The phenotype of human Th17 cells and their precursors, the cytokines that mediate their differentiation and the role of Th17 cells in inflammation

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Abstract

T helper 17 (Th17) cells represent a new subset of CD4+ effector T cells which have been described in both mice and humans. However, some differences seem to exist between murine and human Th17 cells with regard to their features, origin and role in immunopathology. Murine Th17 cells share their developmental origin with Foxp3+ Treg cells, indeed naive T-cell precursors can be differentiated to regulatory T (Treg) cells by transforming growth factor-β (TGF-β) alone, whereas the contemporaneous presence of TGF-β and IL-6 gives origin to Th17 cells. Human Th17 cells which consistently express the CC chemokine receptor 6 and the equivalent of the murine NK1.1, CD161, appear to exclusively originate in response to IL-1β and IL-23 from a small subset of CD161+CD4+ T-cell precursors detectable in the thymus and in umbilical cord blood. These cells constitutively express the Th17-driving transcription factor retinoic acid-related orphan receptor (ROR)γt and the IL-23R and can also give origin to Th1 cells or Th2 cells under the appropriate polarizing conditions. By contrast, human CD161-naive T cells only give rise to Th1 and Th2 cells, but not Th17 cells. TGF-β may not exert a direct critical role in human Th17 cell differentiation, but indirectly favours their development by inhibiting the development of Th1 cells, which are much more susceptible than Th17 cells to its suppressive activity on cell proliferation. Moreover, while murine Th17 are pathogenic in some murine models of autoimmunity where Th1 cells seem to play a protective role, both Th17 and Th1 certainly contribute to the pathogenesis of human autoimmune and other chronic inflammatory disorders.

Introduction

The adaptive effector CD4+ T helper (Th)-mediated immune response can be very heterogeneous, because of the existence of distinct subsets characterized by different profiles of cytokine production. Two polarized forms of Th effectors, named as type 1 (Th1) and type 2 (Th2), were initially identified in both mice and humans (1, 2). Th1 cells produce IFN-γ and play a critical role in the protection against intracellular microbes. Th2 cells, which produce IL-4, IL-5, IL-9 and IL-13, but not IFN-γ, are involved in the protection against gastrointestinal nematodes, as well as in the pathogenesis of allergic disorders. Th1 cells originate in response to the production of IL-12 and IFNs by dendritic cells and NK cells, whereas Th2 cells mainly originate from naive Th1 cells because of the early presence of IL-4 and in absence of IL-12 during the primary immune response (1, 2). More recently, a novel subset of CD4+ effector Th1 cells has been described, which has been named as Th17, because of its exclusive ability to produce IL-17A in addition to other cytokines, including another member of the IL-17 family, known as IL-17F (3, 4). Although Th17 cells exist in both mice and humans, some differences seem to exist between the two species. In this review, the main characteristics of human as compared with murine Th17 cells, as well as the possible role of Th17 cells in immunopathology, will be discussed.

Murine Th17 cells

The Th17 lineage was discovered in some murine models of autoimmunity, such as experimental autoimmune...
encephalomyelitis (EAE) and collagen-induced arthritis (CIA) (3, 4), which have been historically associated with Tn1 responses. The dogma of the Tn1 role in the pathogenesis of EAE and CIA was challenged by the discovery of a new IL-12 family member, named as IL-23, which shares with IL-12 the p40 subunit, but includes p19 instead of p35.

Indeed, some studies showed that EAE and CIA did not develop in mice deficient in IL-23p19 subunit, whereas both diseases could develop in IL-12p35 subunit-deficient mice (3, 4), thus suggesting that at least in these murine models of autoimmune IL-23, rather than IL-12, is involved.

A critical role for Tn17 cells in immunopathology and the distinct origin of Tn1 and Tn17 cells under differential IL-12 or IL-23 conditioning was also suggested by findings other than those derived from gene-deficient mice (5). According to the new model, Tn1 and Tn17 cells share their origin from naive CD4+ T-cell precursors and then diverge contingently upon availability during the primary response of IL-12 or IL-23 acting on a common ‘Tn1 precursor’ or ‘pre-Tn1 intermediate’ that co-expresses both IL-12 and IL-23Rs (6-9).

More recently, however, a completely different model of murine Tn17 development has been discovered. Different groups independently demonstrated that transforming growth factor-β (TGF-β) was the critical cytokine for initiation, IL-6 acting as a critical co-factor for Tn17 differentiation (10-12). Notably, TGF-β is also known for its ability to promote the development of T regulatory (Treg) cells that express Foxp3, a transcription factor that acts as the ‘master regulator’ for Treg cells. Nevertheless, the expression of IL-17A or Foxp3 appears to be restricted to separate cell subsets, so that TGF-β-driven Tn17 and Treg development from naive precursors are mutually exclusive. In a more recent study, an IL-6-independent pathway of murine Tn17 differentiation has also been reported, but the nature of the TGF-β co-factor operating in absence of IL-6 remained unclear (13). Moreover, IL-21 has also been found to be involved in murine Tn17 cell differentiation (14, 15).

The transcription factor that acts as a Tn17 master regulator and directs the differentiation program of murine naive Tn1 cells into Tn17 cells is the retinoic acid-related orphan receptor (ROR)t (16). Up-regulation of RORyt is signal transducer and activation of transcription (STAT) 3-dependent since both RORyt expression and in vitro Tn17 differentiation are greatly impaired in STAT3-deficient T cells (17). Indeed, STAT3 is activated by IL-6, IL-21 and IL-23 which are also critical for Tn17 development and maintenance (18, 19) and directly binds to the promoter of IL17a/t loci (19). Despite the importance of STAT3 signaling, this stimulus alone appears not to be sufficient to drive Tn17 differentiation. Mice deficient in Rorc gene, which encodes RORyt, are unresponsive to IL-23 stimulation, have reduced numbers of Tn17 cells and are resistant to autoimmune diseases (20). However, STAT3 also regulates the expression of RORyt, but it is unclear whether this is a direct or indirect effect of STAT3 (20). More recently, high levels of another related nuclear orphan receptor, namely RORα induced by TGF-β and IL-6 and which is also dependent on STAT3, were found in murine Tn17 cells. RORα synergizes with RORyt to promote differentiation and function of Tn17 cells (20). Finally, the transcription factor IFN regulatory factor 4 was also recently shown to be essential for murine Tn17 differentiation probably acting upstream of RORyt (21). Other factors, such as retinoic acid (22) and aryl hydrocarbon receptors (23), have also been shown to regulate murine Tn17 differentiation. Recent important progress on this point has been achieved with the demonstration that the development of murine Tn17 cells is also regulated by Foxp3 (24-26). Interestingly, Foxp3+ Treg cells were found to be able to produce IL-17 (27).

Murine Tn17 cells produce a large series of cytokines: IL-17A, IL-17F, IL-21, IL-22, IL-6 and tumour necrosis factor (TNF)-α (28). IL-17A and IL-17F appear to be the key cytokines for the recruitment, activation and migration of neutrophil granulocytes by inducing the production of colony stimulatory factors and CXCL8, which are produced by several cell types, including resident cells (28). IL-21 seems to play an autocrine-amplifying role on Tn17 responses. IL-22 can induce acantosis and dermal inflammation, although in the liver it exhibits a protective role by counteracting the destructive nature of the inflammatory response. The exact role of IL-26 in the Tn17 response has not yet been established (28). Because of their functional properties, Tn17 cells have been suggested to be protective against infections sustained by extracellular Gram-negative bacteria and fungi, in which granulocyte infiltration is usually observed. Accordingly, preferential IL-17 production by T cells has been found during infection by Klebsiella pneumoniae, Bacteroides fragilis, Citrobacter rodentium, Escherichia coli, Borrelia burgdorferi and fungal species, whereas IL-17 plays a modest role (if any) in protecting against intracellular mycobacteria (28).

As mentioned above, Tn17 cells seem to be essential for the induction and propagation of autoimmunity in different animal models. IL-17-deficient mice or mice treated with an IL-17 receptor antagonist are more resistant to the induction of CIA and develop EAE with delayed onset and reduced severity. In this context, the presence, and sometimes the prevalence, of Tn1 cells in the inflammatory tissues of murine autoimmune disorders has been interpreted as a protective, rather than pro-inflammatory, mechanism. This interpretation is based on the following observations: (i) IFN-γ-deficient or IFN-γ receptor-deficient mice are still susceptible to EAE and CIA (29) and (ii) IFN-γ inhibits development of Tn17 cells (30).

However, in addition to an impressive series of previous observations clearly demonstrating a pathogenic, rather than protective, role of IFN-γ in various murine models of autoimmune disorders, very recent findings clearly argue against the exclusive pathogenic role of Tn17, as well as against the protective role of Tn1 cells in all murine models of autoimmunity. Indeed, both IL-12p70-polarized (Tn1) and IL-23-polarized T cells (Tn17) appeared to be able to induce EAE after adoptive transfer (31). Moreover, proteoglycan-induced arthritis, unlike CIA, appears to be completely independent of IL-17 (32). More importantly, it has been clearly established that either Tn1 or Tn17 cells may be pathogenic in murine models of experimental autoimmune uveitis (33). Thus, the Tn17 pathway cannot be called as critical mediator of immune-mediated tissue damage (34), because even Tn1 cells contribute to the inflammatory process.
Recent discoveries about human Th17 cells

Recent extensive studies have been performed to identify Th17 cells in humans and to characterize their phenotype and functions. These studies revealed the presence in these cells of RORγt, IL-23R and the high expression of the CC chemokine receptor 6 (CCR6), whereas Th1 cells poorly express CCR6 and highly express the CXC chemokine receptor 3 (CXCR3) (35, 36).

In one of the two studies, Th17 cells were also found to express the β2 chain of the IL-12R (36). The expression of CCR6 by Th17 cells has also been described in a murine model of rheumatoid arthritis (RA), where the CXCR3 expression has not been reported (37). Thus, although CCR6 and CXCR3 cannot be considered as selective markers of Th17 and Th1 cells, respectively, their detection may be useful for the recognition of the prevalence of each of the two subsets in blood (Fig. 1) or even in inflamed tissues.

Human Th17 cells exhibited poor proliferative capacity and cytotoxic potential, could induce the production by B lymphocytes of IgG, IgM and IgA, but not IgE and appeared to be less susceptible than Th1 or Th2 clones to the suppressive activity of an autologous Foxp3+ Treg clone (36). Moreover, the existence of a remarkable number of either double positive (IFN-γ+IL-17+) cells in the context of freshly derived blood cells or T-cell clones (named as ‘Th17/Th1’ cells) was reported, whereas no clones producing both IL-17 and IL-4 were observed (36). More importantly, both Th17 and Th1/Th1 clones consistently exhibited at both mRNA and protein level not only the expression of RORγt but also of T-bet (36), a transcription factor that is the master regulator of Th1 cells. The incubation of Th17 clones with IL-12 allowed these cells to produce IFN-γ in addition to IL-17, and this effect was associated with reduced RORγt and increased T-bet expression, suggesting the existence of a flexibility of Th17 towards Th1 cells and a possible developmental relationship between the two cell types (36).

More recently, by using a microarray analysis, we provided evidence that human Th17 cells consistently express on their surface CD161 (38), which is the human homologue of the murine NK1.1 (39). CD161 is expressed on most NK cells and NKT cells and on some T cells and thymocytes. The human CD161+ Th17 cells were not CD1-restricted NKT cells (40), but CD4+ T cells showing a broad T-cell receptor repertoire and MHC Class II restriction, known as NKT-like T cells (40). Despite the fact that human IL-17-producing cells are not iNKT but NKT-like cells, our findings may appear at variance with those reported in mice showing that a subset of iNKT cells produce IL-17, but curiously while most murine iNKT cells express NK1.1 (NKR-P1C), the IL-17-producing iNKT cells are NK1.1 negative (41, 42). However, by using the microarray assay on murine NKT cells, production of IL-17 by both NK1.1+ and NK1.1− cells upon activation in vitro has also been reported (43). The meaning of CD161 expression by human Th17 cells is still unclear. One possibility is that this molecule plays an important role in favouring transendothelial migration of Th17 effectors into tissues, where they are recruited in response to the CCR6-binding chemokine, CCL20. Although the function of CD161 on human Th17 is unknown, this may represent together with CCR6 an important marker for human Th17 detection and isolation (Fig. 2).

By looking at the results of the same microarray analysis on human Th17 clones, among all the genes analyzed, clusterin (CLU) appeared to be down-regulated, whereas Bcl-2...
ing that Th17 cells are less susceptible to the suppressive effect of circulating CD4+ T cells producing IL-4, but neither IL-17 nor IFN-β), whereas the proliferation of Th10 or Th2 cells, respectively. The cytokine profile of T cells clones was assessed by flow cytometry following stimulation with PMA plus ionomycin. The majority of T-cell clones obtained by CCR6+CD161+ cells were composed of IL-17A-producing cells.

was up-regulated in Th17 compared with both Th1 and Th2 clones (38). Recently, it has been shown that CLU is also a modulator of TGF-β signaling, inasmuch as it is involved in the nuclear translocation of Smad2/3 complex (44), which is critical for the transduction of the TGF-β signaling (45). Proteins of the Bcl-2 family are essential for protecting against apoptosis (46). On the basis of these findings, we evaluated the effect of TGF-β on the proliferation of human Th17 (i.e., producing IL-17, but neither IFN-γ nor IL-4), Th1 (producing IFN-γ, but neither IL-17 nor IL-4) and Th2 (producing IL-4, but neither IL-17 nor IFN-γ) clones, as well as, of circulating CD4+ T cells stimulated by a combination of anti-CD3 and anti-CD28 mAbs. The proliferation of both Th17 clones and circulating IL-17A-producing T cells was virtually not affected by TGF-β, whereas the proliferation of Th1 clones and of circulating IFN-γ-producing cells was strongly suppressed (V. Santarlasci et al., unpublished data), suggesting that Th17 cells are less susceptible to the suppressive activity of TGF-β than Th1 or Th2 cells, probably because of their reduced sensitivity to TGF-β signaling and/or increased resistance to apoptotic stimuli.

Th17 cell precursors and their differentiation seem to differ in humans compared with mice

The origin of human Th17 cells, and in particular the role of TGF-β, in their differentiation is still object of an intense debate. Different studies have denied the role of TGF-β in human Th17 differentiation, rather suggesting the role of IL-1β, IL-23 or IL-6 (47–49). Subsequently, however, three independent studies (50–52) showed that even the differentiation of human Th17 cells requires the activity of TGF-β, suggesting that previous studies in humans (47–49) have underestimated the role of TGF-β because CD4+ T cells were cultured in media comprising human or bovine serum, which usually contains TGF-β. However, the results of the more recent studies (50–52) are somehow contradictory. Manel et al. (50) found that TGF-β, IL-1β and IL-6, IL-21 or IL-23 were necessary and sufficient to induce IL-17 expression in naive umbilical cord blood (UCB) human CD4+ T cells. TGF-β up-regulated RORγt expression but simultaneously inhibited its ability to induce IL-17 expression, an activity which was antagonized by the inflammatory cytokines. Volpe et al. (51) found that TGF-β, IL-23, IL-1β and IL-6 were all essential for human Th17 differentiation, but they differentially modulated the cytokines produced by Th17 cells. More importantly, the absence of TGF-β induced a shift from a Th17 profile to a Th1-like profile. By contrast, Yang et al. (52) found that TGF-β and IL-21 uniquely promoted the differentiation of human naive CD4+ T cells into Th17 cells accompanied by expression of RORγt.

More recently, we have shown that human IL-17A-producing cells exclusively originate from CD161+CD4+ T-cell precursors present in both UCB and thymus when these cells are activated in presence of a combination of IL-1β plus IL-23 (that could also induce the development of Th1 cells) (38). No other cytokine or cytokine combinations (including TGF-β, IL-6 and IL-21) was able to induce IL-17A mRNA expression and IL-17A production. Unlike CD161+, CD161−, naive CD4+ T cells from both UCB or thymus could be induced to differentiate into Th1, Th2 cells under appropriate polarizing conditions (IL-1β plus IL-23, or IL-12 alone, for Th1 cells and IL-4 for Th2 cells), but they did never differentiate into IL-17A-producing cells (38). Thus, it seems that the small subset of CD161+CD4+ naive T cells present in the thymus and in UCB can give origin to both Th1 and Th17 (and also to Th2) effectors under appropriate microenvironmental conditions, whereas all the other (CD161−) CD4+ naive T cells lack the ability to differentiate into Th17 cells and can only be induced to differentiate into Th1 or Th2 cells. Whether CD161+ and CD161− naive CD4+ T cells represent two distinct lineages or CD161− originate from CD161+ cells remains to be established (Fig. 3).

The fact that CD161+, but not CD161−, naive CD4+ T cells from both UCB and thymus were found to express constitutively RORγt and IL-23R even before their culturing (38) suggests that RORγt expression by these cells was not dependent upon exogenously added TGF-β. Moreover, when UCB CD161+ T cells were stimulated in absence or presence of TGF-β alone, or IL-1β plus IL-23, in serum-free cultures, only the addition of IL-1β plus IL-23 significantly enhanced both RORγt and T-bet expression, whereas when TGF-β was added together with IL-1β and IL-23 the expression of RORγt further increased and T-bet expression strongly decreased. Likewise, the addition of either IL-12 or IL-4 inhibited RORγt expression and increased T-bet or GATA-3 expression, respectively (V. Santarlasci et al.,
Human Th17 cells originate only from CD161+CD4+ T-cell precursors, whereas Th1 and Th2 cells can originate from both CD161+ and CD161− T cells. CD161+CD4+ T cells present in the human thymus or UCB can give rise to Th17. Th1 and Th17/Th1 cells in response to IL-1β and IL-23 and can also differentiate into Th1 cells, in response to IL-12, or to Th2 cells in response to IL-4. CD161−CD4+ T cells can only differentiate into Th1 or Th2, but not Th17, cells. Whether CD161− cells originate from CD161+ cells or they are two distinct lineages is still unknown.

TGF-β alone suppressed the ability of cells to produce IFN-γ, but it did not induce the appearance of IL-17A-producing cells. When TGF-β was added together with IL-1β and IL-23, the proportions of IFN-γ-producing cells were strongly reduced, whereas those of IL-17A-producing cells were enhanced (V. Santaralasci et al., unpublished data). Notably, also in the studies of both Volpe et al. (51) and Yang et al. (52), the induction of IL-17A by TGF-β is associated with a strong decrease of IFN-γ production.

Our data suggest that TGF-β is not required for RORγt expression because CD161+ precursors of IL-17A-producing cells constitutively express RORγt. Moreover, TGF-β does not exert a direct critical role on the differentiation of IL-17A-producing cells because the development of IL-17A-producing cells that is induced by IL-1β plus IL-23 could be observed in serum-free cultures even in absence of exogenous TGF-β. The increase of T-bet that was induced by IL-1β plus IL-23 was suppressed when TGF-β was also added and the proportions of IFN-γ-producing cells were strongly reduced, thus resulting in a relative increase in the numbers of Th17 cells (V. Santaralasci et al., unpublished data). Taken together, these findings support the concept that TGF-β does not have a direct and critical effect on the development of human Th17 cells, but it can indirectly favour their development by selectively inhibiting both T-bet expression and the development of Th1 cells (Fig. 4).

Role of human Th17 cells in immunopathology

So far, the pathogenic role of Th17 cells has only been surely established in the so-called hyper-IgE (HIES) or Job’s syndrome. Dominant-negative mutations in the DNA-binding domain of STAT3 have been shown to cause this syndrome, because they result in the impaired Th17 differentiation and the deficiency of Th17 cells (53). Since Th17 cells are believed to be critical in the clearance of fungal and extracellular bacteria infections, their deficiency provides the mechanism underlying the susceptibility to the recurrent infections commonly seen in HIES (53–55).

By contrast, the pathogenic role of Th17 cells in human autoimmune and other chronic inflammatory disorders still needs to be definitively established. Chronically inflamed human tissues in subjects with multiple sclerosis, RA, Crohn’s disease (CD) or psoriasis are infiltrated by highly differentiated Th17 lymphocytes, which produce several inflammatory cytokines, such as IL-17A, IL-22, IL-26, TNF and lymphotoxin-β (56). However, which cytokines produced by human Th17 cells are involved in the different inflammatory processes, as well as the respective role of Th1, cells, are still unclear. Th17 cells appear to enhance osteoclast differentiation, which is required for bone destruction in patients with RA (57). High IL-17 levels have also been found in the sera and colonic biopsies of patients with CD, in whom IL-17F appears to play an important role (58).

Notably, genome-wide association studies have identified the IL-23R gene as being associated with inflammatory bowel disease (59). However, very recently, an IL-23–IFN-γ axis induced by abnormal intestinal macrophages, more than the IL-23–IL-17 axis, has been found to be important in the pathogenesis of patients with CD (60). High IL-17 levels have also been found in the affected skin of patients with inflammatory skin disorders such as nickel-induced dermatitis, psoriasis and atopic dermatitis (38, 61).

However, some of these findings have been challenged. For example, in a recent study, the frequency of Th17 cells was significantly decreased in the joints compared with peripheral blood from the same RA patients, whereas Th1 cells were more abundant in the joints than in peripheral blood (62). Even in psoriasis, which is considered a prototypic Th17-mediated disease, due to their ability induce skin acanthisis via the production of IL-22 and IL-23 (63), not only Th17 but also Th1 cells must be eliminated for final disease resolution (64). With regard to the possible pathogenic role of Th17 cells in allergic disorders, it has been claimed that...
these cells may play a critical role in the granulocyte infiltration that is present in the bronchi of some asthmatic patients (65). Obviously, because Th17 cells have a particular ability to recruit granulocytes, it cannot be excluded that IL-17-recruited cells can enhance bronchial inflammation in severe asthma complicated by bacterial infections and especially in non-allergic asthma. However, it is highly unlikely that Th17 plays a role in classic IgE-mediated allergic disorders, since the presence of IL-4 is among the most effective inhibitory signals for the differentiation of Th17 cells in both mice (8) and humans (66).

**Conclusions**

The discovery in both mice and humans of a new member of the CD4+ effector T-cell family (Th17 cells) has provided exciting and novel insights into the immune mechanisms that are responsible for protection and immunopathology. However, some critical differences appear to exist with regard to the mechanisms that are involved in the differentiation of murine and human Th17 cells, which render it difficult to establish new therapeutic procedures to target these cells or the cytokines that are responsible for their development. In particular, in some murine experimental models of autoimmunity, Th17 cells share their origin with Treg cells and are pathogenic, whereas Th1 cells appear to play a protective role. However, other murine models of autoimmunity demonstrate the critical contribution of Th1 cells to the pathogenesis of the inflammatory process.

Human Th17 cells appear to have a different origin than in mice. First, human Th17 cells appear to exclusively originate from a small subset of CD161+ T-cell precursors detectable in UCB and thymus, which constitutively express RORγt and IL-23R and develop into Th17 cells in response to IL-1β and IL-23 in the apparent absence of TGF-β. Notably, the same cytokines also induce the development of Th1 cells from both the CD161+ and the CD161-naive T-cell subsets, whereas Th17 cells cannot be generated from the CD161− population. Moreover, even established Th17 cells can be induced to produce IFN-γ in addition to IL-17A (Th1/Th17).
cells), suggesting a common developmental relationship between Th17 and at least part of Th1 cells. Whether classic Th1 cells play a protective role against the pathogenic activity of Th17 cells or contribute alongside them to the pathogenesis of human autoimmune as well as other chronic inflammatory disorders remains matter of debate. These findings represent another impressive example of how murine models, although extremely useful, cannot dogmatically be regarded as optimal for the development of novel immunotherapeutic strategies in humans.

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Abbreviations

CCL6 CC chemokine receptor 6
CD Crohn's disease
CIA collagen-induced arthritis
CLU clusterin
CXCR3 CXC chemokine receptor 3
EAE experimental autoimmune encephalomyelitis
HIES hyper-IgE syndrome
RA rheumatoid arthritis
ROR retinoic acid-related orphan receptor
STAT signal transducer and activation of transcription
TGF-β transforming growth factor-β
Th T helper
TNF tumour necrosis factor
Treg cell regulatory T cell
UCB umbilical cord blood

References

et al.


