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Review

Cytokines and effector T cell subsets causing autoimmune CNS disease

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ABSTRACT

Although experimental autoimmune encephalomyelitis (EAE) is limited in its potency to reproduce the entirety of clinical and histopathologic features of multiple sclerosis (MS), this model has been successfully used to prove that MS like autoimmunity in the CNS is orchestrated by autoantigen specific T cells. EAE was also very useful to refute the idea that IFN-γ producing T helper type 1 (Th1) cells were the sole players within the pathogenic T cell response. Rather, "new" T cell lineages such as IL-17 producing Th17 cells or IL-9 producing Th9 cells have been first discovered in the context of EAE. Here, we will summarize new concepts of early and late T cell plasticity and the cytokine network that shapes T helper cell responses and lesion development in CNS specific autoimmunity.

1. Introduction

Multiple sclerosis (MS) is the most common inflammatory demyelinating disease in adult humans. Although its prevalence is only about 1 in 1000 in Europe and the US, MS imposes a heavy medical and economic burden on the society since it affects young individuals in the most productive years of their lives [1]. The clinical course of MS is relapsing remitting (RRMS) in about 70–80% of patients. However, after a disease duration of 10 years, almost half of the affected individuals experience a deterioration of symptoms independently of relapses and enter into the secondary progressive phase of the disease [2]. Many hypotheses have been put forward on the etiology of MS and all of them have been disproved except for one: the autoimmune hypothesis that argues in favor of the idea that the myelin sheath is attacked by autoantigen specific immune cells [3–6]. First, all the gene polymorphisms that have been validated in genome wide association studies to be associated with increased risk of developing MS affect immune genes. Prominent examples are HLA class II DRB1*1501, IL2R, IL7R, CD58, and IL12p35 [7]. None of these genes has a role in the development or homeostasis of oligodendrocytes, astrocytes, or neurons. Second, animal models of primary oligodendropathies do not recapitulate histopathological hallmark features of MS [8–11]. Third (and perhaps most importantly), therapeutic strategies that have been derived from the animal model of inflammatory demyelination, i.e., experimental autoimmune encephalomyelitis (EAE) are at least partially efficient in MS patients [12–15].

The current concept of the pathologic cascade in MS has largely been developed in EAE and the most important key feature of this concept is that immunological tolerance of autoreactive T cells is broken [16–18]. Breach of tolerance can be due to a multitude of reasons including elevated frequencies of autoreactive T cells, molecular mimicry of foreign antigens that activate T cells that have degenerate T cell receptors (TcR), true cross reactivity of T cells that express two different TcRs, one of which recognizes a foreign antigen while the other one is autoreactive, or failure of regulatory T cells. Once autoreactive T cells are triggered in the peripheral immune compartment, a chain of events is started. Every step in this sequence of events, i.e. crossing of the blood brain barrier, re-activation in the perivascular compartment, infiltration into the CNS parenchyma, immune cell/target cell interaction within the CNS parenchyma, lesion development, and resolution of inflammation as well as tissue repair have all been extensively studied in EAE [18,19]. During the last 30 years, EAE has become one of the most successful animal models in preclinical research and basic T cell immunology. Indeed, EAE in its multiple variants does not only recapitulate histopathological features of MS as a prototypic organ specific autoimmune disease but is also a suitable model to study T cell development during immune reactions in vivo. Here, we will focus on the development of various species of effector T cells and the cytokine network involved in their generation as well as the effector cytokines that eventually induce immunopathology during autoimmune CNS inflammation.

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2. T Helper cell subsets

Upon recognition of their cognate antigen in the context of MHC class II molecules and in the presence of co-stimulatory signals as well as cytokine cues provided by innate immune cells, $CD4^+$ T cells are activated and initiate a developmental program that leads to the commitment of the T cell to a specific effector cell phenotype. It has long been recognized that there are at least two distinct effector T helper cell phenotypes that are defined by a characteristic cytokine signature. This categorization into IL-4 producing Th2 and IFN-γ producing Th1 cells was first introduced by Mosmann et al. who were looking for $CD4^+$ T cell subsets that were particularly suited to give B cell help and found that IL-4 producers but not IFN-γ producers were very efficient in promoting the production of IgG1 in murine B cells [20]. Besides IL-4, Th2 also secrete IL-5 and IL-13 but no IFN-γ. In contrast Th1 cells produce IFN-γ, TNF, and lymphotoxin, but no IL-4. Th1 cells activate macrophages and thus mediate phagocyte-dependent protective immune responses.

The generation of Th1 cells from a naïve $CD4^+$ T cell precursor requires IL-12, a cytokine that is strictly T cell-extrinsic and is produced by activated antigen-presenting cells (APCs) [21]. Upon sensing small amounts of IFN-γ derived from innate immune cells in combination with TcR signaling, the transcription factor T-bet is upregulated in a Stat1 (signal transducer and activator of transcription 1) dependent manner. T-bet, in turn, induces the expression of IL-12Rβ2 rendering nascent Th1 cells responsive to IL-12. IL-12, via Stat4, further transactivates T-bet, which is the most important transcription factor to stabilize the production of large amounts of IFN-γ determining the terminal commitment of T cells to the Th1 lineage [22]. Because T-bet and Gata3, the master transcription factors for Th1 and Th2 cells, respectively [23,24], cross-inhibit each other [25], it has long been thought that the commitment of T cells to the Th1 vs Th2 lineages was mutually exclusive, but this view has recently been changing (see below).

Since the histopathological and clinical features not only in EAE and MS but also in other organ-specific autoimmune diseases like rheumatoid arthritis or psoriasis, could be explained by Th1 effector mechanisms, these cells and their key cytokine IFN-γ were thought to be the major mediators of organ-specific autoimmunity. IFN-γ was identified in the lesions of MS patients and administration of recombinant IFN-γ triggered MS-relapses [26,27]. The fact that myelin antigen specific T cell lines that had a pure Th1 phenotype were very potent in inducing EAE upon adoptive transfer into recipient animals was also a very strong argument in favor of EAE (and putatively also MS) as being a "Th1" disease. Consistent with this idea, *Tbx21*$^{-/-}$ (T-bet deficient) mice were resistant to MOG_{35-55} induced EAE and neutralizing antibodies to the p40 subunit of IL-12 reduced the disease severity in EAE mice [28,29]. However, as of the mid 1990s it was difficult to reconcile the Th1 concept of EAE with the observation that the newly generated *Ifng*$^{-/-}$ mice and *Ifngr*$^{-/-}$ mice as well as *Il12p35*$^{-/-}$ mice were not resistant to EAE, but were even hypersusceptible to the disease [30–32]. It was later discovered that the p40 subunit of IL-12 not only paired with p35 to form the biologically active heterodimeric molecule of IL-12, but also with a p19 subunit to form a cytokine that was termed IL-23 [33]. IL-23 did not induce Th1 cells but promoted the secretion of a phylogenetically ancient cytokine, IL-17, in $CD4^+$ T cells. IL-17 had been cloned in 1993 [34,35]but did not receive a lot of attention because it had not been associated with adaptive T helper cell responses up to then. *Il23p19*$^{-/-}$ mice (which do not produce IL-23, but whose production of IL-12 is not impaired) were completely resistant to any model of induced autoimmunity including EAE [36]. Thus, as of 2003 the IL-23/IL-17 axis rapidly moved into the focus of research interest in autoimmunity and chronic inflammation. Since IL-17 cannot be classified according to the Th1/Th2 paradigm, IL-17 producing $CD4^+$ T helper cells were termed Th17 cells. However, whether or not Th17 cells are a T helper cell lineage of their own, kindled a serious debate among T cell immunologists. Even though the minimal requirements for the definition of a "new" lineage, i.e. identification of the differentiation factors that induce Th17 cells from naïve T cells, characterization of a distinct cytokine signature that is linked to distinct effector functions of Th17 cells, and identification of a "master" transcription factor that controls the transcription of the signature cytokines of Th17 cells have all been met [37–39], it remains a concern that Th17 cells, in contrast to Th1 cells, do not seem to be stable in vivo and it is still not entirely clear whether long lived memory T cells can be generated from the Th17 lineage [40]. Yet, Th17 cells are found in the inflamed CNS of EAE mice and IL-17 is one of the cytokines that is strongly upregulated in MS lesions [41], in the skin of psoriasis patients [42], in the gut of patients with chronic inflammatory bowel disease [43], and in the joints of patients with rheumatoid arthritis [44].

Further T helper cell subsets such as Th9 cells or Th22 cells have recently been described based on their signature cytokines IL-9 and IL-22, respectively [45–48]. However, for these Th subsets it is even less clear than for Th17 cells whether they represent stable lineages. Th9 cells are induced by TGF-β plus IL-4 and produce exceptionally large quantities of IL-9, high levels of IL-10 but only trace amounts of IL-17 or IFN-γ. Since IL-9 was formerly thought to be a Th2 specific cytokine, most of the effector functions of Th9 cells were observed in models of allergic diseases. Indeed Th9 cells act as key players in onset and progression of asthma serving as strong inducers of mast cell responses [47]. However, despite major differences in differentiation modes and functions, Th1, Th17 and Th9 cells are able to contribute to the pathogenesis of EAE and MS [49]. Each T helper cell subset produces specific cytokines which act as critical components of the immune inflammatory process and are the key means by which T helper cells amplify immune responses and recruit other effector cells of the adaptive and innate immune system to shape specific types of immunity (Fig. 1). In order to understand the coordinate recruitment of various effector cell subsets to the site of inflammation, it has been an important focus in EAE research to elucidate the temporal and spatial pattern of cytokine expression in the CNS during an autoimmune response (see also Table 1).

3. IFN-γ

IFN-γ, the hallmark Th1 cytokine, plays a significant role both in immunostimulation and immunomodulation. IFN-γ was first described by Wheelock as an interferon-like virus inhibitor produced by human leukocytes [50]. IFN-γ, the only member of the type II class of interferons, has been cloned and is located on human chromosome 12 [51] and mouse chromosome 10 [52]. The *Ifng* gene is highly conserved among species and contains four exons and three introns [53]. The biologically active IFN-γ protein is built from two monomers in an anti-parallel inter-locking manner.

IFN-γ is produced by NK and NKT cells that belong to the innate immune system but is also a major product of activated T cells (see above). The IFN-γ receptor is composed of two subunits: the ligand-binding α-chain [54] and the transmembrane β-chain, that is essential for intracellular signaling [55,56]. Whereas the α-chain is ubiquitously and constitutively expressed, the expression of the β-chain is induced by distinct stimuli [57]. Upon binding of IFN-γ to its receptor the receptor associated Janus kinases Jak1 and Jak2 become phosphorylated and phosphorylate in turn the downstream transcription factor Stat1a which binds to specific DNA elements (IFN-γ-activation sites) [58]resulting in rapid direct or

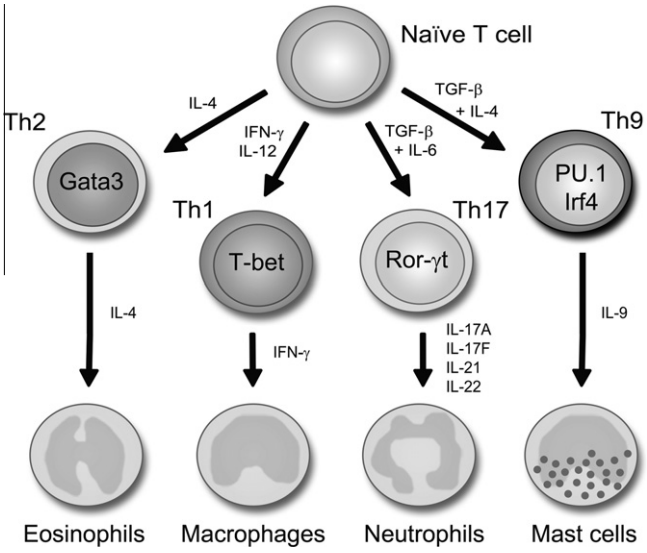

Fig. 1. Model of T helper cell differentiation. Naïve T cells can differentiate into T helper type 1 (Th1), Th2, Th17 or Th9 cells depending on the cytokine environment. The transcription factors Gata3, T-bet, Ror-γt or PU.1, and Irf4 are among others required for the induction of Th2, Th1, Th17, or Th9 cells, respectively. Each T helper cell subset secrets a distinct panel of effector cytokines, which in turn, affects distinct types of target cells.

indirect transcriptional activation of IFN-γ target genes including Fcγ receptor or MHC class I and II [59].

IFN-γ has a great impact on the regulation of the immune response [60] since many immune cells express the IFN-γ receptor and respond to IFN-γ: IFN-γ stimulates the differentiation of Th1 cells, inhibits the differentiation of Th2 cells [61] and activates cytotoxic T cells and NK cells [62]. Furthermore IFN-γ influences antibody production by promoting the secretion of IgG2a by B cells [63] and stimulates macrophages to produce tumor necrosis factor (TNF), IL-1, IL-6 and IL-8 [64]. Because of its influence on Th1 cells and macrophages, IFN-γ was thought to be crucial for the induction of EAE. Indeed, in mice, high levels of IFN-γ could be detected in the CNS at the peak of EAE disease, but declined during recovery [65]. However, unexpectedly, mice deficient for IFN-γ or IFN-γ receptor were fully susceptible to EAE and even experienced an EAE with higher morbidity and mortality [30,31]. Although it is now known that IFN-γ is also pro-apoptotic and initiates the contraction of effector T cell populations [66,67], development of EAE in the genetic absence of IFN-γ eliminated this cytokine as unique non-redundant pathogenic factor in T cell mediated organ-specific autoimmunity.

4. IL-17

IL-17 (IL-17A) is the prototypic cytokine of the IL-17 family which contains IL-17, IL-17B, IL-17C, IL-17D, IL-17E (also called IL-25), and IL-17F, which share 16–50% amino acid identity [68,69]. Members of the IL-17 family of cytokines are structurally homologous to the cysteine knot family of proteins. IL-17A and IL-17F are the best characterized family members and have distinct but overlapping (mostly proinflammatory) functions. IL-17F is more important in mucosa associated immune responses [70]. IL-17A and IL-17F are secreted by several cell types including subsets of $CD4^+$ T cells, $CD8^+$ T cells, γδ T cells, NKT cells, NK cells and neutrophils. In contrast, IL-17E (also called IL-25) is associated with Th2 responses and is secreted by Th2 cells, mast cells, but also intestinal epithelial cells. The receptor complex for IL-17E consists of a IL-17RA/IL-17RB heterodimer and thus, shares the IL-17RA subunit with the receptor for the proinflammatory family members IL-17A and IL-17F, which is a heterodimeric molecule composed of IL-17RA and IL-17RC. Sharing of IL-17RA by IL-17A, IL-17F, and IL-17E might be one of the reasons why the clinical phenotype of *Il17ra*$^{-/-}$ mice that are not resistant to EAE, has been difficult to interpret. In fact, IL-17A (more than IL-17F) plays a disease promoting role in EAE while IL-25 is protective [70,71].

Through IL-17RA binding, IL-17A activates NFκB signaling and MAP kinases. Because IL-17A treatment failed to induce NFκB as

Table 1
Effector cytokines in EAE.

Cytokine	Source	Receptor/receptor distribution	Refs.
IFN-γ	T cells, NKT cells, NK cells	Heterodimer: IFN-γRα/β: inducible on all nucleated cells	[180–183]
IL-17A	Th17 cells, $CD8^+$ T cells, γδ T cells, NKT cells, NK cells, LTi cells, LTi-like cells, neutrophils, eosinophils, monocytes	Functional heterodimer: IL-17RA/C IL-17RA: on hematopoietic cells, osteoblasts, fibroblasts, endothelial cells, epithelial cells IL-17RC: on epithelial cells, fibroblasts and other stromal cells, low amounts on hematopoietic cells	[34,36,147,148,159,184–191]
IL-21	Th17 cells, T follicular helper cells, NKT cells, NK cells	Functional heterodimer: γ_c/IL-21R γ_c: on lymphoid, but not on non-lymphoid and non-hematopoietic cells IL-21R: on B cells, T cells, NK cells, some populations of myeloid cells	[87–89,192–195]
IL-9	Th9 cells, Th2 cells, Treg cells, NKT cells, mast cells	Functional heterodimer: γ_c/IL-9Rα γ_c: on lymphoid, but not on non-lymphoid and non-haematopoietic cells IL-9Rα: T cells, B cells, mast cells, macrophages, dendritic cells, airway epithelial cells, immature neurons	[45,46,90,96,196–203]
IL-22	Th17 cells, activated T cells, γδ T cells, NKT cells, NK cells, LTi cells, LTi-like cells	Functional heterodimer: IL-10R2/IL-22R1 IL-10R2: ubiquitously expressed on hematopoietic and non-hematopoietic cells IL-22R1: on a variety of epithelial and parenchymal tissues, but not on lymphoid cells	[108,118,120,204–209]
TNF	Activated T cells, B cells, NK cells, monocytes, macrophages (main producers), dendritic cells, astrocytes, microglia	TNFR1 (p55): on all nucleated cells (not on unstimulated T cells or unstimulated oligodendrocytes) TNFR2 (p75): expression on hematopoietic cells and oligodendrocytes	[62,124,210–215]
GM-CSF	Activated T cells, macrophages, dendritic cells ($CD103^+$), endothelial cells, fibroblasts, mesothelial cells	Functional heterodimer: β_c/GM-CSF(CSF2)Rα On neutrophils, eosinophils, basophils, monocytes, macrophages, dendritic cells, microglia, endothelial cells	[139,145,146,216–223]

well as IL-6 production in embryonic fibroblasts deficient in the E3 ubiquitin ligase TRAF6, TRAF6 has been suggested to be involved in the IL-17A induced NFκB activation [72]. TRAF6 is recruited to the IL-17RA chain by the adaptor protein Act1, which binds directly to the SEFIR domain of IL-17RA [73]. Thus, Act1 and TRAF6 mediate downstream signaling of IL-17RA [74,75]. IL-17A induces several proinflammatory cytokines (IL-6, IL-1β, TNF, GM-CSF) and chemokines, in particular CCL20, which can attract CCR6 expressing Th17 cells in a positive feed forward loop, and ELR$^+$ (glutamic acid (E), leucin (L), arginine (R)) members of the CXC family of chemokines (CXCL1 and CXCL2) that are strong attractants for neutrophils [76,77]. Moreover IL-17R engagement increases the generation of reactive oxygen species (ROS) in brain endothelial cells resulting in disorganization of tight junctions and subsequently in blood brain barrier impairment [78,79]. Furthermore IL-17A is thought to activate microglial cells [80]. Since upon stimulation with IL-17, innate immune cells produce IL-1β and IL-6 which are factors that promote the differentiation of adaptive immune cells towards the Th17 phenotype, this cytokine network might constitute a feed forward loop resulting in enhanced tissue inflammation [81].

5. IL-21

IL-21 is a member of the IL-2 family of cytokines. IL-21 plays a significant role in the activation of NK cells and promotes the expansion of B cells and T cells that have been activated by their cognate antigen [82]. It is produced by NKT cells, but also by activated CD4$^+$ T cells, especially by Th17 cells and follicular T helper cells. The functional IL-21 receptor is a heterodimer composed of the common γ-chain (γ_c) which is shared by the receptors for IL-2, IL-4, IL-7, IL-9, and IL-15, and the unique IL-21 receptor α chain (IL-21Rα) [83]. Upon receptor binding, IL-21 activates both Jak1 and Jak3 resulting in signal transduction via Stat3 and Stat1 and to a weaker extent via Stat5.

IL-21 is a T cell derived cytokine that has a prominent role in the communication of T cells with other immune cells. IL-21 is involved in the regulation of immunoglobulin production and terminal differentiation of B cells into plasma cells [84,85]. IL-21 induces the expression of killer inhibitory receptors (KIRs) on NK cells and thus augments their cytolytic activity. A combination of IL-15 and IL-21 increases the production of IFN-γ by NK cells [86]. Among effector T helper cells, the largest quantities of IL-21 are produced by Th17 cells. And similar to IL-4 for Th2 cells and IFN-γ for Th1 cells, IL-21 serves as an autocrine amplifier molecule for the generation of Th17 cells since IL-21 together with TGF-β is able to drive the generation of Th17 cells from naïve T cells [87–89]. Thus, IL-21 acts back on T cells to increase the Th17 precursor frequency and also on other immune cells to promote specific effector functions. Due to the restricted expression of the functional IL-21 receptor, which is not expressed on non-hematopoietic cells, IL-21 – unlike IL-17 – does not induce a broad tissue response.

6. IL-9

Like IL-21, IL-9 is a member of the common γ-chain receptor cytokine family. Cellular sources of IL-9 are mast cells but also T cells. IL-9 has been thought to be part of the Treg signature but more recently it has been confirmed that IL-9 may be produced by a specific subset of T helper cells (Th9 cells) that can be induced in vitro with a combination of TGF-β and IL-4 [45,46,90]. Minor amounts of IL-9 may also be produced by Th2 and Th17 cells. IL-9 activates a heterodimeric receptor consisting of the cytokine-specific IL-9 receptor α chain (IL-9Rα) and the common γ-chain [91]. Upon binding of IL-9 to its receptor, the kinases Jak1 and Jak3 are phosphorylated and subsequently activate Stat1, Stat3 and Stat5 [92–94].

IL-9 was initially described as a cytokine that promotes the expansion of mast cells [95]. *Il9*$^{-/-}$ mice harbor normal steady state concentrations of mast cells, but show defects in the expansion and recruitment of mast cell populations after intestinal nematode infections or EAE induction [96,97]. The proinflammatory characteristics of IL-9 are further supported by the observation that antigen-specific, adoptively transferred Th9 cells are able to induce EAE [49]. However, the net effect of IL-9 depends on the cellular context. There are hints that IL-9 may act directly on Tregs (which express IL-9Rα), enhancing their suppressive function and indirectly on Th17 cells (which do not express IL-9Rα), promoting their proliferation and/or accumulation [98]. IL-9 induces the expression of the chemokine CCL20 by astrocytes, which enhances the migration of Th17 cells into the CNS. Accordingly mice treated with a neutralizing anti-IL-9 antibody showed reduced expression of CCL20 in astrocytes and decreased numbers of infiltrating Th17 cells resulting in reduced EAE [99].

7. IL-22

IL-22, which is part of the Th17 cytokine signature, is induced upon IL-23R engagement and is also produced by NK cells, NKT cells, γδ T cells and lymphoid tissue inducer (LTi) cells. IL-22 is a member of the IL-10 family of cytokines, which also includes IL-10, IL-19,IL-20, IL-24, IL-28a, and IL-28b as well as IL-26 and IL-29, two IL-10 family members that are only expressed in humans [100–103]. Whereas the *Il29* gene exists in mice, but is non-functional due to the existence of a stop codon within the first exon [104,105], the *Il26* gene is disrupted in rodents [106]. The unique IL-22R is a heterodimeric transmembrane receptor complex consisting of IL-22R1 and IL-10R2. Binding of IL-22 to its receptor activates Jak-Stat signaling pathways, in particular Stat3. In addition to the cell surface receptor complex, there is a secreted IL-22 binding receptor, termed IL-22 binding protein (IL-22BP), which is encoded by an independent gene that lacks sequences for the intracellular and transmembrane domains of IL-22R [107–110]. In vitro, IL-22BP binds IL-22 and inhibits the binding of IL-22 to its cell membrane associated receptor. Interestingly, IL-22BP expression is downregulated under inflammatory conditions [111,112]. This suggests that IL-22 is the only IL-10 family member whose functional activity can be regulated even after its secretion.

Similar to IL-17, IL-22 has a broad impact on epithelial cells. However, in contrast to IL-17RA and IL-17RC, the functional IL-22 receptor complex is not expressed on hematopoietic cells. Thus, IL-22 modulates local tissue responses and targets cells of the skin, the digestive tract, the lungs and the kidney and promotes cell proliferation and differentiation, thereby enhancing host defence and wound-healing responses [113]. Moreover IL-22 exhibits protective functions by limiting tissue damage during inflammatory processes of the liver [114], the gut [115,116]and the myocardium [117]. The role of IL-22 in autoimmunity is not yet clear. Whereas IL-22 exacerbates the inflammatory skin response in psoriasis [118–120], the effector functions of IL-22 in EAE are not well understood. While IL-22 contributes to breaching of the blood brain barrier [78], IL-22 KO mice do not show a reduced phenotype in the EAE model [121].

8. TNF

TNF is mainly produced by activated mononuclear phagocytic cells, but also by NK cells, B cells, activated T cells, as well as by resident cells of the CNS including astrocytes and microglial cells. TNF is generated as a 27 kDa membrane-bound protein. Upon

proteolytic cleavage by the matrix metalloprotease TNF-α converting enzyme (TACE), the resulting 17 kDa fragments form homotrimers and thus build the soluble active form of the cytokine. Both the transmembrane and the soluble forms are biologically active. There are two types of TNF receptors: TNF receptor 1 (TNFR1, p55) is broadly expressed and can be activated by either soluble or transmembrane TNF. TNF receptor 2 (TNFR2, p75) is preferentially activated by the transmembrane form of TNF [122,123] and is expressed by cells of the immune system including microglia but also by macroglial cells. Oligodendrocytes express TNFR2 in a constitutive manner and are induced to express TNFR1 by inflammatory stimuli [124]. While TNFR1 confers cytotoxic effects and promotes apoptosis, TNFR2 mediated signaling modulates apoptosis but can also result in cell growth and proliferation [125].

More than 15 years ago, TNF was identified in active MS brain lesions, both on the protein and mRNA level [126,127]. Thus, TNF was considered to be involved in Th1 mediated tissue damage. Accordingly, elimination of TNF producing macrophages, application of a neutralizing anti-TNF antibody or of a soluble p55 molecule prevented the induction of EAE [128–130] whereas administration of recombinant TNF exacerbated clinical symptoms. [131]. Similarly, transgenic mice overexpressing TNF in the CNS developed a spontaneous inflammatory demyelinating disease and this demyelination was completely reversed by a neutralizing anti-TNF antibody [132]. In line with these findings, *Tnfr1*$(p55)^{-/-}$ mice were totally resistant to EAE. However, *Tnfr2*$(p75)^{-/-}$ mice exhibited exacerbated EAE, with increased Th1 cytokine production, and increased infiltration of $CD4^+$ T cells and macrophages in the CNS [133]. Also, mice deficient for TNF were not protected from EAE; they even developed a more severe variant of EAE, characterized by extensive inflammation and demyelination [134].Indeed, after toxic demyelination, *Tnfr2*$(p75)^{-/-}$ mice showed reduced proliferation of oligodendrocyte precursor cells and thus, impaired remyelination as compared with wild type littermates or *Tnfr1*$(p55)^{-/-}$ mice suggesting that TNF promotes remyelination by acting directly on $TNFR2^+$ oligodendrocyte precursors [135].Taken together, these observations support the hypothesis that TNF may not only be a myelinolytic effector molecule of exaggerated Th1 responses but also have a role in immunoregulation (by inducing apoptosis) and tissue repair (by modulating remyelination).

9. GM-CSF

Granulocyte macrophage-colony stimulating factor (GM-CSF) was originally defined by its ability to promote the proliferation and differentiation of macrophages, granulocytes, and dendritic cells from precursors [136,137]. GM-CSF is secreted by cells of the innate immune system but also by T cells in response to inflammatory stimuli such as IL-1, TNF and LPS [138,139].Notably, GM-CSF is also a target of IL-23 and is part of the cytokine signature of Th17 cells. GM-CSF binds to a high-affinity heterodimeric receptor composed of a GM-CSF specific α-chain and the common signal-transduction subunit β (β_c), which is shared with the receptors for IL-3 and IL-5 [140,141]. GM-CSF mediates its effects through different signaling pathways, including the Jak-Stat-pathway, the MAP kinase pathway and the phosphoinositol-3-kinase (PI3K) pathway.

GM-CSF has important functions in both physiological and inflammatory conditions. In particular, it is critically involved in the development of organ-specific autoimmune diseases including EAE and collagen-induced arthritis. Mice that are deficient for GM-CSF or received a neutralizing anti-GM-CSF antibody developed attenuated EAE [142,143] whereas local administration of GM-CSF leads to exacerbated EAE [144]. Interestingly, GM-CSF seems to be a particularly important effector molecule of Th17 cells because anti-GM-CSF antibody treatment selectively suppressed IL-23-driven forms of EAE while EAE induced by adoptive transfer of IL-12p70 polarized PLP specific T cells (Th1 cells) developed irrespective of GM-CSF blockade [143]. GM-CSF promotes inflammation in the CNS probably by enhancing the expression of MHC class II and costimulatory molecules by local and/or infiltrating APCs. Kopf and coworkers demonstrated that GM-CSF facilitates the secretion of IL-6 and IL-23 by DCs and macrophages and thus regulates the generation and maintenance of Th17 cells [145]. In summary, GM-CSF appears to play a profound proinflammatory role in EAE. However, while some evidence points to T cells, there are still uncertainties on the most relevant cellular sources of GM-CSF under conditions of chronic inflammation in the CNS [143,146].

10. Individual effector cytokines and T helper cell subsets are not equivalent

Cytokine knockout mice or mice that transgenically overexpress a specific cytokine have been invaluable tools in deciphering the role of cytokines in chronic inflammation and organ specific autoimmunity. Unexpected observations like unimpaired susceptibility to EAE of *Ifng*$^{-/-}$ mice, *Tnf*$^{-/-}$ mice, or *Il17f*$^{-/-}$ mice prompted conceptual debates on whether or not it is possible to define one solitary cytokine that is responsible for the induction of tissue inflammation in a non-redundant manner. The answer to this question might rather be no. The finding that both IFN-γ and IL-17 might be dispensable for induction of EAE, respectively, has even fueled the swan song by some researchers of Th1 and Th17 cells as pathogenic T cells in EAE and other organ specific autoimmune diseases. However, it must be considered that distinct T helper cell subsets do not only produce one solitary signature cytokine but a panel of factors whose combined effects might be responsible for a specific mode of immunity, i.e. IFN-γ is not equivalent to Th1 cells and IL-17 is not equivalent to Th17 cells. Although there has been a tendency to rush into lineage assignment to particular subsets of T helper cells (perhaps regarding Th9 and Th22 cells), there is still a large body of experimental evidence to suggest that the concept of distinct T helper cell lineages is valid. Th1 and Th17 cells are clearly distinct. In the initial reports on Th17 cells, it was shown that Th17 cells develop in the genetic absence of Stat1, Stat4, and T-bet that are necessary and sufficient to induce Th1 cells [147,148]. Moreover, IFN-γ and IL-4 are both inhibitory to the development of Th17 cells. Thus, Th1 cells and Th17 cells are fundamentally different and induce different types of immunity in vivo. While Th1 mediated immunity results in inflammatory infiltrates dominated by activated macrophages, Th17 cells induce neutrophilic inflammatory responses (Fig. 1).

11. Plasticity of T helper cells in EAE

T helper subsets (or even lineages) might be more plastic than anticipated [149]. Plasticity might be dictated by factors in the ambient milieu and adapt the T helper cell response to the requirements of a specific niche or compartment. But here too, T cell biology is not completely arbitrary but follows specific rules and is dependent on specific nodal points of T cell development. Upon initial commitment to a specific developmental program, a T cell will become responsive to modulatory cytokines in the ambient milieu based on its receptor equipment. It will be essential whether WSX1 or IL-6Rα will pair with the constitutively expressed gp130 to form a functional IL-27 receptor or a functional IL-6 receptor in this T cell [150,151]. Similarly, expression of IL-23R that pairs with IL-12Rβ1 to form a functional IL-23R or expression of IL-12Rβ2 that also associates with IL-12Rβ1 but builds a

functional IL-12 receptor will dictate terminal differentiation or plasticity of a T cell that has already been committed to a developmental program [152]. Yet, it depends on the lineage commitment how fundamental the fate decisions of a given T cell can be. For example, Th1 cells are relatively stable and cannot easily be reprogrammed while Th2 cells might be switched into a Th1 phenotype in a biased experimental system [153]. Adoptively transferred LCMV specific Th2 cells can be reprogrammed to express T-bet and produce IFN-γ upon subsequent in vivo infection with LCMV resulting in protective immunity and memory T cells that co-express T-bet and Gata3 [153]. Th17 cells appear to be even less stable. Although it is now clear that in vitro generated Th17 cells and in vivo generated Th17 cells might be different in terms of developmental plasticity [154], it remains to be determined whether memory T cells that express a classic Th17 phenotype really exist [40]. Using reporter mouse/fate tracking systems, it has been shown that IL-17A or IL-17F producing T cells are reprogrammed to produce both IL-17 and IFN-γ or IFN-γ only in the spleen and within the CNS [155,156]. Yet, these reprogrammed "Th17" cells (even if they do not produce anything else but IFN-γ) seem to be distinct from classical Th1 cells. Although they lost expression of IL-17, the expression of IL-23R, IL-1R, and CCR6 that are not usually expressed by Th1 cells was kept up. Thus, the homing behavior of reprogrammed Th17 cells and their response to the innate cytokine milieu in the inflamed tissue as well as their mode of cell death and way of regulation by Tregs might be fundamentally different from Th1 cells.

The contraction of T helper cell populations is an active process and is regulated differentially depending on the compartment (lymphoid tissue vs target tissue) and probably also depending on the effector T cell lineage. While it has long been known that Th1 cells are very susceptible to Fas/FasL induced cell death [157]and Th2 cells to GrzB mediated apoptosis [158], it remains to be determined whether there is a preferred mode of cell death for Th17 cells. It appears that Th17 cells express high amounts of IL-10Rα and are more susceptible to IL-10 mediated suppression than Th1 or Th2 cells. It is likely that IL-10 which might be provided by Foxp3$^+$ Tregs at the site of inflammation, signals directly into Th17 cells. However, it is not yet clear whether sensing of IL-10 leads to reprogramming of the inflammatory properties of Th17 cells or triggers their physical attrition.

12. Alternative sources of T helper cell associated cytokines

Expression of IL-23R, IL-1R, or CCR6 is highly linked to the "Th17 phenotype" in the inflamed tissue. But IL-23R is not only expressed on Th17 cells. In fact, cells of the innate immune system like LTi cells, LTi like cells, NK cells, NKT cells, and γδ T cells express large amounts of IL-23R and respond to IL-23 with extensive secretion of IL-17 and IL-22 [159]. We and others could recently show that IL-23R$^+$ γδ T cells enter into the CNS at the time of onset of clinical signs of EAE and accumulate in the CNS at the peak of EAE followed by rapid contraction of the γδ T cell population [160,161]. Although CNS derived IL-23R$^+$ γδ T cells produce large amounts of IL-17, γδ T cell-derived IL-17 is unlikely to further contribute to IL-17 induced immunopathology because large quantities of this cytokine are produced by antigen specific Th17 cells that are also present in the CNS. However, an effector function unique to γδ T cells which is not shared with Th17 cells might be their capacity to repress Treg responses [161]. IL-23 activated γδ T cells inhibit the generation of Foxp3$^+$ Tregs from conventional T cells in the peripheral immune compartment and in the target tissue of the inflammation independently of IL-6 or IL-21. In addition, IL-23 activated γδ T cells also inhibit the capacity of pre-existent thymus-derived Tregs to suppress adaptive immune responses by antigen specific conventional effector αβ T cells (Fig. 2). Thus, IL-23 shapes αβ T cell responses in a cell intrinsic manner by guiding and stabilizing their transcriptional program towards pathogenic effector T cells and in a cell extrinsic manner by tipping the Treg/effector T cell-balance against Tregs.

Even less is known about the role of IL-23R$^+$ NKT cells. IL-23R$^+$ NKT cells in the spleen rapidly produce large amounts of IL-17 upon stimulation with IL-23 or TcR triggering by aGalCer in an IL-6 independent manner [162]. However, their contribution to EAE is unknown while the role of IFN-γ or IL-4 producing NKT cells has been investigated in EAE. Depending on the timing and mode of their activation with aGalCer, NKT cells can exacerbate EAE [163] or downmodulate the inflammatory response [163–166]. While NKT cells home to secondary lymphoid tissue, gut associated lymphoid tissue, and liver, recruitment to the CNS is under debate [162,167,168].

In summary, we propose that the definition of the temporal pattern of cytokine expression in the inflamed tissue can only be the first step to understand the principles of immunopathology in chronic inflammation and autoimmunity. It may be more important to define the cellular sources of effector cytokines and understand their plasticity in response to the environment of a specific niche in order to predict immunopathology.

13. Concluding remarks

EAE has been an extremely useful model to study T cell development and T cell fate decisions in vivo. Nevertheless, during the last 2 decades, we have experienced many unexpected results when analyzing EAE development in cytokine or transcription factor knock-out animals. Most of the time – after an initial shock – these experiments promoted our understanding of T cell biology and brought our concepts of T cell development and effector functions to a higher level of understanding. Thus, where do we stand

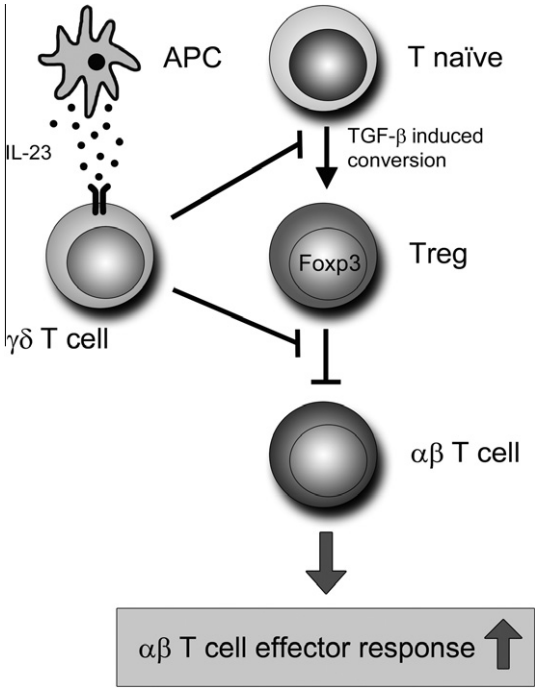

Fig. 2. γδ T cells restrain regulatory T cell responses. γδ T cells sense IL-23 produced by antigen-presenting cells (APC) via a constitutively expressed IL-23 receptor. In response to IL-23 γδ T cells prevent the TGF-β driven conversion of naïve T cells into Foxp3 expressing regulatory T cells (Tregs) and antagonize Treg mediated suppression of αβ T cells. This enhances the adaptive immune response by effector αβ T cells.

at the moment? *Il12p35*$^{-/-}$ mice, *Il12rb2*$^{-/-}$ mice, *Ifng*$^{-/-}$ mice, *Ifngr*$^{-/-}$ mice, *Il17*$^{-/-}$ mice, *Il21*$^{-/-}$ mice, *Il21r*$^{-/-}$ mice, *Il22*$^{-/-}$ mice, *Tnf*$^{-/-}$ mice, and *Tnfr*(*p75*)$^{-/-}$ mice are not resistant to EAE although all of these cytokines are either required for the development of Th1 responses or are signature effector cytokines of Th1 or Th17 cells [31–33,121,133,134,169–171]. On the other hand, *Il23p19*$^{-/-}$ mice, *Il23r*$^{-/-}$ mice, *Il6*$^{-/-}$ mice, T cell conditional *gp130*$^{-/-}$ mice, and *Gmcsf*$^{-/-}$ mice are resistant to EAE corroborating the importance of the IL-23/Th17 axis for the development of chronic inflammation and autoimmunity [36,87,142,172,173]. One conclusion to be drawn from these results is that it might be unlikely that there is a unique non-redundant effector cytokine that is the sole pathogenic factor in organ specific autoimmunity. Furthermore, T helper cells maintain a certain degree of plasticity even after commitment to a specific T helper cell lineage. In addition, pathogenic effector programs within T helper cells may be driven by transcription factors like Stat3 or T-bet, and it may be oversimplified to exclusively allot the expression of these transcription factors to just one T cell subset. For example Th17 cells and even Th2 cells are able to express the Th1 transcription factor T-bet upon sensing particular cytokine cues and only then take on proinflammatory and productive effector functions [153,156].

The development of proinflammatory T cell responses has several checkpoints. Early during the response – perhaps during T cell priming in secondary lymphoid tissue and also due to high amounts of IL-6 receptor expression on naïve conventional T cells – the availability of IL-6 might dictate whether a pathogenic or a regulatory adaptive T cell response is primed [38,87]. A late checkpoint might be the decision whether a pathogenic response will be transient or sustained. Here, the responsiveness to IL-23 whose receptor is not expressed on naïve T cells but on effector T cells that are committed to the Th17 lineage, will determine the acquisition of sustained effector functions which may no longer be exclusively associated with the expression of IL-17.In contrast, it has been shown that committed Th1 cells that keep sensing IL-12 together with sustained TcR stimulation turn on downmodulatory programs and start producing IL-10, which has been shown to be an effector T cell intrinsic mechanism to limit immunopathology [174–178]. This may offer a plausible explanation why the administration of an anti-p40 antibody (ustekinumab) that neutralizes both IL-12 and IL-23, had a zero net effect in patients with RRMS and did not reduce the number of gadolinium enhancing lesions after 23 weeks [179]. It will be important to understand the molecular mechanism of these late checkpoints in order to identify targets for interventional approaches in autoimmune diseases like MS where the initial steps of T cell commitment have already occurred when the diagnosis is made. We feel that for these particular questions of T cell development, EAE – despite all its shortcomings in mimicking the exact clinical course and histopathology of MS – might be an excellent model.

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