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The Interleukin (IL)-23/T helper (Th)17 Axis in Experimental Autoimmune Encephalomyelitis and Multiple Sclerosis

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T helper (Th)17 cells are responsible for host defense against fungi and certain extracellular bacteria but have also been reported to play a role in a variety of autoimmune diseases. Th17 cells respond to environmental cues, are very plastic, and might also be involved in tissue homeostasis and regeneration. The imprinting of pathogenic properties in Th17 cells in autoimmunity seems highly dependent on interleukin (IL)-23. Since Th17 cells were first described in experimental autoimmune encephalomyelitis, they have been suggested to also promote tissue damage in multiple sclerosis (MS). Indeed, some studies linked Th17 cells to disease severity in MS, and the efficacy of anti-IL-17A therapy in MS supported this idea. In this review, we will summarize molecular features of Th17 cells and discuss the evidence for their function in experimental models of autoimmune diseases and MS.

The first report of interleukin (IL)-23 in 2000 (Oppmann et al. 2000) paved the way for the discovery of T helper (Th)17 cells (Aggarwal et al. 2003; Harrington et al. 2005; Park et al. 2005). Indeed, *Il23p19*$^{-/-}$ mice lack a population of IL-17-producing T cells at the site of chronic inflammatory lesions (Cua et al. 2003). Notably, IL-17 had already been cloned in 1993 (Rouvier et al. 1993) and its receptor, IL-17RA, in 1995 (Yao et al. 1995). However, only when IL-17 was identified as a product of Th cells that appeared to be induced by IL-23, interest in the IL-23/Th17 axis grew massively in the scientific community because it provided a potential pathogenetic framework for a variety of severely disabling organ-specific autoimmune diseases, including rheumatoid arthritis, diabetes mellitus, and multiples sclerosis (MS). The discovery of Th17 cells expanded the Th cell paradigm of Th1 and Th2 cells, and challenged the idea that chronic inflammatory diseases and organ-specific autoimmune diseases were caused by exaggerated Th1 responses. Th17 cells were first explored in experimental autoimmune encephalomyelitis (EAE), an animal model of MS, and were defined by their unique cytokine profile of IL-17A (IL-17), IL-17F, IL-21, IL-22, and their prototypical transcription factor retinoid-related orphan receptor-γt (ROR-γt) (Ivanov et al. 2006; Korn et al. 2009). However, Th17 cells

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are neither the only target of IL-23 (which is also sensed by γδ T cells, natural killer [NK] T cells, and innate lymphoid type 3 cells [ILC3s]), nor are they the only source of IL-17, which is also produced by γδ T cells, NK T cells, and ILC3s (reviewed in Cua and Tato 2010).

Early work suggested that IL-17 might be important in driving MS pathology because this cytokine was identified within lesions in the central nervous system (CNS) (Lock et al. 2002). However, the evidence for the correlation of Th17 frequencies in the peripheral blood or cerebrospinal fluid with disease activity in MS is limited. Even though genome-wide association studies (GWAS) have identified single nucleotide polymorphisms (SNPs) in the *IL23* and *IL23R* genes in patients with inflammatory bowel disease (IBD) and psoriasis (Duerr et al. 2006; Cargill et al. 2007), associations of SNPs in genes involved in the IL-23R signaling pathway are only now beginning to be associated with MS with increasing numbers of patients and controls fed into GWAS analyses. Yet, an antibody that neutralizes both IL-12 and IL-23 was inefficient in MS patients as to the suppression of magnetic resonance imaging (MRI) activity (Segal et al. 2008). Nevertheless, neutralization of IL-17 suppressed disease activity in MS patients (Havrdová et al. 2012), and some reports propose that other products of Th17 cells (besides IL-17) play an important role in the inflammatory process in the CNS during MS.

In this review, we will highlight the factors that are responsible for the differentiation of pathogenic and nonpathogenic Th17 cells and compare the evidence for a role of IL-23 and Th17 cells in the pathogenesis of EAE and human MS.

THE BIOLOGY OF Th17 CELLS IN ANIMAL MODELS OF MS

Th17 cells were first discovered in EAE, and a substantial amount of knowledge about Th17 cell biology was gathered by using this model. It is the most common animal model for MS and is induced by immunization with a CNS-derived autoantigen emulsified in complete Freund's adjuvant (CFA). Because transfer of CNS antigen-specific Th1 cells induced EAE and interferon (IFN)-γ was found in CNS lesions of EAE mice, EAE was believed to be a Th1-driven autoimmune disease. Moreover, neutralizing polyclonal antibodies to IL-12 in rodents, and a monoclonal antibody to the p40 subunit of the human IL-12 heterodimer (p40/p35) in marmosets were able to suppress the induction of EAE (Leonard et al. 1995; Brok et al. 2002). Because IL-12 is crucial for Th1 differentiation, this further supported the idea that EAE was a Th1-mediated autoimmune disease. However, p35-deficient mice were still susceptible to EAE (Becher et al. 2002), and this was also true for a variety of other factors required for the differentiation of Th1 cells, including IFN-γ itself, fundamentally challenging the concept of EAE as a Th1 disease (Ferber et al. 1996; Zhang et al. 2003; Bettelli et al. 2004; Gutcher et al. 2006). IL-23 is a heterodimer that comprises the p40 subunit of IL-12 and a private p19 subunit. IL-23 promotes the expansion of Th17 cells (Aggarwal et al. 2003; Harrington et al. 2005; Park et al. 2005). Thus, it appeared an appealing idea to implicate Th17 cells (and not Th1 cells) as major inducers of autoimmune tissue inflammation because IL-23p19-deficient mice (in contrast to IL-12p35-deficient animals) were resistant to EAE (Cua et al. 2003).

Adoptive transfer studies showed that both in vitro–differentiated and restimulated myelin oligodendrocyte glycoprotein (MOG)-specific Th1 and Th17 cells were able to induce EAE in recipient mice. However, host animals that received antigen-specific Th17 cells had more lesions in the meninges and parenchyma and showed a mix of classical and atypical signs of EAE compared to recipients of Th1 cells (Jäger et al. 2009).

It has been difficult to address which are the main effector cytokines of Th17 cells in EAE pathogenesis. EAE onset was delayed in *Il17a*$^{-/-}$ mice, and disease severity was significantly reduced (Komiyama et al. 2006). Moreover, EAE severity was suppressed in wild-type (WT) SJL mice that were immunized with myelin proteolipid protein and received IL-17-neutralizing antibodies (Langrish et al. 2005). Because IL-17-deficient mice are only partly protected from EAE, the pathogenicity of

Th17 cells can likely not be merely narrowed down to this one signature cytokine. IL-23 induces the expression of granulocyte macrophage colony-stimulating factor (GM-CSF) in Th17 cells (Codarri et al. 2011; El-Behi et al. 2011), although the expression of GM-CSF is not restricted to Th17 cells (Grifka-Walk et al. 2015). However, because GM-CSF-deficient mice are resistant to EAE (McQualter et al. 2001), GM-CSF was proposed to be a major effector molecule during Th17-mediated CNS inflammation. GM-CSF triggers a positive feedback loop, inducing the production of IL-23 by antigen-presenting cells (APCs) (El-Behi et al. 2011). However, there has been some debate on the major cellular targets of GM-CSF. Recently, a subset of monocyte-derived dendritic cells (DCs) was identified to be crucially activated by GM-CSF to promote inflammation in the CNS (Ko et al. 2014; Croxford et al. 2015).

Besides IL-23, IL-1β has also been involved in the expansion and late differentiation of pathogenic Th17 cells because the induction of Th17 cells in IL-1 receptor type 1 (IL-1R1)-deficient mice was abrogated and was not restored by IL-23 alone (Sutton et al. 2006). Expression of IL-1R1 in Th17 cells is induced by IL-6, and IL-1R1 signaling promotes expression of ROR-γt by maintaining high levels of IFN regulatory factor 4 (Irf4) (Chung et al. 2009). Co-overexpression of Irf4 and ROR-γt restored Th17-cell polarization in the absence of IL-1β-mediated signaling (Chung et al. 2009). In fact, Irf4 is essential for the production of IL-17 and IL-21, and Irf4-deficient mice are completely protected from EAE (Brüstle et al. 2007; Chen et al. 2008; Huber et al. 2008). Moreover, a recent study showed that IL-1β was able to skew T-cell development toward Th17 cells in the gut, where it was required to override retinoic acid–mediated Foxp3 expression in T cells and thereby tipped the Th17 cell/induced $CD4^+$ regulatory T (iTreg) cell balance toward Th17 cells (Basu et al. 2015).

Interestingly, mice deficient for the Th1-associated transcription factor T-bet are protected from CNS autoimmunity (Bettelli et al. 2004). Fate-mapping studies showed that previous IL-17-producing T cells started expressing IFN-γ at sites of chronic inflammation (Lee et al. 2009; Kurschus et al. 2010; Hirota et al. 2011), raising the question whether the production of IFN-γ by late Th17 cells was dependent on T-bet (Duhen et al. 2013; Wang et al. 2014; Krausgruber et al. 2016). Because infections with *Candida albicans* supported sustained expression of IL-17 in antigen-specific T cells, the induction of effector cytokines previously unrelated to the Th17 signature portfolio, including IFN-γ, GM-CSF, and tumor necrosis factor (TNF), in "historic" IL-17 producers in autoimmunity was surprising and triggered a debate on the stability of the "Th17 lineage." However, the presence of IL-17/IFN-γ double producing exTh17 cells in the inflamed CNS is a robust finding and is tightly dependent on IL-23 (Hirota et al. 2011).

In summary, the EAE model has been instrumental in the research of the IL-23/Th17 axis in CNS autoimmunity. The difficulties to translate some EAE findings into MS might, in part, be because of the strong bias toward Th17 responses induced by the adjuvants used for the induction of EAE. However, plasticity and effector mechanisms of Th17 cells were intensively studied in EAE and revealed a variety of molecular mechanisms that also applied in MS (Fig. 1).

CYTOKINE MILIEUS FOR Th17-CELL DIFFERENTIATION AND PLASTICITY

Despite the fact that IL-23 is necessary for the induction of EAE (Cua et al. 2003; Bettelli et al. 2006), it is no bona fide differentiation factor for Th17 cells because naïve T cells lack IL-23R and do not respond to IL-23 (Mangan et al. 2006). Instead, a cocktail of transforming growth factor-β (TGF-β) and IL-6 is sufficient to differentiate murine naïve T cells into Th17 cells (Bettelli et al. 2006; Mangan et al. 2006; Veldhoen et al. 2006). In addition, IL-21 cooperates with TGF-β to induce Th17 cells in a milieu devoid of IL-6, and thus presents an IL-6-independent mode of Th17-cell generation (Korn et al. 2007; Nurieva et al. 2007).

The role of TGF-β for Th17-cell differentiation has been controversial. Human T cells were reported to require IL-1β, IL-6, and IL-23 to differentiate into Th17 cells, and TGF-β even

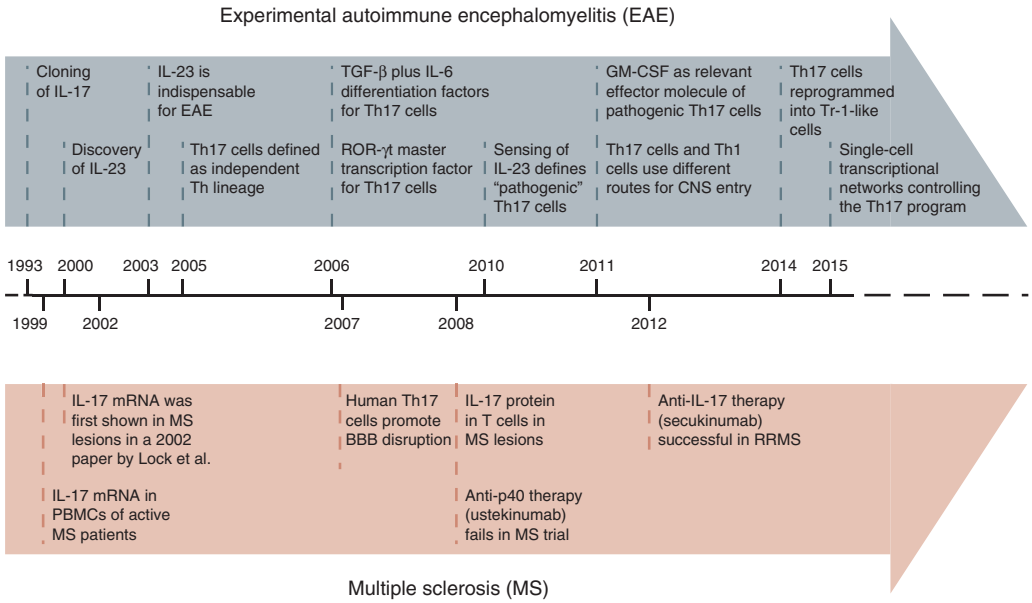

Figure 1. Timeline. Scientific discoveries that led to the concept of the "interleukin (IL)-23/T helper (Th)17 axis" in experimental autoimmune encephalomyelitis (EAE) and multiple sclerosis (MS). TGF, Transforming growth factor; GM-CSF, granulocyte macrophage colony-stimulating factor; CNS, central nervous system; PBMCs, peripheral blood mononuclear cells; BBB, blood–brain barrier; RRMS, relapsing remitting multiple sclerosis.

inhibited Th17 cell polarization (Acosta-Rodriguez et al. 2007; Wilson et al. 2007). However, TGF-β was clearly required for the differentiation of naïve human T cells into Th17 cells and in particular for the induction of RORC (the human homolog of ROR-γt) in serum-free medium (Manel et al. 2008; Yang et al. 2008). IL-1β and IL-6 alone only induced IL-17 secretion in precommitted central memory $CD4^+$ T cells. Because T cells produce TGF-β themselves, an autocrine or paracrine TGF-β-dependent loop must be considered during Th17 differentiation (Li et al. 2007; Gutcher et al. 2011), and more recent reports have shown that Th17 cell differentiation can occur in the absence of exogenous TGF-β in murine T cells. A combination of IL-1β, IL-6, and IL-23 may induce Th17 cell differentiation (Ghoreschi et al. 2010), and these Th17 cells coexpressed T-bet and ROR-γt and were highly pathogenic in inducing EAE upon adoptive transfer.

These experiments supported the idea that distinct "stable" subsets of Th17 cells might exist (Lee et al. 2012). It had earlier been proposed that naïve T cells that were stimulated with TGF-β1, and IL-6 produced IL-17 and IL-10 but did not induce autoimmunity upon adoptive transfer into host animals unless previously exposed to IL-23 (McGeachy et al. 2007). In fact, IL-23R signaling was shown to be essential for the pathogenicity of Th17 cells (McGeachy et al. 2009). It is currently under investigation whether pathogenic versus nonpathogenic Th17 cells represent terminally differentiated Th cell subsets or are different stages of the Th17 developmental program. Also, the conditions under which different subsets of Th17 cells are generated in vivo remain to be determined.

One concept, which has been elaborated to some extent, is the idea that different subsets of Th17 cells likely reflect Th17 differentiation at different priming sites in vivo. For instance, Th17 differentiation in draining lymph nodes and mucosal tissues, like the intestinal lamina propria, is IL-6-dependent, whereas Th17 priming in the spleen seems to be independent of IL-6 (Hu et al. 2011). The need for IL-6 in Th17 differentiation was associated with the presence

of CD103$^+$ DCs, which produce retinoic acid and are proficient in inducing iTregs. CD103$^+$ DCs are relatively abundant in the gut but only comprise a small fraction of splenic DCs. Thus, the local milieu in the spleen is less permissive for iTreg programming of naïve conventional T cells obviating the need for IL-6 to start the Th17 developmental program. However, it remains to be determined how naïve T cells sense IL-6 and whether IL-6, which is produced by many cellular sources, must be provided by the same APC that also presents antigen in the context of major histocompatibility complex (MHC) class II molecules to result in productive Th17 differentiation. IL-1β appears to be essential for the differentiation of Th17 cells in all tissue compartments, which is in line with previous studies and the finding that pertussis toxin promotes Th1/Th17 cell differentiation by inducing the production of IL-1β (Ronchi et al. 2016). However, in contrast to IL-6, IL-1β might have more "mitogenic" properties rather than representing an instructive cue for the specific differentiation of Th17 cells (see below and Kim et al. 2006).

In contrast to Th1 cells that only express IL-12R (heterodimeric IL-12Rβ1/IL-12Rβ2) but lack IL-23R (heterodimeric IL-12Rβ1/IL-23R), Th17 cells express both receptors and respond to both IL-12 and IL-23. In addition, Th17 cells also respond to IL-27, another IL-12 family cytokine (Stumhofer et al. 2006, 2007; Diveu et al. 2009). This exquisite responsiveness to IL-12 family cytokines might in part explain the plasticity of Th17 cells. For example, IL-12 and IL-27 have been shown to "reprogram" precommitted Th17 cells to a Tr1-like phenotype by inducing the transcriptional modulator Blimp1 (Heinemann et al. 2014). IL-23 failed to induce Blimp1, but promoted the expression of ROR-γt and induced the generation of pathogenic Th17 cells, characterized by the production of IL-17, IFN-γ, and GM-CSF (Heinemann et al. 2014). Another pathway to skew Th17 cells into Tr-1 like cells is dependent on the aryl hydrocarbon receptor (Ahr) (Gagliani et al. 2015). Tr-1 cells are defined by the expression of IFN-γ and IL-10, but lack of IL-17 has been shown to critically contribute to the containment of immunopathology in the context of chronic inflammatory diseases (Groux et al. 1997; Battaglia et al. 2004, 2006; Mayo et al. 2016).

Other "nonimmune" (environmental) cues, including salt concentration and even fatty acids, were also reported to modulate the differentiation and plasticity of Th17 cells (Kleinewietfeld et al. 2013; Wu et al. 2013; Berod et al. 2014). Although this has not been rigorously tested, it appears that Th17 cells are more responsive to a variety of external factors than Th1 cells or Th2 cells, suggesting that interventional strategies targeting these instructive cues (many of which are modulated by lifestyle) might exert their effects via modulation of Th17 immunity.

TRANSCRIPTION FACTOR NETWORKS IN Th17 CELLS

The idea that Th17 cells are a Th cell lineage of their own received a lot of attention when it was shown that IL-17 production in CD4$^+$ T cells could be induced in the absence of the master transcription factors for Th1 and Th2 cells, T-bet and Gata-3, respectively (Harrington et al. 2005; Park et al. 2005).

Later, ROR-γt was discovered to be the "key" transcription factor for Th17 cell differentiation (Ivanov et al. 2006). Besides genetic loss-of-function studies, small-molecule ROR-γt antagonists were shown to impair Th17 cell differentiation, emphasizing the role of ROR-γt as a crucial transcription factor for Th17 cells (Xiao et al. 2014). Network analyses of Th17 cells that were differentiated with TGF-β and IL-6 showed the involvement of Irf4 and basic leucine zipper transcription factor ATF-like (Batf), enabling transcriptional activity of Stat3 and ROR-γt (Ciofani et al. 2012). Irf4-deficient mice were protected from EAE and showed crippled Th17 development, as a result of reduced ROR-γt expression (Brüstle et al. 2007). Batf is a member of the activator protein 1 (AP-1) transcription factor family and is believed to inhibit AP-1 activity. Batf-deficient mice are also resistant to EAE and *Batf*$^{-/-}$ T cells fail to induce ROR-γt and IL-21 (Schraml et al. 2009). Overexpression of ROR-γt or IL-21 could not fully restore IL-17 production in *Batf*$^{-/-}$ T cells, sug-

gesting that ROR-γt and Batf may have to cooperate in Th17 development. There is remarkable overlap between Batf and Irf4 promoter regions and cooperative binding of Batf and Irf4 promotes chromatin accessibility for Stat3 and ROR-γt (Ciofani et al. 2012; Li et al. 2012). Moreover, ROR-γt only exclusively regulates a few Th17 genes, namely, *Il17*, *Il17f*, and *Il23r*, but modulates and fine tunes expression at key loci in T cells with a preestablished Th17 lineage program, suppressing alternative fate decisions toward other lineages (Ciofani et al. 2012). Importantly, this suggests that a transcription factor complex regulates lineage fate decisions in Th17 cell development instead of only one master transcription factor.

IL-1β signaling in Th17 cells contributes to reinforcing Th17 responses. Mechanistically, IL-1β promotes the phosphorylation of mammalian target of rapamycin (mTOR), a central regulator of cellular metabolism, and therefore enhances the metabolic fitness of Th17 cells during inflammation (Gulen et al. 2010). In detail, mTOR induces the expression of myelocytomatosis oncogene (Myc), which switches the metabolic pathway from fatty acid β-oxidation to the glycolytic, pentose phosphate, and glutaminolytic pathways to provide enough energy for proliferating cells during T-cell priming. Moreover, signaling through mTOR induces the expression of hypoxia-inducible factor 1α (Hif1α), a transcription factor that promotes Th17 cell differentiation by direct transcriptional activation of ROR-γt and forms a complex with ROR-γt and p300 to induce IL-17 expression (Dang et al. 2011). Additionally, the Th17/Treg balance (Bettelli et al. 2006) is skewed by Hif1α toward Th17 cells by binding Foxp3 and targeting it for proteasomal degradation (Dang et al. 2011).

Recent years have shed some light on the underlying molecular processes that are executed during Th17 cell differentiation. The Th17 transcriptional program is more complex than originally envisioned and is not only dependent on Stat3 and ROR-γt to generate fully committed Th17 cells. Despite all these insights, the role of IL-23 in producing pathogenic Th17 cells is still not fully understood and cannot merely be reduced to its induction of Stat3.

THE PIVOTAL ROLE OF IL-23 IN Th17 CELL PROGRAMMING

IL-23 has been described in the context of the differentiation of pathogenic Th17 cells in many studies and it seems clear that the IL-23/Th17 axis and autoimmunity are strongly intertwined in EAE. The spectrum of actions of IL-23 in the context of Th17 cell development includes expansion and stabilization of pathogenic Th17 cells, maintenance of IL-17 production, induction of GM-CSF expression, and generation of IL-17/IFN-γ double-positive T cells.

Whereas *Il23r*$^{-/-}$ mice are resistant to EAE (Awasthi et al. 2009; McGeachy et al. 2009), mixed WT plus *Il23r*$^{-/-}$ bone marrow chimeric mice develop EAE with regular disease severity, which allows for the analysis of IL-23R functions on T cells in an inflammatory milieu. Here, *Il23r*$^{-/-}$ T cells started expressing IL-17, but were arrested at an early activation stage (marked by impaired down-regulation of IL-2 and CD27 expression) (McGeachy et al. 2009). Eventually, *Il23r*$^{-/-}$ Th17 cells failed to be recruited to the inflamed CNS. In contrast to CD4^{+} T cells, the IL-23R-deficient myeloid compartment was fully functional as compared to its WT counterpart. Thus, while *Il23r*$^{-/-}$ T cells exhibit impaired effector functions, the mechanistic underpinning for this phenomenon remains to be identified.

In a model of colitis, IL-23R signaling in T cells in the gut increased the accumulation of Th17 cells, as well as the percentage of IL-17/IFN-γ double-positive T cells, and inhibited the differentiation of Foxp3-positive T cells (Ahern et al. 2010). However, while in the CNS, IL-23 signaling in Th17 cells is believed to promote IL-17/IFN-γ double producers in a T-bet-dependent manner (Hirota et al. 2011; Wang et al. 2014); T-bet was dispensable for the IL-23-dependent induction of pathogenic IL17/IFN-γ-positive T cells in the colon (Krausgruber et al. 2016). Notably, T cells from T-bet-deficient donors injected into *Rag1*$^{-/-}$ mice showed even higher frequencies of IL-17/IFN-γ double-positive T cells in the colon. Interestingly, this is in contrast to earlier studies wherein transfer of T-bet-deficient T cells into host mice failed to in-

duce colitis (Neurath et al. 2002). Whereas different genetic backgrounds and microbial differences, such as colonization with segmented filamentous bacteria, might in part be responsible for these conflicting results, further investigation is required to identify the "nonredundant" pathogenic function of IL-23 in the context of T-cell-mediated autoimmunity.

The serum glucocorticoid kinase 1 (Sgk1) was identified in a transcriptional profiling study to be an essential node downstream of IL-23 signaling (Wu et al. 2013). Sgk1 is a serine/threonine protein kinase (Waldegger et al. 1997) and its expression is increased by elevated salt concentrations (Wu et al. 2013). The increase in salt concentrations was associated with higher levels of Th17 cells in mice and humans, and resulted in a more severe form of EAE in mice fed with a high-salt diet (Kleinewietfeld et al. 2013). Mechanistically, Sgk1 inhibits a direct repressor of IL-23R expression (i.e., Foxo1), and thereby stabilizes the Th17 phenotype through enhanced induction of IL-23R expression (Wu et al. 2013). However, Sgk1 is also a stress response gene (Miyata et al. 2011; Yuen et al. 2011) and might constitute a more general link between environmental stressors and inflammatory responses.

Furthermore, recombination of signal-binding protein for the immunoglobulin κJ region (RBPJ), which is a downstream regulator of Notch signaling, has been linked to the development of Th17 cells (Yosef et al. 2013). In fact, inhibition of Notch signaling results in a reduction of Th17-associated cytokines in murine and human Th17 cells and ameliorates EAE (Keerthivasan et al. 2011). The role of RBPJ-mediated Notch signaling in the development of Th17 cells has recently been addressed in more detail. RBPJ was found to promote the differentiation of pathogenic Th17 cells by directly up-regulating IL-23R expression through binding and transactivating the *IL23r* promoter together with ROR-γt. Conversely, RBPJ repressed *Il10* in Th17 cells (Meyer Zu Horste et al. 2016).

Taken together, multiple upstream signals that are associated with enhanced pathogenicity of Th17 cells converge (either directly or indirectly) in the transactivation of the *Il23r* gene. Yet, despite the clear evidence of IL-23 being associated with the development of pathogenic Th17 cells and the recent advances in how the expression of IL-23R is induced in Th17 cells, its functions and downstream transcriptional targets in T cells in different settings of inflammation still remain to be fully determined.

THE IL-23/Th17 AXIS IN HUMAN MULTIPLE SCLEROSIS

While GWAS in MS patients indicated that MS is a T-cell-mediated disorder, a predominant role of Th17 cells in MS has not been directly evident (International Multiple Sclerosis Genetics Consortium (IMSGC) et al. 2011, 2013). Interestingly, an SNP within the *STAT3* gene was even protective and was linked to a decreased odds ratio for the development of MS while the same SNP (rs744166) constitutes a risk allele for Crohn's disease (Jakkula et al. 2010). However, replication in independent MS cohorts has been difficult (Cenit et al. 2010; Lill et al. 2012), and two other SNPs (rs9891119 and rs4796791) within the *STAT3* gene were associated with marginally increased risks for MS (International Multiple Sclerosis Genetics Consortium (IMSGC) et al. 2011, 2013). For none of these haplotypes, immunologic analyses as to the modulation of Th17 responses are available in MS patients. In contrast to MS, both GWAS data and functional analyses of the IL-23/Th17 pathway provide clear evidence of its importance in the pathogenic process of IBD and psoriasis (Duerr et al. 2006; Cargill et al. 2007).

In fact, in early work, no SNP in the *IL23* gene or *IL23R* gene was found to be associated with MS susceptibility (Roos et al. 2008). However, larger GWAS now provide evidence for the association of several molecules involved in the IL-23R signaling pathway (including *STAT3* and *TYK2*) with MS. Despite the efficacy of IL-12/IL-23p40-neutralizing antibodies in EAE, treatment in human MS with ustekinumab, a human monoclonal antibody against the p40 subunit (shared between IL-23 and IL-12), did not lower the cumulative number of new gadolinium-enhancing T1-weighted MRI lesions in a phase II clinical trial with relapsing-remitting multiple sclerosis (RRMS) patients (Segal et al. 2008).

This lack of efficacy might at least in part be a result of the inclusion of patients with advanced disease where inflammation may no longer be driven by T-cell activation (reviewed in Longbrake and Racke 2009; Mahad et al. 2015). In addition, IL-23 is likely involved in the programming of pathogenic Th17 cells at the site of inflammation and it is unknown to what extent ustekinumab is able to cross the blood–brain and blood–cerebrospinal fluid barriers to access relevant anatomical compartments and block IL-23 at these sites (see comment by Martin 2008).

A number of correlative studies linked Th17 cells with human MS. IL-17 messenger RNA (mRNA) and protein were detected in perivascular lymphocytes and in $CD4^+$ and $CD8^+$ T cells in active brain lesions of MS patients (Lock et al. 2002; Tzartos et al. 2008). Early studies with small numbers of MS patients indicated that mononuclear cells expressing Th17-associated molecules, including IL-17 mRNA, were more frequent in the peripheral blood and cerebrospinal fluid of RRMS patients as compared with controls and further increased during clinical exacerbations (Matusevicius et al. 1999; Hedegaard et al. 2008; Brucklacher-Waldert et al. 2009). Molecules identified to specifically shape the Th17-expression profile, such as, for example, microRNA-326, showed a higher expression in peripheral blood lymphocytes of MS patients as compared with healthy controls (Du et al. 2009). Furthermore, the ex vivo frequency of Th17 (but not Th1) cells in the cerebrospinal fluid (but not in the peripheral blood) correlated with disease activity in early MS and RRMS patients (Brucklacher-Waldert et al. 2009). Also, in comparison to Th1 clones, Th17 clones generated from the peripheral blood and cerebrospinal fluid of RRMS patients showed higher levels of activation markers, costimulatory molecules, as well as molecules involved in homing of lymphocytes to the CNS (Brucklacher-Waldert et al. 2009). Even more convincing correlations of Th17-associated molecules with disease severity were detected when myelin-specific T-cell populations instead of polyclonal repertoires were interrogated for the expression of Th17-associated factors. Chemokine receptors were used as surface markers to identify Th cell subsets in humans, and Th17 cells express CCR6 while Th1 cells express CXCR3 (Sallusto et al. 1998; Annunziato et al. 2007). Comparing myelin-reactive $CCR6^+$ $CD4^+$ T cells in the peripheral blood of MS patients versus healthy controls on the single-cell level revealed that MS-derived $CCR6^+$ T cells expressed more IL-17 and GM-CSF while control-derived $CCR6^+$ T cells were higher in IL-10 expression (Cao et al. 2015).

Whereas many studies focused on "classic" effector cytokines of Th17 cells to account for immunopathology in MS, it is increasingly becoming clear that Th17 cells also have additional functions during chronic inflammatory processes. Interestingly, Th17 cells have been suggested to be particularly well equipped to give help to B cells (Mitsdoerffer et al. 2010) and, in pediatric patients with demyelinating events (acute disseminated encephalomyelitis and transverse myelitis), the amount of Th17-associated cytokines (including IL-17) were significantly higher in the cerebrospinal fluid of those patients with positive-serum anti-MOG antibodies as compared with seronegative patients (Kothur et al. 2016). It remains to be determined whether antigen-specific Th17 cells contribute to the formation of tertiary lymphoid follicles that have been observed in the meningeal compartment of chronic MS patients (Magliozzi et al. 2007, 2010; Howell et al. 2011). Some results from mechanistic studies in experimental models indicated that Th17 cells might indeed be involved in the formation of these structures and, by analogy, human Th17 also expressed some of the molecules, including IL-17 itself and lymphotoxin β receptor ligands that are responsible for the induction of tertiary lymphoid follicles (Peters et al. 2011; Lee et al. 2015; Pikor et al. 2015).

As in animal models of autoimmunity and chronic inflammation, Th17 cells are not the only cellular source of IL-17 in humans. In mice, γδ T cells have been reported in numerous studies to produce IL-17 in response to IL-23 (Shibata et al. 2007; Nakamura et al. 2008; Reinhardt et al. 2016) and, just recently, the gut microbiota was linked to affect migration of IL-17-

producing γδ T cells from the small intestine into the brain (Benakis et al. 2016) in a model of poststroke inflammation. γδ T cells were also shown to restrain Tregs in an IL-23-dependent manner and thereby increased EAE severity (Petermann et al. 2010). Interestingly, IL-17-producing γδ T cells accumulate in the cerebrospinal fluid of MS patients (Schirmer et al. 2013) and γδ T cells have long been found within MS lesions (Wucherpfennig et al. 1992). Yet, it remains to be determined whether γδ T cells are relevant sources of IL-17 in the CNS during human disease.

Interestingly, efficient therapeutic interventions in MS patients were associated with the reduction of Th17 cells in the peripheral blood. While this phenomenon has been observed in the treatment of acute relapses with steroids (Liu et al. 2009) and also in treatment strategies with disease-modifying drugs, including type I IFNs (Durelli et al. 2009) and fingolimod (Mehling et al. 2010), none of these trials allow for the conclusion of a causal relationship of Th17 cells with immunopathology in MS because no specific effector molecules of Th17 cells were direct targets of these therapies. Conversely, the most striking evidence for a pathogenic role of IL-17 in MS comes from the clinical and radiologic benefit noticed in RRMS patients treated with a neutralizing antibody to IL-17. Secukinumab showed efficacy in a phase II clinical trial with RRMS patients (Havrdová et al. 2012), and more advanced antibodies to IL-17 with improved pharmacodynamic properties are being considered as disease-modifying therapies in MS patients (Wiendl et al. 2015).

In summary, it is highly likely that Th17 cells play a pathogenic role in MS. Th17 cells are elevated at sites of inflammation-mediated tissue damage in the CNS of MS patients and are capable of inducing a broad tissue response with widespread immunopathology by recruitment of other lymphoid and myeloid cells (Carlson et al. 2008). Of course, the mechanistic underpinning of Th17-mediated tissue damage in humans is not worked out to the same extent as in mouse models. However, many hints point to similar functions of effector molecules of Th17 cells in mice and men.

Th17 CELLS IN NEUROMYELITIS OPTICA

Th17 cells have also been linked to the pathogenesis of neuromyelitis optica (NMO) and NMO spectrum disorder (NMOSD), which are characterized by serum antibodies to aquaporin-4 (AQP4) (Wingerchuk et al. 2015; Hinson et al. 2016). A study with patients with RRMS, relapsing NMO, and healthy control participants showed that Th17- and IL-17-producing $CD8^+$ T cells were elevated in the blood of both RRMS and relapsing NMO patients compared to healthy control participants, but this elevation was more profound in NMO patients (Wang et al. 2011). In a recent study in which a wide range of cytokines, chemokines, and growth factors were measured in the cerebrospinal fluid of patients with NMO/NMOSD, RRMS, primary progressive MS (PPMS), and noninflammatory neurological diseases (ONDs), increased expression of Th17- and Th1-mediated proinflammatory cytokines was detected in the cerebrospinal fluid of NMO/NMOSD patients compared to OND patients, whereas proinflammatory cytokines were only mildly elevated in the cerebrospinal fluid of RRMS patients during relapses (Matsushita et al. 2013).

It is widely accepted that the immunopathology in NMO is mediated by binding of anti-AQP4 antibodies to target epitopes within the CNS, mainly astrocytic foot processes at the glia limitans, followed by complement-dependent lysis of astrocytes (reviewed in Papadopoulos and Verkman 2012). Therefore, the role of Th17 cells in NMO is likely restricted to Th functions in the formation of anti-AQP4 antibodies in the peripheral immune compartment and to the inflammation of the glial vascular unit to facilitate the access of anti-AQP4 antibodies to their target structures in the CNS. Interestingly, cortical pathology and tertiary lymphoid follicles in the meninges have never been observed in NMO patients (Lucchinetti et al. 2002; Popescu et al. 2010; Misu et al. 2013). Again, this points to a differential role of pathogenic T cells in MS and NMO. Consistent with these observations, a series of therapeutic strategies that are beneficial in MS have failed in NMO patients, including type I IFNs and nata-

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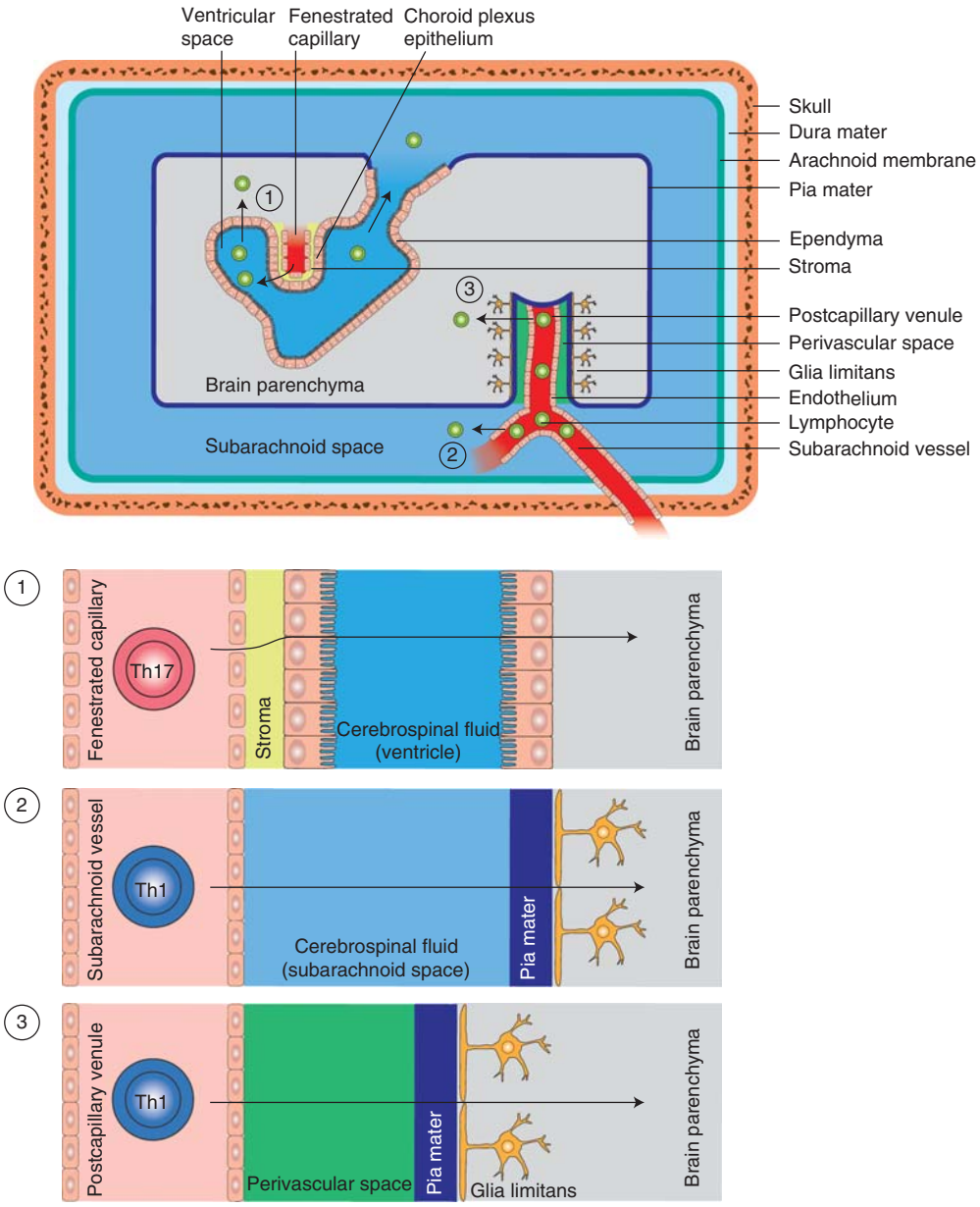

Figure 2. Potential entry routes of lymphocytes into the central nervous system (CNS) in multiple sclerosis. The CNS compartment is separated from the systemic immune compartment by the blood cerebrospinal fluid and blood–brain barriers. In homeostasis and during inflammation, three distinct routes of entry of immune cells into the CNS have been described: (1) T cells may enter the brain parenchyma through the choroid plexus by crossing the choroid plexus epithelium; this route is potentially VLA-4 (α4β1-integrin)-independent and might favor T helper (Th) 17 cell entry. (2) T cells are also able to access the cerebrospinal fluid space through subarachnoid vessels. Once in the cerebrospinal fluid, certain lymphocytes are able to cross the glia limitans (pia mater) to directly infiltrate into the cerebrospinal fluid parenchyma. This route of entry is likely VLA-4-dependent. (3) Finally, entry of T cells into the brain parenchyma also occurs through postcapillary venules of the cerebrospinal fluid parenchyma (via the perivascular space [Virchow–Robin space]). This route has previously been considered as the most important port of entry for lymphocytes in CNS inflammation.

lizumab (Tanaka et al. 2009; Palace et al. 2010; Barnett et al. 2012). Indeed, some NMOSD patients even reacted with adverse effects when treated with natalizumab (Barnett et al. 2012; Kleiter et al. 2012; Kitley et al. 2014). Natalizumab blocks α4-integrins and has been shown to disrupt VLA-4 (α4β1)-mediated Th1 migration into the spinal cord in EAE and MS, while being less efficient in preventing the access of Th17 cells to the CNS compartment (Fig. 2) (Rothhammer et al. 2011). Thus, Th17 cells might be particularly important for the induction of an inflammatory milieu at the blood–brain barrier in NMOSD, an idea that is also supported by the infiltration of NMO lesions by neutrophils, which are bona fide effector cells that are typically recruited into Th17-type responses (Liang et al. 2007; Pelletier et al. 2010; Griffin et al. 2012).

CONCLUDING REMARKS

Over a decade of research on Th17 cells has yielded exciting new therapy options by neutralizing either IL-17 or IL-17RA in psoriasis (Leonardi et al. 2012; Papp et al. 2012). These therapeutic strategies might also become available for rheumatoid arthritis and ankylosing spondylitis. While IL-17 is a primordial pathogenicity factor in the skin and in the joints, the CNS is less prone to support IL-17-driven inflammation. Still, it is likely that immune cells that produce IL-17 and perhaps other cytokines like GM-CSF (as Th17 cells do as well) are important mediators of disease in MS. However, targeting individual cytokines might be insufficient in MS and the recent success of B-cell-depleting therapies (Hauser et al. 2017; Montalban et al. 2017) supports the idea that elimination of B cells as APCs might be an efficient means to inhibit pathogenic T cells altogether. In fact, Th17 cells closely interact with B cells (Mitsdoerffer et al. 2010), and it remains to be determined whether depletion of B cells is particularly inhibitory to the reactivation of Th17 cells. For example, anti-CD20 therapy might affect Th17 responses by depleting a subset of APCs (i.e., B cells) that produce IL-6 and thus particularly promote Th17 responses.

Many studies were performed to elucidate the connection of Th17 cells with human MS. To date, the understanding of mechanistic processes of Th17 cells and its hallmark cytokine IL-17 in the context of MS is still elusive and needs further effort to depict the role of Th17 cells in the early phases of the disease, during relapses, and in remission. Whether Th17 cells drive the disease, whether they sustain neuroinflammation, whether they just act as bystanders, or even have a role in tissue regeneration is not yet definitively answered. Solving these questions will provide the means for designing more advanced treatment options.

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