Induction and effector functions of T$_H$17 cells

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Abstract

T helper (T$_H$) cells constitute an important arm of the adaptive immune system because they coordinate defence against specific pathogens, and their unique cytokines and effector functions mediate different types of tissue inflammation. The recently discovered T$_H$17 cells, the third subset of effector T helper cells, have been the subject of intense research aimed at understanding their role in immunity and disease. Here we review emerging data suggesting that T$_H$17 cells have an important role in host defence against specific pathogens and are potent inducers of autoimmunity and tissue inflammation. In addition, the differentiation factors responsible for their generation have revealed an interesting reciprocal relationship with regulatory T (T$_{reg}$) cells, which prevent tissue inflammation and mediate self-tolerance.

The hallmark of adaptive immunity in advanced vertebrates is the existence of lymphocytes, which induce and regulate immune responses. When activated by pathogens in a specific cytokine environment, naive CD4$^+$ T cells differentiate into different subsets with distinct effector functions aimed at orchestrating and mobilizing other cell types to effectively clear invading pathogens. Based on cytokine phenotypes, initially the existence of two distinct effector T$_H$ subsets was proposed: T$_H$1 and T$_H$2 (ref. 1). T$_H$1 cells produce interferon-γ (IFN- γ) and mediate protection against intracellular pathogens, whereas T$_H$2 cells produce interleukin-4 (IL-4), IL-13 and IL-25 (also known as IL-17E) and orchestrate the clearance of extracellular pathogens[1,2] (Fig. 1). Recently this paradigm has been updated following the discovery of a third subset of T$_H$ cells; these cells, known as T$_H$17 cells (ref. 3), produce IL-17 and exhibit distinct effector functions. In the past four years there has been an explosion of information regarding this T-cell subset: the cytokines for their differentiation have been identified, the key transcription factors that are involved in their generation have been recognized and their function in tissue inflammation has been established. This review summarizes this information to develop a comprehensive view of the generation and function of T$_H$17 cells.

T$_H$17 cells and T$_H$17-specific effector cytokines

T$_H$17 cells are characterized by the production of IL-17A (also called IL-17), IL-17F and IL-22 (Box 1) and are thought to clear extracellular pathogens not effectively handled by

either T_H1 or T_H2 cells (Fig. 1). Because T_H17 cells produce large quantities of IL-17A, most T_H17-mediated effects are attributed to this cytokine. IL-17A is the prototypic cytokine of the IL-17 family, which includes six members: IL-17A, B, C, D, E and F[4]. IL-17 is a phylogenetically old cytokine that is also detected in non-mammalian vertebrates[5].

In addition to IL-17A, T_H17 cells co-produce IL-17F[3,6]. IL-17A and IL-17F have similar functions. They induce the production of proinflammatory cytokines, chemokines and metalloproteinases from various tissues and cell types (Box 1). As a result, they recruit neutrophils to tissues.

Although there is often a coordinated expression of IL-17A and IL-17F in T_H17 cells and other cell types, it is now clear that there are T_H cells expressing only IL-17A, IL-17F or an IL-17A–IL-17F heterodimer[7,8]. In addition to IL-17A and IL-17F, T_H17 cells produce other effector cytokines, namely IL-21 and IL-22 (refs 6, 9–12). Neither IL-21 nor IL-22 are T_H17-exclusive cytokines, but are preferentially expressed in T_H17 cells.

Recent work from our group and others showed that IL-21, a member of the IL-2 family of cytokines, is produced in large amounts by T 17 cells and ICOS$^+$CXCR5$^+$CCR7$^+$ T follicular helper cells[13]. These T follicular helper cells home to the B-cell areas of secondary lymphoid tissue and provide cognate help to B cells. However, it remains to be seen whether T follicular helper cells could represent activated or memory T_H17 cells that help B cells in secondary or tertiary lymphoid organs.

IL-22 is a member of the IL-10 family of cytokines, produced by activated T cells and natural killer cells. It mediates its effects through a receptor complex composed of the IL-10R2 and the IL-22R chains. Interestingly, high concentrations of transforming growth factor-β (TGF-β) can inhibit IL-6-induced IL-22 expression[9]. Furthermore, whereas the combination of TGF-β plus IL-6 induces large quantities of IL-17A and IL-17F by T_H17 cells, the secretion of large amounts of IL-22 by T_H17 cells requires the addition of IL-23 *in vitro*[6,9]. This suggests that IL-22 could represent an end point effector cytokine produced by terminally differentiated T_H17 cells.

An important role for T_H17 cells in host defence

So far it is unclear which class of pathogens preferentially induces a T_H17 response because pathogens as diverse as the Gram-positive *Propionibacterium acnes*, the Gram-negative *Citrobacter rodentium*, *Klebsiella pneumoniae*, *Bacteroides* spp. and *Borrelia* spp., the acid-fast *Mycobacterium tuberculosis*, and fungi such as *Candida albicans* can all trigger a substantial T 17 response[14–19]. The fungal-cell-wall-derived product zymosan or other dectin-1 ligands as well as muramyldipeptide (a derivative of bacterial peptidoglycan) are able to promote IL-17 production in T cells[20]. Therefore, T_H17 responses are likely to emerge as an early response to a number of pathogens not handled well by T_H1- or T_H2-type immunity and which require robust tissue inflammation to be cleared.

Indeed, T_H17 cells appear at sites of inflammation with rapid kinetics. Through the potent induction of chemokines, T_H17 cells could bridge the gap between innate and adaptive immunity and attract other subsets of T helper cells to sites of infection at later stages of the

inflammatory process. This has most convincingly been shown for *M. tuberculosis* infection, for which an early T_H17 response is required to bring T_H1 cells into the infected lung tissue to control the infection[18].

T_H17 cells in autoimmune diseases

It is widely conceived that organ-specific autoimmune diseases are the result of dysregulated autoantigen-specific T_H1 responses. In many animal models of human autoimmune diseases, T_H1 cells have been shown to be pathogenic[21]. However, the concept that auto-immune diseases were exclusively mediated by T_H1 cells has been challenged, and the idea that T_H17 cells are an important part of the autoimmune reaction has emerged in light of the following observations: first, mice deficient for the T_H1 effector cytokine IFN-γ develop enhanced experimental autoimmune encephalomyelitis (EAE)[22]; second, deficiency in the IL-12p35 subunit (specific for IL-12) does not alter the progression of EAE, but deficiency in either p40 or p19, which form IL-23, results in a decreased number of T_H17 cells and protection from EAE and collagen-induced arthritis[23,24]; third, the transfer of myelin-reactive IL-17-producing T cells expanded with IL-23 *in vitro* induces severe EAE[3]; and fourth, IL-17 has profound pro-inflammatory effects and induces tissue damage during the course of various autoimmune diseases. Indeed, IL-17 can directly or indirectly promote cartilage and bone destruction[25]. Conversely, IL-17-deficient mice develop attenuated collagen-induced arthritis[26] and EAE[27]. Increased levels of IL-17 have been observed in patients with rheumatoid arthritis[28], multiple sclerosis[29], inflammatory bowel disease[30] and psoriasis[31]. Furthermore, IL-22 produced by T_H17 cells mediates IL-23-induced acanthosis and dermal inflammation[9]. In addition, IL-22, similarly to IL-17, can disrupt tight junctions between endothelial cells of the blood–brain barrier[32]. These data indicate a pathogenic role of T_H17-associated cytokines and T_H17 cells in inducing autoimmune tissue inflammation both in experimental animals and in humans.

Despite the recent major interest in T_H17 cells, these cells may not be the only T_H cells that can induce autoimmunity because T_H1 cells can readily transfer organ-specific autoimmune disease[33]. It is therefore possible that there is a sequential involvement and different functions of T_H17 and T_H1 subsets rather than an exclusive role of these subsets during the development of autoimmune diseases and other tissue inflammation[34]. In this scenario, T_H17 cells might facilitate the migration of other T_H cells (such as T_H1 cells) into the target tissue, which could further propagate and modulate inflammation and tissue damage.

Taken together, these data suggest that T_H17 cells are potent inducers of autoimmunity through the promotion of tissue inflammation and the mobilization of the innate immune system. However, in some tissues, such as the gut and perhaps the liver[35], T_H17 cells, as potent early players of the adaptive immune system, might also have modulatory and protective roles.

At least two cytokines are needed to differentiate T_H17 cells

In contrast to T_H1 and T_H2 cell differentiation, which depend on their respective effector cytokines (IFN-γ and IL-4) for differentiation, T_H17 differentiation does not require IL-17.

Instead, IL-6 and TGF-β—two cytokines with opposing effects—together induce the development of T_H17 cells[15,36,37]. IL-6 is a pro-inflammatory cytokine strongly induced in cells of the innate immune system on engagement of specific pattern-recognition receptors such as Toll-like receptors and C-type lectin receptors. Thus, infection or local inflammation induces large amounts of IL-6. In the immune system, TGF-β is regarded as an anti-inflammatory cytokine because the loss of TGF-β is associated with a fatal lymphoproliferative disease[38]. In mice, TGF-β plus IL-6 have also been shown to be the differentiating factors for T_H17 cells *in vivo*. First, TGF-β transgenic animals immunized with the myelin oligodendrocyte glycoprotein $MOG_{35–55}$ in complete Freund's adjuvant, which induces high amounts of IL-6, develop exacerbated EAE owing to enhanced frequencies of T_H17 cells[37]. Second, mice with a defect in TGF-β responsiveness in T cells are protected from EAE owing to the lack of generation of T_H17 cells[39]. Third, when TGF-β is not secreted by T cells as a result of a conditionally disrupted *Tgfb* gene in CD4 cells, T_H17 cells cannot be generated and the mice are relatively protected from developing EAE[40]. Consistent with the idea that T_H17 cells require both TGF-β and IL-6, we showed that IL-6-deficient mice fail to develop a T_H17 response and are resistant to the development of EAE[10,37].

In humans, IL-17-producing T cells have been detected in the memory population of peripheral blood mononuclear cells (PBMCs); in one report they were characterized by the combined expression of CCR4 and CCR6 (ref. 41), and in another they were characterized by the expression of CCR2 and lack of CCR5 (ref. 42). A heterogeneous population of IL-17 and IFN-γ double-producers resided in the $CCR6^+CXCR3^+$ human memory-T-cell compartment[41]. It has been reported that in naive human T cells, the combination of TGF-β plus IL-6 or TGF-β plus IL-21 failed to induce the differentiation of T_H17 cells[43,44]. Recent findings suggested that $CD45RA^+$ human $CD4^+$ T cells can be more efficiently differentiated into T_H17 cells by a combination of IL-1β plus IL-6 (ref. 43) or IL-1β plus IL-23 (ref. 31). However, the presence of TGF-β in fetal calf serum or human serum used in these culture conditions cannot be totally excluded. Interestingly, another study indicated that the combination of TGF-β plus IL-6 is capable of inducing the expression of ROR-γt, a transcription factor important for T_H17 cells (see below), but not the expression of IL-17 in human T cells[45]. More recently, TGF-β in combination with IL-1β, IL-6 or IL-21 was shown to induce the differentiation of human T_H17 cells[99,100], thus highlighting the role of TGF-β in T_H17 differentiation. This also underscores the similarities in the differentiation of mouse and human T_H17 cells.

IL-21 and other cytokines as amplifiers of T_H17 cells

Although IFN-γ and IL-4 produced by T_H cells reinforce, T_H1 and T_H2 differentiation, respectively[46], IL-17 does not act on the differentiation and expansion of T_H17 cells. Three independent groups reported simultaneously that IL-21, a member of the IL-2 family of cytokines, is produced in overwhelming amounts by T_H17 cells and could, in combination with TGF-β, induce T 17-differentiation[10–12]. Therefore, IL-21 produced by natural killer cells and natural killer T cells could induce the differentiation of T_H17 cells in the absence of IL-6 (ref. 10). When IL-6 is present, however, IL-21-receptor-deficient mice show a reduced but detectable T_H17 response *in vitro* and *in vivo*[10]. These findings point to a

relevant function of IL-21, produced by newly generated T_H17 cells, in amplifying the precursor frequency of differentiating T_H17 cells (Fig. 2). In addition to IL-21, other cytokines such as tumour-necrosis factor alpha (TNF-α) and IL-1, which are not specifically produced by T_H17 cells, have been proposed to have an additional role in the amplification of T_H17 responses[36,47].

What is the role of IL-23?

The observation that IL-23p19-deficient animals, which did not develop EAE, lack IL-17-producing T cells[24] and the fact that IL-23 could expand a population of IL-17-producing pathogenic cells[3] pointed to an important role of IL-23 in the development of pathogenic T_H17 cells. It is now clear, however, that IL-23 does not act on naive T cells to induce their differentiation, but instead acts on already differentiated T_H17 cells. The maintenance of T_H17 cells *in vitro* for extended periods of time appears to require IL-23, which might also modulate effector functions of T_H17 cells both *in vitro* and *in vivo*. Recently it has been shown that T cells cultured in the presence of TGF-β plus IL-6 did not induce tissue inflammation unless they are further cultured in the presence of IL-23, which could decrease the secretion of IL-10 by these cells[48,49].

Although IL-23 was described eight years ago[50], little is known about the role of IL-23 for T_H17 cells *in vivo*. IL-23 signals through a receptor composed of the IL-12Rβ1 chain (which it shares with the IL-12 receptor) and a unique IL-23R subunit[51]. *IL23R* mRNA expression has mainly been detected in T cells, natural killer cells and natural killer T cells, but low levels of this receptor can also be found in monocytes, macrophages and dendritic cells[52]. Both IL-6 and IL-21 are strong inducers of IL-23R in T cells[12]. Furthermore, IL-23 can enhance the expression of its own receptor through an auto-crine or paracrine feedback loop in mouse[3] (M. Oukka, unpublished observation) and human[45] T cells. The understanding of the regulation of IL-23R expression on naive T cells as they develop into T_H17 cells and on cells of the innate immune system will shed light on the role of this cytokine.

There is new evidence that IL-23 may have a profound impact on the innate immune system as well. Recent work has demonstrated that the development of gut inflammation in T-cell-deficient mice was dependent on IL-23, in that the loss of IL-23 but not IL-12 was associated with a decrease in gut inflammation mediated by anti-CD40-antibody-activated cells of the innate immune system[53]. IL-23 appears to induce IL-17, IL-1 and IL-6 from cells of the innate immune system[47,53]. Whether IL-23-mediated gut inflammation is entirely dependent on IL-17 produced by cells of the innate immune system has not been addressed. Consistent with this finding, a genome-wide scan revealed that particular SNPs in the coding sequence (rs11209026, c.1142G > A, p.Arg381Gln) of the *IL23R* gene conferred strong protection from Crohn's disease[54]. It has not been tested whether the different IL-23R variants affect the innate or adaptive immune systems or both.

We propose that the full differentiation of T_H17 cells requires three different steps: induction, amplification and stabilization/maintenance (Fig. 2). (1) The differentiation is initiated by the combined actions of IL-6 and TGF-β; (2) the amplification of the T_H17

response is driven through the production of IL-21 by T_H17 cells; (3) the stabilization/ maintenance of the T_H17 phenotype is achieved by IL-23. Whereas the first two steps in the development of T_H17 cells seem to be distinct, it is possible that the stabilization and the amplification phases overlap or take place simultaneously.

T_H17-specific transcription factors

The differentiation of effector T_H cells is initiated by proximal signals from the T-cell receptor, co-stimulatory molecules and cytokine receptors. These integrated signals then lead to the induction of lineage-specific transcription factors. T_H17 cells have emerged as a truly independent subset because their differentiation was shown to be independent of the T_H1- or T_H2-promoting transcription factors T-bet, STAT1, STAT4 and STAT6 (refs 55–57). Consistent with the role of IL-6 in the differentiation of T_H17 cells, STAT3 appears to be critical for the differentiation of T_H17 cells because conditional deletion of STAT3 in T cells prevents the development of T_H17 cells[58]. Activation in the presence of TGF-β1 alone normally induces FOXP3 and generates induced T_{reg} cells (iT_{reg} cells). In T_{reg} cells, the interaction of TGF-β1 with its receptor induces the phosphorylation of SMAD2/3 proteins and the formation of a complex with SMAD4, which then translocates to the nucleus. Whether similar molecules are involved in the differentiation of T_H17 cells remains to be determined.

Analogously to T_H1 and T_H2 subsets, T_H17 development relies on the action of a lineage-specific transcription factor, identified as the orphan nuclear receptor ROR-γt. ROR-γt is selectively expressed in T_H17 cells differentiated in the presence of TGF-β plus IL-6, and transduction of naive T cells with a retroviral vector containing ROR-ct induces the development of T_H17 cells[59]. Conversely, loss of ROR-ct in T cells prevents the generation of myelin-specific T_H17 cells and subsequently the development of EAE in mice immunized with myelin antigens. Furthermore, the analysis of ROR-γt–GFP (green fluorescent protein) reporter mice revealed the existence of a population of IL-17[1] cells that are constitutively present in the intestinal lamina propria and whose development depends on ROR-γt expression[59]. These observations argue in favour of a critical role of ROR-γt in the differentiation of the T_H17 lineage (Fig. 2). However, the mechanisms by which ROR-γt drives T_H17 development have not yet been fully elucidated. A recent report indicates that, similarly to T-bet inducing IL-12Rβ2, ROR-γt would induce IL-23R. More precisely, IL-6-mediated activation of both STAT3 and ROR-γt would promote the production of IL-21 by T_H17 cells, and IL-21 would then induce the expression of IL-23R and establish responsiveness of T_H17 cells to IL-23. In this model, a sequential involvement of IL-6, IL-21 and IL-23 would lead to the differentiation of T_H17 cells[12]. Another report suggested that the induction of IL-21 required STAT3, but not ROR-γt[11]. In addition, it has not yet been formally addressed whether ROR-γt directly transactivates the *IL17A, IL17F, IL22* and *IL21* genes in T_H17 cells. A more recent report suggested that T_H17 differentiation might be mediated by the combined effect of ROR-γt and ROR-α, both of which are expressed at high levels in differentiated T_H17 cells. Loss of only one of these transcription factors resulted in partial loss of T_H17 cytokine expression, and loss of both ROR-γt and ROR-α abrogated T_H17 differentiation[60].

Reciprocal relationship between iT$_{reg}$ and T$_H$17 cells

TGF-β induces the T$_{reg}$-specific transcription factor FOXP3 and is required for the maintenance of iT$_{reg}$ cells in the peripheral immune compartment. However, addition of IL-6 to TGF-β inhibits the generation of T$_{reg}$ cells and induces T$_H$17 cells. On the basis of these data, we first proposed[37] that there is a reciprocal relationship between T$_{reg}$ cells and T$_H$17 cells, and that IL-6 has a pivotal role in dictating the balance between these two cell populations[10,37].

This reciprocal relationship between T$_{reg}$ and T$_H$17 cells is further supported by recent data from other laboratories[61,62]: IL-2, which is a growth factor for T$_{reg}$ cells, has also been shown to inhibit the generation of T 17 cells[61]. Consistent with these data, mice that lack IL-2 or in which IL-2 signalling is compromised (*Stat5*$^{-/-}$), harbour reduced numbers of T$_{reg}$ cells and an increased proportion of T$_H$17 cells in the peripheral repertoire[61]. Moreover, these mice develop multi-organ inflammatory diseases, which can be prevented by the passive transfer of T$_{reg}$ cells[63].

Additional evidence for a reciprocal developmental relationship between FOXP3[1] T$_{reg}$ cells and T$_H$17 cells came from the discovery that retinoic acid, a vitamin A metabolite, could drive the generation of T$_{reg}$ cells[64] by enhancing TGF-β signalling and enhancing FOXP3 promoter activity while abrogating the differentiation of T$_H$17 cells, but not of T$_H$1 cells, through the inhibition of IL-6 signalling[62]. These findings indicate that retinoic acid can regulate the balance between pro-inflammatory T$_H$17 cells and anti-inflammatory T$_{reg}$ cells (Fig. 3).

Finally, it has been found that ROR-γt and RORα, the transcription factors for T$_H$17 cells, and FOXP3, the transcription factor for T$_{reg}$ cells, can physically bind to each other and antagonize each other's functions[65,66]. In line with this concept, conditional deletion of FOXP3 protein in 'T$_{reg}$ cells' *in vivo* resulted in an increase in ROR-γt, IL-17 and IL-21 expression[67,68], further corroborating the reciprocal relationship between T$_H$17 cells and T$_{reg}$ cells.

More than one way to inhibit T$_H$17 cells

So far, several cytokines and pathways have been shown to inhibit the development and expansion of T$_H$17 cells. T$_H$1- and T$_H$2-specific cytokines can antagonize each other. Correspondingly, IL-4, IL-25 (IL-17E) and IFN-γ also inhibit the expansion of T 17 cells[55,56,69].

Similarly, IL-27, a member of the IL-12 heterodimeric family of cytokines produced by cells of the innate immune system, can suppress the development of T$_H$17 responses. Consistent with this observation, a lack of IL-27 signalling resulted in an increased T$_H$17 response and enhanced inflammation of the central nervous system in two different disease models[70,71]. Two recent studies showed that IL-27 together with TGF-β induces the differentiation of IL-10-producing T cells with Tr-1-like properties and that IL-27R-deficient mice (*Wsx1*$^{-/-}$) have a defect in generating IL-10-producing Tr-1 cells[48,72]. Thus, IL-27 might also be

necessary to control exaggerated immunopathology indirectly by inducing Tr-1 cells (Fig. 3).

Role of TGF-β in inducing novel T_H subsets

Since the discovery of TGF-β and IL-6 as the differentiation factors for T_H17 cells, we have proposed that the dual cytokine interaction (TGF-β plus a cytokine X) might be operational in the induction of other novel T-cell subsets as well. Tr-1 differentiation induced by a combination of TGF-β plus IL-27 supports this hypothesis[48,72]. When TGF-β is involved in the differentiation of novel T_H subsets, T_H commitment might be accomplished either by TGF-β acting together with another cytokine, where the two cytokines will inhibit each other's functions and result in the generation of a totally new gene programme (for example, T_H17 differentiation induced by TGF-β plus IL-6), or by quantitatively scaling back each other's functions, thereby resulting in the production of only dominant cytokines in the responding T cells (for example, Tr-1 cells induced by TGF-β plus IL-27; Fig. 4). These observations suggest that T cells would sense multiple cytokine inputs simultaneously from the environment to initiate the differentiation of new T-cell subsets with distinct cytokine phenotypes and effector functions.

Concluding remarks

It is now established that T_H17 cells constitute an independent T-helper-cell subset with major functions in the induction of tissue inflammation and host protection against extracellular pathogens. Since their initial description, substantial progress has been made in the understanding of T_H17 differentiation and effector functions. On the basis of recent reports, we propose a three-step model for the differentiation of T_H17 cells: induction, amplification and maintenance/stabilization, where TGF-β plus IL-6 induce the differentiation of T_H17 cells, IL-21 amplifies the frequency of T_H17 cells and IL-23 stabilizes the phenotype of previously differentiated T_H17 cells. Loss of any one of the members in this pathway (IL-6, IL-21 or IL-23) limits the T_H17 response, and only the combination of these factors leads to a robust and stable T_H17 response. The understanding of how different cytokine signalling pathways are integrated to induce the differentiation of novel T_H subsets, including T_H17 cells, will represent a major step forward in our understanding of T-cell-subset differentiation. Because multiple lines of evidence suggest that there is a reciprocal relationship between T_{reg} cells and T_H17 cells, manipulation of this differentiation pathway might result in the generation of pro-inflammatory T_H17 cells and induce tissue inflammation or induce protective T_{reg} cells and therefore inhibit autoimmunity and induce tolerance. Targeting nodal points in this pathway will allow one to shift the balance between pro-inflammatory T_H17 cells and inhibitory T_{reg} cells and thus provide exciting new targets for the treatment of multiple inflammatory and autoimmune diseases.

Acknowledgements

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Effector cytokines produced by T_H17 cells

IL-17A

Source. T_H17 cells[3,55,56], CD8[1] T cells[73], cd T cells[74], neutrophils[75], eosinophils[76] and monocytes[77].

Receptor(s). IL-17RA is the cognate receptor for IL-17A. It is expressed at high levels on haematopoietic cells, and at lower levels on osteoblasts, fibroblasts, endothelial cells and epithelial cells[78]. Human IL-17RC binds human IL-17A with high affinity, but mouse IL-17RC does not bind mouse IL-17A[79]. Human IL-17RA–IL-17RC can form a heterodimer that binds human IL-17A[80].

Effects. IL-17A induces pro-inflammatory cytokines (IL-6, TNF-α and IL-1β[78]) and chemokines (CXCL1, GCP-2, CXCL8 or IL-8, CINC, MCP-1; ref. 81). It increases the production of prostaglandin E2 (ref. 81), nitric oxide[82] and matrix-metalloproteinases[55], increases the recruitment of neutrophils[14,75] and modulates neutrophil homeostasis[83].

IL-17F

Source. T_H17 cells[3,6,9], monocytes[84] and possibly other cell types.

Receptor(s). IL-17RC is the cognate receptor for IL-17F. It is expressed at low levels on haematopoietic cells, and at high levels on nonhaematopoietic cells[80]. Human IL-17RA–IL-17RC heterodimers can bind human IL-17F[80].

Effects. IL-17F induces pro-inflammatory cytokines (IL-6, ref. 85) and chemokines (CXCL1, GCP-2, CXCL8 or IL-8, ref. 85), and increases the recruitment of neutrophils[86].

IL-22

Source. T_H17 cells[6,9], activated T cells and natural killer cells[87].

Receptor(s). The receptor for IL-22 is a heterodimer consisting of IL-22R1 and IL-10R2 (ref. 88). IL-10R2 is ubiquitously expressed in haematopoietic and non-haematopoietic cells[89]. IL-22R1 (CRF2–9) is expressed on a variety of epithelial and parenchymal tissues (skin, liver, kidney, pancreas, intestine and lung)[90].

Effects. IL-22 increases acute-phase reactants in hepatocytes[91] and protects them from acute liver inflammation[35]. It induces the expression of b-defensins in epithelial cells[6,90] and promotes epidermal hyperplasia[9].

IL-21

Source. CD4[1] T cells stimulated with IL-6, T 17 cells[10–12], T follicular helper cells[13], natural killer cells and natural killer T cells[10,92].

Receptor(s). The receptor for IL-21 is a heterodimer consisting of common cytokine-receptor γ chain ($γ_c$) and IL-21R[93] $γ_c$ is expressed in lymphoid, but not in non-lymphoid and non-haematopoietic cells[94]. IL-21R is restricted to haematopoietic cells with highest

levels of expression on B cells, but also on T cells, natural killer cells, and some populations of myeloid cells[92].

Effects. IL-21 participates in the differentiation/amplification of T_H17 cells[10–12]. In combination with IL-7 or IL-15, IL-21 stimulates the proliferation and differentiation of CD8[1] T cells[95,96]. It promotes B-cell differentiation and antibody class switching (IgG1, IgG3)[96], induces the differentiation and cytotoxic programme of natural killer cells[92] and natural killer T cells[97], and induces CXCL8 in macrophages[98].
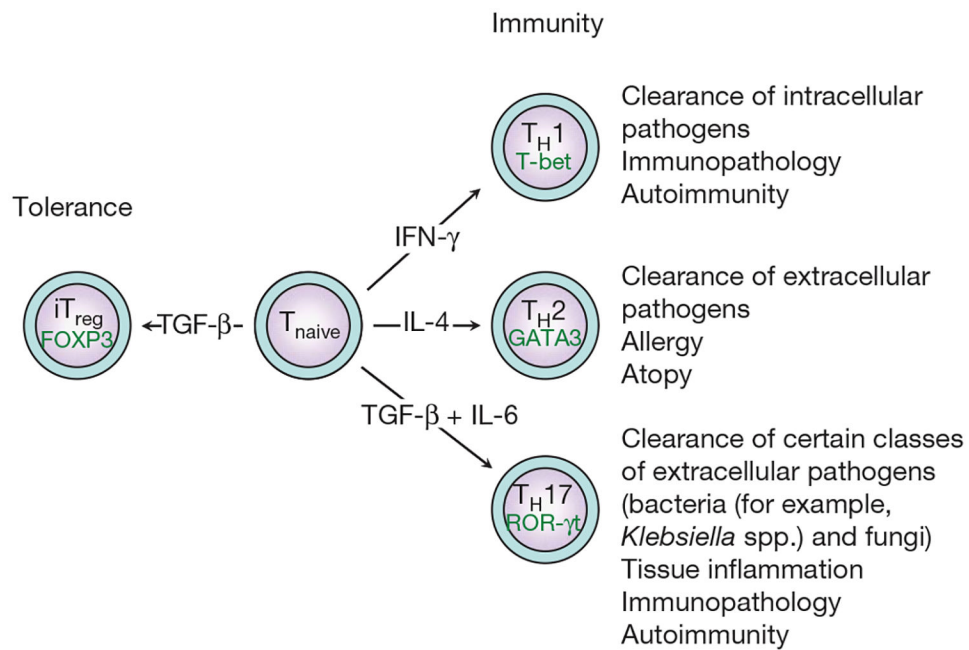
Figure 1 |. Subsets of T helper cells.
Depending on the cytokine milieu present at the time of the initial engagement of their T-cell receptor and costimulatory receptors in the peripheral immune compartment, naive CD4[1] T cells can differentiate into various subsets of T helper cells (T_H1, T_H2 and T_H17). However, in the presence of TGF-β, naive T cells convert into FOXP3-expressing induced T_{reg} (iT_{reg}) cells. For each T helper cell differentiation programme, specific transcription factors have been identified as master regulators (T-bet, GATA3 and ROR-γt). Terminally differentiated T helper cells are characterized by a specific combination of effector cytokines that orchestrate specific and distinct effector functions of the adaptive immune system.
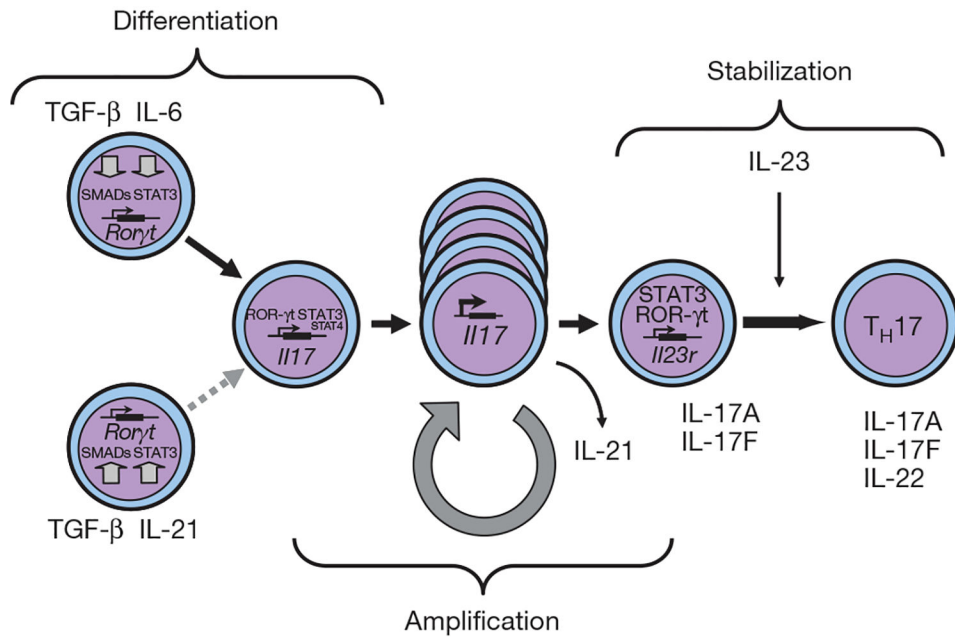
Figure 2 |. Steps in the differentiation of T$_H$17 cells.
Different factors control the initial differentiation of T$_H$17 cells from naive T cells, the amplification of T$_H$17 precursor cells, and finally the stabilization and effector phenotype of T$_H$17 cells. Whereas TGF-β together with IL-6 are the differentiation factors for T$_H$17 cells, IL-21, which is produced by T$_H$17 cells themselves, acts in a positive feedback loop to increase the frequency of T$_H$17 cells. STAT3 is the essential signalling molecule for the differentiation of T$_H$17 cells because the induction of IL-21 is absolutely dependent on STAT3, and STAT3 is also critical in the signal transduction cascades of IL-6, IL-21 and IL-23 receptors. IL-23 expands and stabilizes T$_H$17 cells to produce their effector cytokines IL-17, IL-17F and IL-22.
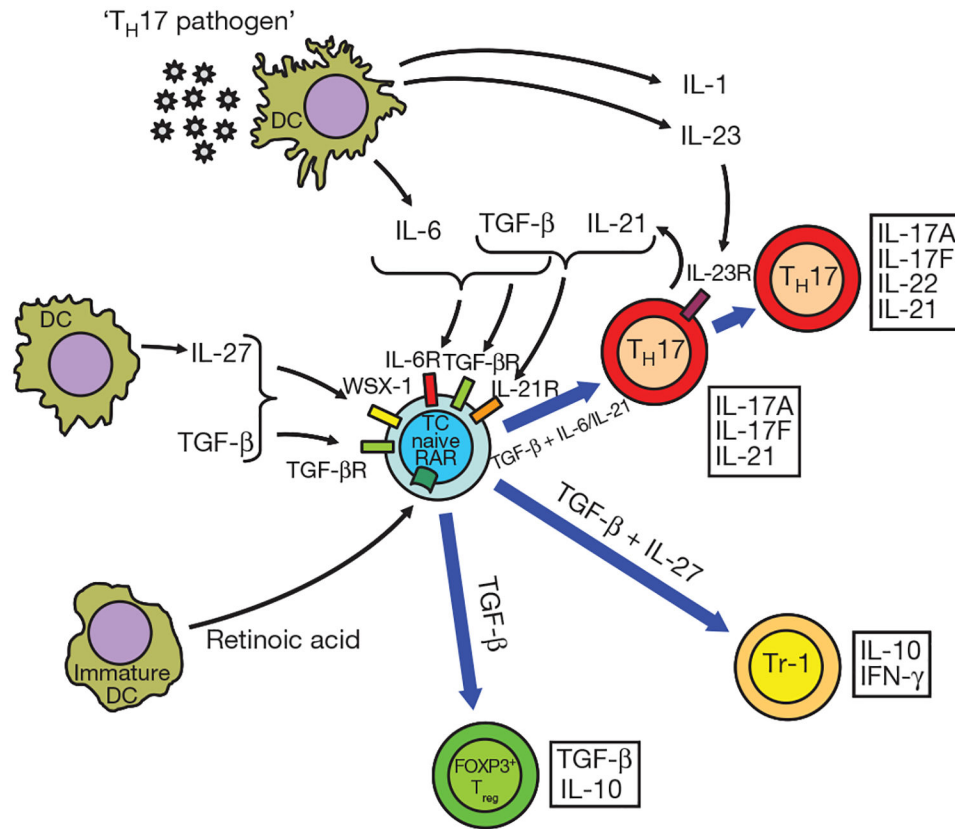
Figure 3 |. The developmental pathways of T$_H$17 cells and FOXP3$^+$ T$_{reg}$ cells require TGF-β signalling and are reciprocally regulated.

TGF-β is ubiquitous although its most relevant source in regulating immune reactions is still unclear. Other factors such as retinoic acid or cytokines such as IL-6, IL-1, IL-23 or IL-27 are provided by cells of the innate immune system (immature or activated dendritic cells (DCs), respectively) and dictate whether a naive T cell (TC) develops into a FOXP3$^+$ T$_{reg}$ cell, a T$_H$17 cell or an IL-10-secreting T cell of the Tr-1 phenotype. IL-6R, IL-6 receptor; IL-21R, IL-21 receptor; IL-23R, IL-23 receptor; RAR, retinoic acid receptor; TGF-βR, TGF-β receptor; WSX-1, IL-27 receptor).
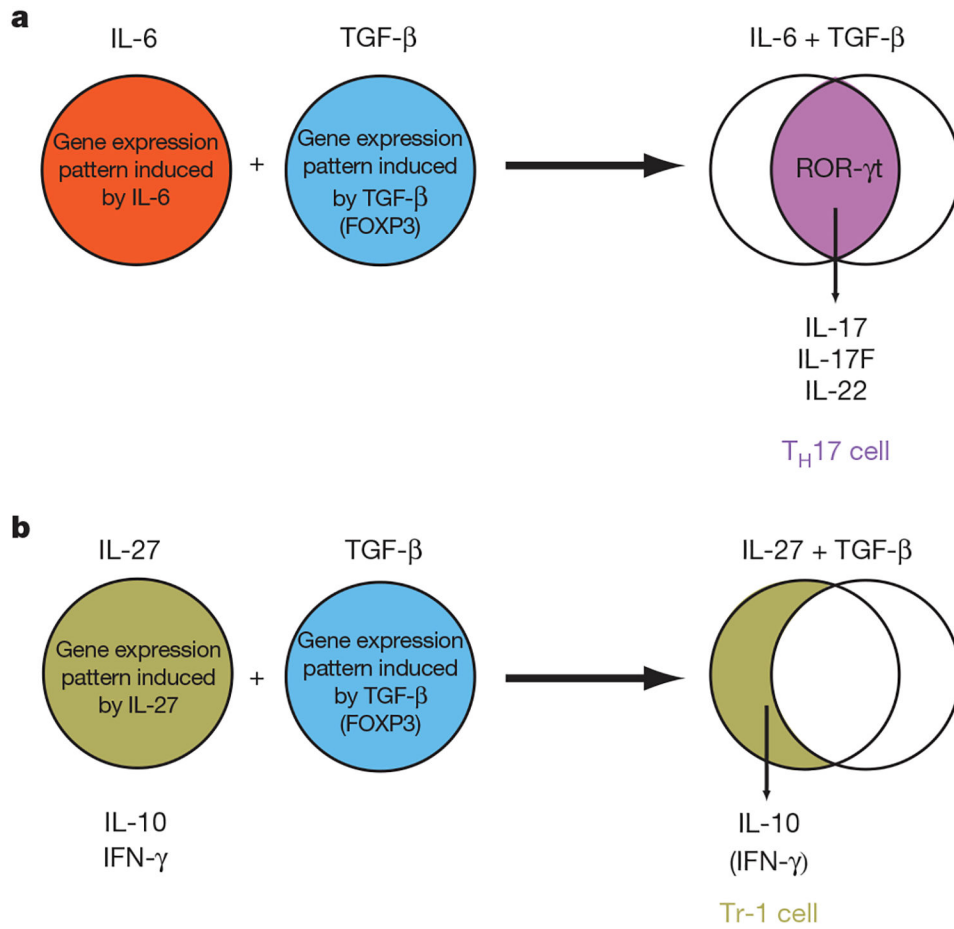
Figure 4 |. Effects of TGF-β in shaping the transcriptional programme of developing T helper cell subsets.

a, IL-6 and TGF-β independently induce specific gene expression programmes in T cells. However, when both cytokines act in concert, an essentially novel and distinct gene expression programme is induced resulting in a qualitatively different outcome such as the T$_H$17 transcriptional programme (*IL-17, IL-17F* and *IL-22*). **b**, In contrast, when TGF-β acts in combination with cytokines such as IL-27, IFN-γ expression is scaled down and IL-10 expression is increased resulting in a Tr-1-like phenotype.