

Reciprocal Modulation Between TH17 and Other Helper T Cell Lineages

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T helper 17 (TH17) cells have well-described roles in autoimmune disease. However, TH17 is not stable in some physiological or pathological courses. Also, TH17 cells can reciprocally modulate and convert into other helper T cell subpopulations. The fully exploring the reciprocal regulatory effects and its immunoregulatory mechanisms are becoming interesting topics in the immunological study. In this review, we summarized reciprocal modulation pattern between TH17 cell and other helper T cell subpopulations in the mouse model of autoimmune diseases and human diseases.

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The differentiation of naïve CD4⁺ T cells into lineages with distinct effector functions has been considered to be an irreversible event. T helper type 1 (TH1) cells stably express interferon (IFN)- γ , whereas TH2 cells express IL-4 (Dong, 2008). The more recently defined TH17 cells, follicular helper T (T_{fh}) cells and induced regulatory T (iT_{reg}) cells have been added into the CD4⁺ T cell subpopulations (Weaver and Hatton, 2009). The cytokines interleukin (IL)-12 and interferon (IFN)- γ and the transcription factors STAT1, STAT4 and T-bet promote the development of TH1 cells, which produce IFN- γ as their “signature” cytokine (Dong, 2008; Annunziato et al., 2009). The cytokine IL-4, together with the transcription factors STAT6 and GATA-3, promotes the development of TH2 cells, which produce IL-4, IL-5, and IL-13 (Dong, 2008; Zhu et al., 2010). Natural regulatory T (nT_{reg}) cells, which develop in the thymus, gained acceptance as a bona fide CD4⁺ T cell lineage with the discovery that the transcription factor Foxp3 reliably marks these cells and directs their development (Bettelli et al., 2006a). Induced Treg (iT_{reg}) cells, which also express Foxp3 and share many if not all of the functions of nT_{reg} cells, are generated by transforming growth factor (TGF)- β and retinoic acid in the periphery and, can produce TGF- β , IL-10, and IL-35 (Bettelli et al., 2006a,b; Horwitz et al., 2008). Follicular helper T (TFH) cells can develop under the influence of IL-6 by induction of the transcription factor Bcl-6 (Rolf et al., 2010). Largely through their capacity to induce expression of the transcription factors ROR γ t, ROR α , and STAT3, the cytokines TGF- β , IL-6, and IL-23 promote the development of TH17 cells, which produce IL-17A, IL-17F, and IL-22. IL-21 is principally a product of TH17 and TFH cells and further promotes, through an autocrine feedback loop, the development of these cells (O’Quinn et al., 2008). The differentiation of TH17 cells from naïve CD4⁺ T cells is regulated directly by cytokines and transcriptional factors and indirectly by other immune cells (O’Quinn et al., 2008) (Fig. 1). The discovery and investigation of accumulating TH17 evidences suggests TH17 cells, is not stable, and more flexible, can be redirected their functional differentiation programs, and thus finally affecting in vivo homeostasis (Bettelli et al., 2006a; Dong, 2008; Yao et al., 2009). In this review, we will summary the recent findings that demonstrate the reciprocal modulation between TH17 and other helper cell types and clarify the plasticity of TH17 cells and the biological implications of this flexibility.

TH17 Cells and its Immune Regulation

The identification of the TH17 subset of effector CD4⁺ T cells has provided a new understanding as to the underlying mechanisms of autoimmunity (Weaver and Hatton, 2009; Buonocore et al., 2010). This TH17 cells is a potent producer of IL-17A and IL-17F, both of which belong to the IL-17 family of cytokines that includes IL-17B, IL-17C, IL-17D, and IL-17E (also known as IL-25) (Mucida et al., 2007). In terms of function, IL-17A and IL-17F target various (mostly nonlymphoid) cell types, including fibroblasts, endothelial cells, epithelial cells, keratinocytes, and macrophages, and induces the production of a milieu of cytokines, such as IL-6, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage CSF (GM-CSF), IL-1, transforming growth factor (TGF- β),

Abbreviations: APCs, antigen presenting cells; cLP, lamina propria of the colon; DCs, dendritic cells; EAE, experimental autoimmune encephalomyelitis; TFH, Follicular helper T cells; LPS, Lipopolysaccharide; MS, multiple sclerosis; nTregs, Natural regulatory T cells; OVA, ovalbumin; ROR γ , retinoic acid receptor related orphan receptor γ ; STAT3, signal transducer and activator of transcription 3; SLE, systemic lupus erythematosus; TCR, T cell receptor; TGF- β , transforming growth factor- β ; IBD, inflammatory bowel disease. Yujing Bi and Guangwei Liu contributed equally to this work.

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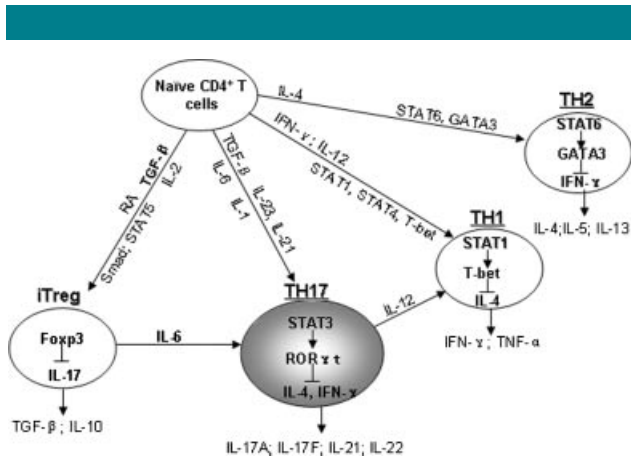


Fig. 1. CD4⁺ T cell differentiation. Naïve CD4⁺ T cells, after activation by signaling through the T cell receptor and co-stimulatory molecules initiate the process by which naïve CD4⁺ T cells begin to differentiate towards one of several fates. IL-12 activates STAT4 and drives naïve CD4⁺ T cells to become TH1 cells, which produce IFN- γ . Naïve CD4⁺ T cells are induced to become TH2 cells through IL-4 by innate immune cells, which signal through STAT6. Treg cells can develop from thymic CD4⁺ T cell precursors in the presence of TGF- β and IL-2. In the periphery, naïve CD4⁺ T cells can also be converted to inducible Treg cells by signaling through STAT5 in the presence of TGF- β , which up-regulate the Foxp3, and produce IL-10, IL-35, and TGF- β . TH17 cells develop from naïve CD4⁺ T cells in response to IL-6, IL-21, TGF- β , and IL-1 β . IL-6 and IL-21 activate STAT3, which increases transcriptional factor ROR γ t and ROR α , which promote IL-17A, IL-17F, IL-21, and IL-22.

tumor necrosis factor (TNF- α), and a series of chemokines, such as monocyte chemoattractant protein (MCP)-1, macrophage inflammatory protein (MIP)-2, and prostaglandins (e.g., PGE2) (van den Berg and Miossec, 2009; Korn et al., 2009). An important outcome of these effects is the stimulation and attraction of neutrophils to the site of inflammation. In addition to IL-17A and IL-17F, TH17 cells also produce IL-6, TNF- α , IL-21, and IL-22 (Korn et al., 2009).

In parallel to Th1 and Th2 cells, Th17 cells have their own distinct set of differentiation factors. Naïve CD4⁺ T cells, after activation by signaling through the T cell receptor and co-stimulatory molecules such as CD28 and inducible T cell co-stimulator (ICOS), can differentiate into TH17 cells. TGF- β , IL-6, IL-23, and IL-1 contribute to the differentiation of TH17 cells (Bi et al., 2007; O'Quinn et al., 2008; Romagnani, 2008). And then, the transcriptional factors ROR γ t, one subtype of ROR γ , are the transcription factor that directs the differentiation of inflammatory TH17. ROR α , another ROR family member, is also up-regulated during in vitro TH17 differentiation (Lee et al., 2009; Zhou et al., 2009). Although the over-expression of ROR α is sufficient to induce IL-17, lack of ROR α has only a minor effect on TH17 cell differentiation (Lee et al., 2009). These two closely related transcription factors, which presumably share the same DNA binding sequence, may have similar function in TH17 cell differentiation (Buonocore et al., 2010). IL-6, IL-21, and IL-23 signaling all utilize the Jak-Stat pathway and activate signal transducer and activator of transcription 3 (Stat3) (Eddahri et al., 2009; Hruz et al., 2010). Stat3 binds to the IL-17A promoter and Stat3 is also required for induction of ROR γ t by cytokines.

Now, some other factors have been confirmed to contribute to the TH17 cell differentiation and modulation. IRF4-deficient mice were protected from EAE and T cells from these animals failed to differentiate into TH17 cells (Chung et al., 2009; Kriegel et al., 2009). ROR γ t and ROR α induction were impaired in IRF4-deficient T cells, but over-expression of IRF4 could partially restore induction of IL-17, suggesting that IRF-4

may function upstream of the nuclear receptors (Huber et al., 2008). AhR, a mediator of the effects of environmental toxins (e.g., dioxin, a polycyclic aromatic hydrocarbon xenobiotic compound), is a ligand-dependent transcription factor that is structurally distinct from the nuclear receptor superfamily. Analysis of AhR-deficient cells has shown that it is required for IL-22 and, to a lesser extent, IL-17 expression in TH17 polarizing conditions in the presence of either dioxin or FICZ (Martin et al., 2009; Horvat et al., 2010). The transcriptional repressor protein Bcl-6 regulates T cell differentiation by repressing TH2 responses and promoting follicular TH cell responses. Recently, researcher also found that memory T cells from Bcl-6-deficient mice had increased IL-17 production. Additionally, Bcl-6 expression is up-regulated in CD4⁺ T cells cultured under TH17 conditions (Yu et al., 2009).

TH17 cell have an important function in the host-defense-response against extracellular pathogens, but they also have become notorious for their role in the pathogenesis of many autoimmune and allergic disorders. Animal models of autoimmune disorders have shown that TH17 effector molecules and transcription factors play a crucial role in both development and maintenance of the disease. Accumulating evidences is showing that TH17 and other helper T cell subpopulations can be regarded as a linker between innate and adaptive immune responses and regulating the sequent adaptive immunity. However, recent study indicates TH17 always is not be stable and there are many facets of plasticity in their differentiation statuses, whose studies will contribute to fully to understand and demonstrate TH17 immunoregulatory effects and biological implications.

TH17 and Treg

Current study suggests TH17 and iTreg is more flexible than other helper T cells subpopulation. The below listed factors contribute to access the reciprocal modulation between TH17 and iTreg in immune responses.

TGF- β

TGF- β is significant important linker to regulate the reciprocal modulation between TH17 and Treg cells, at least in part because it is required for the differentiation of iTreg cells and for maintenance of nTreg cells after development from the thymus. And, also TGF- β is also essential for the differentiation of inflammatory TH17 cells. Research results showed that although TGF- β induces the expression of Foxp3, IL-6 inhibits its expression (Bettelli et al., 2006a). Moreover, IL-6 together with TGF- β induced the optimal expression of IL-17 by activated T cells. So, inducible regulatory T cells and TH17 cells are reciprocally regulated during the differentiation and share TGF- β as a common inducer (Bettelli et al., 2006a; Ziegler and Buckner, 2009; Yang et al., 2009a). Further studies, researcher reported that over-expression of TGF- β in T cells resulted in increased differentiation to TH17 cells and in TH17 cell mediated experimental autoimmune encephalomyelitis (EAE) (Bettelli et al., 2003, 2006b). More clearly, from T cell specific TGF- β 1 gene knock out mouse, results showed that T cell derived TGF- β was indispensable for TH17 cell differentiation and induction of EAE in mice (Bettelli et al., 2003; Korn et al., 2007; Jager et al., 2009). Basically, researchers have believed that TGF- β orchestrates in vitro TH17 and Treg cell differentiation programs in a concentration dependent manner. IL-6 was believed to be necessary for the induction and maintaining of TH17 cells. And the loss of IL-6 during autoimmune responses resulted in significantly increased numbers of Foxp3⁺ Treg (Korn et al., 2007). Due to most of these studies used IL-17 expression as a marker of TH17 cell differentiation, but it is becoming evident that although TGF- β and IL-6 synergistically regulate transcription of the genes

encoding IL-17 and IL-17F, many other TH17 cell specific genes are regulated by either exogenous TGF- β or IL-6. So, TGF- β dose dependent modulation effects can be summarized about the reciprocal differentiation between TH17 and iTreg cells. At lower concentrations, together with IL-6 or IL-21, TGF- β synergistically induces IL-23R and thus promotes TH17 cell differentiation in the presence of IL-23. However, at higher concentrations, TGF- β inhibits IL-23R, IL-22 and IL-17 expression and favors induction of Foxp3 and, thus, Treg lineage differentiation. In spite of the absolute requirement of TGF- β , little is known about its precise signaling pathways in TH17 and Treg cell differentiation. Smad4 appears not to be required for TH17 cell differentiation (Yang et al., 2008a; Lu et al., 2010). But recent research report that neither Smad2 nor Smad3 gene deficiency abrogates TGF- β -dependent iTreg induction by a deacetylase inhibitor trichostatin A in vivo, although the loss of the Smad2 or Smad3 gene partially reduces iTreg induction in vitro. Similarly, Smad2 and Smad3 have a redundant role in development of TH17 in vitro and in EAE (Xiao et al., 2008; Qin et al., 2009; Lu et al., 2010). So, the involvement of Smad dependent or independent pathways in TH17 and Treg cell differentiation still needs to be carefully examined.

ROR γ t and Foxp3

Results have been shown that the orphan nuclear receptor retinoic acid receptor related orphan receptor γ t (ROR γ t), one subtype of ROR γ , is the transcription factor that directs the differentiation of inflammatory TH17. TH17 development in the gut requires ROR γ t expression in CD4⁺ T cells (Annunziato et al., 2007; Cha et al., 2010). In vitro, IL-6 plus TGF- β treatment-induced IL-17 expression requires induction of ROR γ t, and forced expression of ROR γ t is sufficient to induce IL-17 expression in the absence of any exogenous cytokines (Cha et al., 2010). Interestingly, ROR γ t-deficient mice develop less severe autoimmune diseases and specifically lack TH17 cells in the inflammatory tissues (Yang et al., 2008b; Kwan et al., 2009; Buonocore et al., 2010). Moreover, exposure of antigen-activated naive CD4⁺ T cells to TGF- β results in transcriptional upregulation of both Foxp3 and ROR γ t. T cells of coexpress ROR γ t and Foxp3 have been identified in vivo in both and humans. Foxp3⁺ ROR γ t⁺ cells from the small intestine produce less IL-17 compared with Foxp3⁻ ROR γ t⁺ cells, whereas Foxp3 deficiency results in a marked increase in IL-17. This indicates Foxp3 may antagonize ROR γ t mediated IL-17 expression in a cell-intrinsic manner.

As already mentioned, the numbers of Treg and TH17 cells are inversely associated in the autoimmune disease. This suggests that there could be a dynamic interaction between TH17 and Treg cells in the autoimmune disease microenvironment (Oukka, 2007). In vivo experimental results showed that Foxp3⁺ ROR γ t⁺ T helper intermediates display suppressive function against autoimmune diabetes. Traces of double-positive Foxp3⁺ ROR γ t⁺ T cells were identified and viewed as dual programming differentiation intermediates geared toward development into Tregs or TH17 cells. Results showed that Foxp3⁺ ROR γ t⁺ intermediates arise in the NOD mouse T cell repertoire prior to inflammation and can be expanded without further differentiation (Nistala and Wedderburn, 2009; Weaver and Hatton, 2009). Furthermore, Foxp3⁺ ROR γ t⁺ cells express both CD62L and membrane-bound TGF- β and use the former to traffic to the pancreas and the latter to suppress effector T cells both in vitro and in vivo. The cells perform these functions as Foxp3⁺ ROR γ t⁺ intermediates, despite being able to terminally differentiate into either Foxp3⁺ ROR γ t⁻ T regulatory or Foxp3⁻ ROR γ t⁺ TH17 cells on polarization (Nistala and Wedderburn, 2009). This indicates that the intermediates are poised to traffic to sites of

inflammation and target diverse pathogenic T cells, likely without prior conditioning by effector T cells, thus broadening efficacy against autoimmunity. So, the Foxp3⁺ ROR γ t⁺ cells probably are a transient population that can differentiate into Treg or TH17 (Fig. 2).

IL-17 and Foxp3

The dynamic interaction between TH17 and Treg cells in the autoimmune disease microenvironment could be further explored. Consistent with previous study, mouse peripheral mature Treg cells can be converted into TH17 cells (Nistala and Wedderburn, 2009; Weaver and Hatton, 2009). This event is favored by inflammation and IL-6 production. In addition Foxp3 also inhibits the expression of IL-17, and IL-17⁺ Foxp3⁺ T cells can be detected in vitro and in mice or humans (Beriou et al., 2009; Kryczek et al., 2009). However, it is not known whether these IL-17⁺ Foxp3⁺ T cells originate from TH17 cells or from Treg cells and also cannot make sure these cells have the functions of conventional TH17 cells (Voo et al., 2009; Buonocore et al., 2010). These IL-17⁺ Foxp3⁺ T cells also express CD25 and the TH17 lineage specific transcription factor ROR γ t, and have suppressive functions (Ratajczak et al., 2010). This indicates that IL-17⁺ Foxp3⁺ cells have certain functional characteristics of Treg and TH17 cells. Specifically, in tumor, notably, despite the high levels of IL-6 detected in some human epithelial cancers, the number of TH17 cells is limited in the tumor. Therefore, the positive effect of IL-6 in inducing TH17 cells might be subverted by an unidentified mechanism. Interestingly, in the presence of retinoic acid, which enhances TGF- β signaling and inhibits IL-6 signaling, IL-6 could not induce IL-17 production from Foxp3⁺ T cells (Mucida et al., 2007; Mukherjee et al., 2009). However, it is unknown whether retinoic acid affects the balance between Treg and TH17 cells in the tumor and autoimmune diseases. Nonetheless, the plasticity of the Treg cell lineage might allow the initial skewing of Treg cells towards an IL-17⁺ Foxp3⁺ phenotype and eventually into potentially protective Foxp3 and TH17 cells that can promote anti-tumor immunity and protect from autoimmune diseases.

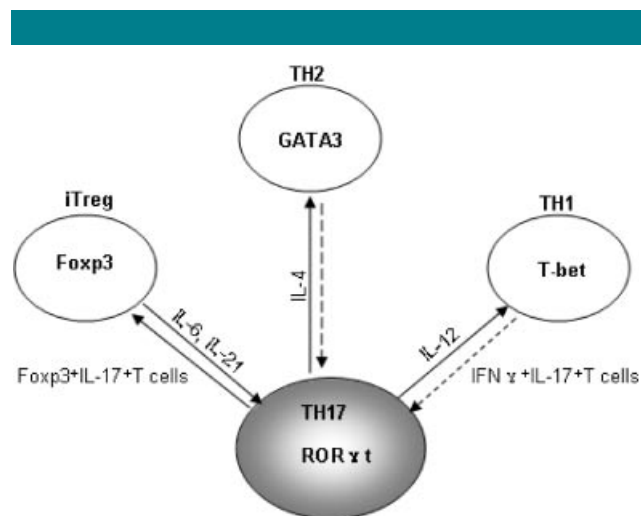


Fig. 2. Modulation and plasticity of TH17 cells. TH1 and TH2 cells are thought of as terminally differentiated cell types. However, TH17 cell have capacity to produce the TH1 cytokine IFN- γ , and converted into TH1 cells; also TH17 cells can intermediately express Foxp3 and converted into iTreg cells; TH17 cells also can convert into TH2 cells. In contrast, Foxp3⁺ Treg and TH1 cells can be converted into TH17 cell.

TH17 and TH1

Although there are no experiments directly demonstrating the lineage association between TH17 and TH1 cell development, there is evidence indicating that TH17 cells and TH1 cells might be phenotypically, developmentally and functionally linked in the autoimmune diseases. Autoreactive effector $CD4^+$ T cells have been associated with the pathogenesis of autoimmune disorders (O'Quinn et al., 2008; Homs et al., 2009; Korn et al., 2009; Zhu et al., 2010). Early studies implicated the TH1 cells as the causal agents in the pathogenesis of autoimmunity (O'Quinn et al., 2008). However, further studies have suggested a more complex story. In models thought to be driven by TH1 cells, mice lacking the hallmark TH1 cytokine IFN- γ were not protected but tended to have enhanced susceptibility to disease. Identification of the TH17 has helped shed light on this issue. TH17 effector cells are induced in parallel to TH1, and, like TH1, polarized TH17 cells have the capacity to cause inflammation and autoimmune disease. This, together with the finding that deficiency of the TH17-related cytokine IL-23 but not the TH1-related cytokine IL-12 causes resistance, led to the notion that TH17 cells are the chief contributors to autoimmune tissue inflammation (Matsushita and Higashi, 2008; Korn et al., 2009). Nevertheless, mice lacking IL-17 are not protected from disease and display elevated numbers of TH1 cells, and, in some cases, lack of IFN- γ does confer resistance. Recent studies report overlapping as well as differential roles of these cells in tissue inflammation, which suggests the existence of a more complex relationship between these two effector T-cell subsets than has hitherto been suspected. It causes the interest of regarding interaction, balance, and collaborative potential between the TH1 and TH17 effector lineages.

Antagonism and cooperation of TH1 and TH17 responses

Now, researchers basically believed that TH1 is significantly different from TH17, which have a distinct transcriptional factor, and "signature" cytokines. Also, researchers also realize that TH1 and TH17 lineages are antagonistic. Expression of the TH1 master regulator T-bet is implicated in ablation of the TH17 response and its absence inhibits TH1 polarization of $CD4^+$ T cells. Furthermore, activation of STAT1 by IFN- γ can suppresses TH17 development by antagonizing STAT3, a positive regulator of TH17 cells. Moreover, results also showed this antagonism is bidirectional regulatory effects. In the presence of APC and ovalbumin (OVA) peptides, IL-12 promotes the TH1 cells markedly more in the IL-17 $^{-/-}$ mice than WT (Annunziato et al., 2009; Ramgolam et al., 2009; Teng et al., 2010). This indicates IL-17 inhibit the TH1 development during T cell priming. The development of TH17 cells is suppressed by IFN- γ produced by TH1 cells, suggesting cross-regulation between TH17 and TH1 cells (Stockinger and Veldhoen, 2007). Thus, researcher analyzed the balance of TH17 and TH1 cell responses in peripheral blood from patients with systemic lupus erythematosus (SLE) and healthy subjects. Results showed that patients with SLE had an increased frequency of TH17 compared to healthy subjects (Yang et al., 2009b). However, the frequency of TH1 cells was similar between the two groups, indicating an altered balance of TH17 and TH1 cell responses in SLE. Patients with SLE also had an increased frequency of $CD4^+$ CCR4 $^+$ CCR6 $^+$ T cells that are known to produce IL-17. The frequency of $CD4^+$ IL-17 $^+$ T cells and $CD4^+$ CCR4 $^+$ CCR6 $^+$ T cells correlated with disease activity. In measuring plasma levels of the TH17-polarizing cytokines, levels of IL-6 were higher in patients with SLE than in healthy subjects (Cui et al., 2009). This suggests an enhanced TH17 cell response that correlates with disease activity in patients with SLE, suggesting a role for IL-17 in the pathogenesis of lupus. The mechanisms involved in balancing TH1 and TH17

regulation, as well as in producing IL-6, are aberrant in SLE, leading to an increased TH17 response.

Although either TH1 or TH17 effector T cells can drive immune-mediated pathology, the disease induced by each effector population is distinct in terms of the type of inflammatory leukocytes recruited to the site of inflammation and in terms of the preferential tissue location of the pathology. Adoptive transfer of TH1-polarized myelin-specific T cells results in heavy macrophage infiltration in EAE mice, whereas transfer of TH17-polarized cells leads to an infiltrate rich in neutrophils (Annunziato et al., 2007; Awasthi et al., 2009; Bai et al., 2009; Lin et al., 2009). The chemokine profile at the site of inflammation reflected the nature of the infiltrating cells, with monocyte chemoattractants CXCL9, 10, and 11 found in TH1-caused lesions and neutrophil-attracting chemokines CXCL1 and CXCL2 found in TH17-caused lesions (Blaschitz and Raffatellu, 2010). Moreover, TH1 and TH17 cell immune effects always show some time-sequence characters. Research showed that in the CNS of mice with EAE, only myelin-specific IFN- γ producing TH1 cells had the capacity to accumulate within the CNS and cause disease if transferred alone, whereas the TH17 cells could not (Ousman et al., 2007; Nath et al., 2009; Yang et al., 2009c). This also suggested that in the course of EAE, TH1 cells accumulate first in the CNS and subsequently allow for the entry of pathogenic TH17 cells. And the TH1 and TH17 sequence cooperation take important effects in diseases.

Reciprocal conversion between TH17 and TH1

Interestingly, TH1 "signature" cytokine IFN- γ , is also expressed by primary TH17 cells in TH17-polarized mouse cells. IFN γ^+ IL-17 $^+$ T cells are also found in patients with autoimmune diseases. It is possible that IFN γ^+ IL-17 $^+$ T cells can develop from TH1 cells and/or TH17 cells (Fig. 2). Consistent with this, adoptive transfer of antigen-specific IL-17 $^+$ CD8 $^+$ T cells into antigen-bearing hosts result in their conversion to IFN γ^+ CD8 $^+$ T cells (Huber et al., 2009). In mouse models, under lymphopenic conditions, TH17 cells can re-differentiate into TH1 cells (Jager et al., 2009). Given that after chemotherapy and radiotherapy, patients with cancer might mimic lymphopenic hosts, and given that there are substantial numbers of IFN- γ^+ IL-17 $^+$ T cells, TH17 cells could initially express low levels of IFN- γ but gradually be converted into TH1 cells in vivo (Klemann et al., 2009). However, although IFN- γ inhibits TH17 cell differentiation from naive T cells in mice, TH1 cell derived IFN- γ might drive APCs to promote memory TH17 cell expansion through inducing the production of IL-1 and IL-23 by APCs (Mangini et al., 2007; Locksley, 2009). Study showed that IFN- γ conditioning enhances the capacity of APC to drive the expansion of memory TH17 cells but not the commitment of naive $CD4^+$ T cells to the TH17 lineage. Similar study demonstrates that IFN- γ diminishes TH1 polarization by up-regulating co-stimulatory molecule B7-H1 on APCs. Therefore, modification of APC expression may be mechanism by which IFN- γ creates a local environment conducive to the TH17 lineage, especially to TH17 memory cells. Much more study also showed that incubation with IFN- γ significantly induces expression of IL-23 in APC from both healthy individuals and patients with psoriasis, driving differentiated T cells to up-regulate IL-17 and providing a mechanism for their trafficking into inflamed tissues. In EAE model, there are complex relationship between TH1 and TH17. At the same time of adoptive transfer, there are three populations, TH1, TH17, and IFN- γ^+ IL-17 $^+$ T cells, which appears to related with the expression of T-bet (Hermann-Kleiter and Baier, 2010). And silencing of T-bet inhibits the differentiation of both TH1 and TH17 cells by direct inhibition of IL-23 receptor (Yu et al., 2009; Hermann-Kleiter and Baier, 2010). This

suggests TH17 cells probably synergize with local TH1 cells in autoimmune response independent of TH1 intrinsic modulation. The functional interaction between TH1 cells and TH17 cells has been appreciated in the autoimmune disease models. To fully explore this interaction might be functionally relevant and therapeutically meaningful.

TH17 and TH2

TH17 cells can be converted into TH2 inflammation. Recent results showed that TH17 can be converted into TH2 inflammation by acetyl salicylic acid via the adenosine and uric acid pathway in the lung. Allergen-specific T-cell responses orchestrate airway inflammation, which is a characteristic of asthma (Bettelli et al., 2006b; Soroosh and Doherty, 2009; Saito et al., 2010). Recent evidence suggests that noneosinophilic asthma can be developed by mixed TH1 and TH17 cell responses when exposed to LPS-containing allergens. TH1 + TH17 asthma and TH2 asthma mouse models were generated by intranasal sensitization with OVA and LPS and intraperitoneal sensitization with OVA and alum, respectively (Korn et al., 2009; Peron et al., 2009). Therapeutic or adverse effects were evaluated after allergen challenge using pharmacologic and transgenic approaches. Results showed that Lung infiltration of eosinophils was enhanced in OVA/LPS-sensitized mice by ASA treatment, which was accompanied by the enhanced production of eotaxin. These changes were associated with the down-regulation of TH17 cell response, which was partly dependent on adenosine receptor, but up-regulation of allergen-specific IL-13 production from T cells, a TH2 associated cytokine. Lung inflammation induced by LPS-containing allergen was markedly reduced in IL-13-deficient mice in the context of ASA treatment, but not without ASA. Meanwhile, adenosine levels in the lung were enhanced by ASA treatment (Finotto, 2008; Caruso et al., 2009). Moreover, lung infiltration of eosinophils induced by ASA treatment was reversed by co-treatment of a xanthine oxidase inhibitor (allopurinol) (Hausding et al., 2008; Schmidt-Weber, 2008; Traves and Donnelly, 2008). These findings suggest that ASA changes TH17 into TH2 inflammation mainly via the adenosine and uric acid metabolic pathway in the lung (Fig. 2).

Also, TH2 can antagonize the TH17 lineage in vivo and in vitro. Results showed that over-expression of GATA3, a specific transcriptional factor of TH2, inhibit the IL-17 production, and down-regulate the expression of STAT3 and ROR γ t, which partially dependent on TH2 "signature" cytokine IL-4. Anti-IL-4 alone or combination with anti-IFN- γ treatment promotes the TH17 differentiation, whereas, addition of exogenous IL-4 inhibits TH17 differentiation. Similarly, GATA3 transgenic mice exhibit reduced joint destruction in experimental arthritis in which significantly increased TH2 cytokine expression and significant decrease of TH17 cell and IL-17⁺ IFN- γ ⁺T cells.

Conclusive Remark

T helper cell lineage commitment was regarded as an endpoint differentiation status of TH1 and TH2 cells. Each T helper cells have specific lineage-specific transcriptional factors and functional cytokines. However, accumulating reciprocal modulation evidences between TH17 and other T helper cell populations suggest the commitment of T helper cell lineages is more flexible, which probably contribute to the in vivo immunoregulatory mechanisms and maintaining the in vivo homeostasis. A better understanding of the complex the reciprocal courses between TH17 and other T helper cells will also helpful for developing and refining the new immunological therapies.

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