

Metabolic Control of Th17 Cell Generation and CNS Inflammation

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Abstract

Multiple sclerosis (MS), an inflammatory demyelinating disease of the central nervous system (CNS), results from uncontrolled auto reactive T cells that infiltrate the CNS and attack the myelin sheath. Th17 cells play a prominent role in the pathogenesis of MS and experimental autoimmune encephalomyelitis (EAE), a mouse model of MS. Extensive studies have focused on understanding the roles of cytokine signaling and transcriptional network in the differentiation of Th17 cells and their pathogenicity in CNS inflammation. Aside from these events, activated T cells dynamically reprogram their metabolic pathways to fulfill the bioenergetic and biosynthetic requirements for proper T cell functions. Emerging evidence indicates that modulation of these metabolic pathways impinges upon the differentiation of Th17 cells and the pathogenesis of EAE. Thus, a better understanding of the functions and mechanisms of T cell metabolism in Th17 cell biology may provide new avenues for therapeutic targeting of MS. In this review, we discuss the recent advances in our understanding of T cell metabolic pathways involved in Th17 cell differentiation and CNS inflammation.

Keywords: CNS inflammation; Autoimmune disease; T cell metabolism

Introduction

To ensure proper electrical activity of neurons, the central nervous system (CNS) strictly controls immune cell entry across the blood-brain barrier (BBB). Multiple sclerosis (MS) is an autoimmune disease initiated by auto reactive T cells, which break down BBB and gain the access to CNS where they cause inflammation and demyelination. MS is one of the most common idiopathic inflammatory demyelinating diseases in young adults, affecting more than 2.5 million people worldwide. On the basis of clinical symptoms and course, MS is divided into relapsing remitting (RR), primary progressive (PP), and secondary progressive (SP) subtypes [1].

The principal animal model of MS, experimental sclerosis encephalomyelitis (EAE), has been widely utilized to investigate the function of myelin antigen-specific CD4⁺ T helper (Th) cells that mediate dysregulated immune functions in the CNS. Based on unique cytokine production, effector Th cells are categorized into various subsets, such as Th1, Th2 and Th17 cells, which are implicated in distinct protective and pathogenic immune responses [2]. Although Th1 cells were originally considered as the pathogenic effector cells for neuroinflammation, recent studies indicate that Th17 cells play a key role in the pathogenesis of MS [3]. Th17 cells are characterized by producing IL-17A, IL-17F, IL-21 and IL-22, and mediate protective functions for the clearance of extracellular pathogens during infection [3]. The differentiation of Th17 cells can be induced by proinflammatory cytokines in TGF- β dependent and independent ways [4,5]. The proinflammatory cytokine IL-6, together with TGF- β , drive the expression of Th17-specific transcription factor ROR γ t and the differentiation of Th17 cells. In the absence of TGF- β , a combination of proinflammatory cytokines IL-1 β , IL-6 and IL-23 induces differentiation of Th17 cells and promote the pathogenesis of EAE [5]. Blockade of TGF- β or IL-23 signaling markedly suppresses Th17 differentiation and ameliorates EAE progression [6,7]. Moreover, genome-wide associated studies of MS patients reveal that several genetic risk factors are associated with IL-23/Th17 axis [1]. Recent studies also uncovered the critical role of the cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF) in IL-23-mediated

EAE pathogenesis. IL-23 induces the expression of GM-CSF by Th17 cells, which in turn enhances the production of IL-23 by dendritic cells (DCs) [8,9]. This IL-23-Th17-GM-CSF circuit promotes both sustained Th17 responses and the de novo generation of pathogenic Th17 cells. These studies indicate that the complex interaction of various cytokines and inflammatory factors dictates the pathogenicity of Th17 cells and disease outcome.

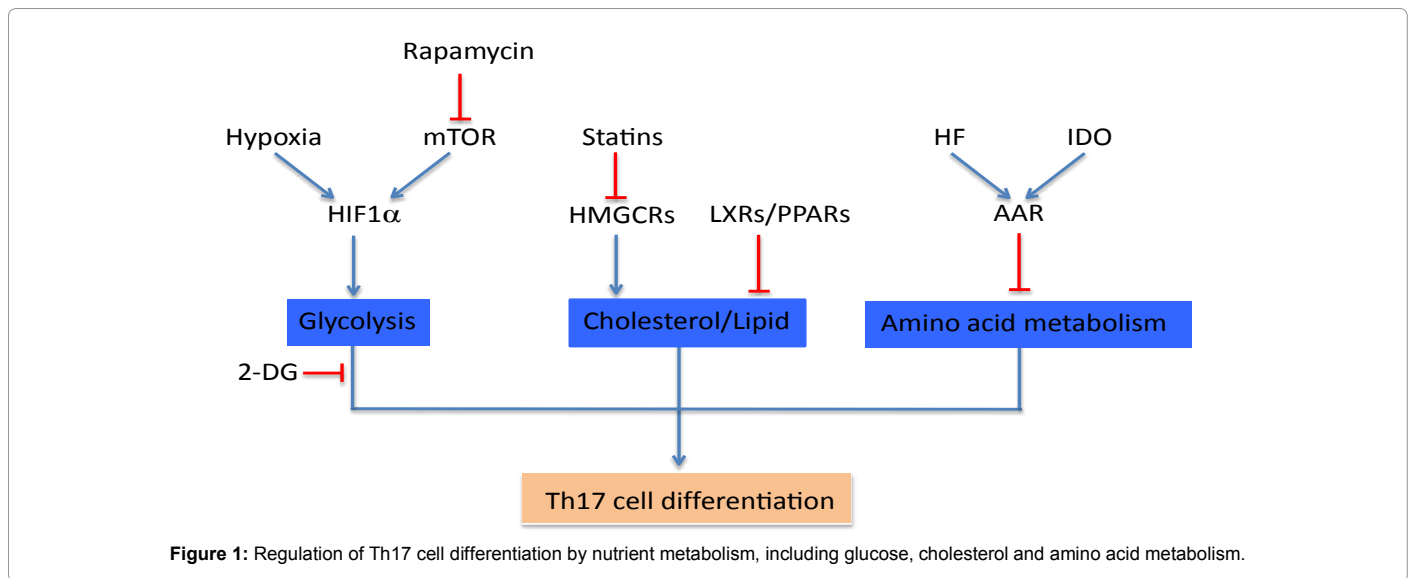
Aside from the regulation by cytokine signaling, emerging evidence highlights that T cell metabolism is an important regulator of T cell fate decisions and functions. To meet the bioenergetic and biosynthetic demands at various states, including development, maintenance, activation and differentiation, T cells dynamically reprogram cellular metabolic pathways [10-13]. In the quiescent state, naive T cells generate ATP through catabolic metabolism, including oxidative phosphorylation (OXPHOS) of glucose, amino acid and lipids in mitochondria. In contrast, antigen-primed T cells switch from catabolism to anabolism, characterized by marked upregulation of glycolysis, glutaminolysis and biosynthetic activities, for rapid clonal expansion [14]. Distinct metabolic requirements have also been implicated in the control of different T cell subsets for their specific functions in immunity and inflammation [15,16]. Conversely, modulation of specific metabolic pathways can suppress pathogenic T cell responses, for example, the differentiation of Th17 cells and EAE pathogenesis [16]. In this review, we discuss the current understanding of the regulation, function and targeting of T cell metabolism and the associated regulatory pathways in Th17 cell differentiation and CNS inflammation (Figure 1).

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Glucose Metabolism and the mTOR-HIF1 α Signaling Axis

Glucose metabolism provides critical bioenergetic and biosynthetic support for proper T cell functions. Quiescent T cells catabolically utilize glucose-derived pyruvate along with lipids and amino acids to generate ATP for their survival. Upon antigen stimulation, activated T cells upregulate glucose transporter Glut1 and hence elevate glucose availability. Further, they switch to aerobic glycolysis to provide essential metabolic intermediates for biosynthesis of macromolecules. This metabolic shift is required to meet the increased bioenergetic and biosynthetic demands for rapid clonal expansion during immune responses. Blockade of glucose metabolism markedly suppresses T cell activation and proliferation [14,17].

Aside from its role in T cell activation and proliferation, glucose metabolism also impinges upon Th17 cell differentiation and the pathogenesis of EAE. As compared with induced Treg (iTreg) cells, Th17 cells have much higher glycolytic activity, associated with elevated expression of metabolic genes involved in the glycolytic pathway [15,16]. Glut1-transgenic T cells enhance glucose uptake and glycolytic activity, and manifest increased IL-17 production in aged mice [17]. Compared with other Th subsets, Th17 cells selectively express the transcription factor HIF1 α that regulates the expression of genes involved in the glycolytic pathway. The specific ablation of HIF1 α in T cells reciprocally affects Th17 and iTreg cell generation, indicated by reduced expression of the Th17 family cytokines IL-17A, IL-17F, IL-21 and IL-22, and upregulated expression of Treg-specific transcription factor Foxp3 [16]. Additionally, HIF1 α -deficient T cells have defective expression of IL-23R, but maintain expression of Th17 transcription factors ROR- γ t and ROR- α . Analysis of global gene expression profiles reveals that glycolytic or related metabolic pathways are significantly diminished in HIF1 α -deficient T cells [16]. Similar as HIF1 α deficiency, inhibition of glycolysis by the pharmacological inhibitor 2-deoxyglucose (2-DG) also results in reciprocal changes of Th17 and iTreg cell generation [16]. In EAE mice, increased glycolysis has been observed in infiltrating lymphocytes in the spinal cord [18]. Blockade of glycolysis by HIF1 α deletion or 2-DG treatment ameliorates the development of EAE [16,19]. These results demonstrate that HIF1 α -dependent glycolysis functions as a metabolic checkpoint for the differentiation of Th17 cells.

HIF1 α expression in T cells is regulated at both transcriptional and post-transcriptional levels. Shi et al. revealed that signaling via mechanistic target of rapamycin (mTOR) acts as an important upstream pathway to induce HIF1 α transcription [16]. mTOR, an evolutionally conserved serine and threonine kinase, has been recently implicated in the integration of immune signals and metabolic cues in lymphocyte proliferation, differentiation and survival [10,11,13]. Rapamycin, a specific mTOR inhibitor, inhibits the transcription of HIF1 α . Similar as HIF1 α deficiency, treatment of cells with rapamycin suppresses the expression of glycolytic genes and IL-17 [16]. Genetic evidence also indicates the important role of mTOR in Th17 cell differentiation [20,21]. In agreement with these observations, rapamycin treatment ameliorates the clinical course of EAE [22-24]. Given the similar effects of blocking mTOR, HIF1 α and glycolysis on Th17 cell differentiation and the relationship between these pathways, these studies highlight the important roles of the mTOR-HIF1 α -glycolysis axis in Th17 cell differentiation. The stability of the HIF1 α protein is tightly regulated by hypoxia. Dang et al. described that hypoxia-stabilized HIF1 α promotes Th17 cell differentiation via promoting ROR γ t activity and inducing Foxp3 degradation [19]. In agreement with the role of hypoxia in Th17 cell differentiation, a recent study indicates that hypoxia followed by reoxygenation accelerates Th17 cell differentiation in an mTORC1-HIF1 α -dependent manner [25]. These studies indicate that mTOR signaling and hypoxia conditions are critical regulators of HIF1 α expression in Th17 cell differentiation, and highlight that modulation of HIF1 α function or the glycolytic pathway is a potential therapeutic strategy for the treatment of MS patients.

Amino Acid Metabolism and IDO Functions

T lymphocytes regulate uptake of essential amino acids from microenvironment to meet the metabolic demands of an immune response [14,26]. Blockade of amino acid metabolism in T cells induces metabolic energy, indicated by defective proliferation upon TCR stimulation [27]. The relative abundance of amino acids in the immune microenvironment may therefore establish a fundamental metabolic requirement for proper T cell-mediated immune responses.

A recent study by Sundrud et al. reported that induction of amino acid starvation response (AAR) by a small molecule compound halofuginone (HF) attenuates Th17 cell differentiation and EAE

pathogenesis [28]. HF is a derivative of the plant alkaloid febrifugine used in traditional Chinese medicine to reduce malarial fever [29]. Treatment of T cells with HF selectively impairs Th17 cell differentiation without affecting other Th subsets, and reciprocally promotes iTreg generation. HF induces AAR by downregulating expression of genes involved in amino acid transports, biogenesis and protein synthesis. The starvation of amino acids activates the kinase GCN2, which has been recently shown to mediate the remission phase of EAE in mice [30]. Addition of excess amino acids restores the defective Th17 cell differentiation in HF-treated cells. In line with these observations, HF treatment significantly ameliorates the pathogenesis in an active EAE mouse model; however, it cannot provide protection in the passive EAE model, indicating that HF inhibits Th17 cell differentiation, but not the effector function of developed Th17 cells [28].

Metabolism of tryptophan, one of the essential amino acids, by the enzyme indoleamine 2,3-dioxygenase (IDO) plays an important role in the control of EAE pathogenesis. IDO is an inducible tryptophan-degrading enzyme, expressed by DCs and other immune cells. IDO causes the breakdown of tryptophan and induces localized amino acid depletion, leading to cytoprotective AAR and activation of GCN2 [31]. IDO promotes immune tolerance in part by affecting generation of T effector cells and iTreg cells [32-34]. Specifically, IDO suppresses the differentiation of Th1 and Th17 cells, but enhances the generation of iTreg cells and maintains Treg cell function [32,33]. Consistent with the effects of IDO on T cell differentiation in vitro, IDO expressed by DCs suppresses EAE [34,35]. Moreover, IDO-deficient mice develop more severe EAE, associated with the enhanced generation of Th17 cells but reduced Treg cells [34]. The Tryptophan metabolite 3-hydroxyanthranilic acid (3-HAA) plays an important role in mediating IDO-induced immune tolerance via affecting the generation of Treg cells [34]. Administration of 3-HAA at the early phase of EAE ameliorates the disease progression, but starting the treatment at the peak of EAE has no therapeutic effects [34]. Whereas the underlying mechanism remains to be further investigated, these studies establish the link of regulation of amino acid availability to the fate decisions of Th17 and Treg populations.

Lipid and Cholesterol Metabolism and LXR/PPAR Functions

Cholesterol is a vital constituent of cell membrane and modulates membrane fluidity and permeability. Activated T cells markedly enhance cholesterol synthesis, and blockade of cholesterol synthesis suppresses the differentiation of Th17 cells and neuroinflammation. 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase (HMGCR), a rate-limiting enzyme of the mevalonate pathway that produces cholesterol and other isoprenoids, is the molecular target of the cholesterol-lowering drugs statins. Administration of statins inhibits Th17 cell differentiation by directly suppressing the expression of Th17-transcription factor ROR γ t [36,37], as well as indirectly by targeting DCs to modulate cytokine expression and antigen presentation [36,37]. Mevalonic acid, a downstream metabolite of HMGCR, restores Th17 cell differentiation in statin-treated cells [36,37]. Statins also suppress Th17 cell differentiation in CD4⁺ T cells derived from patients with multiple sclerosis [38]. In line with these observations, statin treatment ameliorates the pathogenesis of EAE [39-41].

Transcriptional regulators of cholesterol and lipid metabolism have been also implicated in the control of Th17 cell differentiation. Liver X receptors (LXRs), a member of nuclear receptors, are activated by endogenous oxysterols (oxidized derivatives of cholesterol) and thus act as cholesterol sensors. When cellular oxysterols accumulate

due to increasing concentration of cholesterol, LXRs are activated and induce expression of genes required to eliminate cellular cholesterol [42]. Systemic administration of LXR agonists GW3965 and T0901317 inhibits Th17 cell differentiation [43,44] and ameliorates EAE progression [44]. In contrast, LXR deficiency promotes the generation of Th17 cells and exacerbates the disease [44]. Another type of nuclear receptors, peroxisome proliferator-activated receptors (PPARs), play a well-defined role in regulating lipid homeostasis, and can function as coactivators of LXRs. PPARs are important negative regulators of Th17 cell differentiation. Accordingly, treatment of mice with synthetic agonists of PPARs ameliorates EAE, and deficiency of PPAR γ or PPAR δ exacerbates EAE pathogenesis [45-47]. These studies highlight that modulation of cholesterol and lipid synthesis is a promising therapeutic approach for MS.

High Salt Diet and SGK1 Functions

The etiology of MS is driven by multiple factors, such as genetics, immunity and environment. Genetic risk factors are associated with the IL23-Th17 axis that is pivotal for the pathogenicity of Th17 cells and the development of EAE [1]. How environmental factors contribute to these processes remains less understood. Two recent studies reported that high salt diet is an environmental risk factor in the development of EAE through enhancing the pathogenicity of Th17 cells, in a manner dependent upon IL-23R signaling [48,49].

Kleinewietfeld et al. reported that high concentration of NaCl selectively enhances the differentiation of Th17 cells, but not Th1 or Th2 cells [48]. Microarray analysis reveals that NaCl treatment markedly promotes expression of key signature molecules of Th17 cells, including IL-17A, IL-17F, ROR γ t, and IL-23R, as well as GM-CSF and CCR6 that mediates the enhanced pathogenicity of Th17 cells. In agreement with the in vitro observations, mice with high-salt diet exhibit accelerated onset and increased severity of EAE, associated with augmented infiltration of Th17 cells into the spinal cord [48]. Mechanistically, increased NaCl concentration activates the p38 MAPK pathway to enhance the expression of SGK1 and NFAT5, both of which contribute to Th17 cell differentiation, although whether p38 MAPK signaling in T cells directly regulates Th17 cell generation is unclear [50]. Wu et al also studied the effects of high salt diet on EAE pathogenesis and the underlying molecular basis [49]. From transcriptional profiling of developing Th17 cells, the authors identified SGK1 as a critical signaling node downstream of IL-23R signaling. SGK1 expression is specifically induced and maintained by exposure to IL-23. In turn, SGK1 promotes IL-23R expression through inactivating transcription factor Foxo1, which is an inhibitor of IL-23R expression.

Furthermore, SGK1 deficiency impairs IL-17A expression in response to IL-23 stimulation but not in response to TGF- β and IL-6 stimulation, indicating the critical role of SGK1 in mediating IL-23R-dependent stability and maintenance of Th17 cells. Importantly, SGK1 expression is induced by high salt, and loss of SGK1 in T cells protects the mice from high-salt-mediated exacerbation of EAE [49]. These studies establish the pathogenic effects of high salt diet in EAE pathogenesis and the underlying signaling mechanisms. They further highlight that reduced intake of high salt diet may prevent the development of MS, and targeting SGK1 or related molecular pathways may have beneficial effects in MS patients.

Concluding Remarks

For the development of effective drugs to target autoimmune neuroinflammation, much emphasis is placed on understanding the mechanisms underlying the differentiation and pathogenicity of Th17

cells. These studies have led to the identification of the pivotal role of the IL-23/Th17/GM-CSF axis in the generation of pathogenic Th17 cells. Emerging evidence also highlights the fundamental importance of T cell metabolism in the regulation of T cell responses, such as T cell survival, proliferation and differentiation. In particular, recent studies have established the roles of specific metabolic pathways in Th17 cell differentiation, and modulation of these pathways manifests therapeutic opportunities to target CNS inflammation. Continued investigation on the interplay of immune signals and metabolic cue and metabolic signatures of pathogenic Th17 cells will likely facilitate the development of novel therapeutic strategies to restore the dysregulated immune responses in MS. At the mechanistic level, the integrated use of mouse genetic and pharmacological approaches and the EAE model will be a powerful strategy to further define the regulation and function of specific metabolic pathways in the generation and pathogenicity of Th17 cells.

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