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T cell subsets and their signature cytokines in autoimmune and inflammatory diseases

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INTRODUCTION

T helper (Th) cells are characterized by different cytokine profiles which are used to define their subsets. However, it is still an area of debate if pathogenic Th cells can be defined by simple cytokine profiles.

Over a quarter of a century ago, Mossman and Coffman made the seminal observation that long-term Th clones could be distinguished based on their cytokine profiles, which afforded Th subsets different functional properties[1]: Th1 cells, characterized by the secretion of Interferon-gamma (IFN-γ) and tumor necrosis factor alpha (TNF), and Th2 cells, which secrete interleukin (IL)-4, IL-5 and IL-13. This observation was novel and advanced the understanding of how the immune system adapts to specific pathogens and that Th subsets have unique roles in mediating protection. For example Th1 cells are responsible for cell-mediated immune responses, while Th2 are responsible for humoral-mediated immunity[2]. Interestingly, each of these Th subsets can promote immunopathology; for instance an excessive Th1 response will result in tissue damage, while excessive Th2 responses can result in atopy/hypersensitivity[2].

Since the discovery of the Th1/Th2 dichotomy, many additional Th subsets were discovered, each one with a unique cytokine profile, functional properties and presumed roles in autoimmune tissue pathology. These “new” Th subsets include IL-17 producing Th17 cells, regulatory Th cells (Tregs), and, recently, IL-9 producing Th9 cells and IL-22 producing Th22 cells. This article will review the different Th subsets in terms of cytokine profiles, how these cytokines influence and shape the immune response, and their relative roles in promoting pathology in autoimmune and inflammatory diseases. Furthermore, we will discuss whether Th cell pathogenicity can be defined solely based on their cytokine profiles and whether rigid definition of a Th cell subset by its cytokine profile is helpful.

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Shown in Figure 1 is an illustration of the pro-inflammatory and anti-inflammatory functions of the signature cytokines of each T cell subset.

Th1 cells

Th1 cells are the quintessential cell type involved in cell mediated inflammation and delayed-type hypersensitivity reactions. They are thought to be important for immunity to intracellular pathogens. Th1 cells are most often defined by their production of IL-2 and IFN-γ but have been reported to produce a number of cytokines including: TNF, lymphotoxin, and granulocyte-macrophage colony-stimulating factor (GM-CSF). Committed Th1 effectors express the transcription factor T-bet. Factors favoring Th1 differentiation includes IFN-γ/STAT1 signaling, IL-2/STAT5 signaling, IL-12/STAT4 signaling and strong T cell receptor (TCR) signals. The signature cytokine of the Th1 subset, IFN-γ, has long been associated with pathology of several autoimmune diseases including autoimmune type 1 diabetes (T1D), multiple sclerosis (MS) and rheumatoid arthritis (RA)[3,4]. It was not surprising, though, that IFN-γ-secreting Th cells were associated with immunopathology: IFN-γ is a potent proinflammatory cytokine which has a number of important roles including increasing the expression of toll-like receptors (TLR) by innate immune cells[5], promoting immunoglobulin (Ig) G class switching[6], increasing major histocompatibility gene complex (MHC) class I (MHC-I) and class II (MHC-II) antigen presentation[7], and induction of chemokine secretion, macrophage activation and increased phagocytosis[8].

However, even before the discovery of Th1 cells, evidence for IFN-γ having detrimental effects in autoimmune diseases was provided by the observation that administration of IFN-γ to MS patients was deleterious and resulted in exacerbation of the disease[9]. The negative outcome of IFN-γ treatment was unexpected since it was believed to have similar beneficial effects as had been seen with type-I IFN treatment. Subsequently, data accumulated from experimental autoimmune encephalomyelitis (EAE) studies, the animal model for MS, which supported a pathogenic role for IFN-γ and Th1 cells. Olsson et al. showed that autoreactive, myelin-specific, T cells produced high amounts of IFN-γ[10]. Similarly, myelin basic protein (MPB)-specific Th cells from both mouse and human were found to produce IFN-γ and TNF, but not IL-4[11], and adoptive-transfer of myelin-specific Th1 cells resulted in the development of EAE[12,13]. Importantly, knockout of the master regulator of the Th1 subset, T-bet, which is induced by IFN-γ signaling in a positive-feedback loop, results in resistance to EAE[14,15]. The observation that elevated serum levels of IFN-γ and TNF, derived from Th1 cells, were measured in patients with autoimmune demyelinating diseases, including MS, further supported that Th1 cells were pathogenic[16]. Hence for many years it was assumed that Th1 cells promote immunopathology in MS/EAE, conceivably by secreting IFN-γ, and that IFN-γ plays an essential role in promoting autoimmune pathology[17].

Additional support for Th1 cells being pathogenic came from studies in systemic lupus erythematosus (SLE) and its animal models. For instance, administration of IFN-γ to (NZB/W) F1 mice resulted in accelerated autoimmune disease[20]. Additonaly, in lupus-prone mice, IFN-γ was augmented and its increase corresponded to development of lupus-like

disease and increased mortality[18]. Furthermore, there was a significant reduction in the severity of murine lupus in IFN-$\gamma^{-/-}$ or IFN-γ-receptor (IFN-γR)$^{-/-}$ mice[19,20]. Importantly, IFN-γ signaling, but not Th2 cytokines, was found to be crucial for the generation and production of autoantibodies targeting intracellular molecules, similar to those found in SLE[21,22]. Similar to the observations in the SLE animal models, IFN-γ production was found to be elevated in serum of patients with SLE[23]. Indeed, administration of IFN-γ to patients with chronic myelogenous leukemia resulted in the manifestation of lupus-like disease, characterized by antinuclear antibody (ANA) formation and development of rheumatoid symptoms[24]. Likewise administration of IFN-γ to RA patients resulted in life-threatening multi-organ flare-ups of SLE[25]. These results highlighted the pathogenic role of IFN-γ in autoimmune diseases, even in a disease like SLE that was initially considered to be a Th2/type-2 mediated autoimmune disease (i.e. humoral-mediated).

However, there is some debate whether Th1 cells only play a pathogenic role in autoimmune diseases, or whether they also contribute to protective or anti-inflammatory immune responses. Experiments testing the impact of genetic deletion of IFN-γ on EAE showed a paradoxical but striking phenotype: animals lacking IFN-γ developed disease with increased severity compared with IFN-γ sufficient controls. The counterintuitive observation that IFN-γ was dispensable for the induction of EAE[26,27] was similarly noted in other models of autoimmune and inflammatory diseases including asthma[28], insulin-dependent diabetes mellitus[29] and experimental autoimmune uveitis (EAU)[30].

Several hypotheses have been proposed to account for the apparent anti-inflammatory properties of IFN-γ including the downregulation of lymphocyte trafficking into the draining lymph-nodes (dLN)[28], and control of T cell clonal expansion via induction of apoptosis[31,32]. IFN-γ is important for the induction of indoleamine2,3-dioxygenase (IDO), which exerts anti-inflammatory effects in lymph nodes and tissues[33,34]. IFN-γ can also suppress differentiation of T cells towards other Th subsets, for example towards Th17 cells. In this scenario IFN-γ would be protective by preventing the generation of T cells of a more pathogenic phenotype. This model of immune regulation has been observed in EAE models, where IFN-γ deficient mice exhibited strongly enhanced disease severity, which correlated with an increase in IL-17 producing T cells[35]. Indeed, during infection, IFN-γ regulates the induction and expansion of pathogenic Th17 cells[36]. These properties of IFN-γ seem to be pivotal in downregulating the inflammatory responses mediated by other Th cells and pathology promoted by these cells, in particularly Th2 and Th17 cells[28,37,38], but also by influencing other Th subsets such as Th9 cells via modulating IL-27 secretion by dendritic cells[39]. Additional work has identified a role for IFN-γ and STAT1 in the generation and maintenance of self-tolerance through the induction of Foxp3^{+} regulatory T cells[40]. These observations are supported by a report showing that adoptive transfer of IFN-γ-treated autoreactive Th cells suppressed EAE[41]. Taken together, IFN-γ can suppress autoimmune inflammation and pathogenic Th cells via direct and indirect mechanisms.

Recently another regulatory circuit was described that involves the actions of IFN-γ-inducible GTPase 1 (GBP-1), which acts as an important switch for cellular events during chronic virus infection which are responsible for promoting oxidative killing and delivery of antimicrobial peptides to autophagolysosomes[42]. Interestingly, GBP-1 can also be induced

by other Th1 cytokines such as TNF[43], and thus there is redundancy between IFN-γ and other Th1 cytokines. Thought-provoking, GBP-1 also acts as a negative regulator of TCR signaling and decreases the production of IL-2 in an IFN-γ-dependent manner[44]. Thus, conceivably, similar mechanisms could take place during other chronic inflammatory conditions, such as autoimmune diseases, in which IFN-γ acts as an autocrine and/or paracrine anti-inflammatory cytokine that inhibits T cell activation. It remains to be determined which Th cell subsets are most affected by IFN-γ via GBP-1. It also remains an enigma as to how regulatory Th cells abolish Foxp3 expression and convert into pathogenic IFN-γ producing Th1-like cells in the presence of high levels of IFN-γ [45,46], and why Th17 cells are differentiating into IFN-γ producing cells which are highly encephalitogenic in EAE[47]. The pleiotropic effects of Th1 cells in autoimmune disease pathology are associated not only with IFN-γ, but also with TNF, which was shown to be an important mediator in the induction of EAE[41], but it can also mediate CNS remyelination[48] and modulate the function of Tregs, both in EAE[49] and SLE[50].

Th2 cells

Th2 cells are recognized for their role in host defense against multi-cellular parasites and their involvement in allergies and atopic illnesses. To a large extent, Th2 cells function in epithelial tissues, most notably the intestinal tract and lungs. Perhaps as a direct result, Th2 differentiation and function are intimately regulated by innate and epithelial cell types that inhabit these tissues[51]. Recent work has identified the actions of innate cytokines IL-25, IL-33 and thymic stromal lymphopoietin (TSLP) as playing a critical role in developing Type 2 immune responses[52]. Th2 cells are best known for the production of IL-4, IL-5 and IL-13, as well as IL-9 and IL-10[53].

IL-4 is a multifunctional, pleiotropic cytokine discovered in the early 1980s', which is mainly produced by activated Th2 cells, but also by mast cells, basophils, eosinophils and γδT cells[54,55]. In the adaptive immune system, IL-4 is an important survival factor for lymphocytes. In B cells it promotes plasma cell differentiation and induces antibody class switching to IgG1 and IgE[56,57]. In the innate immune system, IL-4 has been shown to promote the differentiation of dendritic cells (DCs) from stem cells and to promote their maturation. IL-4R is expressed by monocytes and macrophages and IL-4 signals are thought to elicit macrophage activation against parasites. Interestingly, in experimental models of helminth infection, Th2 cells are thought to promote tissue repair by promoting the function of M2 macrophages through secretion of IL-4[58,59].

In autoimmune diseases, Th2 cells were initially described as anti-inflammatory based on their ability to suppress cell-mediated or Th1 models of disease[2,3]. Th2 cells have been described in lesions of MS patients[60], and IL-4 and IL-4R expression has been reported in several cell types in close proximity to active demyelinating lesions[61]. Over the years, however, a number of reports established a role for Th2 cells in tissue inflammation and implicated their cytokines in immunopathology. Initially, Genain et al. reported that in marmoset monkeys with EAE the cytokine production was shifted from a Th1 to a Th2 pattern, and titers of autoantibodies to myelin oligodendrocyte glycoprotein (MOG) were enhanced. They concluded that induction of Th2 responses may exacerbate autoimmunity by

enhancing production of pathogenic autoantibodies[62]. Indeed, autoantibodies against neuronal proteins are often observed in MS patients[63] and elevated levels of IL-4 (as well as IFN-γ and TNF) in serum of MS patients during the acute stage are positively correlated with increased demyelination[16]. Additionally, in the rat and marmoset models of MOG-induced EAE, demyelination is partially antibody-mediated, similar to immunopathology observed in some MS patients[64]. However, questions remain about the pathogenic functions of Th2 cells in the marmoset and rat models of EAE. It will be interesting to determine the pathogenic antibody isotypes as well as developing a clearer phenotype of the autoreactive T cell effector subsets in these models. The involvement of Th2 cells and pathogenic antibodies contrast the prevailing models of murine EAE which are considered to be Th1 and Th17-effector T cell-mediated diseases. However, pathogenic roles for Th2 cells have also been reported in murine EAE. Lafaille et al. showed that adoptive transfer of Th2-polarized MBP-specific T effector cells elicited EAE in immunocompromised recipient mice (RAG-1 or TCRα deficient), but not immune-sufficient hosts[65]. When compared with other T effector subsets, mice receiving Th2 cells developed EAE with delayed onset and milder symptoms. Jager et al. have also reported that 2D2 MOG-specific Th2 cells can induce EAE with delayed onset and low severity[66]. Taken together, these reports support that Th2 cells can promote pathogenicity, but ensuing disease may be less severe. Alternatively, but not mutually exclusive, development of EAE may not have been mediated by “Th2” cytokines, but might have been due to the switch of Th2 cells to a Th1-like phenotype and secretion of proinflammatory cytokines such as IFN-γ[67]. As previously mentioned, Th2 cytokines are associated with the pathogenesis of antibody-mediated autoimmune diseases such as SLE[68,69]. In some lupus-susceptible strains it was shown that there is an increased number of IL-4 producing cells[70] and treatment of animals in two mouse models of SLE ((NZB/W)F_1; MRL-*Faslpr* mice) with blocking anti-IL-4 antibody or soluble IL-4R reduced autoantibody production and nephritis[71]. Furthermore, IL-4 knockout MRL-*Faslpr* mice showed less lymphadenopathy and end-organ disease as compared with their wild-type littermates[71].

Consistent with a pathogenic role, blocking IL-4 with anti-IL-4 monoclonal antibody reduced the severity of experimental autoimmune myocarditis (EAM), which was also associated with a shift from a Th2 to a Th1 phenotype represented by reduction of IgG1 antibodies specific for cardiac myosin autoantigen and increased IFN-γ production. However, in the mercury-induced model of systemic autoimmunity, where IL-4 induces anti-nucleolar IgG1 and IgE antibodies (ANoA), knockout of the IL-4 gene had no effect on disease induction. Under these conditions, IFN-γ was found to compensate for the lack of IL-4 and induce ANoA IgG2a and IgG2b antibodies to drive disease pathology[69,72]. Nevertheless, much evidence supports that IL-4 promotes antibody-mediated autoimmune disease, whereas IFN-γ seems to limit pathology in these models[73]. IL-4, besides suppressing IFN-γ, may contribute to disease by activating B cells and enhancing IgG1 and IgE production, and IgG1 is indeed the predominant antibody response that correlates with the severity of EAM[56,74].

In contrast to their pathogenic role in type-2 autoimmune responses, much speculation centers on the protective role of Th2 cells in type-1 mediated immune pathology, since IL-4

is known to strongly suppress the development of Th1 cells even in an environment with high levels of IFN-γ, thereby antagonizing Th1 cell functions[75]. Anti-inflammatory properties of IL-4 include the inhibition of Th1-activated macrophages and suppression of the secretion of several potent proinflammatory mediators including IL-1, TNF, and reactive oxygen species (ROS) or reactive nitrogen species (RNS)[76]. Indeed, Heeger and colleagues showed that autoantigen in complete Freunds' adjuvant (CFA), but not in incomplete Freunds' adjuvant (IFA), induced organ-specific pathology, and that this was associated with the induction of type-1 immune responses by CFA and type-2 responses by IFA[77]. Furthermore, IFA promotes tolerance by inducing Th2 cells and suppressing IFN-γ production[77]. In support of this view, studies by Racke et al. showed that when EAE was induced by adoptive transfer of MBP- specific T cells and the mice were treated with IL-4, T cells differentiated into Th2-like cells which subsequently suppressed the expression of inflammatory cytokines in the CNS, ameliorated EAE symptoms and decreased demyelination[78]. Similar results were reported by Kuchroo et al. demonstrating that adoptive transfer of myelin proteolipid protein (PLP)-specific Th2 cells prevented EAE and abrogated established disease[79]. In addition, another group reported that prevention of adoptive transfer-induced EAE with an altered peptide ligand (APL) was dependent on the availability of IL-4, and that anti–IL-4 treatment reversed tolerance induced by APL[80]. Recent studies showed that local expression of IL-4 delivered into the central nervous system (CNS) by a *Herpes simplex* virus vector was able to convert a disease promoting condition into an IL-4-dependent, disease-limiting condition. Indeed, the increased expression of IL-4 in glial cells was associated with reduced severity of EAE, indicating that upregulation of Th2 cytokines can prevent the propagation of inflammation in EAE/MS[81]. Another anti-inflammatory effect of Th2 cells is through the induction of antigen (Ag)-specific Tregs via IL-4 and IL-5[82]. It was shown that IL-4 released by antigen-specific Th2 cells promotes the polyclonal expansion of Tregs, and that these cells then express the IL-5 receptor and proliferate and expand in the presence of IL-5[82]. These discoveries and others lead to the assumption that IL-4 administration can potentially be used for autoimmune disease therapy, thereby counteracting the harmful effects of Th1 cells and converting Ag-specific Th1 cells into "suppressive" Th2 cells[76]. Several different subsequent observations in humans further supported that Th2 immune-deviation via IL-4 could have a protective effect in autoimmune conditions. For instance, low levels of IL-4 are found in tissues affected by organ-specific autoimmune diseases[83], and early treatment with IL-4 has shown to ameliorate development of several autoimmune disease conditions[84].

IL-5 and IL-13 are two other major cytokines produced by the Th2 subset. IL-5 was initially described as 'T-cell replacing factor' which is secreted by Th2 cells to stimulate antibody production from activated B cells, and it also enhances proliferation and differentiation of eosinophil precursors into mature eosinophils[85]. IL-13 is primarily produced by Th2 cells, but also by $CD8^+$ T cells, mast cells, DCs, and eosinophils. It is known to inhibit the production of proinflammatory cytokines including IL-1β, IL-12, and TNF by monocytes, and it also serves as a B cell co-stimulator that facilitates B cell activation and maturation, and it promotes mucus production[86,87]. Both IL-5 and IL-13 are capable of driving allergic type inflammatory responses and to promote pathology of Th2-mediated immune diseases such as asthma[87,88].

In regards to MS and EAE, no significant differences were observed in the levels of IL-5 between MS and control groups[89], and also no differences were noted in the types of cells infiltrating the CNS between IL-5 knockout and wild-type (Wt) EAE mice[90]. These results suggest that IL-5 does not play an important role either in the pathogenesis or induction of MS/EAE, and also, that IL-5 is not directly involved in the initiation or effector phase of $MOG_{35–55}$ peptide-induced EAE in immune-competent mice. It is possible that IL-5 may have an immunomodulatory function in MS, as relapsing-remitting MS patients treated with glatiramer acetate (Copaxone) showed reduced relapse frequency with a concomitant increase in IL-5 producing T cells[91]. In SLE patients with severe skin involvement, IFN-γ and IL-5 were the most commonly overexpressed cytokines in skin lesions, implying that both Th1 and Th2 subsets may be involved in the pathophysiology of SLE inflammation[92]. However, an earlier report suggests that IL-5 may play a protective role as overexpression of IL-5 in SLE-prone mice suppresses the disease[93].

IL-13 is known to promote protection from Th1-mediated pathology, as shown in several different models. For instance, IL-13 was found to protect against myocarditis in BALB/c mice, either induced by immunization with cardiac myosin or by viral infection. In these studies, most of the IL-13 knockout mice displayed severe cardiac infiltration in over 50% of heart tissue leading to fibrosis, cardiac dysfunction and death. Furthermore, these mice showed increased numbers of classically activated macrophages and decreased numbers of alternatively activated macrophages infiltrating the heart as compared with Wt mice. It must be noted, however, that IL-13 also has profibrogenic effects either directly, or through upregulation of transforming growth factor beta (TGF-β) synthesis[94]. Taken together, most of the evidence points towards a protective role for IL-13 in myocarditis by modulating macrophage populations and regulating their function[95]. These results are in accordance with a report by Elnaggar et al. demonstrating amelioration of EAM via delivery of an IL-13-gene vector into heart tissue[96]. In EAE, IL-13 is known to promote protection by several different mechanisms[97,98]. However, some studies suggested that this cytokine, under certain conditions, could potentially be pathogenic. For instance, IL-13-producing T cells were significantly increased in $CD4^+$ T cells from MS patients at relapses and returned to normal levels during remission, and additionally, IL-13 upregulated the expression of vascular cell adhesion molecule-1 (VCAM-1), which plays an important role in mediating adhesion and migration of inflammatory cells into the CNS and has been detected in active MS lesions[99,100]. This suggests that IL-13 may facilitate the migration of inflammatory cells into the CNS and thus could indirectly promote pathology. Additionally, since IL-13 induces B cells to produce antibodies, it may promote demyelination via anti-myelin autoantibody production in MS lesions[86,101].

In summary, Th2 cells can promote pathology of several different autoimmune diseases, particularly those which are associated with humoral immune responses. Indeed, studies have demonstrated that aberrant and continued IL-4 expression *in vivo* can rescue autoreactive B cells from apoptosis, enhance their survival, and induce activation of autoreactive B cells and thereby promote autoimmune disease[102]. Additionally, even in type-1 mediated immunopathology, Th2 cells may induce the generation of autoantibodies and enhance pathology. In contrast, Th2 cytokines can mediate protection either by directly

suppressing Th1/Th17 development via IL-4/IL-13 respectively, or by counteracting Th1-mediated inflammation.

Th17 cells

The IL-17 family of cytokines comprises potent inflammatory mediators involved in host defense against extracellular bacteria, fungi and other eukaryotic pathogens. IL-17 cytokines have been implicated in a broad spectrum of inflammatory conditions and autoimmune diseases[103]. Currently, there are six known IL-17 family members: IL-17A (commonly referred to as IL-17), IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F[104]. Specialized $CD4^+$ T helper cells (Th17) are the major source of IL-17 and IL-17F, although more recently other cells were also shown to express IL-17 including γδT cells, natural killer (NK), NKT cells, macrophages and others[104–106]. IL-17 secreting T cells were later defined as key mediators of autoimmunity. Cua and colleges first showed that IL-23 was indispensable for the generation of organ-specific autoimmunity[107], and that IL-23 promoted the generation of IL-17 producing Th cells[108]. Shortly thereafter, Park et al. and Harrington et al. showed that IL-17-producing T cells belonged to an independent Th subset which was designated "Th17" cells[109,110]. Since their initial description, Th17 cells have been shown to play a critical role in promoting and enhancing inflammation including autoimmune tissue injury.

Much of the pathogenic functions of Th17 cells have been attributed to the secretion of IL-17, including: the recruitment of neutrophils, activation of innate immune cells, enhancing B cell functions, and inducing release of proinflammatory cytokines including TNF, GM-CSF and IL-1β[111,112]. Additionally, IL-17 signaling induces the expression and/or release of chemokines and other inflammatory mediators, including intercellular adhesion molecule 1 (ICAM-1), prostaglandin E2 (PGE2), as well as promoting tissue damage through the induction of matrix metalloproteinases (MMPs) and antimicrobial-peptides[113]. Importantly, these events initiate several positive-feedback loops that further increase IL-17 production, sustain a proinflammatory environment, and can cause excessive tissue damage[114]. In addition to IL-17, Th17 cells can also secrete IL-21, IL-22, IL-25, and IL-26 (human)[103].

Even prior to the discovery of Th17 cells, IL-17 was noted to be overexpressed in a number of inflammatory/autoimmune conditions including MS[115], RA[116], SLE[117,118] and airway inflammatory diseases [119], and it has been implicated in their pathogenesis. The discovery of Th17 cells and extensive research in many laboratory models of autoimmune diseases have substantiated Th17 cells as important contributors to tissue pathology and the promotion of antibody responses. In a mouse model of RA where mice spontaneously develop autoantibodies, IL-17 was found to be elevated in the serum and increased numbers of Th17 cells were observed in the spleen[120]. In this model, IL-17 promoted the spontaneous formation of germinal centers and the generation of autoantibodies in an antigen independent manner[120,121]. IL-17 has also been shown to promote B cell responses in murine models of SLE by enhancing the proliferation and reducing apoptosis of B lymphocytes and enhancing their maturation into plasma cells[118].

In addition to promoting antibody-mediated pathology, IL-17 was also found to mediate autoimmunity and tissue damage in a B cell-independent fashion, including in models of $MOG_{35–55}$ peptide-induced EAE[122], collagen-induced arthritis (CIA), an animal model of RA[123], and type 1 diabetes in NOD mice[124]. For instance, in CIA, IL-17 was found to promote cartilage tissue damage by induction of aggrecanase activity and inhibition of proteoglycan synthesis[125]. Additionally, IL-17 induces the chemotaxis of neutrophils and monocytes into synovial tissue through the induction of several chemokines[126]. Likewise, IL-$17^{-/-}$ mice exhibit reduced disease severity in acute and chronic allergic airway responses through the lack of induction of CXCL5 and inability to recruit neutrophils to the lungs[127]. Similarly, EAE induced by either adoptive transfer of IL-$17^{-/-}$ Th cells or induction of disease in IL-$17^{-/-}$ mice, exhibited delayed disease onset with reduced severity and early recovery[35,127] as a result of decreased chemokine expression in the CNS, including CCL2 and CXCL1, which are crucial for the recruitment of activated monocytes and granulocytes[128,129]. Importantly, similar results were shown in RAR-related orphan receptor gamma (ROR-γt) deficient mice, the master regulator of the Th17 subset, which maintains the production of IL-17[130]. Th17 cells are also responsible for the disruption of the blood-brain barrier (BBB), which promotes immune cell traffic into the CNS and mediates tissue inflammation through the action of IL-17 and IL-22, most likely helped by the secretion of CCL2 by BBB epithelial cells[131].

Under certain conditions, Th17 cells may also have anti-inflammatory functions as shown for EAU, in which mice treated with anti-IL-17 antibody exhibited more severe disease symptoms[132]. Indeed, it was shown that Th17 cells can produce the potent anti-inflammatory cytokine IL-10, as well as IFN-γ (which can also have protective effects) and thereby down-regulate inflammation and decrease pathology[133,134].

In summary, Th17 cells promote pathology and enhance inflammation and tissue damage, conceivably via the cytokine IL-17. Nonetheless, the picture may be more complicated than that since IL-17 may be dispensable for the development of organ-specific autoimmunity (e.g. EAE)[135]. In contrast, obligatory for autoimmune diseases are (i) IL-23 signaling, which promotes the stability of Th17 cells, and (ii) T-bet, the master regulator of Th1 cells, which regulates the expression of IL-23 receptor[3].

Th22 cells

Th22 cells are recent siblings of Th17 cells which produce predominantly the cytokine IL-22 and represent a separate Th subset with distinct gene expression and functions, and were initially associated with immunopathology of skin diseases[136–138]. IL-22 is a member of the IL-10 family of cytokines and it is produced by activated T cells, notably Th17 and Th22 cells, as well as by NK cells and γδ T cells, and it acts primarily on non-immune cells[139]. Recent evidence indicates that IL-22 plays an important role in the pathogenesis of autoimmune diseases including psoriasis, SLE, MS, RA, and allergic diseases, thereby implicating Th22 cells and IL-22 as a potential therapeutic target in autoimmune diseases[140,141].

In RA, evidence points to a detrimental effect of IL-22 in promoting pathology. First, IL-22 mRNA was found upregulated in RA synovial tissues and positively correlated with the increase of IL-23R in RA synovial fibroblasts. It was also reported that IL-22 increased the proliferation of synovial fibroblasts, and induced the expression of CCL2 by these cells[142]. Second, Geboes et al. showed that sera of CIA mice contained high levels of IL-22 and showed increased expression of IL-22R in splenocytes[143]. In addition, IL-22 deficient mice are less susceptible to CIA, showing reduction in disease penetrance and severity of arthritis symptoms including pannus formation. Interestingly, the loss of IL-22 was associated with increased production of collagen-specific and total IgG antibodies, whereas cellular responses were unchanged. IL-22 regulates antibody production and also has a proinflammatory role in CIA by promoting osteoclastogenesis[143]. This is in line with a recent report showing that IL-22 induces osteoclastogenesis through the upregulation of receptor activator of nuclear factor kappa-B ligand (RANKL) via the p38 MAPK/NF-κB and JAK-2/STAT-3 signaling pathways[144]. Lastly, several studies showed that higher frequencies of Th22 cells were detected in patients with RA as compared with healthy controls, and that plasma levels of IL-22 producing Th cells were elevated in patients with RA[145,146] and that the higher frequencies of Th22 cells in patient blood positively correlated with the degree of disease severity (higher disease activity score)[147].

In neuroinflammatory autoimmune disease the role of IL-22 seems to be more complex. For instance, Olsson and colleges identified an increased risk for MS associated with the IL-22Rα2 gene[148]. In addition, an increase of IL-22 and Th22 cells was detected in patients with MS and neuromyelitis optica (NMO), further supporting a pathogenic role for IL-22 during neuroinflammation[149]. However, studies by Becher and colleges demonstrated that IL-22 deficient mice are fully susceptible to $MOG_{35–55}$ peptide-elicited EAE [150], thus, further investigation is necessary to clarify the exact function of IL-22 in autoimmune inflammatory diseases of the CNS.

Similar to MS and EAE, there are somewhat contradicting reports for SLE. Decreased levels of IL-22 were reported by several groups in the serum of SLE patients[151,152]. The decreased serum IL-22 levels were positively correlated with the SLE disease activity index (SLEDAI), and interestingly, IL-22 levels were inversely correlated with the levels of IL-17 and IL-23[152]. In contrast, Qin et al. reported that frequencies of $IL\text{-}22^+$ Th cells in peripheral blood mononuclear cells (PBMCs) from patients with SLE were increased and showed a strong positive correlation to SLEDAI scores[153]. A recent report by Lin et al. may explain these contradictory reports by showing that the levels of IL-22 in plasma from SLE patients were markedly decreased during onset of SLE as compared with relapses and healthy individuals, and a positive correlation between IL-22 and Th22 cells was observed, which correlated inversely with SLEDAI scores. Interestingly it was also shown that autoantibodies in the plasma of SLE patients bind to IL-22 and thus the decreased IL-22 plasma concentrations and correlation with the percentage of Th22 cells may be features of SLE and correlate with SLEDAI[154].

Of note, IL-22 is important for its roles in protective immunity. In the gut, IL-22 was found to restrict commensal bacteria to their tissue niches, thereby preventing inflammation and providing protection from chronic inflammatory and autoimmune diseases[155–157]. In the

liver, IL-22 expressing Th cells were found to protect hepatocytes during acute liver inflammation[158]. This is in line with a report showing that mice with liver-specific transgenic expression of IL-22 were resistant to acute and chronic pancreatitis and that treatment of Wt mice with IL-22 or retrovirus-induced IL-22 attenuated the severity of acute and chronic pancreatitis[159]. Interestingly, IL-22 was also found to play a role in the prevention of systemic inflammation provoked by LPS by inducing the expression of lipopolysaccharide (LPS)-binding protein.

Overall, IL-22 may have both anti-inflammatory and proinflammatory effects, though it seems that the respective function of this cytokine is influenced by environmental cues such as other cytokines and the tissue microenvironment. Nonetheless, IL-22 is considered a member of the “pathogenic Th17-cytokines” and can promote inflammatory and autoimmune conditions and Th22 cells are widely considered to be pathogenic. However, the exact mechanism by which Th22 cells are involved in the development and pathogenesis of autoimmunity remains to be elucidated. Furthermore, the differentiation, regulation, downstream pathways of Th22, and the relationship between Th22 and other Th cells, in particularly Th17 cells, need further investigation. Overall, despite conflicting evidence for the involvement of IL-22 in autoimmune diseases, this cytokine remains a possible therapeutic target in certain autoimmune conditions, in particular those involving the skin such as psoriasis[160,161, 162].

Th9 cells

IL-9 was first described as a T cell and mast cell growth factor and it is important in promoting mucus production and activation of mast cells as well as eosinophils[163]. It was initially viewed as a Th2 cell cytokine, however, more recently, IL-9 has been identified in a subset of T cells distinct from Th2 cells, now delineated as Th9 cells[164]. The development of Th9 cells requires the combination of TGF-β (which also promotes Tregs) and IL-4 (known to induce Th2 cells)[165]. Interestingly, Th9 cells, which are strongly associated with the immunopathology of asthma, also produce IL-10[164].

Several independent reports demonstrated the involvement of IL-9-producing Th cells in the development and pathogenesis of EAE. Li et al. studied EAE in IL-9 knockout mice and found that these animals developed significantly less-severe disease as compared with their wild-type littermates, both after immunization with $PLP_{180–199}$ peptide and upon adoptive transfer of $PLP_{180–199}$ peptide-specific T cells from wild-type mice[166]. IL-9 knockout mice showed decreased numbers of infiltrating immune cells in the CNS and lower levels of IL-17 and IFN-γ than Wt control mice[166]. In addition, null mutation of the IL-9 gene resulted in significantly lower levels of $PLP_{180–199}$ peptide-specific IL-17 and IFN-γ production[166]. In support of these findings, earlier studies demonstrated that T cells transferred from the CNS of Th9 cell recipient mice maintained production of their original cytokines IL-9 and IL-10, although they also showed increased production of IFN-γ[66]. Kuchroo and colleagues showed that MOG-specific Th1, Th17, and Th9 cells can induce severe EAE upon adoptive transfer[66]. These results indicate that IL-9 is important for T cell activation and differentiation into encephalitogenic T cells in neuroinflammatory diseases like EAE, and that IL-9 promotes CNS pathology. In addition to the pathogenic roles of Th9

cells in EAE and asthma, studies in SLE indicate that the IL-9/IL-9R pathway may exert both proinflammatory and anti-inflammatory effects, but the outcome may be biased towards proinflammatory conditions[167]. Patients with SLE-induced glomerulonephritis showed mast cell infiltrates in affected tissues[168], and IL-9 is associated with the recruitment and/or accumulation of mast cells as demonstrated by Forbes and colleagues[169]. Indeed, increased levels of IL-9 mRNA, serum IL-9 levels and the percentages of $CD4^+$ $IL\text{-}9^+$ T cells were shown to correlate with disease activity and severity, implying an important role for IL-9 in the pathogenesis of SLE[170]. Furthermore, treatment with high-dose methylprednisolone, an immunomodulatory corticosteroid drug, reduced serum IL-9 levels and the percentage of Th9 cells, thereby implicating that Th9 cells are involved in the inflammatory process in SLE[170]. These results are in line with IL-9 mediated immunopathology in asthma, which is also characterized by an increase of Th9 cells in inflamed tissues leading to excess mast cell reaction and eosinophilia[171].

Taken together, Th9 cells seem to be pathogenic, and thus blocking the IL-9 pathway may be a promising strategy to attenuate immunopathology in certain autoimmune and inflammatory diseases. However, as previously mentioned, Th9 cells are also a source for the potent anti-inflammatory cytokine IL-10, and may harbor immune regulatory functions.

Tregs

The concept of a specialized subset of T lymphocytes with suppressive function has been around since the early 1970s[172]. In the mid-1990s a novel subset of Th cells with “regulatory” function was identified and designated Tregs[173]. Tregs were later found to express the signature Foxp3 transcription factor, which is critical for their development, lineage commitment, and regulatory functions[174,175]. Foxp3 expressing Treg subsets include thymically derived or natural Tregs (nTregs) and Tregs that are induced via post-thymic maturation (iTregs)[176]. Later, iTregs were further discriminated into $Foxp3^+$ cells (Th3) and $Foxp3^-$ cells (Tr1)[176,177]. Numerous studies have identified Tregs as important immunoregulators in many inflammatory and autoimmune disease conditions including asthma[178], MS[179], and type-I diabetes[180].

Several mechanisms of Treg-mediated immune suppression have been identified, including: the secretion of anti-inflammatory cytokines, expression of inhibitory receptors, and cytokine deprivation[181]. For the purpose of this review we will focus on regulatory cytokine production. The two cytokines mostly associated with Tregs are IL-10 and TGF-β[177,181]. Importantly, Tregs can themselves secrete these cytokines and use them to carry out their suppressive function[176].

TGF-β is produced by both nTreg and Th3 cells, however other cells including B cells, macrophages, DCs, and many other non-immune cells, can also produce this cytokine[176,182,183]. TGF-β is required for the generation of iTregs by inducing the expression of Foxp3 in a paracrine feedback loop that will convert naive T cells (Th0) to differentiate into iTregs[184]. The positive feedback loop between TGF-β and Foxp3 plays a critical role in maintaining peripheral tolerance[185] and is key to the generation and maintenance of Tregs[186,187]. *In vivo*, TGF-β producing Tregs have been shown to suppress

EAE by inhibiting autoimmune T cell responses in the CNS of EAE mice[188]. This coincides with reports showing that there is a greater number of TGF-β-expressing Tregs during the recovery phase in EAE[189], that anti-TGF-β treated mice do not recover from EAE[190], and, importantly, that TGF-β producing Tregs inhibit IL-17 production and enhance the expression of Foxp3 in Th cells[188]. Furthermore, a unique subpopulation of Tregs suppressed the development of diabetes in NOD mice in a TGF-β-dependent manner[191], and TGF-β blockade impaired the immunoregulatory function of Tregs and resulted in increased disease incidence and early manifestation of diabetes[192].

IL-10 is expressed by cells of the innate and the adaptive immune system, including $CD4^+$ and $CD8^+$ T cells, macrophages, mast cells, NK cells, eosinophils, and neutrophils[193]. Among the $CD4^+$ T cells, Tr1 cells are a dominant source for this cytokine[176]. IL-10 is critical for the generation and maintenance of Tr1[194] cells through an autocrine process[195]. The immunosuppressive effects of IL-10 are largely mediated through its impact on antigen presenting cells (APCs) where it has been shown to downregulate the expression of MHC-II[196] and co-stimulatory molecules (CD80/CD86 and CD28)[197]. Additionally it reduces the release of proinflammatory cytokines by mast cells and macrophages as well as suppressing their function and activation[197–199].

IL-10 production by Tregs has been studied in models of inflammatory bowel disease (IBD), EAE, T1D in the NOD mouse, and hypersensitivity/allergy[176]. Evidence for a regulatory role of IL-10 in IBD was provided by studies showing that IL-$10^{-/-}$ mice developed chronic colitis[200]. Subsequent studies showed that transfer of Tregs from IL-$10^{-/-}$ mice, but not Wt mice, failed to prevent IBD and established a link between Tregs and IL-10 in IBD[201]. The regulatory function of IL-10-producing Tregs is further illustrated by adoptive transfer studies in EAE where IL-10-deficient Tregs did not suppress EAE to the same extent as was observed with IL-10-sufficient Tregs[202]. Treatment with IL-10 antagonists reversed the suppressive effect of nTregs, which resulted in increased EAE severity[202]. Treatment of mice with vitamin D supplementation ameliorated disease severity, but when the IL-10 signaling pathway was disrupted, EAE symptoms were increased and vitamin D treatment did not show a beneficial effect[203]. The transfer of Tregs has also been shown to suppress Th2-mediated allergic responses in an IL-10 dependent manner[204]. This is possibly mediated by Tr1 cells, which contribute to the suppression of allergy by suppressing IgE production[205].

In contrast to the suppressive functions of TGF-β and IL-10 produced by Tregs, these cytokines can, under certain conditions, enhance the function and activity of pathogenic cells. This phenomenon seems to be a mechanism by which the immune system maintains its balance. For example, IL-10 activates B cells and increases their function as APC by upregulating MHC-II mediated antigen presentation[183,184]. IL-10 drives the maturation of B cells into plasma cells[206] and stimulates the proliferation of mature B cells and B cell precursors[207,208]. IL-10 was shown to enhance the production of IgG4[205,207,209]. Interestingly, however, IgG4 was reported to exert anti-inflammatory activity in some autoimmune models such as experimental autoimmune myasthenia gravis in rhesus monkeys[210]. TGF-β is also associated with some proinflammatory effects involving the development and subset commitment of IL-17-producing Th17 cells[211], which promote

inflammation and augment immunopathology[103]. TGF-β can reprogram T cell subset commitment and generate IL-9 producing Th cells which promote tissue pathology[212,213]. Finally, TGF-β and IL-10 enhance the survival of $CD8^+$ T cells and increase the production of IL-17 and IFN-γ by those cells[214]. Additionally, IL-10 producing $CD4^+$ T cells were shown to contribute to the pathology of diabetes via a $CD8^+$ T cell pathway, and modulation of the requirement for CD40-CD40L costimulation. Thus, it is worth considering that some of the cytokines produced by/linked to Tregs, including IL-10 and TGF-β, may not always have anti-inflammatory properties, and under certain conditions, may promote immune pathology.

Discussion - or the enigma of the "Th1-like" Th17 cell

Here, we have summarized the most recent understanding of $CD4^+$ Th cell subset "signature" cytokines in promoting autoimmune tissue pathology and/or mediating protection. Since a sustained and uncontrolled inflammatory response will be detrimental to the host, it must be self-limiting. As a result it seems that there is a switch point at which anti-inflammatory pathways are activated. Thus, instead of an elusive "pathogenic" T cell subset which secretes harmful cytokines, most Th cell subsets can promote protection, often via the same "pathogenic" cytokines. An illustration of this is Th1 cells secreting IFN-γ and TNF, which have pleiotropic effects in autoimmune diseases and promote tissue inflammation on one hand, and protection on the other. Another example is TGF-β which is required for the induction of both "suppressive" Tregs and "pathogenic" Th17 cells, possibly in an attempt to maintain the balance between tolerance and immunity during steady-state and inflammatory conditions[215].

An additional aspect in support of this view is the plasticity of different T cell subsets and emerging evidence that subset-signature cytokine expression is not as stable as initially believed. For instance, most Th subsets, including Th2 cells, Th17 cells and Tregs, can acquire Th1 cell-like properties such as production of IFN-γ. Many different mechanisms are underlying T cell plasticity, including cytokines, metabolic regulation, diverse epigenetic modifications, microRNA expression, expression of subset "master regulators" and "fine-tuning" transcription factors, tissue specific environmental cues and others, which have been extensively reviewed[67,216,217]. Of note, the stability of signature-cytokine production is preserved by epigenetic modifications and induced by one of the subset master regulators. For example the IFN-γ and IL-4 genes show similar CpG demethylation patterns in their promoter region during Th1/Th2 cell differentiation. Also, different cytokines can influence the expression of a master regulator, which will influence the expression of the signature-cytokine(s) and will create a positive feedback loop that favors subset commitment[218]. Nonetheless, expression of one signature cytokine, such as IL-17, may not tell the full story about Th subset commitment, since the stability of its expression may be influenced by different factors as mentioned above. Along these lines, IL-17 is enhanced by IL-23, which promotes the pathogenic potential of Th17 cells and enhances the expression of IL-17 by these cells[3,219]. Thus, adoptive transfer of IL-23-induced Th17 cells results in severe EAE, and in the absence of IL-23 signaling the mice are resistant to EAE[107,108]. However, the disease resistance seen in the absence of IL-23 signals was not due to the lack of expression of IL-17[135] or IL-22[150] by Th17 cells, but rather by the failure of these cells to produce GM-

CSF[220,221], a cytokine that was initially believed to be produced by encephalitogenic, IFN-γ producing Th1 cells[222]. Indeed both Th1 cells and Th17 cells can produce GM-CSF. Interestingly, induction of GM-CSF expression by human Th cells is constrained by the IL-23/ROR-γt/Th17 cell axis but promoted by the IL-12/T-bet/Th1 cell axis[223]. Thus the enigma remains as to why IL-23-induced Th17 cells are indispensable for the induction of EAE. As it turns out, IL-23-induced Th17 cells not only produce GM-CSF, but are also producing IFN-γ[47]. The observation of IFN-γ producing Th17 cells lead to the realization that IL-17 and IFN-γ double-producing cells, belonging to the Th17 subset, developed under the influence of IL-23 and converted into IL-17 producing Th1-like cells, and later to "exTh17" cells, while discontinuing the production of IL-17[47]. Not surprisingly, exTh17 cells are expressing the transcription factor T-bet and as a result IFN-γ, in an IL-23 dependent manner, which is important for the pathogenic potential of exTh17 cells[47]. Furthermore, IFN-γ acts as a potent negative regulator of ROR-γt, the master regulator of the Th17 subset that drives the production of GM-CSF[220]. Similar observations were made in other inflammatory and autoimmune conditions, illustrating the transition of Th17 cells into Th1-like cells[224]. These observations further support the view of a switch point at which anti-inflammatory pathways are activated by the same Th subsets that initially promoted pathogenicity. In this scenario, IFN-γ inhibits GM-CSF production by Th17 cells in the target tissues. In Figure 2 we propose a possible model for a switch point for GM-CSF production by "pathogenic" Th-17 cells which is mediated by IL-23 and IFN-γ in EAE.

Taken together, the one cytokine, one pathogenic Th cell, does not fit the bill anymore. The discovery of Th1-like Th17 cells, exTh17 cells, etc. complicates the question as to whether targeting a single cytokine or pathogenic T cell subset will ever result in the cure for autoimmune diseases.

Concluding remarks

The immune system seems to favor a balance between pathogenic and protective Th cells via dual roles for "subset-specific", or "signature cytokines", as well as allowing plasticity for subset differentiation and expression of "signature" cytokine(s) by other Th subsets. The observation that many Th subsets can convert into IFN-γ secreting Th1-like cells illustrates this fact since IFN-γ can be both pathogenic and protective. Targeting cytokines as therapy for autoimmune and/or inflammatory disorders remains a conceptual challenge more than ever. Clearly, cytokine therapy proved successful in some cases, such as anti-TNF therapy of RA[225], with the caveat that surprising adverse effects were observed in some patients indicative of the additional roles of this cytokine[226].

Where do we stand then and *quo vadis* Th17 cells[227]? We would answer "*Novas portas pandamus, et post nos occudamus*", open new doors and close the one behind you, and realize that the life of a T cell is complicated. Not only the cytokines produced by a Th cells, but also the influence of other cytokines and other factors in the tissue microenvironment must be included in our analysis of pathogenic T cells.

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Highlights

- T helper (Th) cells provide host defense, but can also promote autoimmune diseases.
- The original description of Th subsets considered Th1 and Th2 cells.
- New Th subsets have since been described including Th17, Th22, Th9, and Treg cells.
- Th subsets have been defined based on their “signature” cytokine profiles.
- New models of Th subset biology may have to incorporate T cell subset plasticity.

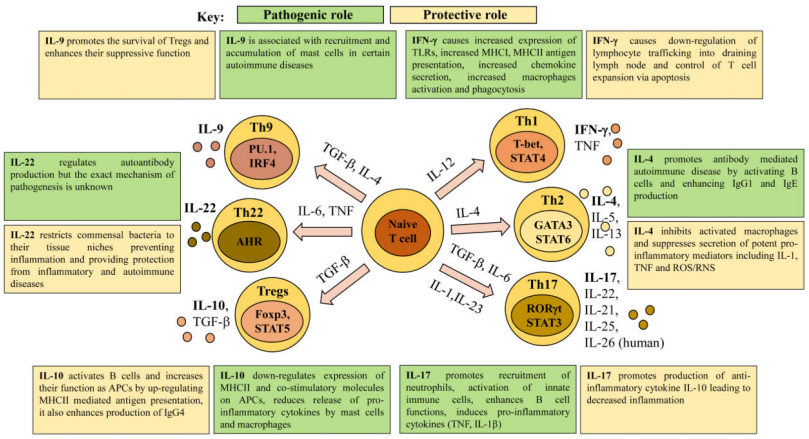

Figure 1. T helper cell subset differentiation and the protective and pathogenic roles of their lineage-signature cytokines

The signature cytokines for each subset are shown in bold. IL-12 induces the expression of T-bet and differentiation into the Th1 subset which produces IFN-γ and TNF; Th2 differentiation and GATA3 expression is induced by IL-4, leading to the production of IL-4, IL-5 and IL-13, whereas TGF-β and IL-4 induce PU.1 expression which causes differentiation into the Th9 subset leading to the production of IL-9. TGF-β induces the expression of Foxp3, which leads to differentiation into the Treg lineage; Th17 differentiation is a result of RORγt expression induced by TGF-β, IL-6 and IL-23, leading to the production of IL-17, IL-22, IL-21, IL-25 and IL-26 (human); IL-6 and TNF induce AHR and differentiation into the Th22 subset and production of IL-22. STAT: Signal transducer and activator of transcription; RORγ: RAR related orphan receptor gamma, AHR: Aryl hydrocarbon receptor, Foxp3: forkhead box P3.

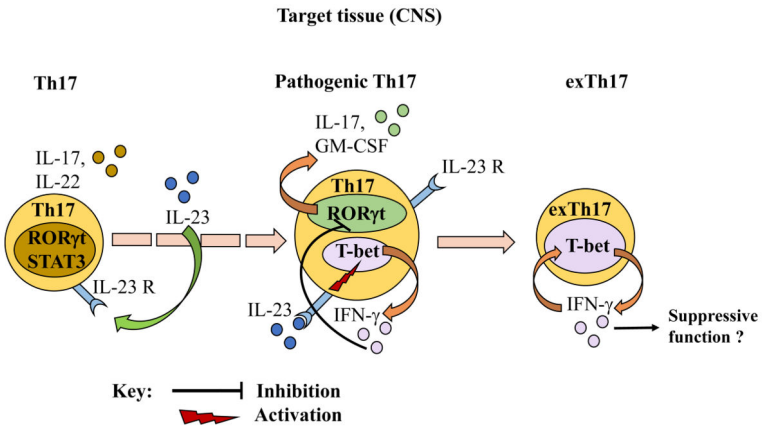

Figure 2. Proposed model of an immune switch point from pathogenic Th17 cells to suppressive exTh17 cells in EAE

TGF-β, IL-6 and IL-23 induce the differentiation of Th17 cells in the immune periphery. In the CNS, signaling by IL-23 induces the expression of GM-CSF and IFN-γ in Th17 cells, thereby rendering these cells pathogenic. In an autocrine signaling loop, IFN-γ suppresses the expression of RORγt and the production of GM-CSF (as well as IL-17) by pathogenic Th17 cells, thereby inducing a switch to “suppressive” exTh17 cells.