous and endogenous insults. To cope with exogenous insults such as infectious pathogens, coordinated and optimized effector functions from T cells (T_{eff}) are required. On the other hand, to mitigate the detrimental effects from an overexuberant immune response to endogenous insults as in autoimmune diseases (*e.g.*, multiple sclerosis, psoriatic arthritis, Crohn's disease, as well as ulcerative colitis), suppression of immune responses by regulatory T cells (T_{reg}) is necessary to maintain immune homeostasis. Since the original proposal of the IFN-γ-producing T_H1 and IL-4-producing T_H2 dichotomy in 1986 (Mosmann et al., 1986), $CD4^+$ helper T cell differentiation has significantly evolved with the identifications of IL-17-producing T_H17 (Harrington et al., 2005), follicular helper T cells T_{FH} (Breitfeld et al., 2000; Schaerli et al., 2000) and less-defined IL-9-producing T_H9 (Dardalhon et al., 2008) and IL-22-producing T_H22 (Eyerich et al., 2009). The discovery of T_{reg} cells in 1995 (Sakaguchi et al., 1995) that produce the anti-inflammatory signature cytokine TGF-β further expanded the $CD4^+$ T cell network by installing a counterbalance control of T_{eff} functions, forming a balanced Yin-Yang immune system. Analogous to $CD4^+$ T cell subsets, a similar paradigm in $CD8^+$ T cells is appearing including T_C1 (IFN-γ-producing $CD8^+$ T cells), T_C2 (IL-4-producing $CD8^+$ T cells), T_C17 (IL-17-producing $CD8^+$ T cells), and regulatory $CD8^+$ T cells (Croft et al., 1994; Hamada et al., 2009; Lu and Cantor, 2008). In addition to their signature cytokines, $CD4^+$ T cell subsets express different master transcriptional factors: T-bet for T_H1 (Szabo et al., 2000), Gata-3 for T_H2 (Zheng and Flavell, 1997), RORγt for T_H17 (Ivanov et al., 2006), Bcl-6 for T_{FH} (Johnston et al., 2009; Yu et al., 2009), and Foxp3 for T_{reg} (Fontenot et al., 2003; Hori et al., 2003), but unequivocal master transcriptional factors for T_H9 and T_H22 cells remain to be identified. Furthermore, these T cell lineages exert distinct functions. For example, T_H1 cells play an essential role in the clearance of intracellular pathogens and can mediate some organ-specific autoimmune diseases; T_H2 cells are more closely involved in the clearance of extracellular parasites as well as asthma and other allergic reactions; T_H17 cells have been affiliated with many autoimmune diseases but also play important roles in combat against extracellular bacteria and fungi (Zhu and Paul, 2008); T_{FH} cells specialize in promoting B cell-mediated humoral immunity (Crotty, 2014); T_H9 cells have been suggested to be involved in allergy, autoimmune and inflammatory bowel diseases, and cancer (Li et al., 2016); and T_H22 cells can provide help in mucosal wound healing, epithelial proliferation and repair (Eyerich et al., 2009). On the flip side, T_{reg} can suppress functions of all the effector T cells and play an essential role in the self-tolerance and immune modulation (Sakaguchi, 2008).

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While it has long been recognized that the aforementioned fate decisions (T_{eff} vs T_{reg}) of activated T cells, in response to TCR ligation and CD28-mediated costimulation, are orchestrated by distinct sets of cytokines: IL-12/IFNγ for T_H1; IL-4/(IL-2, IL-7, TSLP) for T_H2; TGFβ/(IL-6, IL-21, IL-23) for T_H17 and TGFβ/IL-2 for T_{reg} (Zhu and Paul, 2010), in recent years, accumulating evidence indicates that, at a fundamental level, it is the cellular metabolism that coordinates T cell activation (Wang et al., 2011), differentiation (Michalek et al., 2011; Shi et al., 2011) and function (Chang et al., 2013; Peng et al., 2016), and shapes the final outcome of T cell-mediated immune response, an emerging concept termed "immune-metabolism" linking two previously-regarded disparate physiological systems of immunity and metabolism (Jones and Thompson, 2007; Pearce, 2010; Siska and Rathmell, 2015). Quiescent naïve T cells have a catabolic metabolism where they mainly catabolize glucose, fatty acids, and amino acids to generate ATP through the TCA cycle (Krebs cycle) and oxidative phosphorylation (OXPHOS). Upon activation, naïve T cells undergo a growth phase that lasts about 1–2 days, followed by extensive clonal expansion and differentiation that are essential for appropriate immune defense and regulation (Wang and Green, 2012). Both the initial growth and subsequent rapid proliferation of T cells have dramatically increased bioenergetic and biosynthetic demands over the resting state. To meet these demands, T cells rewire their metabolic machinery to engage certain metabolic pathways including glycolysis (Michalek et al., 2011; Wang et al., 2011), which is largely anabolic. This phenomenon of reliance on glycolysis even when oxygen concentration is ample was initially observed by Dr. Warburg in most cancer cells, known as the Warburg effect (Warburg, 1956). Although glycolysis is a rather ineffective means to generate ATP as compared to OXPHOS, it is believed that T cells prefer glycolysis over OXPHOS because of its expedited production of ATP (100 times faster) and provision of necessary building blocks for the biosynthesis of fatty acids, nucleic acids, and amino acids. However, it becomes apparent that activated T cells also upregulate OXPHOS and cooperate both glycolysis and OXPHOS to meet the energetic demands, albeit the former becoming the dominant metabolic pathway (Fracchia and Walsh, 2015). Furthermore, mitochondrial OXPHOS-derived ROS is required for optimal T cell activation and expansion (Sena et al., 2013) and intact functional mitochondria serve as critical "bridges" between glycolytic metabolites to biosynthetic reactions such as lipogenesis that have been shown to be essential for T_{eff} cell differentiation. On the basis of these findings, we propose the glycolytic-lipogenic axis (connected by mitochondrial TCA cycle) as a key pathway in driving T cell function and differentiation (Fig. 1). We will dedicate our review by primarily focusing on this axis. For other metabolic regulation mechanisms, readers are encouraged to read other great recent reviews (Angajala et al., 2018; Hesterberg et al., 2018; Raud et al., 2018).

Among the four well-established T cell lineages (T_H1, T_H2, T_H17, and T_{reg}), T_H17 cells represent the newest member and have been widely ascribed as the culprit for the autoimmune pathology in patients with multiple sclerosis (MS), rheumatoid arthritis (RA), psoriasis, Crohn's disease, and ulcerative colitis (Han et al., 2015), which lack effective therapeutic interventions. Therefore, suppressing T_H17 cells as a cure to these autoimmune conditions has attracted intensive research endeavors. Interestingly, T_H17 cells are largely distributed to barrier sites like the intestine, lung, and skin with greater plasticity compared to other T cell subsets. This equips them an intrinsic adaptability to combat opportunistic pathogens and maintain epithelial barrier function by transdifferentiating into T_H1-like or T_{reg}-like cells (Ueno et al., 2018). In addition, some T_H17 cells display stemness markers and construct the $CD4^+$ T cell memory pool (Karmaus et al., 2019). Thus, T_H17 cells represent a functionally heterogenous effector T cell population. Understanding the metabolic control of T_H17 cell development and functional heterogeneity may manifest effective approaches to selectively impact T_H17 cells and cure autoimmune diseases. Given the intimate relationship between T_H17 and T_{reg} cells (shared requirement of TGF-β for their development and the functional and physical interaction of their respective master transcriptional factors: RORγt and Foxp3), T_{reg} cells will be also discussed in some studies.

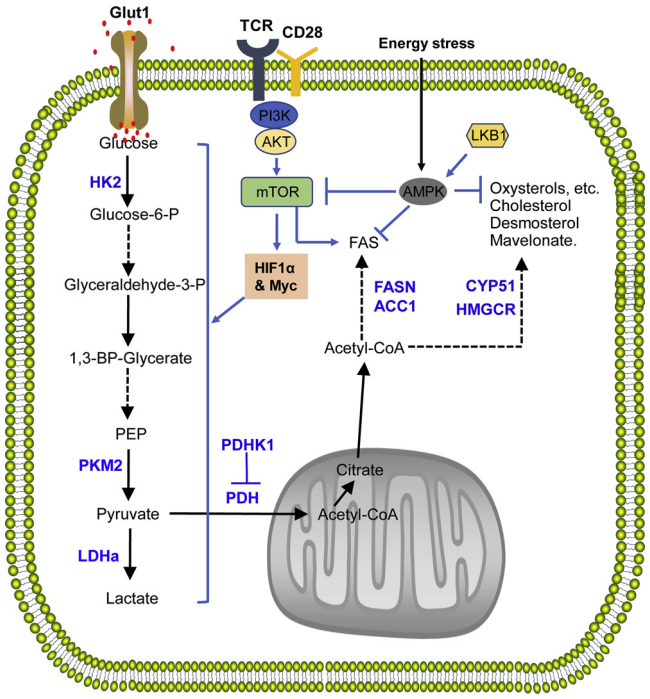

Fig. 1. The glycolytic-lipogenic pathway in T_H17 cells. HK2: hexokinase 2; PKM2: pyruvate kinase muscle isozyme M2; LDHa: lactate dehydrogenase A; PDH: pyruvate dehydrogenase; PDHK1: pyruvate dehydrogenase kinase 1; ACC1: acetyl-CoA carboxylase 1; FASN: fatty acid synthase; HMGCR: 3-hydroxy-3-methylglutaryl CoA reductase. Metabolic enzymes highlighted in **blue** are the ones that have been shown to be involved in T_H17 differentiation and function. Solid arrows indicate single-step reactions; dashed arrows indicate multiple steps involved (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

2. The mTOR-HIF1α/myc-glycolysis axis in T_H17 cells

During T_H17 differentiation, the signaling cascades initiated by TCR ligation, CD28-costimulation, cytokines, and other environmental cues (*e.g.*, nutrient, oxygen, energy, and stress levels) activate PI3K/Akt and the mechanistic target of rapamycin (mTOR), a central regulator of cell metabolism. mTOR signaling is transmitted *via* two complexes, mTORC1 containing the scaffolding protein RAPTOR and mTORC2 containing a distinct scaffolding protein RICTOR (Chi, 2012). Intriguingly, multiple studies using genetic mouse models revealed a selective role of mTORC1 (but not mTORC2) in T_H17 differentiation both *in vivo* and *in vitro* (Delgoffe et al., 2011; Sasaki et al., 2016). Correlative upregulation of mTORC1 but not mTORC2 has been observed in human autoimmune diseases mediated by T_H17 cells (Perl, 2016). The AMP activated protein kinase (AMPK), activated by low energy levels and regulated by liver kinase B1 (LKB1), can suppress the mTOR signaling by phosphorylating the TSC1/2 complexes, negative regulator of mTORC1. As such, deletion of upstream AMPK regulator LKB1 (MacIver et al., 2011) and AMPK downstream target TSC-1 (Mathis and Shoelson, 2011) in T cells predisposed naïve T cells to differentiate into T_H17, associated with greater mTORC1 activity. On the contrary, AMPK activation with AICAR (a direct activator) and metformin led to impaired T_H17 differentiation, associated with suppressed mTOR activation and its downstream target HIF1α (hypoxia inducible factor-1 α subunit) (Gualdoni et al., 2016; Sun et al., 2016). Besides inhibiting mTOR pathway and glycolysis, AMPK activation also increased fatty acid oxidation (FAO), a catabolic process with known inhibitory effects on

effector T cells, including T_H17 cells. Taken together, these studies indicated that the PI3K/AKT-mTORC1 (but not mTORC2) pathway and the LKB1-AMPK pathway serve as the interconnection mechanisms between environmental metabolic cues (*e.g.* nutrient and energy levels) and T cell commitment to effector T_H17 cells.

In line with a potential role of HIF1α in T_H17 cell differentiation, HIF1α expression in mouse T_H17 cells at both the mRNA and protein level is higher than other T cell subsets (T_H1, T_H2, and T_{reg}) (Dang et al., 2011; Shi et al., 2011). Further clear evidence comes from studies using mice with selective deletion of HIF1α in T cells, wherein HIF1α$^{-/-}$ T cells exhibit diminished T_H17 development and concomitantly enhanced T_{reg} induction (Dang et al., 2011; Shi et al., 2011). Although these independent studies reached similar conclusions, different underlying mechanisms were proposed: decreased glycolysis in HIF1α$^{-/-}$ T_H17 cells (described in details below) in our study (Shi et al., 2011) and differential interactions of HIF1α with RORγt and Foxp3 in the other (Dang et al., 2011) with transactivation of the former and proteasomal degradation of the latter. However, the precise mechanisms of how HIF1α exerts this reciprocal regulation of RORγt and Foxp3 remain to be determined. Consistent with these mouse studies, human T_H17 cells also require HIF1α for IL-17 production (Kastirr et al., 2015). Another important downstream target of mTOR signaling is Myc. While a prominent role of Myc in controlling metabolic reprogramming upon T cell activation has been reported (Wang et al., 2011), its role in T cell differentiation (including T_H17) is largely unknown. Our unpublished results using mice with T cell-specific Myc deletion (indicated by YFP expression) revealed that Myc deficient (YFP$^+$) T cells are impaired to differentiate into T_H17 cells and prone to become T_{reg} cells, similar to HIF1α$^{-/-}$ T cells, suggesting that T cell-intrinsic expression of Myc is also required for T_H17 differentiation.

mTOR, Myc, and HIF1α work in concert to ensure a smooth transition of T cell metabolism from FAO and pyruvate oxidation *via* the TCA cycle to the glycolytic, pentose-phosphate, and glutaminolytic pathways, during T cell activation and subsequent functional commitment to T_H17 cells. Perhaps, Myc initiates the metabolic reprogramming process and HIF1α sustains it (Shi et al., 2011; Wang et al., 2011). Although some recent studies suggest that enhanced activity of the pentose phosphate pathway and glutaminolysis, *via* integrating with glycolysis also contribute to T_H17 development by generating cellular building materials (Johnson et al., 2018; Yang et al., 2016), the majority of studies focus on the requirement of glycolysis in T_H17 differentiation. We reason that HIF1α in T cells drives T_H17 differentiation while simultaneously suppressing T_{reg} induction through maintaining the glycolytic activity in activated T cells (Shi et al., 2011). In support of this mechanism, we found that deletion of HIF1α reduced the expression of multiple glycolytic molecules, including Glut1 (the dominant glucose transporter on T cells), Hexokinase 2 (the first rate-limiting enzyme in glycolysis), pyruvate kinase muscle (the enzyme catalyzing the final step of glycolysis), and lactate dehydrogenase (the enzyme converting pyruvate to lactate) (Fig.1). Consistent with this notion, a recent study reported that acute myeloid leukemia cancer cells carrying gain-of-function mutation of isocitrate dehydrogenase (IDH) led to increased secretion of D-2-hydroxyglutarate (D-2HG), which was taken up by T cells, causing HIF1α destabilization and subsequent reduction of T_H17 and increase of T_{reg} cells (Bottcher et al., 2018). Moreover, inhibition of glycolysis with 2-DG (an inhibitor of all hexokinases) phenocopied the effect of HIF1α deficiency (Shi et al., 2011). Similarly, the HK-2 specific inhibitor 3-bromopyruvate also impaired T_H17 differentiation coupled with increased T_{reg} induction, pointing to an important role of hexokinase isoform HK-2 in this process (Okano et al., 2017). Pyruvate dehydrogenase (PDH) is a key bifurcation enzyme in the glycolytic pathway, which in its active dephosphorylated form moves pyruvate into mitochondria for TCA cycle and OXPHOS. Because of its crucial bifurcating function, PDH is under tight regulation of PDH kinases (PDHKs) that phosphorylates PDH to be inactive phosphorylated-PDH and PDH phosphatases (PDHPs) that dephosphorylates p-PDH to active dephosphorylated PDH. Intriguingly, PDHK1 was found to be only expressed in T_H17, but not T_H1 cells, and at low levels in T_{reg}. Inhibition or knockdown of PDHK1 selectively inhibited T_H17 and promoted T_{reg} (Gerriets et al., 2015). On the flip side, the inducible cAMP early repressor (ICER), overexpressed in CD4$^+$ T cells from patients with systemic lupus erythematosus (SLE, a type of autoimmunity), binds to PDHP2 and suppresses its expression, leading to reduced PDH activity, enhanced glycolysis, and subsequently increased T_H17 differentiation. PDHP2 overexpression reduced and shRNA-based suppression of PDHP2 increased T_H17 differentiation (Kono et al., 2018). The selective expression of PDHK1 (and thus inhibited PDH activity) in T_H17 cells directs pyruvate flow through lactate dehydrogenase-mediated reactions to produce the end product, lactate, which has long been regarded as a "waste" byproduct of glycolysis. However, a recent report showed that lactate accumulation in the synovial fluid of rheumatoid arthritis patients was actually responsible for CD4$^+$ T cell entrapment in the inflammatory site. Treatment of polarizing CD4$^+$ T cells with sodium lactate preferentially enhanced the production of IL-17 but not T_H1 and T_H2 signature cytokines (Haas et al., 2015). Collectively, these studies indicate a critical role of the mTOR-HIF1α/Myc-glycolysis axis in T_H17 differentiation, which is negatively regulated by AMPK activation.

3. The lipogenic pathway in T_H17 differentiation

We previously showed that in addition to increased glucose metabolism, activated T cells also promote lipid metabolism as an integral component of their metabolic reprogramming (Wang et al., 2011). This is not surprising, given that proliferating T cells have a massive need for building blocks such as fatty acids, phospholipids, and cholesterols to feed various cellular processes including membrane synthesis, ATP production, and signal transduction. What is more interesting is that a recent study reported that T_H17 cells primarily engaged de novo fatty acid synthesis (FAS) rather than utilizing already-available extracellular fatty acids for proliferation and differentiation (Berod et al., 2014). This is mediated by acetyl-CoA carboxylase 1 (ACC1) (catalyzing the carboxylation reaction of acetyl-CoA to malonyl-CoA, the first step in FAS), but not ACC2, which can be explained by their respective functions in FAS and fatty acid oxidation (FAO). Deletion of ACC1 in T cells or treated with an ACC1 pharmacological inhibitor, soraphen A (SorA) blocked T_H17 development. In association with reduced T_H17 differentiation, ACC1$^{-/-}$ T cells and SorA treatment strongly favored differentiation toward a functional T_{reg} phenotype, supported by enhanced uptake of exogenous fatty acid (favoring T_{reg} induction). Using the glucose tracing system, the authors revealed that T_H17 cells readily synthesized lipids from glucose, with increased expression of enzymes in the citrate-pyruvate shuttle system that transfer the final glycolytic product pyruvate into mitochondria to form acetyl-CoA and then citrate (part of TCA cycle), which then move out of mitochondria into the cytosol. In cytosol, citrate is converted to acetyl-CoA, which subsequently fuels FAS (Berod et al., 2014). More recently, another study found that fatty acid synthase (FASN), the multienzyme complex that mediates the conversion of acetyl-CoA and malonyl-CoA to saturated long-chain fatty acids, downstream of ACC1 also governs T_H17 differentiation (Young et al., 2017).

In addition to FAS, cytosolic acetyl-CoA can be catalyzed in the mevalonate-cholesterol synthetic pathway. Published studies found that statins, which inhibit the 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase (HMGCR), a rate-limiting enzyme in the mevalonate-cholesterol pathway, reduced T_H17 differentiation and decreased IL-17 production (Kagami et al., 2009; Zhang et al., 2008). Further mechanistic studies revealed that the cholesterol precursor (desmosterol) (Hu et al., 2015) and cholesterol derivatives, oxysterols (7β, 27-dihydroxy-cholesterol < 7β, 27−OHC > and 7α, 27−OHC) (Soroosh et al., 2014) can act as potent endogenous RORγt agonists to drive T_H17 differentiation and function. Using Azole-based inhibitors of CYP51 (an

enzyme downstream of HMGCR in the mevalonate and cholesterol synthesis pathway) and desmosterol (and desmosterol sulphate), Hu, et al. found that desmosterol exhibited selective activation of RORγt and T_H17 cells without overt effects on Foxp3 and IFN-γ expression during T_{reg} and T_H1 differentiation (Hu et al., 2015). The liver X receptor (LXR) is a negative regulator of T_H17 cells (Cui et al., 2011), which can be potentially activated by desmosterol. Interestingly, the authors did not observe LXR activation in their system, likely due to the low-affinity of desmosterol for LXR and the suppression of LXR by desmosterol sulphation (Hu et al., 2015). In the second study, Soroosh, et al. identified naturally occurring oxysterols (7β,27−OHC), derivatives of cholesterol as the most potent and selective activators for RORγt. They found that 7β,27−OHC directly binds to RORγt ligand binding domain (LBD) to enhance the differentiation of both murine and human T_H17 differentiation in a RORγt-dependent manner. T_H17, but T_H1 cells, preferentially produce these oxysterols. Furthermore, mice with deletion of CYP27A1, a key enzyme in generating these oxysterols, showed significant reduction of IL-17-producing cells (Soroosh et al., 2014). Collectively, these results establish a prominent role of lipogenic pathway in dictating T_H17 differentiation. However, a puzzling question arises, *i.e.*, why do T_H17 cells preferentially engage this futile and energy-wasteful FAS pathway for their differentiation and function, even in the presence of available exogenous fatty acids?

The glycolysis (under the regulation of mTOR, HIF1α and Myc) produces pyruvate, which can be either fermented to lactate by LDHa or enter the mitochondrial matrix where it gets oxidized and decarboxylated to acetyl-CoA *via* PDH. Mitochondrial acetyl-CoA combines with oxaloacetate (OAA) to produce citrate, a substantial proportion of which is transported out into the cytoplasm, where it is lysed *via* citrate lyase to generate cytosolic acetyl-CoA that serves as the precursor for downstream fatty acids, cholesterol and lipid biosynthesis. These biosynthetic processes are delicately regulated by coordinated actions of sterol response element binding proteins (SREBPs) and LXRs, with SREBPs increasing and LXRs removing intracellular cholesterol. Peroxisome proliferator-activated receptors (PPARs) are also involved in lipid homeostasis acting as coactivators of LXRs. As such, SREBPs induce cholesterol and lipid synthesis to meet the increased demands of rapid proliferation of activated T cells and T_H17 differentiation (Kidani et al., 2013). Conversely, activation of LXR with agonists GW3965 and T0901317 inhibits T_H17 cell differentiation and ameliorates T_H17-dependent EAE progression (Cui et al., 2011; Xu et al., 2009). Furthermore, activation of PPARs and deletion of PPARγ ameliorates and exacerbates EAE pathogenesis, respectively ((Dunn et al., 2010; Klotz et al., 2009). It is noteworthy to mention that mTOR signaling, in addition to boost glycolysis, also activates SREBPs (Kidani et al., 2013), constructing a closely-interacting loop between glycolysis and lipogenesis, namely, the glycolytic-lipogenic pathway in T_H17 development. As expected, activation of AMPK by madecassic acid inhibited ACC1 expression in T_H17 cells, leading to downregulation of RORγt and reduced T_H17 differentiation, associated with increased T_{reg}, but not much impact on T_H1 and T_H2 cells (Xu et al., 2017) (Fig. 1).

4. The glycolytic-lipogenic pathway in T_H17 pathogenicity

T_H17 cells exhibit diverse functions spanning from induction of tissue inflammation and autoimmune diseases (pathogenic) to maintenance of tissue homeostasis by enhancing barrier function of gut epithelial cells and preventing invasion of gut microflora (non-pathogenic). With the identified critical roles of the glycolytic-lipogenic pathway in T_H17 differentiation, a pertinent question to ask is whether it also controls the pathogenicity of T_H17 cell. In support of this, an early study showed that loss of Rheb, a critical regulator of mTORC1 signaling, in T cells impaired T_H17 differentiation and EAE progression (Delgoffe et al., 2011). To further pinpoint the downstream targets of mTORC1 signaling in regulating the pathogenicity of T_H17 cells, Sasaki et al. reported that deletion of $p70^{S6KI}$ downregulated T_H17-associated genes such as *Il17a*, *Il17f*, and *Il23r* without overt reduction of T_{reg}, T_H1, or T_H2 differentiation, supporting a selective role of $p70^{S6KI}$ in T_H17 cell differentiation (Sasaki et al., 2016). Consistent with reduced T_H17 differentiation and pathogenicity, EAE progression in $p70^{S6KI}$ knockout mice was delayed (Sasaki et al., 2016). HIF1α in T cells is also required for the pathogenicity of T_H17 cells. Using a T_H17-polarized transfer model of EAE, we found that deletion of HIF1α in T_H17 cells led to delayed development of EAE, indicative of reduced pathogenicity of $HIF1\alpha^{-/-}$ T_H17 cells (Shi et al., 2011). In support of a role of glycolysis in driving pathogenicity of T_H17 cells, our unpublished results showed that administration of glycolytic inhibitor 2-DG significantly suppressed pathogenesis of EAE *in vivo*. Most recently, Hongbo Chi group characterized heterogeneous T_H17 cells based on the expression of CD27, TCF-1, and T-bet. While $CD27^{+}TCF\text{-}1^{hi}$ T_H17 cells possess stemness-associated features but lower anabolic metabolism (non-pathogenic T_H17 cell-like), $CD27^{-}T\text{-}bet^{hi}$ T_H17 cells have higher metabolic activity that supports their transdifferentiation into T_H1-like cells (analogous to pathogenic T_H17 cells). More importantly, disruption of mTORC1 or glycolytic inhibition with 2-DG prevented the development of T_H1-like $CD27^{-}T\text{-}bet^{hi}$ T_H17 cells and failed to induce autoimmune inflammation, but instead upregulated TCF-1 expression and acquired stemness-associated features, clearly supporting that mTORC1 and glycolysis control the pathogenicity of T_H17 cells (Karmaus et al., 2019). Paradoxically, a recent study indicated that too strong co-stimulation with anti-CD28 actually suppressed induction of T_H17 transcriptional program and rendered T_H17 cells more immunosuppressive (at least in human T cells activated under *in vitro* conditions). Instead, cytokines (IL-23 and IL-1β) provided sufficient (just right) stimulation for metabolic reprogramming and avoidance of anergy, representing a Goldilocks principle of metabolic reprogramming in T_H17 cell differentiation (Revu et al., 2018). Furthermore, Volchenkov, et al. reported that isolated human T cells that were exposed to hypoxia *in vitro*, a commonly-encountered feature in inflammatory conditions and tumor microenvironment, increased HIF1α expression and reduced AMPK activities, coupled with greater glycolysis and reduced OXPHOS and ETC (electron transport chain). However, no obvious increase of IL-17 was observed, but the production of anti-inflammatory cytokine IL-10 in T_H17 cells was significantly augmented (Volchenkov et al., 2017), indicating hypoxia drives a more immunosuppressive phenotype of human T_H17 cells. How these *in vitro* results in human T_H17 cells are related to *in vivo* settings awaits further investigations, as clearly there are some distinct metabolic features differing between *in vitro* differentiated T_H17 cells (more glycolytic) and *in vivo* formed T_H17 cells (more oxidative) (Franchi et al., 2017). *In vitro* generated T_H17 cells displayed greater metabolic flexibility than *in vivo* developed T_H17 cells when treated with oligomycin (an inhibitor of OXPHOS) by increasing their glycolytic activity, which is controlled by PDHK1 but not HIF1α (Franchi et al., 2017).

In terms of the importance of lipid metabolism in T_H17 cell pathogenicity, Vijay Kuchroo group conducted single-cell RNA-sequencing of T_H17 cells isolated from *in vivo* autoimmune lesions or generated *in vitro* under pathogenic or non-pathogenic polarizing conditions. Their results implicated *Cd5l*, encoding CD5 antigen-like (CD5L) protein, as a regulator of T_H17 cell pathogenicity (Gaublomme et al., 2015). Loss of CD5L converts non-pathogenic T_H17 cells into pathogenic ones (disease-inducing). Considering CD5L is a member of the scavenger receptor cysteine-rich superfamily involved in lipid metabolism with specific function in inhibiting fatty acid synthase (FASN) (Kurokawa et al., 2010), the authors profiled the lipidome of WT and $CD5L^{-/-}$ T_H17 cells and revealed that CD5L maintains the intracellular balance between polyunsaturated and saturated fatty acids by decreasing the level of the former and by downregulating *Cyp51* and *Sc4mol*, two enzymes of the cholesterol synthesis pathway responsible for synthesizing ligands for RORγt. These authors argued that these alterations of fatty acids might promote RORγt binding at the anti-inflammatory genes (*Il10)* and prevent binding at the *Il17a* and *Il23r* loci (pro-inflammatory

genes) in T_H17 cells (Wang et al., 2015), thus modulating T_H17 pathogenicity.

5. Concluding remarks

Provided the prominent role of T_H17 cells in many autoimmune conditions (Han et al., 2015), how to specifically targeting T_H17 cells without imparting other T_{eff} and T_{reg} is the key to inventing novel therapies to treat these refractory diseases. Exciting advents in immunometabolism indicate that cellular metabolism underpins the fate decisions of T cells (T_H17 vs T_{reg}) (Jones and Thompson, 2007; Michalek et al., 2011; Shi et al., 2011). Here, we reviewed studies on how the glycolytic-lipogenic axis orchestrates T_H17 differentiation and function. Three potential targets have been identified in this pathway with selective effects on T_H17 cells and can be potentially utilized to treat T_H17-mediated autoimmune conditions: 1. $p70^{S6K1}$ (a downstream target of activated mTORC1 signaling): $p70^{S6K1}$ blocks T_H17-cell development by limiting chromatin accessibility through acetylation of histone 3 in the regulatory sequences near the *Il17* gene (Sasaki et al., 2016), which represents a reversible reaction and likely has limited and controllable toxicity; however, how to selectively suppress $p70^{S6K1}$ remain to be explored. 2. The PDH-PDHK1 pair: PDH is the key bifurcation enzyme in the glycolytic-lipogenic pathway whose activity controls the metabolic flow of pyruvate either through LDHa-mediated fermentation to lactate or into the mitochondria and subsequent lipogenesis; PDH activity is under tight control of PDHKs and PDHPs; PDHK1 inhibitor DCA showed impressive results in mice bearing autoimmune disease (Gerriets et al., 2015) and has been tested in clinical trials (James et al., 2017); additional results will become available in the near future. 3. Desmosterol: desmosterol is the precursor of cholesterol synthesis; strong experimental evidence exists in support of a selective role of desmosterol in T_H17 differentiation in animal studies (administration of statins as inhibitors of HMGCR or Azole-based ketoconazole, clotrimazole and econazole as CYP51 inhibitors resulted in reduction of desmosterol) (Hu et al., 2015; Kagami et al., 2009; Zhang et al., 2008), which need to be further tested in clinical trials. Whether or not these targets represent the Archilles' heel in curing the refractory autoimmune diseases mediated by T_H17 cells awaits further systemic investigations.

Despite the above-identified metabolic checkpoints specific in T_H17 cell differentiation and pathogenicity, several challenges remain: 1. Given the differences between human and mouse T_H17 cells (Annunziato et al., 2009), further characterization and mechanistic understanding are needed to determine the feasibility of targeting these metabolic checkpoints in patients with autoimmune diseases, To this end and provided the impracticability of carrying out *in vivo* studies in patients, a reliable *in vitro* T_H17 system that largely recapitulates the *in vivo* conditions is urgently needed. So far, most of the *in vitro* studies have been conducted in nutrient-rich (*e.g.*, glucose concentration: ~25 mM) and ambient oxygen level (~21%), which are much higher than *in vivo* inflammatory environment (physiological glucose concentration is ~5 mM and oxygen level is less than 2%). Even for those studies that did consider these limitations, in most cases, only a single factor was assessed, be it either hypoxia or glucose depletion or others (pH value, *etc.*). 2. *In vivo* developed T_H17 cells display a more oxidative metabolic phenotype than *in vitro* differentiated T_H17 cells (Franchi et al., 2017), which are predominantly anabolic and glycolytic. In this regard, *in vivo* results hold greater practical value than *in vitro* data, but *in vitro* systems offer powerful tools for mechanistic studies. Currently, *in vivo* studies primarily rely on pharmacological inhibitors and genetic animal models wherein the genes of interest are either specifically deleted in T cells or in all the cells (germ-line deletion). The caveats with these *in vivo* systems are non-specific effects associated with the inhibitors and compensatory upregulation of other genes with overlapping functions of the deleted genes. A combination of both approaches with consistent results would offer greater strength of validity. 3. From the therapeutic standpoint of view, T_H17 cells already pre-exist in the autoimmune pathologies. How to suppress their pathologic functions holds the key to successful cure of autoimmune diseases. While it is important to understand how T_H17 differentiation is metabolically regulated, much more work is warranted to metabolically modulate already fully-differentiated T_H17 cells. 4. In spite of opposite functions of non-pathogenic and pathogenic T_H17 cells, they both require the T_H17 master transcription factor RORγt for their development. Identification of the transcriptional factors that can interact with RORγt and juggle T_H17 cells' functionality from being pathogenic to non-pathogenic will be important in therapeutic development. Fan Pan group reported differential roles of HIF1α when it is bound to RORγt and Foxp3, leading to activation of the former and proteasomal degradation of the latter (Dang et al., 2011). An unanswered question is whether these distinct outcomes of interaction are due to differential metabolic alterations in T_H17 and T_{reg} cells mediated by HIF1α. The results that hypoxia can dramatically increase the expression of anti-inflammatory IL-10 in T_H17 cells (Volchenkov et al., 2017) suggest that environmental metabolic cues also play a key role in governing the functionality of T_H17 cells. Further illustration of the metabolites and binding partners that selectively dampen the pathogenicity of T_H17 cells will shed new light on therapeutic targets. 5. Intriguingly, T cells isolated from SLE patients express much higher level of PFKFB3 (6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3, a rate-limiting enzyme in glycolysis) and are much more glycolytic, as compared to T cells harvested from patients with rheumatoid arthritis (another common autoimmune disorder) (Yang et al., 2013). This observation suggests tailor-made therapeutic strategy should be designed for different types of autoimmunity and the "one-size-fits-all" approach might not be ideal. With the rapid advancement of technology and exciting findings in the immune-metabolism field, we envision promising metabolic therapeutics for autoimmune diseases might be just around the corner, after witnessing the revolutionary changes in the field of cancer care in recent years.

Lastly, although we focus in this review on the glycolytic-lipogenic pathway in T_H17 cells, given the shared the metabolic reprogramming among other effector T cells (T_H1, T_H2, T_H9, T_H22, T_{FH}, *etc.*), some of the discussed regulators might also play important roles in those T cell lineages (those without selective effects on T_H17 cells). In addition, amino acid metabolism also contributes to T_H17 differentiation (Johnson et al., 2018; Sundrud et al., 2009), which is only briefly mentioned here. For further details, please refer to other reviews (Barbi et al., 2013; Ren et al., 2017; Wei et al., 2017).

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