Published in final edited form as:
Semin Immunol. 2013 November 15; 25(4): 305–312. doi:10.1016/j.smim.2013.10.009.

The plasticity of human Treg and Th17 cells and its role in autoimmunity

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Abstract

$CD4^+$ T helper cells are a central element of the adaptive immune system. They protect the organism against a wide range of pathogens and are able to initiate and control many immune reactions in combination with other cells of the adaptive and the innate immune system. Starting from a naïve cell, $CD4^+$ T cells can differentiate into various effector cell populations with specialized function. This subset specific differentiation depends on numerous signals and the strength of stimulation. However, recent data have shown that differentiated $CD4^+$ T cell subpopulations display a high grade of plasticity and that their initial differentiation is not an endpoint of T cell development. In particular, $FoxP3^+$ regulatory T cells (Treg) and Th17 effector T cells demonstrate a high grade of plasticity, which allow a functional adaptation to various physiological situations during an immune response. However, the plasticity of Treg and Th17 cells might also be a critical factor for autoimmune disease. Here we discuss the recent developments in $CD4^+$ T cell plasticity with a focus on Treg and Th17 cells and its role in human autoimmune disease, in particular multiple sclerosis (MS).

Keywords

Autoimmunity; $CD4^+$ T cells; IL-17; Th17; FoxP3; Treg; T cell plasticity

1. Introduction

$CD4^+$ T helper (Th) cells are an essential element of the adaptive immune system, regulating B cell dependent, humoral as well as $CD8^+$ cytotoxic T cell dependent cellular immune responses. Moreover, $CD4^+$ T cells are able to interact with the innate immune system and respond to stimuli in particular from dendritic cells. Upon peptide/MHC-class II TCR mediated antigen encounter, naive $CD4^+$ T cells are activated and differentiate into T effector cells, which can generate long lasting memory T cells. Depending on the antigen

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The authors declare no competing financial interests.

and strength of stimulation, cytokine milieu, co-stimulatory and various additional factors, $CD4^+$ T cells can differentiate into distinct subpopulations with specialized functions [1, 2].

Classically, $CD4^+$ T cells were divided into Th1 and Th2 subsets. Th1 cells produce the signature cytokine interferon (IFN)-γ and are induced in the presence of interleukin (IL)-12. They express the specific transcription factor Tbet (TBX21) and are generated in response to viral infections where they provide help to $CD8^+$ T cells. Th2 cells are primarily linked to humoral immune responses by providing B cell help and are induced in the presence of IL-4. Th2 cells express the transcription factor GATA3 and are characterized by the expression of the signature cytokines IL-4, IL-5, and IL-13. However, since the discovery of Th1 and Th2 cells, several additional Th cell subpopulations have been described. So far, the most prominent additions are the $FoxP3^+$ regulatory T cells (Treg) and IL-17 producing Th17 cells. Regulatory T cells are a distinct lineage of $CD4^+$ T cells, generated during thymic development, which play an important role in maintaining peripheral tolerance. While Th17 cells are induced in the presence of transforming growth factor (TGF)-beta and IL-21, IL-6 or IL-1β and play a major role in fighting extracellular pathogens. Importantly, both of the latter populations are believed to play a major role in human autoimmune diseases [1, 3].

Although $CD4^+$ Th cell polarization based on the Th1/Th2 paradigm was believed to be a stable process with low grade of variability, recent data provided evidence that this is not the case for many Th subpopulations. Indeed, under certain circumstances most of the differentiated Th cells and in particular Th17 and Treg cells show a great magnitude of plasticity and are able to change their phenotype and function. In this review we discuss the recent findings about Th cell plasticity with an emphasis on Treg and Th17 cells and their role in the human autoimmune disease MS.

2. Human Th17 and Treg cells

2.1 Th17 cells

It is now established that Th17 cells represent, in addition to Th1 and Th2 cells, an independent helper T cell lineage [4, 5]. Th17 cells were initially described based on their secretion of IL-17. They express a series of other cytokines including IL-17F, IL-21, GM-CSF and IL-22 [1]. Their lineage specific transcription factor is the retinoic acid receptor-related orphan receptor γt (RORγt, in humans RORc), which controls development and function of Th17 cells [6]. However, RORγt acts in concert with other transcription factors such as the RAR-related orphan receptor α (RORα), signal transducer and activator of transcription 3 (STAT3), Basic leucine zipper transcription factor (BATF) and interferon regulatory factor 4 (IRF4) which also have been described to play an important role in Th17 development and function [1, 7–12]. Recently, a comprehensive study defined the transcription factor dependent network contributing to Th17 generation [13].

Rodent studies helped identify factors involved in the induction of Th17 cells from naïve $CD4^+$ T cells, namely transforming growth factor beta (TGF-β) in combination with IL-6 or IL-21 [14]. TGF-β is important for the induction of RORγt in Th17 cells. Studies in the human system also indicated that the cytokines IL-1β and IL-23 play an important role in the induction of human Th17 cells from memory cells [15–17], while TGF-β and IL-21 induce naïve $CD4^+$ cells to become Th17 cells [17]. The cytokine IL-23 is also critical for the inflammatory potential of Th17 cells [18, 19] and is the most important survival factor for Th17 cells [1]. Although, currently no specific cell surface markers for Th17 cells have been identified, studies have demonstrated that Th17 cells highly express the chemokine receptor CCR6 [20–22]. In addition to CCR6 [20], human Th17 cells also express CD161 [23] and high levels of CD49d, the α-chain of the integrin VLA-4 [24, 25].

Th17 cells can be found under homeostatic conditions, particularly in the lamina propria of the small intestine. However, during infection or under inflammatory conditions, Th17 cells are induced in other tissues [26–28]. Based on these and other data, analyzing the antigen specificity of Th17 cells, the natural role of Th17 cells in the immune system is to protect the host of extracellular bacteria and fungal infections in tissues such as the gut [20, 29]. The physiological role of Th17 cells is more apparent in rare human genetic diseases, which are related to Th17 cells [30]. The autosomal dominant hyper-IgE syndrome (HIES, 'Job's syndrome') is characterized by mutations in the *stat3* gene, which lead to the absence of IL-17 production in T cells and severe fungal and bacterial infection [31, 32]. Moreover, patients with Chronic mucocutaneous candidiasis (CMC) suffering from severe *candida* infection of the skin, nails and mucous membranes, carry a gain of function mutation in *stat1* which blocks effective Th17 generation [33, 34].

2.1.1 The role of Th17 cells in multiple sclerosis—MS is an inflammatory CNS white matter disease where over 100 allelic variants have been identified that, together with a number of environmental factors are associated with the disease. These factors include low vitamin D, smoking, and an increased body mass index [35]. MS is characterized by increases in myelin-antigen reactive T cells, secreting inflammatory cytokines that mediate an attack on the myelin sheaths surrounding axons in the brain and spinal cord. So far, several targets of the immune response have been suggested but the presence of T cells reactive to myelin self-antigens alone is not sufficient for disease to occur. Indeed, T cells reactive to the same antigens can be found in healthy subjects but various mechanisms are available that control these self-reactive T cells in normal individuals [35–37].

Although Th1 cells were previously thought to drive MS, it now appears that pathogenic Th17 cells play an important role in disease pathogenesis. Based on studies on experimental autoimmune encephalomyelitis (EAE), it became clear that IL-23/Th17 mediated responses are critical for the disease [18, 19]. Of note, recent studies suggested that the cytokine GM-CSF plays a fundamental role in the pathogenicity of Th17 cells in EAE [38, 39]. In line with these murine data, there is also increasing evidence that Th17 cells are critically involved in human MS. Almost a decade before the identification of Th17 cells, increased levels of IL-17 were reported to be associated with disease [40] and several more recent studies have supported a role for pathogenic Th17 cells in MS [35, 41–45]. Moreover, genetic variants associated to the IL-23/Th17 pathway are risk factors for disease [35]. Although not completely understood, one potential mechanism as to how Th17 cells contribute to MS might be the disruption and early penetration of the blood-barrier [41], potentially by a CCL20-CCR6 guided mechanism through the choroid plexus [46] which then lead to the recruitment, influx and immune activation of other pathogenic cell types [35, 47].

Recent data indicate that the pathogenicity of Th17 cells, particularly in autoimmune neuro-inflammation, could be directly controlled by environmental factors. The composition of the gut microbiota can greatly impact the host immune system and an imbalance in the gut microbiome could lead to alterations of immune responses both in gut-associated tissues and in the periphery [48, 49]. It was demonstrated that gut residing bacteria such as segmented filamentous bacteria (SFB) can specifically induce Th17 cells [26]. Moreover, luminal ATP, secreted from bacteria was found to indirectly induce Th17 cells [50]. More recently, it was shown that the microbiota could have indeed an impact on the development of EAE [51, 52].

Besides gut bacteria, dietary components itself have been shown to influence the generation of pathogenic Th17 cells. It has long been noted that NaCl-induced hypertonicity can have an impact on immune cells [53]. Moreover, T cells may face different sodium concentrations and hypertonicity in secondary lymphoid tissues [54] and in the interstitium, especially after

a sodium rich diet [55, 56]. Most recently, it was shown that increased sodium chloride concentrations, similar to concentrations that could be found in interstitial tissues after a high-salt diet [56, 57,] boost the differentiation of Th17 cells in mice and humans [58]. The high-salt conditions induced a particularly pathogenic phenotype in Th17 cells, with the upregulation of a pro-inflammatory signature characterized by increases in GM-CSF, TNFα, IL-2 and IL-23R expression. Consequently, a high-salt diet led to a severe worsening of EAE, associated with augmented induction of pathogenic Th17 cells *in vivo* [58, 59]. The effect was dependent on the induction of p38/MAPK, nuclear factor of activated T cells 5 (NFAT5) and serum/glucocorticoid-regulated kinase 1 (SGK1) which in turn regulates indirectly the expression of the IL-23R. Considering the involvement of highly conserved stress induced pathways in this process, the *in vivo* effect is likely to be more complex involving other cell types, including cells of the innate immune system. Moreover, a high-salt diet may change the composition of the gut microbiota and thus can indirectly affect host immunity as well.

However, it remains to be demonstrated whether these environmental factors indeed are contributors to the development of MS and therefore might represent novel environmental risk factors for disease development.

2.2 FoxP3$^+$ regulatory T cells

Studies in the past decades have established that regulatory T cells are a central element for the maintenance of peripheral tolerance. Up to now, several types of regulatory T cells have been identified, which predominantly belong to the CD4$^+$ T cell lineage [3, 60]. Upon activation they are able to neutralize the function of other effector cells, including CD4$^+$ T cells, CD8$^+$ T cells, NK cells, B cells and other antigen presenting cells (APC) [3, 61]. Depending on the type of regulatory T cell, their mechanism of suppression is mainly based on cell/cell contact dependent mechanisms (e.g. CTLA-4, granzymes), the release of suppressive cytokines (e.g. TGF-β or IL-10) or the generation of suppressive metabolites (e.g. adenosine) [3, 60, 61].

The best-characterized regulatory T cell population is the natural regulatory T cell population (Treg or nTreg). Tregs can be identified in humans and rodents by the high expression of the IL-2 receptor alpha chain (CD25) and by the expression of the transcription factor FoxP3 [3, 61, 62]. Tregs are generated in the thymus and are believed to be a specific lineage of T helper cells, imprinted early during development by the expression of FoxP3 in a specific context [63] and by stably induced epigenetic changes [64, 65]. FoxP3 largely controls the phenotype and function of Tregs and mutations in the gene can result in IPEX (Immune dysregulation, Polyendocrinopathy, Enteropathy X-linked syndrome), a severe and rapidly fatal autoimmune disorder [66]. Although it is not completely understood how precisely regulatory T cells work, there is increasing evidence that FoxP3$^+$ Treg cells are able to suppress ongoing immune reactions using several direct or indirect mechanisms [61, 67, 68]. Interestingly, naïve T cells can also be converted to so-called adaptive or induced Treg (iTreg) in the periphery. This process occurs in the presence of TGF-β or at low dose of antigen encounter, most probably also in the presence of a TGF-β rich or inducing milieu [3, 69]. While adaptive Tregs resemble natural Tregs in phenotype and function there are, however, differences between these cell types most prominently regarding their epigenetic status and stability [65, 70]. Besides TGF-β, which seems to be crucial for the development of Tregs, their survival and homeostasis is dependent on the cytokine IL-2 [71].

Recent studies have demonstrated that Tregs can be further subdivided into distinct subsets, partly explaining the functional heterogeneity of Treg cells. Several Treg subsets have been described by differential expression of surface markers such as CD45RA, CD45RO, CD127,

CCR6, HLA-DR, CD39, CD95, ICOS, CD147 or CD31 [72–78] and can be largely subdivided into memory-like or naïve-like Tregs [61]. Memory-like Tregs are presumably induced from naïve-like Tregs after antigen contact in a specific context and appear to resemble a Treg population that exerts its suppressive function directly in inflamed tissues. For this reason, they are equipped with homing and chemokine receptors as well as specific effector functions [72]. In contrast, naïve-like Tregs appear to function in secondary lymphoid tissues [3, 79, 80]. This heterogeneous view of Treg populations was recently extended by a series of murine studies that demonstrated the need for Tbet, IRF4, STAT3 or BCL6 induction in Tregs to effectively control Th1, Th2, Th17 or follicular helper cell (TFh) specific effector cell responses [2]. Of note, it remains unclear if analogues to $CD4^+$ effector Th cells, long lasting central-memory type Tregs exist in humans. There are only a few studies, mainly in experimental animal systems, indicating that Tregs or iTregs can also contribute to relatively long lasting immunologic memory [81–83].

2.2.1 The role of Tregs in Multiple Sclerosis—Based on experimental animal models and studies in human subjects with autoimmune diseases, it became clear that Tregs play a major role in controlling peripheral immune tolerance. Deficits in Treg function appear to be a common cause of human autoimmune diseases. Treg defects have been discovered in patients multiple sclerosis (MS), type I diabetes (T1D), psoriasis, myasthenia gravis and other autoimmune diseases. Similar correlations also have been observed in atopy and allergic diseases [66, 84–87]. There are several observations providing possible mechanisms, which might contribute to the loss of Treg suppression in MS patients. These mechanisms include for instance a lower thymic Treg output, decreased FoxP3 expression, decreases in CD39 expression, decreased CD58/CD2 dependent co-stimulation or subset-specific changes of Tregs [73, 88–91].

Similar to Th17 cells, Tregs are also influenced by the gut microbiota. Studies in mice have proven a connection of particular gut residing bacteria to the generation of Tregs [92–94]. Of note, the specific induction of IL-10 producing Tregs by a polysaccharide of *Bacteroides fragilis* was able to protect mice from EAE induction [95, 96]. However, direct evidence that the microbiota may have impact on human Treg generation and a subsequent effect on disease prevention is absent. Nonetheless, recent data using human microbes for the induction of Tregs in murine models of autoimmune diseases show promising results [97].

2.3 Relationship between Th17 and Treg cells

Both Th17 and Tregs are reciprocally related to each other; for example TGF-β links the development of Th17 cells to that of $FoxP3^+$ Tregs. It was shown that TGF-β induces the differentiation of Tregs, whereas the combination of IL-6 or IL-21 results in the induction of Th17 cells and inhibition of Treg differentiation [1]. On the molecular level it was demonstrated that FoxP3 could bind physically to RORγt and RORα to antagonize each other's function, which appears to be the basis for their reciprocal relationship [98, 99]. Furthermore, the balance between Th17 and Treg differentiation can be influenced by retinoic acid. In the presence of the vitamin A metabolite, Tregs are preferentially induced over Th17 cells, since retinoic acid enhances TGF-β signaling while it blocks the expression of the IL-6 receptor [100]. Additionally, the aryl hydrocarbon receptor (AHR) that is highly expressed on Tregs and Th17 cells, can promote the induction of both cell types by integrating environmental stimuli Thus, depending on the ligand, AHR mediated signaling results in either Treg or Th17 cell differentiation [101, 102]. Another recent example is the balanced regulation of Th17 and Treg development based on metabolic inputs signaled by the transcription factor hypoxia inducible factor 1α (HIF1α). HIF1α can bind to and enhance RORγt expression, while inhibiting FoxP3 expression and thereby promote Th17 differentiation over Treg development [103–105]. Moreover, the close relation between

Tregs and Th17 cells is also evident in a rodent obesity model, where probiotic bacteria shifted the balance from a pro-inflammatory, IL-17 dominated immune response towards an anti-inflammatory, IL-10 and Treg dependent response [106].

These examples underline the close relationship between both cell types and indicate that there is a particular need for a balanced regulation of both subsets in many immunological settings. Although its *in vivo* relevance for the human immune system is not clear yet, several mechanism have apparently evolved, which can, depending on the surrounding signals, regulate the immune response in the direction of either suppression or inflammation.

3. Plasticity and functional variability of Th17 and Treg cells in relation to MS

3.1 Th17 plasticity

It was noted from early on that at least a subset of Th17 cells had the potential to secrete IFN-γ in mice and humans and thus identify a population with Th1-like features [2]. This was surprising, since initial studies have found that IFN-γ can block Th17 development [107]. By using reporter mice for IL-17F this phenomenon was studied in more detail *in vitro* and *in vivo* and it was found that the Th17 stability is dependent on TGF-β and IL-23 but is lost in the presence of IL-12, favoring the expression of IFN-γ in line with the roles of Tbet and STAT4 [108]. This flexibility of Th17 cells is underlined by the epigenetic status of these cells. Th17 cells presented for instance a semi-permissive/bivalent histone modification status of the *Tbx21* gene [109]. The development of a transgenic system to map the fate of IL-17 expressing cells further demonstrated the *in vivo* plasticity of murine Th17 cells [110]. Strikingly, as demonstrated in the EAE model, almost all of the pathogenic cells in the spinal cord that expressed IFN-γ or other pro-inflammatory cytokines were derived from IL-23 dependent Th17 cells. Evidence from repertoire analyses of human T cells suggests that a similar mechanism exists in humans [111] and it was proposed that these cells could be distinguished from Th1 cells by the expression of CD161 [112]. Moreover, these observations are in line with the high frequency of IFN-γ and IL-17 co-expressing cells in human memory Th17 cells [21, 25, 43]. Thus, the flexibility and plasticity of Th17 cells to gain a Th1-type phenotype is highly dependent on the cytokine micro-environment and inflammatory situation and the pathogenicity of Th17 cells in autoimmune diseases seems to be related to this phenotype. Of note, studies in the EAE model indicated that only Th17 generated in the presence of particular stimuli and cytokines adopt a pathogenic phenotype and gain the ability to induce disease. It was for instance shown that the cytokines TGF-β3 and IL-23 play a key role in this process [113, 114].

A similar differential Th17 cell induction into a pathogenic or an anti-inflammatory phenotype was described in humans by using different antigenic stimuli. *Staphylococcus aureus*-specific Th17 cells were induced to produce the anti-inflammatory cytokine IL-10, whereas *Candida albicans*-specific Th17 cells displayed a more pathogenic phenotype with the induced expression of IFN-γ. This phenomenon was dependent on *C. albicans* triggered IL-1β secretion of monocytes [115]. In line with these data, the induction of IL-10 expression by Th17 cells in the small intestine with an immune suppressive capacity was also described in mice [116]. It was suggested that this process could serve as a control mechanism for excessive inflammation.

Analogous to the Th17/Th1 plasticity, recent data indicated that Th17 cells can also acquire a Th2-type phenotype and potentially play a role in asthma [111]. Interestingly, a study using a helminthic infection model demonstrated the *in vivo* conversion of Th17 cells into IL-4 expressing Th2-type cells, which might be a partial explanation for the inverse

correlation of helminth infection and protection from autoimmunity [117]. However, the information on Th17/Th2 plasticity needs more investigation (Figure 1).

3.2 Plasticity of Treg cells

Recent findings indicate that there is an unexpected plasticity between both Tregs and T effector cells [118]. Although information on this phenomenon is still limited there are indications that this plasticity might play a key role in the control of the immune system, enabling a rapid switch from suppression to active immunity. Moreover, this phenomenon might be a critical factor for the development of autoimmune diseases. Since the conversion of Treg cells, enriched for autoreactive TCR specificities into pathogenic effector T cells could be an in particular harmful threat to the host [119], this process must be tightly regulated on several levels.

3.2.1 Treg-Th1 plasticity—The potential of Tregs to convert into Th1-like cells, co-expressing FoxP3 and Tbet was first described in mice almost a decade ago [120]. Several other studies made similar observations, mainly in murine *in vivo* models of lymphophenia or inflammation [121–124]. Direct evidence that this population was related to natural Tregs come from experiments where the *in vivo* deletion of FoxP3 led to the development of pro-inflammatory IFN-γ secreting cells, which retained self antigen specificity [122]. The phenomenon of Tbet induction in Tregs was also observed in models of infection [125] and colitis [126] and it was noted that this *in vivo* plasticity was highly dependent on IL-12. This data indicated that the conversion to pathogenic Th1-like Treg cells can occur *in vivo* and thus can have the potential to induce autoimmunity. This data is also supported by the epigenetic regulation of Th1-associated loci in Treg cells [109].

Although a pro-inflammatory cytokine expression profile in human $CD25^+$ Tregs was noted from early on [127], these data were complicated due to the absence of valid Treg markers and thus by potential contaminations of effector T cells in Treg preparations. The presence of IFN-γ producing cells was also observed in FoxP3 expressing cells after PMA/ionomycin stimulation [24] or after prolonged *in vitro* expansion of $FoxP3^+$ Tregs [128, 129]. However, since FoxP3 can be also transiently upregulated on human effector T cells [130], it was unclear if the IFN-γ producing cells derived from Tregs or contaminating effector T cells. Nonetheless, using a more detailed analysis, it has been shown that a subset of human natural $FoxP3^+$ Tregs is capable of inducing Tbet and IFN-γ expression [131]. Of note, IFN-γ producing Treg displayed an almost fully demethylated TSRD region in the *FoxP3* locus, similar to IFN-γ negative Treg, which was indicative of a functional nTreg [64]. The IFN-γ production correlated with the upregulation of Tbet, CXCR3 and other classical Th1 marker and could be induced *in vitro* by IL-12 and IL-2. Moreover, the suppressive activity of this population was dramatically decreased in an IFN-γ dependent fashion (Figure 1). Importantly, untreated patients with relapsing remitting MS (RRMS) displayed significantly increased levels of IFN-γ secreting Th1-like Treg in peripheral blood [131] and it is likely that this, at least in part, contributes to the observed loss of suppression in MS patients [86]. Interestingly, a similar population could be observed in humans with T1D [132], indicating that IL-12 dependent Th1-like Tregs are associated with several autoimmune diseases in humans. It remains to be seen, if the Th1-Treg plasticity plays a role for disease pathogenesis. Moreover, the question whether this Treg subset has a physiological role in non-autoimmune conditions remains open.

3.2.2 Treg-Th17 plasticity—Apart from the reciprocal relationship of Th17 and Treg cells (see 2.3), plasticity has been observed between both antagonistic cell types [133–136]. This phenomenon was first reported in mice, where it was shown that IL-6 was able to induce Th17 producing cells from $FoxP3^+$ Treg in the presence of TGF-β [133]. Other

groups reported similar findings, although based on different stimuli and models [135, 136]. The study by Osorio et al. showed that the conversion seems to be dependent on RORγt expression in a subset of murine FoxP3$^+$ Tregs that can be modulated to express IL-17 by dendritic cells (DC). Yang et al. demonstrated that this phenomenon partly depends on IL-6 and IL-1β mediated signals affecting STAT3, RORγt and RORα function. Another study analyzed this process *in vivo* and demonstrated the potential pathogenicity of converted Tregs in murine models of T1D [124]. Most recent data indicated the additional importance of RUNX transcription factors for the induction of a Th17-like phenotype [137].

A similar phenomenon was reported for human FoxP3$^+$ Treg cells. IL-17 expression in *ex vivo* stimulated human FoxP3$^+$ Tregs was found to be mainly restricted to a subset of CCR6$^+$ and CD49d$^+$ cells and the *in vitro* conversion to Th17-like Tregs was dependent on the presence of IL-1β and on epigenetic modifications [24, 134, 138]. More recent studies confirmed these observations and demonstrated additionally a correlation of the Th17-like phenotype with RORc expression, although it's expression was not restricted to IL-17$^+$ FoxP3$^+$ cells [139, 140]. Interestingly, in contrast to Th1-like Tregs, IL-17 secreting Tregs were still suppressive *in vitro*, but lost their suppressive capacity rapidly upon strong activation in the presence of IL-1β and IL-6 [138] (Figure 1). Another mechanism of Treg-Th17 conversion might occur upon microbial stimuli via TLR2 ligation [141]. Thus, besides the reciprocal relationship in the differentiation of Treg and Th17 cells, there also seem to exist mechanisms that allow the rapid shut down of suppression and the induction of pro-inflammatory responses in Treg cells. The likely occurrence of a Th17-like conversion *in vivo* was recently proposed for tumor infiltrating Tregs isolated from human ovarian tumors [142] and in murine models of cancer, where the conversion to Th17-like Tregs was indirectly dependent on indoleamine 2,3-dioxygenase (IDO) [143].

Of note, the expression of CD39 on a subset of human Tregs [73] might enable them to effectively self-control the induction of Th17-plasticity and Th17 cells *per se*. Extracellular ATP is considered as classical 'danger-signal' that can induce inflammasome activation and IL-1β release from innate immune cells and thus creates the environment for an efficient induction of the Th17 conversion and *de novo* induction. As mentioned above, luminal ATP released from certain bacteria have been shown to be critical for Th17 generation [50]. Thus, CD39 activity on Tregs might control this process through the removal of extracellular ATP [73, 144] (Figure 1). This is in line with the observation that CD39$^+$ Tregs are most effective in controlling Th17 cells [88], moreover a similar mechanism was recently proposed for the effects of IL-27 on DC mediated suppression of Th17 responses and EAE [145].

In summary, although the information on the relevance of Th17-like Tregs for autoimmune disease is still sparse, the subset was recently associated with psoriasis [146, 147], autoimmune hepatitis [148, 149] and systemic sclerosis [150], while so far no direct association could be detected in MS [131]. Thus, It will be an important issue for future studies to clarify the role of this Treg subset in autoimmune diseases.

4. Concluding remarks

The plasticity of CD4$^+$ T cells and in particular of Tregs and Th17 cells might have evolved to keep elasticity in combination with stability to enable the immune system to most flexibly deal with pathogens. The plasticity of CD4$^+$ cells enables the immune system to quickly react to changes in the environment and pathogens. However, this flexibility also comprises a potential threat to the host, since the deregulation of this system enhances the risk of developing autoimmunity. It is therefore not surprising that several mechanisms have evolved to control T cell plasticity and many of them are related to interfaces of mucosal tissues where changes in the environment are most critical.

Thus, factors that regulate Treg and Th17 plasticity would be targets for immune therapies aiming at the manipulation of the immune system in settings of cancer or autoimmune diseases. In this context, the manipulation of the gut microbiota or related factors might have the most favorable potential for being therapeutically used in autoimmune diseases. Promising data from animal studies has already demonstrated that it could influence Th17 and Treg homeostasis and actively induce immune suppression via the induction of Tregs but also through the conversion of Th17 cells into non-pathogenic phenotypes.

In summary, the information on the phenomena of $CD4^+$ T cell plasticity and its relation to human autoimmune disease and cancer is still limited. However, future research applying most up-to-date techniques (e.g. humanized mouse models), under consideration of genetic and environmental factors in human research, are likely to quickly gain more insight into this field to ultimately develop new therapeutic approaches for the treatment of human diseases.

Acknowledgments

This work was supported by a National MS Society Collaborative Research Center Award CA1061-A-18, National Institutes of Health Grants P01 AI045757, U19 AI046130, U19 AI070352, and P01 AI039671, and by a Jacob Javits Merit award (NS2427) from the National Institute of Neurological Disorders and Stroke, the Penates Foundation and the Nancy Taylor Foundation for Chronic Diseases, Inc. (to D.A.H.). The authors would like to thank S. Ni Choileain for critical reading of the manuscript.

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Highlights

- Human $CD4^+$ T cells can display a high grade of plasticity
- Th17 cells can adapt Th1- and Th2-type phenotypes
- $FoxP3^+$ Tregs can differentiate into Th1-, Th2- and Th17-like cells
- These mechanisms may play a role in autoimmune diseases like MS

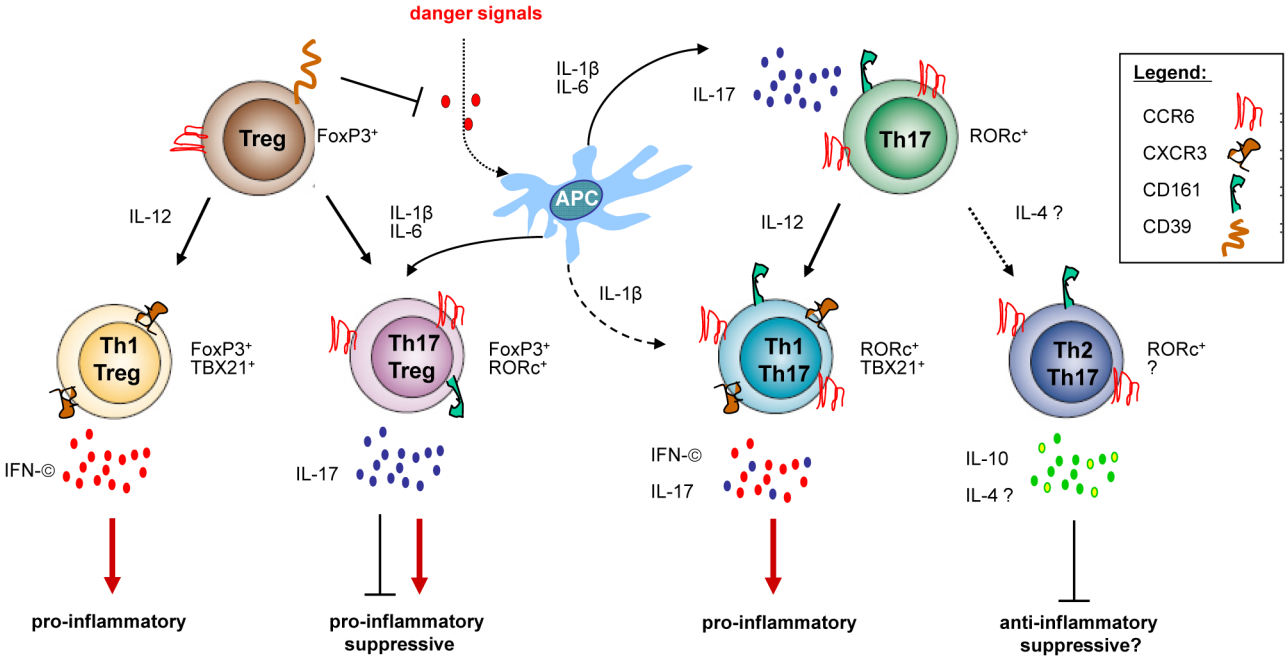

Figure 1. Plasticity of Treg and Th17 cells

Indicated are the major routes of human Treg and Th17 plasticity. Danger signals like extracellular ATP or microbial stimuli can induce cytokine release (e.g. IL-1β) by antigen presenting cells (APC). FoxP3$^+$ Tregs can inhibit this process for instance through CD39-mediated hydrolysis of extracellular ATP. Tregs can be induced by IL-12 to become pro-inflammatory IFN-γ producing cells, expressing TBX21 and CXCR3, which loose suppressive capacity while retaining FoxP3 expression (Th1 Treg). In the presence of IL-1β and IL-6 Tregs can acquire a Th17-like phenotype. These cells secrete IL-17 and express RORc, high levels of CCR6 and CD161 but can retain suppressive capacity and FoxP3 expression (Th17 Treg). Highly pathogenic Th17 cells start to express IFN-γ and upregulate TBX21 and CXCR3 in the presence of IL-12 or of IL-1β when primed by *C.albicans* (indicated by the dotted line) but retain expression of CCR6 and CD161 (Th1 Th17). Th17 cells can also convert into anti-inflammatory IL-4 or IL-10 expressing CD161$^+$ CCR6$^+$ Th17 cells in the presence of IL-4 or when primed by *S.aureus*. Additionally, a similar phenotype was observed when Th17 cells were redirected to the small intestine (Th2 Th17).