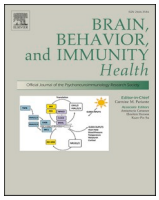
Brain, Behavior, & Immunity - Health 43 (2025) 100928

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx



Interaction between Th17 and central nervous system in multiple sclerosis

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ARTICLE INFO

Keywords:
Multiple sclerosis
CNS
Immune therapy
Th17
Cytokine network

1. Introduction

Multiple sclerosis (MS) is a dominant cause of disability of the nervous system with autoimmune disorders, raising the risks of depression, hypertension, osteoporosis, etc. (Tian et al., 2020; Walton et al., 2020). The high disease incidence of MS has been indicated since 2000. (Koch-Henriksen and Magyari, 2021). Chronic autoimmune neuroinflammation in MS causes the blockade of nerve conduction and various functional disorders such as eye dysfunction (Tian et al., 2020; Marcus, 2022). Currently, a cohort study with approximately seventeen thousand participants indicates that half of MS patients suffer from comorbidities, including depression, anxiety, hypertension, and hyperlipidemia (Salter et al., 2024). These findings indicate that multiple factors may influence the disease activities and outcomes of MS.

Th17 cells, first identified in 2005, are one major component in the neuroinflammation of MS (Harrington et al., 2005). Accumulating evidence has indicated the massive infiltration of Th17 cells into the central nervous system (CNS) with interleukin-17 (IL-17) secretion (Beurel and Lowell, 2018). During the progressive stage of MS, a high proportion of Th17 cells is detected in the CNS lesions and the cerebrospinal fluid (CSF) (Kaskow and Baecher-Allan, 2018). CNS-infiltrated Th17 cells may directly cause neurological disorders in MS. The MS patients with epilepsy show higher IL-17A levels in CSF (Bautista et al., 2003). Importantly, the clinical trials in relapsing-remitting multiple sclerosis (RRMS) patients show reduced relapse rates as well as an obvious decline of lesion activity with the IL-17-neutralized monoclonal antibody treatment (Elain et al., 2014).

The CNS-infiltrated Th17 cells interact with tissue cells. For instance, the IL-17A secreted from infiltrated Th17 cells leads to apoptosis of oligodendrocytes and results in demyelination. Moreover, IL-17 induces neuronal cell death by direct cell-cell interaction and neuronal toxicity with Ca^{2+} overload (Siffrin et al., 2010). Importantly, Th17 cell-related cytokines upregulate the expression of IL-23R in neurons, resulting in increased levels of caspase 3 which marks the apoptosis of neuronal cells (Sonar et al., 2024). In the animal model of MS, experimental autoimmune encephalomyelitis (EAE), mice are immunized with the self-antigen of myelin protein to induce CNS autoimmune inflammation (Procaccini et al., 2015). During the induction, Th17 cells traverse the blood-brain barrier (BBB) *via* the IL-17A secretion and C-C chemokine receptor 6 (CCR6) expression (Y. Shi et al., 2022). CCL20 is upregulated in the EAE choroid plexus and guides the Th17 cells entering CNS *via* the CCL20-CCR6 axis. The number of Th17 cells significantly declines in the CNS of $CCR6^{-/-}$ EAE mice with ameliorated disease progression (Reboldi et al., 2009; Robinson et al., 2014). Therefore, the infiltration of Th17 cells into the CNS is directly linked to disease severity in MS pathogenesis (Robinson et al., 2014). Notably, the direct axonal and neuronal injury are mediated by Th17 cells. Th17 cells form immune-neuronal synapses with neurons, leading to the elevation of intracellular Ca^{2+} in neurons (Siffrin et al., 2010).

The critical function of Th17 cells is also observed in EAE using the two-photon microscopy. Th17 cells directly cause the axonal transection and initiate neuronal death with Ca^{2+} fluctuations. Moreover, Th17 cell infiltration is also related to the recruitment of other immune cells into the CNS, such as neutrophils (Beurel and Lowell, 2018). Therefore, Th17 cells play crucial roles in the neurological damage of MS. The interaction between Th17 cells and CNS tissue cells may provide novel therapeutic targets for the treatment of MS.

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https://doi.org/10.1016/j.bbih.2024.100928
Received 3 October 2024; Received in revised form 18 December 2024; Accepted 21 December 2024
Available online 24 December 2024

2. The Th17 cell generation during MS development

Accumulating evidence indicates that the pathogenicity and plasticity of Th17 cells are dependent on the distinct cytokines, including IL-1β, IL-6, IL-23, TGF-β, TNF-α and so on (B. Wu et al., 2021). Distinct genetic programs related to cytokines trigger the pathogenicity of Th17 cells and the expression of retinoic acid-related orphan nuclear receptor γt (RORγt). Key transportation factors in Th17 cell generation include RORγt, IRF4, Runx1, bHLH, and so on (Ciofani et al., 2012; C. C. Lin et al., 2016a).

2.1. The cytokine related to Th17 cell differentiation in MS

Elevated levels of IL-1β, IL-6, IL-23, TGF-β and TNF-α have been reported in the serum and CNS of MS patients (D. W. Luchtman et al., 2014). IL-1β, IL-6, and IL-23-induced Th17 cells exhibit higher pathogenic features than the TGF-β and IL-6-triggered Th17 subsets (Ichiyama et al., 2016). In EAE mice, Th17 cells driven by IL-23 and IL-1β directly contribute to the disease severity (Mills, 2023) (Fig. 1).

IL-6 is critical in the differentiation of Th17 cells by promoting the expression of RORγt in Th17 cells *via* the phosphorylation of signal transducer and activator of transcription 3 (STAT3) (H. I. Lee et al., 2022). Blocking IL-6 in EAE suppresses Th17 cell induction and disease progression (Serada et al., 2008). Evidence from both EAE and MS patients proves that IL-6 promoter can be activated by inflammatory cytokines like IL-1β, TNF-α, TGF-β1 and TGF-β3 (Ruddy et al., 2004; Eickelberg et al., 1999; Mann et al., 2002). Additionally, it is reported that Th17 cells induced by TGF-β3 and IL-6 are more pathogenic than those induced by TGF-β1 and IL-6 (Y. Lee et al., 2012).

Though IL-6 can induce IL-17 and Th17 cells alone, its induction is limited without other cytokine interactions. Ilona's team reported that IL-1 promoted the differentiation of Th17 cells in the absence of exogenous IL-6 by detecting Th17 cells in the blood, kidney, liver, and immune organs of normal and EAE mice. Moreover, IL-1 can stimulate IL-$6^{-/-}$ T cells into Th17 cells. Therefore, IL-1 may serve as a key inducer, while IL-6 plays a more supportive role (Kryczek et al., 2007). IL-1 further initiates the downstream signaling of transcription factor Bhlhe40 expression and promotes granulocyte-macrophage colony-stimulating factor (GM-CSF) secretion (Lin et al., 2014; C.-C. Lin et al., 2016a). Notably, IL-1β expressed by myeloid cells in EAE, contributes to generating GM-CSF-producing Th17 cells and enhancing their encephalitogenic potential (Mufazalov et al., 2016). However, the function of IL-1β in Th17 cell differentiation can be suppressed by IL-10 and amplified by IL-17 and TNF-α (B. Li et al., 2015).

IL-11, another member of the IL-6 family, also plays a role in inducing the generation of encephalitogenic Th17 cells. During MS pathogenesis, IL-11 in CSF triggers Th17 cell polarization by activating STAT3 and stimulating the secretion of IL-1β, TGF-β, IL-21, and IL-23 (X. Zhang et al., 2015).

IL-21 cooperates with TGF-β to form an alternative pathway in the differentiation of Th17 cells to secrete IL-17 in EAE mice. Accordingly, T cells without IL-21 receptors are disabled to respond as Th17 cells (Korn et al., 2007). The secretion of IL-21 can be triggered by IL-6, IL-7, and IL-15 in Th0 cells, further contributing to the Th17 cell differentiation process (Caprioli et al., 2008). Besides, IL-21 enhances its own expression by recruiting STAT3 to its gene promoter, creating a positive

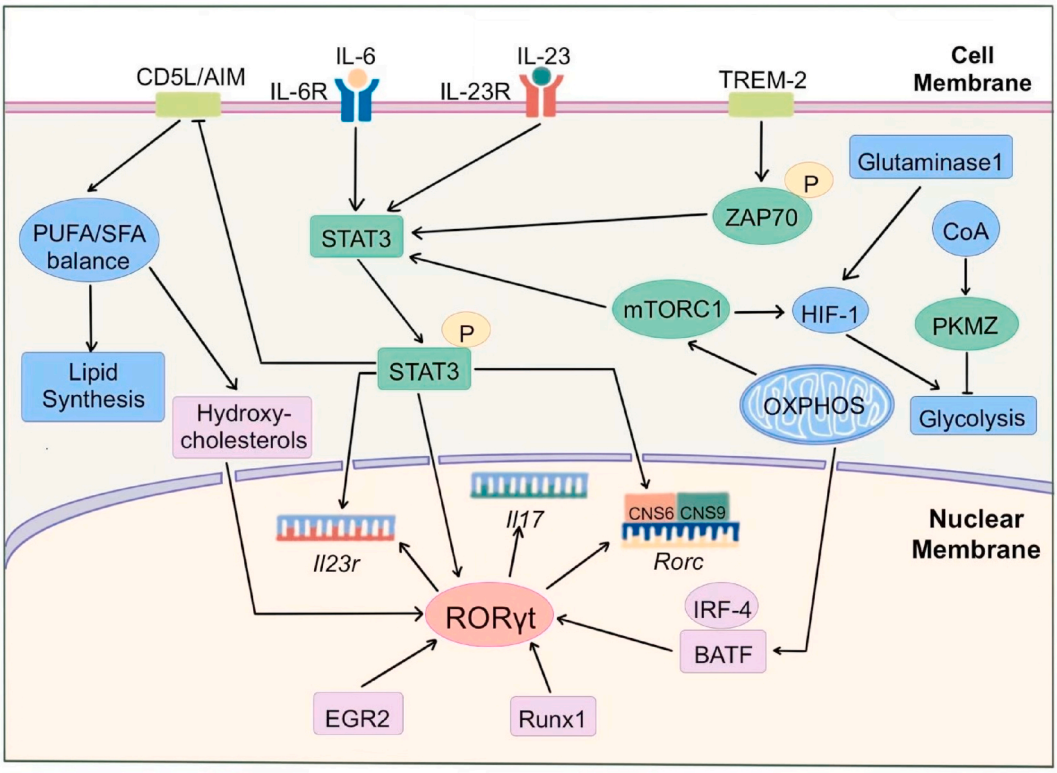

Fig. 1. The cellular immune and metabolic regulation of Th17 differentiation in MS. The ligation of IL-6 and IL-6R, IL-23 and IL-23R, TREM-2 and p-ZAP70 results in the phosphorylation of STAT3. The phosphorated-STAT3 binds to the promoter region, CNS6, and CNS9 regions in *Rorc* to promote the differentiation and maturation of Th17 cells. The p-STAT3 induced by IL-23 inhibit the expression of CD5L/AIM and control the synthesis of fatty acid. In animal model of MS, low expression of CD5L/AIM in the local Th17 cells decreases the cellular PUFA and increases hydroxycholesterols. These hydroxycholesterols can interact with RORγt and promote the expression of *Il17* and *Il-23r*. Transcriptional factors including EGR2, Runx1, BATF, and IRF-4 promote the RORγt transcription and enhance Th17 cell differentiation. The mitochondrial OXPHOS activates mTORC1-HIF-1 pathway and enhances the activation of STAT3. Additionally, OXPHOS also promotes the Th17 cell differentiation in a BATF-dependent manner through TCR signaling regulation. Glutaminase1 increases HIF-1 and promotes glycolysis, contributing to the differentiation of Th17 cells, while CoA combining with PKMZ inhibits glycolysis.

feedback loop that supports Th17 cell differentiation (Caprioli et al., 2008). Interestingly, IL-21 also acts as a regulatory cytokine by inhibiting the secretion of pro-inflammatory cytokines such as IL-6, IL-12, IL-1β, and TNF-α (Foster et al., 2003; Strengell et al., 2006).

IL-23 further amplifies Th17 cell polarization in the presence of TGF-β, IL-6, and IL-21 (Schinocca et al., 2021). It drives the generation of Th17 cells co-expressing RORγt and T-bet, enhancing their encephalitogenic capacity in EAE (Ghoreschi et al., 2010). The upregulation of RORγt and IL-23R by IL-1β further boosts the Th17 cell differentiation when combined with IL-23 (Kryczek et al., 2007; Stritesky et al., 2008).

In contrast to the cytokines that promote Th17 cell differentiation, several cytokines have inhibitory effects on this process, including IL-2, IL-3, IL-19, IL-24, and interferon-beta (IFN-β). IL-2 can inhibit Th17 cell differentiation by the activation of STAT5 *in vitro*. The deficiency of IL-2 is associated with enhanced IL-17 production and Th17 cell generation (Laurence et al., 2007). Similarly, IL-3 inhibits the differentiation of Th17 cells by blocking STAT3 phosphorylation in an IL-2-dependent manner (Rani et al., 2022). This cytokine plays a role in the CNS immune response. The IL-3/IL-3RA axis forms a glial-peripheral immune network that worsens MS by recruiting immune cells to the CNS (Kiss et al., 2023).

IL-19 also exerts an inhibitory effect on Th17 cell differentiation. IL-19-deficient macrophages in EAE mice have increased mRNA levels of IL-1β, IL-6, TGF-β1, IL-12 p40, IL-23 p19, and severe Th17 cell infiltration in CNS. Mechanistically, IL-19 suppresses MS pathogenesis by inhibiting macrophage antigen presentation and Th17 cell expansion (Horiuchi et al., 2021). These findings highlight the importance of IL-19 in suppressing both the initiation and expansion of Th17 cell-driven inflammation.

IL-24 inhibits the pathogenicity of Th17 cells in a STAT3-dependent manner. IL-24 gathers in the inner mitochondrial membrane and interacts with Grim9. Then, the binding of IL-24 and Grim9 promotes the accumulation of STAT3 and the secretion of IL-10 to inhibit the disease development in EAE (Sie et al., 2022).

IL-27 has a complex role in regulating Th17 cell differentiation. It downregulates several Th17-related genes, including *Il-17a, Il-17f, Rorc,* and *Ahr*, and inhibits IL-17 secretion under Th17-polarizing conditions (Chong et al., 2014; Murugaiyan et al., 2009). IL-27R-deficient mice are highly susceptible to EAE development, indicating the protective role of IL-27 (Chong et al., 2014; Stumhofer et al., 2006). However, while IL-27 inhibits Th17 cell differentiation in a STAT1-dependent manner and suppresses the expression of RORγt, it exerts the negligible effects on committed the fate of Th17 cells (El-behi et al., 2009; Yoshimura et al., 2006).

IFN-β is another cytokine with comprehensive effects on Th17 cell differentiation. IFN-$\beta^{-/-}$ mice exhibit increased Th17 cell polarization and greater susceptibility to EAE, proving IFN-β to be a key regulator for Th17 cell differentiation. Mechanistically, IFN-β upregulates IL-27 in macrophages *via* I IFN receptor (IFNAR), contributing to the downregulation of IL-17 (B. Guo et al., 2008). However, the effects of IFN-β on Th17 cell differentiation are not entirely consistent. IFN-β promotes IL-23-driven-Th17 cell differentiation by enhancing RORγt expression and improving their encephalitogenicity in EAE, Besides, it inhibits TGF-β-driven Th17 cell differentiation (Agnieshka Agasing et al., 2021).

Activin-A is a member of the TGF-β superfamily, exhibiting dual roles in Th17 cell regulation. Its role is context-dependent, with contrasting effects observed in different studies of MS and EAE. In MS and EAE, exogenous Activin-A not only activates the aryl hydrocarbon receptor (AhR) to control CD39 and CD73 expression but also inhibits hypoxia-inducible factor-1 α (HIF-1α) to suppress the pathogenicity of Th17 cells (Morianos et al., 2020). However, under inflammatory conditions, autocrine Activin-A-ALK4 signaling is activated in T cells and promotes the pathogenicity of Th17 cells. Correspondingly, blocking this pathway reduces IL-17A production during EAE induction (B. Wu et al., 2021).

In summary, cytokines play different roles in the development of Th17 cells through various mechanisms (Table 1). A better understanding of the interaction and function of these numerous cytokines is helpful in the exploration of new therapeutic targets for MS.

Table 1
Cytokines related to the differentiation of Th17.

	Cytokines	Related signaling cascades and transcriptional factors	Upstream enhanced cytokines	Upstream reduced cytokines
Activators	IL-6	STAT3	TNF-α; IL-1β; IL-17; TGF-β1; TGF-β; IFN-β;	IL-27; IL-21;
	IL-23	STAT3	IL-21; TGF-β; IL-6; IFN-β;	Unknown
	IL-1β	Bhlhe40	TNF-α; IL-17;	IL-10; IL-21;
	IL-21	STAT1; STAT3; STAT5;	IL-6; IL-7; IL-15; IL-21;	Unknown
	IL-11	STAT3	IL-17F; TNF-α; IL-1β; TGF-β; IL-11;	Unknown
	Endogenous Activin-A	ALK4	IL-6; IL-23; IL-1β;	Unknown
Inhibitors	IL-24	STAT3	IL-17	Unknown
	IL-27	STAT1; STAT3;	IFN-β	Unknown
	IL-2	STAT5	IL-3	Unknown
	Exogenous Activin-A	AhR; STAT3; c-Maf;	Not applicable	

2.2. *Th17 cell differentiation-related transcriptional factor signaling pathways*

Previous reviews focus on the complexity of TGF-β signaling in Th17 cell development, including the receptor Activin receptor-like kinase (ALKs), Smad proteins and their crosstalk with RORγt, aryl hydrocarbon receptor (Haghayegh Jahromi et al., 2019), mitogen-activated protein kinase (MAPK) signaling and other important pathways (J. Wang et al., 2023). The MAPK inhibitor PD98059 relieves MS by inhibiting Th1, Th9, and Th17 cells and promoting nTreg to maintain the immune balance. This is confirmed by the downregulation of *Il-17a* and the upregulation of *Foxp3* mRNA and protein levels in the spleen and brain of EAE mice (S. F. Ahmad et al., 2023a,b). PD98059 also downregulates the NF-κB signaling and inhibits the expression of various cytokines including CM-CSF, IL-6 and so on (Alomar et al., 2023).

RORγt is a symbolized transcriptional factor of Th17 cells and its transcriptional activity greatly affects the differentiation of Th17 cells (Y. Shi et al., 2022). Cathepsin B antagonist CA-074 reduces mRNA and protein levels of IL-17A and RORγt in the brain of EAE to lower its clinical scores (M. A. Ansari et al., 2022a,b). Previous studies have demonstrated that Interferon regulatory factor 4 (*Irf4*) could control Th17 cell differentiation by regulating the transcriptional activity of *rorc*. IRF4 is usually bound with Basic Leucine Zipper ATF-Like Transcription Factor (BATF), which is a basic leucine zipper transcription factor of the activator protein-1 (AP-1) family (Nalbant and Eskier, 2016). Schraml et al. finds the disability of Batf$^{-/-}$mice in Th17 cell differentiation and the resistance to EAE (Schraml et al., 2009). During Th17 differentiation, IRF4 and BATF not only improve chromatin accessibility and then start the transcriptional program together with STAT3 but also assist the recruitment of RORγt (Ciofani et al., 2012).

What's more, the Histamine H4 Receptor (H4R) is found to be expressed by Th17 and enhanced the expression of IL-17 (Passani and Ballerini, 2012). H4R antagonist JNJ10191584 alleviates EAE by downregulating the mRNA expression of *IL-17a* and *RORγt*, which sheds light on novel therapeutic targets for MS (Aldossari et al., 2023). In line with this, H4R agonist 4-methylhistamine (4-MeH) increases the expression of NF-κB p65, GM-CSF, and IL-6 mRNA, resulting in more severe EAE (Alsaad et al., 2023). Additionally, acetyl-11-keto-β-boswellic acid (AKBA) also alleviates EAE by suppressing NF-κB signaling in dendritic cells, thus inhibiting the activation of Th17 cells (Nadeem et al., 2022). Similarly, the CCR5 antagonist DAPTA inhibits the NF-κB/NOTCH pathway and downregulates the expression of IL-17A and RORγt in the brain, exerting anti-inflammatory effects (Alghibiwi et al., 2023; Ahmad et al., 2022). In addition to the CCR5 antagonist, the gold compound auranofin AFN also inhibits the NF-κB signaling and enhances the nuclear factor erythroid 2-related factor 2 (Nfr2) signaling which upregulates the expression of IL-17A by Th17 cells (Al-Kharashi et al., 2023).

Moreover, runt-related transcription factor 1 (Runx1) is identified to enhance RORγt expression as well as interact synergistically with RORγt during the transcription of *Il17* (F. Zhang et al., 2008). In addition, a study showed that the absence of early growth response protein 2 (EGR2) prevented the differentiation of Th0 cells towards Th17 cells. This suggests that EGR2 probably encourages the differentiation of Th17 cells through promoting RORγt transcription. EGR2 also is also reported to directly adjust the transcription of other Th17 cells signature genes such as *Il17*a (Gao et al., 2023).

The STAT3 signaling induced by IL-6 and regulated by IL-23 is considered to be one of the most related transcriptional factors in Th17 differentiation. Under the Th17 cell-skewed conditions, IL-6 activates the STAT3 signaling and induces the expression of IL-23R. The combination of IL-23 and IL-23R results in the phosphorylation of STAT3 and STAT4, which form heterodimers to bind to RORγt, generating a complex located in the *IL-17* promoter site and promoting the maturation of the Th17 cells (Samuels et al., 2018; Harris et al., 2007; P. W. Lee et al., 2017). In accordance with this, inhibiting the STAT3 pathway can block the neuroinflammation to alleviate EAE. The selective STAT3 inhibitor S3I-201 downregulates the expression of pSTAT3, IL-17A and RORγt in the brain of EAE (S. F. Ahmad et al., 2023a,b). Similarly, another STAT3 signaling inhibitor, Stattic decreases the levels of Th17-related inflammatory cytokines in EAE including IL-17A and IL-1β. Taken together, these studies have shown that STAT3 is a potential target for MS (Alhazzani et al., 2021).

Other factors related to STAT3 signaling and influencing Th17 cell differentiation include Recombination Signal Binding Protein for Immunoglobulin Kappa J Region (RBPJ) and Conserved Non-coding Sequences 6/9 (CNS6/9). Using CD4CreRBPJ$^{fl/fl}$ mice, researchers demonstrated that RBPJ, a canonical Notch signaling mediator, could bind to the *Il23r* promoter regions and synergize with RORγt. This process maintains the expression of IL-23R, forming the pathogenic phenotype of Th17 cells (Meyer Zu Horste et al., 2016). In addition, CNS6 and CNS9 at the *Rorc* gene are crucial to Th17 differentiation. STAT3 binds to the *Rorc* promoter and CNS6 and CNS9 regions, promoting the differentiation of Th17 cells (Chang et al., 2020).

Moreover, peptidylprolyl Cis/Trans Isomerase, NIMA-Interacting 1 (Pin1), a member of the peptidyl proline isomerase (PPIase) family, is proven to promote pathogenic Th17 cell differentiation (Lu, 2000). Pin1 elevates RORγt expression by interacting with STAT3 in Th17 and directly binds RORγt to increase the transcriptional activation of RORγt to the +11 kb cis-regulatory element of *Rorc* (Fan et al., 2024).

Apart from IL-6 and IL-23, the significance of the TREM-2/ZAP70/STAT3 signal axis for Th17 cell differentiation has been recently discovered in EAE. Researchers have proven that the triggering receptor expressed on myeloid cell 2 (TREM-2) is highly expressed in pathogenic CD4+T cells in MS patients as well as EAE mice. *Trem-2* knockout mice show that TREM-2 could encourage the activation of STAT3 by stimulating the phosphorylation of ZAP70 (zeta-chain associated protein kinase 70) (Qu et al., 2024). Overall activated STAT3 positively regulates RORγt and promotes the differentiation of Th17 cells.

2.3. Th17 cell differentiation-related epigenetic modification in MS

The epigenetic modification related to Th17 cell differentiation and IL-17 secretion mainly includes DNA methylation and histone modification, especially methylation. For instance, the methylation level of the promoter region at *STAT3* is lower and the expression of STAT3 is higher than that in CD4 T cells of RRMS patients (A. Hosseini et al., 2020).

Additionally, H3K4me3 modification marks are evident at the *IL17* and *Rorc* locus in Th17 cells and also evident in Th1 and Th2 cells (Wei et al., 2009). Correspondingly, the H3K27me3 marks are evident at the *Ifng* and *IL4* locus in Th17 cells (Wei et al., 2009). However, 17β-estradiol increases H3K27me3 enrichment and decreases H3K4me1 at *Rorc*, as well as inducing H3K4me3 and H3K4me1 enrichment at *FOXP3* in polarized Th17 cells, limiting the production of Th17 cells (Iannello et al., 2018). Therefore, estrogen plays a critical role in histone modification of the *Rorc* through its α receptor and decreases the relapse rate in pregnant MS patients (Iannello et al., 2018). Since methionine restriction of Th17 cells reduces H3K4me3 and H3K4me1 at *Il17a*, *Il17f*, and *Batf*, as well as *Rorc*, dietary methionine limitation can reduce the expression of IL-17 and release neuroinflammation of EAE (D. G. Roy et al., 2020). Besides, H3K27 demethylase (JmjC domain-containing protein 3) Jmjd3 and histone acetyltransferase (p300) are recruited in the conserved noncoding sequence 2 (CNS2) and promote the chromatin remodeling and gene expression of IL-17A and IL-17F (X. Wang et al., 2012). Additionally, Jmjd3 is enriched at the *Rorc* in Th17 cells and decreases H3K27me3 at the Jmjd3 binding sites (p-4, p-6, and BS1) of *Rorc* locus in Th17 cells (Z. Liu et al., 2015). Due to the important role of jmjd3 in Th17 cell differentiation, Jmjd3 cKO mice exhibit delays in the onset of EAE induction compared to WT mice, and its severity is reduced (Z. Liu et al., 2015). Importantly, the histone H3K27me3 demethylases KDM6A/B also link to metabolic response. Blockades of KDM6A and KDM6B both selectively inhibit the polarization of human Th17 cells in culture. Mechanism study shows KDM6A/B inhibition blocks the H3K27me3-mediated transcriptional activation of multiple metabolic genes, including peroxisome proliferator-activated receptor gamma coactivator-related protein 1 (PPRC1) in Th17 cells (Cribbs et al., 2020).

Tripartite motif-containing proteins (Trims) 28, induced by the IL-6-STAT3 axis, act as an epigenetic activator in Th17 cell differentiation. It binds to the *IL17a* and *IL17f* locus with active H3K4me3 and DNA 5hmc, recruiting RORγt and enhancing Th17 cell differentiation. Trim 28$^{fl/fl}$*Il17f*-Cre mice are less severe than WT mice during EAE induction. And in Trims28KO Th17 cells, p300 binding, the H3K27Ac at Th17 signature SE regions, and the interaction between CNS2 and promotors of *Il17* or *Il17f* are decreased (Jiang et al., 2018; "EGR2 drives TH17 cell pathogenicity in autoimmune neuroinflammation," 2023). Moreover, Trim33 plays a pivotal role in regulating Th17 cell differentiation. In its absence, the severity of EAE and the number of T cells in CNS are reduced. Mechanistically, Trim33 enhances *IL17* expression while decreasing *IL10* expression at the chromatin level in a TGF-β/Smad2-dependent manner. In *Trim33* KO CD4$^+$ T cells cultured under Th17 conditions, H3K9me3 and H3K27me3 at the *Il17* locus are enhanced while H3K4me3 and H3Ac in the *Il17* gene are not affected. In contrast, H3K4me3 is increased in multiple conserved regions at the *Il10* locus (Tanaka et al., 2018). In summary, the cytokine signaling cascades that drive the differentiation of Th17 cells are crucially controlled by epigenetic modification.

2.4. The Th17 cell differentiation-related metabolic reprogramming in MS

Besides genetic and epigenetic factors, metabolic reprogramming and heterogeneity also influence the cytokine network and fate of Th17 cells. Th17 cells exhibit distinct metabolic characteristics, including enhanced glycolysis, lipid synthesis, glutaminolysis, and mammalian

target of rapamycin (mTOR) activation, crucially modulate Th17 cell differentiation (Kanno et al., 2023).

The function of Th17 cells is mainly affected by glycolysis and the related metabolic pathways. Glutaminase1$^{fl/fl}$*Il17*^{Cre} F2 mice display ameliorating disease during EAE induction as inhibition of glutaminase1 decreases HIF-1α, suppressing glycolysis during Th17 cell differentiation (McGettrick and O'Neill, 2020; Kono et al., 2019; Vakili et al., 2023). Since ATP-linked mitochondrial oxidative phosphorylation (OXPHOS) plays a role in naïve T cells and promotes the signaling of ZAP70/STAT3, inhibition of ATP synthase during Th17 differentiation reduces the severity of EAE (Shin et al., 2020; S. Roy et al., 2019). mTORC1, a key integrator of environment signals to coordinate cellular metabolism and immune function, can mediate transcriptional factors like HIF-1 to promote glycolytic metabolism and stabilize the expression of RORγt. Both the T cell-specific HIF-1α$^{-/-}$ mice and mice receiving the HIF-1α$^{-/-}$ T cells show significantly delayed development during EAE induction (Waickman and Powell, 2012; L. Z. Shi et al., 2011; Eric V. Dang et al., 2011). Additionally, NO production decrease regulated by Formyl peptide receptor 2 signaling in DCs promotes Th17 cell differentiation in the context of neuroinflammation (Lim et al., 2024).

Besides, the lipid biosynthesis regulated by CD5L/AIM also alters the non-pathogenic and pathogenic states of Th17 cells through polyunsaturated fatty acid/saturated fatty acid (PUFA/SFA) balance the activity of RORγt ligands. In Th17 cells from the CNS in EAE, IL-23 binds IL-23R and enhances STAT3 function, which suppresses the expression of CD5L. Loss of CD5L decreases the level of PUFA and affects cholesterol biosynthesis enzymes, resulting in high level of RORγt ligands. RORγt ligands like hydroxycholesterols bind to RORγt ligands and promote the expression of IL-17A and IL-23R (C. Wang et al., 2015; Jin et al., 2010). Governed by the mTORC1 activation, ATP-linked OXPHOS promotes the Th17 cell differentiation in a basic leucine zipper ATF-like transcription factor (BATF)-dependent manner through TCR signaling regulation and mTORC1 activation (Shin et al., 2020). Moreover, coenzyme A (CoA) can limit the inflammation caused by Th17 cells in EAE and MS. CoA binds to pyruvate kinase isoform 2 (PKM2) to impede its phosphorylation and nuclear translocation, inhibiting glycolysis and STAT3 phosphorylation in Th17 cells (C. Chen et al., 2022). Vitamin B5 catabolized into CoA in a pantothenate kinase (PANK)-dependent manner to participate in fatty acid metabolism. Notably, it alleviates EAE and its level is reduced in the serum of MS patients (C. Chen et al., 2022). CoA fueling with the CoA precursor pantethine (PTTH) reduces pro-inflammatory cytokine production and limits T cell pathogenicity in EAE and peripheral blood mononuclear cells (PBMCs) from MS patients (Angiari et al., 2024).

Interestingly, dietary intake such as essential fatty acids and salt also affects Th17 cell differentiation. For instance, Eicosapentaenoic Acid-treated EAE mice exhibited lower clinical scores and less production of IL-17 in the CNS (Hoffman et al., 2023; Ramirez-Ramirez et al., 2013). The effect of EPA in Th17 cells is correlated with the activation of peroxisome proliferator-activated receptors (PPARs) including PPAR-α, PPAR-γ, and PPAR-β/δ which inhibit EAE. PPAR-δ-knockout mice show increased Th17 cells in the spinal cord and more severe EAE (Dunn et al., 2010). Besides, EPA-containing fish oil treatment decreases the serum levels of TNF-α, IL-1β, IL-6, and nitric oxide metabolites in RRMS patients (Ramirez-Ramirez et al., 2013). Though mice fed a high salt diet (HSD) show increased EAE severity compared to WT mice, *Cd4*^{Cre}*Sgk1*$^{fl/fl}$ mice are resistant to HSD. Researchers suggest that HSD upregulates the expression of glucocorticoid kinase (SGK1) and IL-23R, resulting in amplified Th17 cell differentiation and accelerating EAE pathogenesis (Wu et al., 2013).

Bile acid biosynthesis also influences Th17 cell fate. The conditional knockout of *Ahr* in mice results in alterations of the gut environment, promoting the formation of taurocholic acid, isovaleric acid, and other bile acids. These changes induce the apoptosis of Th17 cells and prevent EAE (Merchak et al., 2023). Despite the energy-related metabolisms, second messenger cyclic adenosine monophosphate (cAMP) can also influence the function of Th17 cells *via* the cytoplasmic PKA signal pathways. CRTC2 is a co-activator of cAMP-response element binding protein (CREB). Upon exposure to prostaglandin E2 (PGE2), it binds to CREB on the promoter of IL-17A and IL-17F. Therefore, CRTC2-mutant mice are defective in Th17 cell differentiation and resistant to EAE (Hernandez et al., 2015).

In summary, a high glycolytic metabolic state promotes Th17 cell differentiation, significantly contributing to their plasticity and pathogenic potential. Additionally, high salt intake and EPA influence the cytokine network and Th17 cell differentiation, impacting the process of EAE and MS.

3. The interaction between Th17 cells and the central nervous system in MS

Previous studies suggest that Th17 cells in the CNS during MS are mainly derived from the peripheral immune system. A meta-analysis showed increased Th17 cells in peripheral blood and Th17 cell-related cytokines in the serum of MS patients (Y. F. Li et al., 2017). By analyzing single-cell transcriptomes and surface protein, Kaufmann et al. identified CNS-homing T09 cluster of T cells that exhibited the Th17-Tfh phenotype and were enriched in the peripheral immune system in RRMS patients (Kaufmann et al., 2021). In addition to the peripheral immune system, recent studies suggest that the choroid plexus (ChP) acts as a reservoir for Th17 cells and plays an important role in their migration into the CNS. Since Th17 cells expressed CCR6, researchers investigated the CCL20-CCR6 interaction and found that CCL20 possibly assisted Th17 cells in migrating to ChP rather than crossing the BBB (Lazarevic et al., 2023). Th17 cells show a specifically greater ability to reach CNS through the epithelial blood-cerebrospinal fluid barrier (BCSFB) of the ChP and this process mainly relies on the epithelial ICAM-1 expression (Nishihara et al., 2020).

Th17 cells release various cytokines, including IL-17, IL-6, and IL-22, with IL-17 being central to pathogenic damage in the CNS. IL-17 impairs astrocyte function, disrupting glutamine metabolism and promoting glutamine excitotoxicity in MS (Kostic et al., 2017). Notably, the effects of IL-17 on oligodendrocytes are quite comprehensive. Liu et al. found that exposure to IL-17 increased Kv1.3 expression, subsequently inhibited the proliferation and differentiation of oligodendrocyte progenitor cells (OPCs), leading to myelin loss (H. Liu et al., 2021). However, Rodgers et al. suggest that IL-17A enhanced OPC differentiation and maturation by stimulating extracellular regulated protein kinases (ERK)1/2 signaling in a dose-dependent manner. Taken together, the effects of IL-17 depend on the dose, timing, and developmental stage of OPCs. While IL-17A inhibits early multipotent progenitors, it promotes later-stage O4^{+} OPCs (Rodgers et al., 2015). Notably, the IL-17A- and IL-22-double-expressing Th17 cells can secrete granzyme B, which has cytolytic effects on human fetal neurons, potentially by targeting the glutamate receptor, GluR3 (Kebir et al., 2007; Ganor et al., 2007). Additionally, IL-1β also plays an important role in damage to spinal cord white matter (SCWM) (Xue et al., 2023).

Interestingly, although IL-22 is produced by pathogenic Th17, it is not necessary for MS development and IL-22$^{-/-}$ mice also develop similar disease to WT mice (Kreymborg et al., 2007). In addition, a recent study shows that the overexpression of IL-22 could inhibit the generation and invasion of Th17 cells into CNS, being protective for EAE and MS progression (Eken et al., 2021). The cytokines ELISA result demonstrates that in EAE, the level of IL-22 is increased during the induction and peak phase of the disease, but decreased during the recovery phase. One possibility may be that IL-22 exerts its protective effects while the inflammation begins (Villoslada et al., 2011). To localize the IL-22 expression, researchers used immunofluorescent and found that compared to healthy individuals, MS patients showed increased IL-22 expression in astrocytes, blood vessels and MS plagues especially in strong astrogliosis regions. IL-22 protects astrocytes in TNF-α-induced inflammation conditions (Perriard et al., 2015). While

for oligodendrocytes in EAE, exogenous IL-22 induces its apoptosis through the mitogen-and stress-activated protein kinase 1 (MSK-1)/NF-κB pathway (Zhen et al., 2017). These results suggest that IL-22 has comprehensive effects on different cells and the exact mechanisms still need exploration.

Besides, GM-CSF is produced by Th17 cells, promoting the antigen-representing function of antigen-presenting cells (APCs) and boosting the pathogenicity of Th17 cells. (Fleetwood et al., 2007). GM-CSF elevates inflammatory cytokines especially IL-23 from APCs, which in turn promotes Th17 cell differentiation and increases GM-CSF production (El-Behi et al., 2011). Interestingly, GM-CSF regulation differs between humans and mice. In MS patients, GM-CSF expression is constrained by the IL-23/RORγt/Th17 axis but promoted by the IL-12/T-bet/Th1 axis (Noster et al., 2014). Conversely, IL-23 and RORγt can induce GM-CSF production in EAE mice (Codarri et al., 2011).

Besides different cytokines produced by Th17 cells, other inflammatory and cellular elements and molecule pathways are also implicated in the immune dysfunction of CNS in MS. CCR1 is a chemokine detected increased in inflammatory tissues and MS brain lesions. Detected by flow cytometry, EAE mice treated with CCR1 antagonist J-113863 are found to have decreased levels of GM-CSF, NF-κB-expressing $CD4^+$T cells in the spleen, while anti-inflammatory cytokines IL-10 and IL-27p28 are increased (M. A. Ansari et al., 2022a,b). In line with this, EAE mice treated with J-113863 show decreased IL-17-expressing $CD4^+$T cells, IL-17 mRNA expression and STAT3 signaling in brain tissues, proving the pro-inflammatory effects of CCR1 (Al-Mazroua et al., 2022).

3.1. The interaction between Th17 cells and the blood-brain barrier (BBB) in MS

The integrity of BBB is maintained by the neurovascular unit (NVU), including various cells, high expression of tight-junctions (TJs)-related molecules, and low expression of leukocyte function-associated adhesion molecules (LFA) (Nishihara et al., 2022).

Th17 cells interact with BBB-related cells mainly by communicating with vascular endothelial cells (VECs) and astrocytes to alter adhesion molecules and cytokines, inducing inflammation. Th17 cells secrete mass pro-inflammatory cytokines that activate VECs to express receptors, impairing BBB and recruiting more inflammatory cells to CNS through chemokine signaling. Researchers observe that the increased levels of CCL2 and CXCL1 produced by VECs under the stimulation of IL-17 recruit immune cells. These results in further increased levels of pro-inflammatory cytokines in CNS (Wojkowska et al., 2017). Additionally, IL-17A induces VECs to produce reactive oxygen species (ROS), causing a decline in TJs-related molecules (Huppert et al., 2010). Notably, even though IL-17 increases the permeability of BBB, studies demonstrated that IL-26 produced by non-pathogenic Th17 cells could maintain the integrity of BBB. VECs stimulated by IL-26 expressed ascending junctional adhesion molecules (JAM1) and claudin5 (CLDN5) to enhance the tight junctions of BBB (Broux et al., 2020). Collectively, the interaction between Th17 cells and VECs depends on the pathogenicity of Th17 cells. IL-17 secreted by pathogenic Th17 cells can improve BBB permeability, while IL-26 produced by non-pathogenic Th17 cells is involved in BBB homeostasis. Importantly, a current study detected the expression of IL-17 receptor and IL-22 receptor in human BBB-endothelial cells. The treatment of IL-17 significantly induces the secretion of IL-6 and CXCL8 and decreases the expression of tight junction-associated molecules (occludin and zonula occludens-1) in human BBB-endothelial cells. These findings provide crucial pre-clinical evidence of Th17 in BBB disruption during MS pathogenesis (Kebir et al., 2007).

Glial fibrillary acidic protein (GFAP) is a protein highly expressed in activated astrocytes. During EAE, it is observed in the white matter and grey matter of lumbar medullar of WT mice, while is only observed in white matter in $\alpha4^{-/-}$ mice (Prajeeth et al., 2017). Chemokines from Th17 cells can induce an inflammatory phenotype of astrocytes. Th17 cells generally express CCR6, and its ligand CCL20 is faintly expressed in astrocytes of healthy people. However, MS patients are observed to have higher expression of CCL20 in $GFAP^+$ astrocytes, attracting $CCR6^+$ Th17 cells to the inflamed area in the CNS (Reboldi et al., 2009). In primary astrocytes, IL-17A/F promotes IL-6/R-induced CCL20 expression by activating NF-κB and regulating the CCL20 promoter (Meares et al., 2012). However, a recent study using CCR6-KO mice and CCL20-KO mice by CRISPR/cas9 suggests that CCL20/CCR6 axis may not be necessary for Th17 cell migration and may be compensated by other chemokines (Sachi et al., 2023). Therefore, the mechanisms of Th17 cell migration to the CNS by chemokines still need further exploration. Th17 cells also regulate the expression of cytokine receptors in astrocytes to promote their phenotype change. By co-culturing Th17 and astrocytes, researchers reported that the expression of astrocytic IL-17RA was significantly increased in the spinal cord and cerebellum, especially during the onset and peak phase of EAE. In accordance with this, gene ontology analysis suggests that the gene change in activated astrocytes is related to immune activation and pro-inflammatory cytokine signaling (Milne et al., 2024). In the IL-17-activated astrocytes of EAE mice, lncRNA AK018453 is upregulated, promoting the TGF-β receptor-associated protein 1 (TRAP1)/Smad signaling pathway in astrocytes to enhance the secretion of pro-inflammatory cytokines (Q. Zhang et al., 2022). In EAE, the expression of *Rorc* in the astrocyte-deficient spinal cord is lower than in the control group, suggesting that activated astrocytes promoted the infiltration of Th17 cells (Prajeeth et al., 2017). The activated astrocytes promote the secretion of CCL2, CCL20, CXCL10, CXCL12, IL-1β, IL-6, and other cytokines, further recruiting Th17 cells. The synergy between Th17 cells-derived IL-17 and TNF activates astrocytes, creating a vicious cycle of inflammation (Prajeeth et al., 2017; Z. Q. Li et al., 2022; Murphy et al., 2010). Astrogliosis is a typical sign of EAE, accompanied by upregulated expression of connexin 43 (Cx43) gap junction channel proteins. Researchers found that deleting *Cx43* in astrocytes decreases Th17 cell infiltration in the CNS and the CNS-permeable Cx blocker IN-0602 reversed astrocytes into an anti-inflammatory phenotype, providing a novel therapeutic target (Takase et al., 2024). Altogether, the mechanisms of Th17 cells communicating with astrocytes mainly focus on the secretion of chemokines and other cytokines to promote inflammatory phenotypes.

Adhesion molecules crucially control the Th17 cells trafficking across the BBB into the CNS. Increased integrin α3 in Th17 cells promotes the expression of migration-related genes in Th17 cells. Integrin α3 can also interact with laminin α5, an important composition of BBB to mediate the infiltration of Th17 cells into CNS (Park et al., 2023). Th17 cells can also infiltrate the CNS without α4 integrin but require β2 integrin. Nevertheless, under α4 chain and α4β7 integrin blockade, Th17 cells can directly enter the cerebrum but not the spinal cord, causing atypical EAE. This indicates the crucial role of these integrins in Th17 cell adhesion and the development of EAE. In addition, dual immunoglobulin domain-containing cell adhesion molecule (DICAM), which is preferentially produced by Th17 cells, slows Th17 cell movement and promotes their adhesion on BBB-ECs (Charabati et al., 2022). Intercellular cell adhesion molecule (ICAM-1) mediates the adhesion between white cells and VECs. During the primary stage of EAE, ICAM-1 on APCs facilitates the formation of immune synapses between T cells and dendritic cells (DCs), activating the MOG-specific $CD4^+$T cells. The adhesion and rolling process of Th17 cells in VECs cells is blocked in ICAM-1/-$2^{-/-}$ mice during EAE and reveals milder EAE symptoms (Haghayegh Jahromi et al., 2019). Melanoma cell adhesion molecule (MCAM) also plays a key role in the development of EAE. Its depletion delays disease onset, reduces EAE symptoms, and decreases $IL\text{-}17^+$ and $IL\text{-}17^+IFN\text{-}\gamma^+$ lymphocytes, indicating its importance in the invasion of Th17 cells into CNS and EAE progression (Larochelle et al., 2012).

In addition to various adhesion molecules, the low expression of tight and adherens junction-related molecules weakens the BBB, allowing

Th17 cells to invade the CNS. The most studied molecules related to MS/EAE include occludin, claudin5, and ZO-1. Notably, decreased levels of occludin, claudin5, and ZO-1 in EAE mice are observed, together with the infiltration of inflammatory cells and demyelination, indicating the destruction of tight and adherens junctions (Guo Xiuli and Guo, 2018).

3.2. The interaction between Th17 cells and glial cells in MS

In MS pathogenesis, the interaction between Th17 cells and various glial cells in the CNS is responsible for the breakdown of BBB and the aggravation of MS and EAE. Activated leukocyte adhesion molecule (ALCAM) and MCAM are closely involved in the interaction between Th17 cells and oligodendrocytes (Jamann et al., 2024). Blocking ALCAM significantly reduces the interaction between Th17 cells and oligodendrocytes, while MCAM shows no notable change (Jamann et al., 2024). Act1 combines with NICD1 under IL-17A stimulation. This process activates the NOTCH1 pathway, suppresses OPC differentiation, and drives demyelination. The translocation of the Act1-NICD1 complex into the nucleus of OPCs alters OPC proliferation. Furthermore, IL-17R may recruit the Fas-associating protein with a novel death domain (FADD) through one of Act1's domains and promote the apoptosis of OPCs (Kang et al., 2013; C. Wang et al., 2017). During EAE, versican-V1 promotes Th17 cell polarization. Co-culturing OPCs with versican-V1 and Th17 cells results in more severe OPC impairment, shown by more propidium iodide (PI) incorporation (Ghorbani et al., 2022). Additionally, Th17 cells directly impair the myelination in oligodendrocytes by expressing high levels of CD29 and glutamate (Larochelle et al., 2021).

Additionally, IFN-γ/LPS-induced microglia exhibit M1 phenotype to promote Th17 cell differentiation by producing IL-23. A higher concentration of IL-1β, IL-6, and TNF-α is observed while co-culture microglia and Th1/Th17 cells which are characterized by secreting both IFN-γ and IL-17 (Prajeeth et al., 2017; Z. Q. Li et al., 2022; Murphy et al., 2010). Notably, CXCR3 expressed by glial cells, astrocytes and microglia activates extracellular regulates protein kinases (ERK), which inhibit the NF-κB pathway, a key signaling pathway for IL-23 and CCL-20, both critical for Th17 cell expansion and CNS infiltration (Chung and Liao, 2016). In addition to various cytokines, a recent study suggests that bromodomain protein 4 (BRD4) expressed in microglia, contributes to EAE progression by regulating related genes including *Cst7*, *Ccl6* and so on. In *Brd4*-deficient microglia, lower expression of *Cd40* and *Vcam1* are observed, interrupting the T-microglia interaction and resulting in less severe EAE (Dey et al., 2024). Fig. 2 summarizes the interaction between Th17 cells and VECs, glial cells, and neurons in MS.

3.3. The interaction between Th17 cells and CNS-infiltrated B cells in MS

Previous studies confirm that the interaction between Th17 cells and B cells promotes Th17 cell differentiation and maturation, worsening neuroinflammation (Comi et al., 2021). In Samples from MS patients, B cell aggregation in the meninges was observed, which may be driven by Th17 cells, as higher expression of *Il17f* was observed (Schropp et al., 2019). Given that B cells are antigen-presenting cells (APCs), they are capable of presenting myelin antigens and activating brain-homing T cells (Comi et al., 2021). Additionally, B cells are a major source of IL-6, enhancing the Th17 cell polarization (Barr et al., 2012). Bcl-6 in Th17 cells partially regulates the phenotype of meningeal B cells by upregulating transcripts related to meningeal follicular B cells (FOBc) and downregulating transcripts related to antigen presentation. Bcl-6 also influences isotype class switching, convinced by decreased IgG1, IgG2b, and IgG3 in the CSF from Bcl6KO-R compared to wt-R (Hartlehnert et al., 2021). In conclusion, previous studies have focused on the antigen-presenting and molecule-secreting functions of B cells, as well as how Th17 cells regulate B cells at the transcriptional level, yet the exact mechanisms still need further investigation. In conclusion, Th17 cells can interact with various cells including VECs, astrocytes, microglia, oligodendrocytes, and B cells to affect the permeability of BBB and aggravate MS or EAE.

4. The Th17 cells-related immune therapy in MS

For the novel treatment of MS, several immune therapies fail due to unexpected serious adverse events including immunological

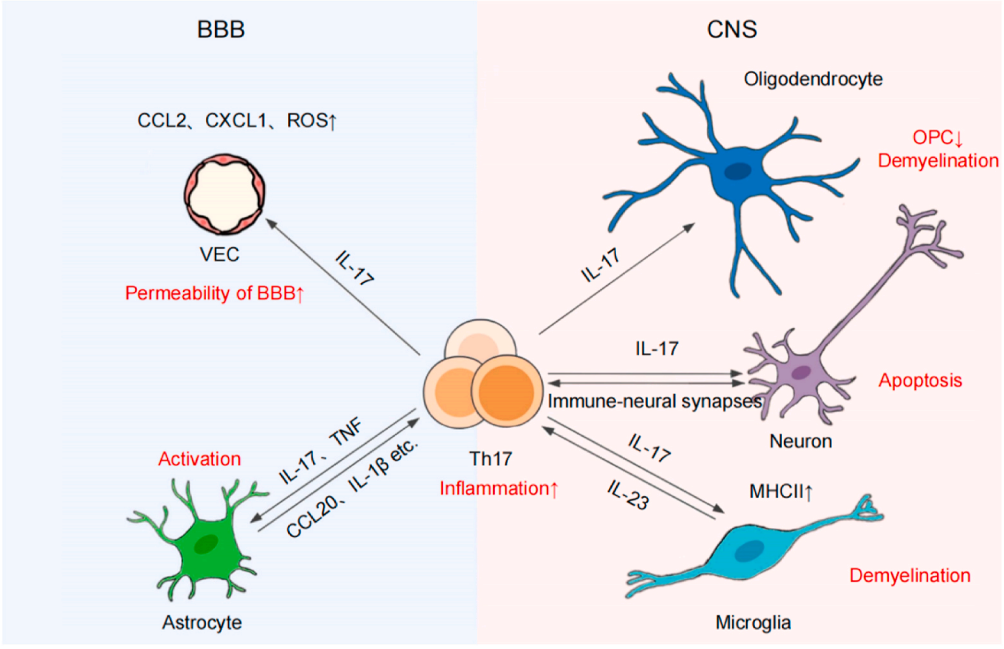

Fig. 2. The interaction between Th17 cells, VECs, neurons, and glial cells in MS. During the migration through the blood-brain barrier (BBB), Th17 cells express IL-17 to upregulate CCL2, CXCL1, and ROS in vascular endothelial cells (VECs). IL-17 and TNF cause the activation of astrocytes which express CCL20, IL-1β, and other cytokines to expand Th17 cell differentiation. IL-17 blocks the maturation from OPCs to oligodendrocytes and impairs oligodendrocytes, thus causing demyelination. Th17 cells damage neurons by producing IL-17 to increase its Ca^{2+} and forming immune-neuronal synapses. IL-17 produced by Th17 cells upregulates MHC II in microglia which present myelin-specific antigen and express IL-23 to stimulate Th17 cells, thus resulting in demyelination during MS development.

complications and potential liver toxicity (Krämer and Wiendl, 2022; Ghosh, 2012; Soleimani et al., 2019; Havla and Hohlfeld, 2022). Daclizumab, a humanized monoclonal antibody targeted at the α subunit of the IL-2 receptor (CD25), was withdrawn in 2018 for its potential liver toxicity and immune-mediated disorders like progressive multifocal leukoencephalopathy (The, 2018). In a phase III clinical trial called ASCEND, natalizumab treatment has no significant effect on secondary progressive multiple sclerosis compared to placebo and 20% of patients have serious adverse events (Kapoor et al., 2018). Furthermore, the α4-integrin antagonist Natalizumab, anti-CD20 mAbs alemtuzumab, and anti-CD52 mAbs cladribine are three disease-modifying therapy (DMT) drugs of MS (J. Guo et al., 2024). mAbs targeting Th17 cell-related cytokines have potential therapeutic implications and are under investigation (D. W. Luchtman et al., 2014; Buttmann, 2010; Deiβ et al., 2013; Gensicke et al., 2012).

Targeting cytokines that promote Th17 cell differentiation is a promising approach for MS. Ustekinumab, which binds to the D1 domain of p40, a subunit shared by IL-12 and IL-23, shows potential in inhibiting EAE (Papp et al., 2008). However, in a phase II study, ustekinumab treatment has no significant difference in the efficacy of RRMS compared to placebo (Martin, 2008; Segal et al., 2008). This discrepancy may be attributed to the interaction between the drugs and BBB and its role in MS. Similarly, ABT-874, a monoclonal antibody against IL-12 receptor β1 shared by IL-12 and IL-23, shows below-average results in MS (Vakili et al., 2023). Despite these setbacks, IL-12/23 blockers may be effective in certain MS subtypes, requiring further exploration (Longbrake and Racke, 2009). Notably, though ustekinumab seems to be ineffective, its tolerability in MS remains important as demonstrated in other diseases. A phase I study confirms that IL-12/23 monoclonal antibody has tolerability in RRMS (Kasper et al., 2006). Given the complexity of cytokines pleiotropy, BBB obstruction, and varying disease phenotypes, more research is needed on the efficacy of the novel drugs in MS.

Among Th17 cells-derived cytokines, GM-CSF and IL-17 are key players in MS. MOR 103, a monoclonal antibody targeting GM-CSF, is tolerated in MS patients in a phase Ib clinical study (Behrens et al., 2015; Constantinescu et al., 2015). Secukinumab, a fully human monoclonal antibody against IL-17A approved in 2015 for the treatment of psoriasis, reduces MRI lesion activity in RRMS and can reduce IL-17A-induced levels of IL-6 in human astrocytes (Elain et al., 2014; Sanford and McKeage, 2015; Havrdová et al., 2016). Despite its effectiveness in treating skin and neurological manifestations, cases of MS exacerbation following secukinumab treatment have been reported (Tsiogkas et al., 2024). Nonetheless, the relationship between MS and psoriasis and the effectiveness of mAbs of IL-17A in MS still need further investment.

Th17 cell differentiation is mainly controlled by JAK/STAT, NF-κB, and PI3K/AKT/mTOR, offering several potential therapeutic targets. For example, JAK1/2 inhibitors baricitinib and ruxolitinib are found effective in ameliorating EAE through suppressing JAK and then STAT phosphorylation, reducing the inflammatory cytokines (C. Dang et al., 2021; Arezoo Hosseini et al., 2021). Previous research showed that the differentiation of Th17 cells could be suppressed by STAT3 inhibitors in EAE (S. F. Ahmad et al., 2023a,b; Alhazzani et al., 2021). The STAT-specific single-domain nanobody (SBT-100) derives from camelids and targets at conserved residues in Src homolog 2 (SH2) domains of STAT1 and STAT3. SBT-100 also suppresses the expansion of Th17 and Th1 cells in the brain and spinal cord, ameliorating EAE (Mbanefo et al., 2024). Additionally, NTG-A-009 (6-aminopyridin-3-ol) reduces the infiltration of Th17 cells in CNS and ameliorates EAE by the inhibition of STAT3 phosphorylation (Acharya et al., 2018). BJ-3105, a 6-alkoxypyridin-3-ol Analog, also inhibits the STAT3 phosphorylation (Ashour et al., 2017). Notably, plant-derived natural compounds are gaining attention for restraining STAT3 phosphorylation, including 4-phenyl coumarin isolated from propolis, named cinnamoyloxy-mammeisin (CNM), Plumbagin (PL), berberine, and Magnolol (Franchin et al., 2022; Tansey et al., 2011; J.-Y. Chen et al., 2023; Qin et al., 2010). Except for targeting at STAT3, PL, and berberine also inhibit NF-κB, while the total flavonoids of Astragalus (TFA), active ingredients in Astragali Radix (AR) regulate both JAK/STAT and NF-κB signaling pathways (Han et al., 2023).

Several pathways are involved in the metabolic modulation of Th17 cells. For instance, the HIF-1α and mTOR are involved in the glycolysis. The blockade of mTOR with rapamycin significantly reduces the IL-17 levels with ameliorated spinal cord damage in EAE mice (Li et al., 2020). Additionally, the supplement of metabolic coenzyme A and Vitamin B5 may also limit T cell pathogenicity in MS patients (Angiari et al., 2024). Interestingly, dietary intake such as essential fatty acids EPA shows therapeutic effects in the animal models of MS as well. Thus, metabolic modulation may apply as a novel therapeutic strategy in the treatment of MS.

Besides, the anti-hCCR6 mAbs targeting at CCR6 on pathogenic Th17 cells are evident in suppressing Th17 cell infiltration in EAE (Richard et al., 2017). The selective cannabinoid 2 (CB2) receptor ligand Gp1a can also alleviate EAE symptoms. CB2 is a cannabinoid receptor expressed primarily on hematopoietic cells and activated microglia and it is selectively activated by Gp1a. Its early effect is the inhibition of Th17 cell differentiation in peripheral immune organs through restraining RORγt expression. Subsequently, Th17 cell accumulation in CNS is observed, along with the reduction of local proinflammatory signals, including IL-1β and TNF-α, chemokines such as CCL2, CCL5, CXCL10, and adhesion molecules like VCAM-1 and iNOS (Kong et al., 2014; G. Y. Liu et al., 2022). Detailed information on Th17 cell-related signaling pathways in MS treatment is summarized in Table 2.

5. Conclusion

Increasing evidence indicates the importance of Th17 cells in MS pathogenesis especially in the local interactions between Th17 and CNS. Comprehensive cytokine networks control the differentiation and function of Th17 cells in MS. For instance, IL -6, IL-23, IL-1β, IL-21 and IL-11 promote the differentiation of Th17 cells, while IL-24, IL-27, IL-19 and IL-2 inhibit the generation of Th17 cells. The transcriptional activity of RORγt is critical for Th17 cell differentiation, and various pathways also crosstalk with RORγt to modify Th17 cell differentiation. Mechanism studies indicate the importance of the epigenetic modification of RORγt in the differentiation and pathogenicity of Th17 cells. Besides, metabolic factors, such as a high glycolytic metabolic state, high lipid biosynthesis state high salt diet, and EPA have comprehensive effects on

Table 2
Drugs targeting Th17-related cytokines and signaling pathways.

Target	Drug	Effect on Th17 differentiation and MS
IL-12/23	Ustekinumab;	No significant reduction of MS
	ABT-874;	Improvement below average level in MS patient
GM-CSF	MOR 103	Tolerability in MS
IL-17A	Secukinumab	Reduction of MRI lesion activity in MS
JAK/STAT	Baricitinib;	Downregulation of IL-6, IL-17, IL-23, TNF-α;
	Ruxolitinib;	Inhibition of STAT3 phosphorylation
	BJ-3105;	
	CNM;	
	PL;	
	Berberine;	
	Magnolol;	
	TFA;	
NF-κB	PL;	Downregulation of iNOS, IL-6 and IFN-γ etc.
	Berberine;	
PI3K	Novel azaindoles	Inhibition of PI3K/AKT/mTOR pathway
mTOR	Sirolimus;	
	Temsirolimus;	
	Everolimus;	
CCR6	Anti-hCCR6 mAbs	Inhibition of Th17 migration to CNS
CB2	Gp1a	Downregulation of RORγt, IL-1β, TNF-α, CCL2, CCL5, CXCL10, VCAM-1 and iNOS

Th17 cell differentiation. Due to the complexity of the CNS microenvironment, the precise mechanisms and kinetic changes of Th17 cells in MS require further investigation.

Importantly, the interaction between Th17 cell-derived cytokines and other cells in the CNS such as VECs, astrocytes, microglia, and oligodendrocytes directly affects the permeability of BBB and aggravates neuroinflammation in MS. Based on the crucial roles of Th17-derived cytokines, potential therapeutic strategies are indicated for the treatment of MS. Additionally, researches on the CNS will provide novel insights into the understanding of neural-immune axis, the differentiation and function of Th17 cells in MS pathogenesis.

Gliosis and glial scar formation are hallmark pathological features of MS. Although relative studies indicated the key pathogenic roles of glial cells in the pathogenesis of MS, the involvement of Th17 cells is still largely unknown (Sen et al., 2022; J. Q. Wang et al., 2024). Thus, further investigation into the interactions between Th17 cells and the CNS will shed light on novel therapeutic interventions for MS treatment.

CRediT authorship contribution statement

Shixin Lai: Writing – review & editing, Writing – original draft, Supervision. **Xiaomin Wu:** Writing – review & editing, Writing – original draft. **Yue Liu:** Writing – review & editing, Writing – original draft. **Bo Liu:** Writing – review & editing, Visualization. **Haiqi Wu:** Writing – review & editing, Supervision. **Kongyang Ma:** Writing – review & editing, Supervision.

Declarations of generative AI and AI-assisted technologies

None of the generative AI and AI-assisted technologies have been used in the writing process.

Funding

This work was supported by funding from the National Natural Science Foundation of China (81901635, 82171782), Shenzhen Science Foundation for Distinguished Young Scholars (RCJC20210706092009004), Guangdong Pearl River Talent Program (2021QN02Y108).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We gratefully thank Prof. Bin Jiang from the School of Medical, Sun Yat-sen University, Shi-wen Lai PhD. from the School of Social Science, Tsinghua University, and Dr. Yong-yu Yin from the Beijing Institute of Pharmacology and Toxicology for their advice and assistance in preparing this article. Graphic abstract, Figs. 1 and 2 were drawn in the Procreate platform (https://procreate.com/cn).

Data availability

No data was used for the research described in the article.

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