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REVIEW

T helper 17 cells: discovery, function, and physiological trigger

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Abstract In the few years since their discovery, T helper 17 cells (T_H17) have been shown to play an important role in host defense against infections, and in tissue inflammation during autoimmunity. T_H17 cells produce IL-17, IL-21, IL-10, and IL-22 cytokines, and thus have broad effects on a variety of tissues. Notably, the requirement for the immunosuppressive cytokine TGF-β along with the pro-inflammatory cytokine IL-6 for T_H17 differentiation supports the intimate relationship between the T_H17 subset and $FOXP3^+$ regulatory T cells. Here, we discuss current knowledge on effector functions and differentiation of the T_H17 lineage. Furthermore, we now know of a physiological stimulus for T_H17 differentiation: innate immune recognition of cells undergoing apoptosis as a direct result of infection induces unique development of this subset. As our knowledge of T_H17 and T regulatory cells grows, we are building on a new framework for the understanding of effector T cell differentiation and the biology of $CD4^+$ T cell adaptive immune responses.

Keywords T_H17 · Effector T cells · Regulatory T cells · Innate immunity · Apoptosis · Tolerance · Autoimmunity · Host defense

Introduction

$CD4^+$ T helper (T_H) cells are a sub-category of T lymphocytes that regulate both innate and adaptive immune processes and help to determine what type of immune response is mounted against a particular pathogen. $CD4^+$ effector T_H cells express T cell receptors (TCR) that recognize antigens bound to major histocompatibility complex (MHC) class II molecules when presented by dendritic cells (DC) or other antigen presenting cells (APC). TCR activation along with co-stimulatory signaling activates the $CD4^+$ T cell and allows it to undergo proliferation and differentiation. Naïve $CD4^+$ T cells, when activated, can differentiate into effector T_H cells or regulatory T cells, or T_{reg} cells. Effector T_H cells can be further subdivided into the T helper 1 (T_H1) and T helper 2 (T_H2) subsets, where each subset has distinct pro-inflammatory functions to orchestrate the immune response to particular pathogens via production of different cytokines. For example, T_H1 cells produce interferon-γ (IFN-γ) and stimulate clearance of intracellular infections, while T_H2 cells produce interleukin-4 (IL-4) and IL-5 and promote clearance of extracellular parasitic infections [1]. T_{reg} cells synthesize anti-inflammatory cytokines such as TGF-β, and these cells serve to limit and control inflammation. Effector T_H cells have also been implicated in pathological responses: T_H1 cells can participate in autoimmune inflammation, while T_H2 cells mediate allergic inflammation.

The process by which an uncommitted, or naïve, $CD4^+$ T cell develops into a mature T_H1 or T_H2 cell is one of developmentally regulated gene expression, influenced by many factors. In general, APC direct differentiation of naïve T cells by translating molecular features on pathogens they encounter into the production of cytokines, which in turn instruct naïve $CD4^+$ T cells towards a particular lineage. IL-12 and IL-4, acting through signal transducer and activator of transcription 4 (STAT4) and STAT6 transcription factors, respectively, are important cytokines in differentiation decisions towards the T_H1 or

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T_H2 lineage [2]. Subsequent activation of specific transcription factors T-bet (for T_H1) or GATA3 (for T_H2) also plays a key role in induction of these subsets. More recent studies have indicated that activation of the Notch pathway by specific ligands expressed on APC can also instruct T_H cell differentiation in the absence of IL-4 or IL-12 [3].

T_H17 cells

Recent advances in the understanding of the development of a subset of $CD4^+$ effector T cells that produce another cytokine, IL-17, have led to substantial modifications in the original T_H cell subset paradigm. In 1986, two landmark papers by Mosmann and Coffman provided a foundation for understanding T cell biology when they proposed the T_H1–T_H2 hypothesis [4, 5]. The theory was based on the observation that subsets of $CD4^+$ T_H cells had distinct cytokine expression profiles that defined their function: T_H1 cells induced cell-mediated inflammatory responses, and T_H2 cells provided B cell help. Coffman also predicted a cross-regulatory element of T_H cell differentiation, where the effector cytokines produced by one subset of cells would regulate the development and activity of the other. This idea has been validated over the past 20 years by molecular and genetic studies demonstrating a complex network of cross-regulatory signaling pathways and transcriptional regulators that co-ordinate genetic and activated programming of the differentiating T cells. On the basis of these kinds of studies [6], it became possible to define the IL-17-producing $CD4^+$ T cells as a distinct subset of T_H cells, T_H17 cells. This distinction was made according to the same general criteria by which T_H cell lineages had been defined: naïve $CD4^+$ T cells differentiate independently into each lineage in vitro and in vivo, and each lineage has a distinct, heritable gene-expression signature.

Even before the definition of T_H17 cells as a separate subset, IL-17 cytokine produced by $CD4^+$ T cells has been associated with host defense against infectious pathogens as well as with autoimmune diseases. However, it was not clear how IL-17 production was regulated. At the turn of the century, Infante-Duarte et al. [7] showed that a population of murine or human $CD4^+$ T cells primed in the presence of *Borrelia burgdorferi* or mycobacterial lysates express IL-17 and do not co-express IFN-γ. Subsequent studies of mice deficient for IL-23, an IL-12 family cytokine that will be discussed presently, in autoimmune disease models showed that although this cytokine was not important for expression of IFN-γ, it was required for expression of IL-17, indicating that IL-17 and IFN-γ are differentially regulated [8]. IL-23 was subsequently shown to selectively induce proliferation of in vivo-primed IL-17-expressing $CD4^+$ T cells [9]. T cells induced to proliferate with IL-23 express a distinctive set of genes: they do not produce IFN-γ or IL-4 but instead express IL-23 receptor (IL-23R) and IL-17. Following this work, two groups independently showed that naïve $CD4^+$ T cells can differentiate into IL-17-expressing T cells in vitro and in vivo, distinct from T_H1 or T_H2 development [10, 11]. Since then, T_H17 cells have been recognized as a separate lineage of T_H cells that plays a crucial role in T cell-mediated adaptive immunity. This idea has been supported in the last 4 years with many studies describing their unique cytokine profile and transcriptional regulation, both in human and mouse systems. T_H17 cells are not only distinct from other T_H cell subsets in terms of gene expression and regulation, but also in their biological function. T_H17 cells are generally thought to be pro-inflammatory, especially through the production of IL-17 [12]. They have been shown to participate in development of autoimmunity, and also to play an important role in host defense against infection, by recruiting neutrophils and macrophages to infected tissues, promoting abscess formation [13], and inducing expression of antimicrobial peptides [14].

Differentiation of T_H17 cells: transcriptional regulation

After the observation that T_H17 cells expressed a distinct subset of cytokines and chemokines as compared to T_H1 and T_H2 cells, several groups performed experiments to look for a T_H17-specific transcription factor. A retinoid orphan nuclear receptor, RORγt (encoded by *Rorc*), was shown to be specifically expressed by mouse and human T_H17 cells [15, 16]. Expression of RORγt in naïve $CD4^+$ T cells was necessary and sufficient to induce IL-17 expression. A related nuclear receptor, RORα, was shown to synergize with RORγt to promote differentiation of T_H17 cells [17]. Binding of a Runx family transcription factor, Runx1, to *Il17* promoter and enhancer regions along with RORγt was shown to be required for optimal IL-17 expression in $CD4^+$ T cells [18]. In vitro, Runx1 could also upregulate expression of RORγt directly in T_H17 polarizing conditions [18]. Interleukin regulatory factor 4 (IRF4), a transcription factor originally reported to be important in T_H2 development [19], was recently shown to be critical for T_H17 induction as well. IRF4-deficient T cells were impaired in T_H17 polarization, and IRF4-deficient mice were resistant to T_H17-mediated induction of experimental autoimmune encephalomyelitis (EAE) [20], a mouse model of multiple sclerosis. T_H17 cell development and function is also critically dependent on the transcription factor STAT3. Upregulation of RORγt is STAT3-dependent [21], and selective deletion of STAT3 in T cells abrogates T_H17 development partly because expression of RORα and RORγt are also abrogated [17]. STAT3 is activated by IL-6

and IL-23 (reviewed in [22]), and STAT3 can also directly regulate the expression of IL-21 and IL-17 [23]. Thus, T_H17 cell differentiation fate, effector functions, and maintenance are all in some part regulated by STAT3 via various cytokine mediators. The regulatory network of transcriptional regulation of T_H17 cells is shown in Fig. 1.

Another factor in the regulation of transcription of T_H17 cytokines is the aryl hydrocarbon receptor (AhR), a ligand-dependent transcription factor that mediates effects of environmental toxins such as dioxin or FICZ (a UV photoproduct of tryptophan) [24]. Experiments with AhR-deficient cells suggested that it is required for expression of IL-22, and to a lesser extent IL-17, in T_H17 polarizing conditions and in the presence of either dioxin or FICZ [25, 26]. However, the requirement for AhR in IL-17 expression remains controversial [27]: while one group found opposing effects on T_H17 and T_{reg} differentiation in response to different AhR ligands (dioxin vs FICZ) [26], another saw no difference between the individual ligands [27]. More recently, an AP-1 transcription factor, BATF [28], was shown to also play a role in T_H17 differentiation. *Batf*$^{-/-}$ mice had a defect specifically in differentiation of T_H17 cells, and were resistant to EAE [29]. This effect is thought to occur via BATF binding to the *Il17a*, *Il21*, and *Il22* promoters; *Batf*$^{-/-}$ T cells are also deficient in induction of the T_H17-specific transcription factor RORγt [29].

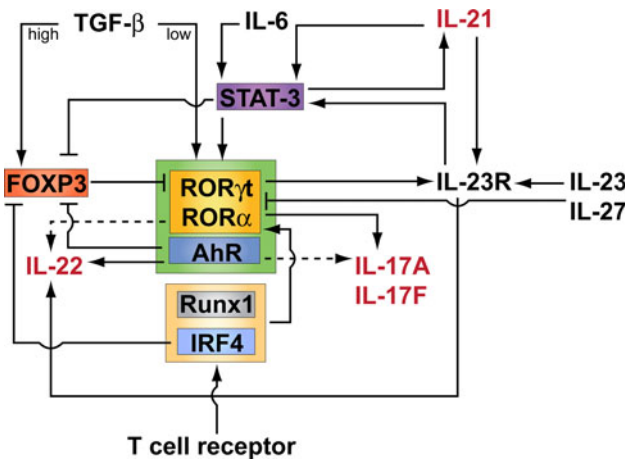

Fig. 1 Schematic representation of the transcriptional regulation of T_H17 cell differentiation. Activation of $CD4^+$ T cells through the T cell receptor (TCR) in the presence of a T cell costimulatory signal results in activation and differentiation of CD4 T cells into different fates depending on the cytokine milieu. Activation of the TCR in the presence of high concentrations of TGF-*β* induces expression of both RORγt and FOXP3, but FOXP3 antagonizes RORγt functions leading to naïve $CD4^+$ T cell differentiation into regulatory T cells (T_{reg}). When the pro-inflammatory cytokine IL-6 is present together with low concentrations of TGF-*β*, the T_H17 specific transcription factors RORγt and RORα are induced in a STAT-3-dependent manner leading to the transcriptional activation of IL-17, IL-22, and IL-23 receptor (IL-23R). Through STAT-3, IL-6 induces IL-21, which acts in a positive autocrine loop in order to amplify T_H17 cell differentiation. Indeed, IL-21 induces IL-23R expression, which imparts responsiveness to IL-23, a cytokine that maintains and expands T_H17 cells. IL-23 is also important in inducing the expression of IL-22 by T_H17 cells. Although IL-6 is dominant in vivo, in its absence and when T_{reg} cells are experimentally depleted, IL-21 together with TGF-*β* can induce T_H17 cell differentiation. Many transcription factors cooperate with RORγt and RORα in inducing maximal IL-17 and IL-22 expression. These include the aryl hydrocarbon receptor (AhR), which is also induced during T_H17 cell differentiation and inhibits FOXP3 expression, TCR-induced interferon regulatory factor IRF-4 which under T_H17 polarizing conditions upregulates RORγt expression and plays a role in IL-6 mediated downregulation of FOXP3 expression, and TCR-induced Runx1 which also upregulates RORγt expression and, together with RORγt, directs *Il17* transcription. IL-27 counters the effects of TGF-*β* and IL-6 on differentiating $CD4^+$ T cells, effectively blocking T_H17 differentiation in a STAT-1-dependent manner, and inhibiting expression of RORγt and IL-17 production. Cytokines shown in *red* are induced upon the initiation of T_H17 cell differentiation and are thus produced by T_H17 cells

Differentiation of T_H17 cells: cytokines

Meanwhile, with the establishment of T_H17 cells as an independent subset of T_H cells, studies were also under way to determine the specific cytokine factors that promote differentiation of these cells. In 2006, three independent studies found that a combination of the prototypical, pleiotropic pro-inflammatory cytokine IL-6 along with the immunoregulatory cytokine TGF-*β* were required to induce IL-17 expression in naïve $CD4^+$ T cells [30–32]. Because the synergistic effect of two cytokines with supposedly opposing consequences was required to activate differentiation of this cell subset, signaling molecules and transcription factors downstream of the TGF-*β* and IL-6 receptors were thought to work together to induce T_H17 differentiation. Two collaborating groups performed experiments using a 2D2 TCR transgenic mouse, which has T cell receptor specificity to myelin oligodendroycte glycoprotein (MOG), crossed to a TGF-*β* transgenic mouse that overexpresses TGF-*β* under the IL-2 promoter (2D2/TGF-*β* Tg mouse). When they injected the mice with MOG peptide alone, the T cells from the 2D2/TGF-*β* transgenic mice were able to suppress EAE on adoptive transfer. This was because T cells activated in the presence of TGF-*β* alone (which was constitutively expressed by the T cells, under the IL-2 promoter) differentiated into anti-inflammatory T_{reg} cells [33]. When the mice were immunized with both peptide and complete Freund's adjuvant (CFA), however, the splenocytes from these mice made high levels of IL-6, and the T cells were much more potent at induction of EAE as compared to T cells from immunized 2D2 mice that did not overexpress TGF-*β* [31]. Although some early reports suggested that T_H17 differentiation in human cells could occur in the absence of TGF-*β*, these results were

revealed to be artifactual by several studies showing the absolute requirement of TGF-β for T_H17 differentiation in human as well as mouse cells [34–36].

Because of this finding, the groups predicted that the T cell repertoire of IL-6-deficient mice would be dominated by T_{reg} cells, and that *Il6*$^{-/-}$ animals would lack the ability to generate T_H17 cells and be resistant to development of EAE. This proved to be the case. In fact, although there were increased numbers of T_{reg} cells in the *Il6*$^{-/-}$ mice [37], these mice were still susceptible to EAE via a pathogenic T_H17 response when the T_{reg} population was depleted, suggesting an IL-6-independent pathway for T_H17 differentiation. By screening for cytokines that might substitute for the effect of IL-6, they identified a cytokine that could do so, the IL-2 family member IL-21[37], a cytokine originally identified as a factor that enhances T cell proliferation and drives differentiation of NK cells [38]. Other groups were able to corroborate the finding that IL-21 could promote T_H17 differentiation, solidifying the notion that IL-21 can pair with TGF-β for induction of T_H17 responses [39, 40]. Several groups also found that IL-21 was equally as effective at induction of RORγt transcription factor and the IL-23 receptor as was IL-6. In further examination of the differences in effect of IL-6 and IL-21, however, it became clear that compared with IL-6-deficient T cells, cells deficient in IL-21 were markedly impaired in induction of IL-23R, RORγt, and IL-17 [40]. IL-21 therefore not only enhances T_H17 cell differentiation by inducing RORγt, but it is also important in helping T_H17 cells to attain a fully inflammatory phenotype by upregulating IL-23R [40]. Expression of IL-21 is not dependent on RORγt, as RORγt-deficient mice express normal levels of IL-21 [40], and IL-21 produced by differentiating T_H17 cells therefore likely acts in a positive feedback loop, amplifying the T_H17 response.

Although T_H17 cells were first described as a result of experiments that suggested IL-23 as an important directive signal for their induction [9], IL-23 was later shown to be unnecessary for generation of T_H17 cells from naïve CD4$^+$ T cells. In fact, the receptor for IL-23 (IL-23R) is expressed on activated or memory T cell populations but not on naïve T cells [41], indicating that IL-23 could not be involved in the initial generation of T_H17 cells. Nonetheless, IL-23 is actually essential for the full and sustained differentiation of inflammatory T_H17 cells. In the absence of IL-23, T_H17 cells demonstrated reduced production of inflammatory cytokines and increased secretion of the immunoregulatory cytokine IL-10, which correlated with an impaired ability to transfer EAE [42]. Thus, IL-23 is required for T_H17 cells to "mature" to their fully inflammatory potential. Besides IL-23, there are other pro-inflammatory mediating events that promote differentiation of T_H17 cells, including release of IL-1, which, like IL-21, can substitute for IL-6 in induction of T_H17 cells [43], and ligation of the tumor necrosis factor receptor family member DR3 by its cognate ligand, TNF family ligand 1A (TL1A, also known as TNFSF15) [44]. A related cytokine, IL-27, counters the effect of TGF-β + IL-6 on differentiating CD4$^+$ T cells, effectively blocking T_H17 differentiation via a mechanism dependent on STAT-1, by directly inhibiting expression of RORγt [45, 46]. IL-27 has anti-inflammatory properties, likely due to its ability to promote IL-10 production by T cells [47], and notably the inhibitory effects of IL-27 on expression of RORγt are specific to differentiating T_H17 cells rather than committed ones [48].

T_H17 cells and cytokine factors

The T_H17 lineage was originally defined by production of the cytokine interleukin-17 (IL-17A) [49], a member of a family of IL-17 cytokines. Additional studies have shown that T_H17 cells are also characterized by the production of IL-17F (another member of the IL-17 family) and an IL-10 family cytokine, IL-22 [9, 50]. Besides acting in concert with TGF-β to promote T_H17 differentiation, IL-21 is also produced by T_H17 cells themselves [37]. T_H17 cells can produce certain cytokines that are expressed by other T_H-cell lineages, including tumor necrosis factor-α (TNFα) and lymphotoxin-β, and the T_H17 subset can also be characterized by expression of chemokine receptor CCR6 and the CCR6 ligand, CCL20 [51].

The IL-17 cytokine family has six members, of which IL-17A and IL-17F, both produced by T_H17 cells, are the best characterized. IL-17A and IL-17F are closely related, with about 50% amino acid identity [9]. However, they appear to have non-redundant roles in inflammation, as mice deficient in IL-17A or IL-17F respond differently in terms of neutrophil recruitment in response to airway challenge, and in colitis models, despite the high homology between the two proteins [52]. In addition to the production of IL-17A and IL-17F homodimers, T_H17 cells can produce IL-17A/F heterodimers, which have biological activity in vitro and in airway neutrophil recruitment in vivo [53]. While IL-17A and IL-17F are clearly associated with inflammation, the precise roles of the different forms of secreted cytokines are yet to be elucidated.

Another cytokine preferentially produced by T_H17 cells is the IL-10 family member IL-22 [50], which is expressed both during primary polarization of naïve CD4$^+$ T cells towards the T_H17 lineage, as well as during restimulation of T_H17 cells, in an IL-23-dependent manner [50]. Although T_H17 cells have the capacity to secrete IL-22 together with IL-17, they do not necessarily all co-express

both cytokines. Expression of IL-22 by T_H17 cells has been shown to be dependent on the AhR transcriptional pathway linking T_H17 induction with environmental factors [25].

IL-22 receptor is not expressed on the surface of immune cells [54], so secreted IL-22 acts to regulate tissue inflammation via induction of signal transduction in non-immune cells. Notably, the downstream effects of IL-22 signaling can be anti-inflammatory, protective, or pro-inflammatory depending on the microenvironment. IL-22 can induce expression of acute phase reactant genes in a mouse model of hepatitis, conferring protection from acute inflammation [55], and the cytokine is also protective in a mouse model of ulcerative colitis [56]. Although IL-22 is induced in EAE, depletion of IL-22 does not affect disease progression [57], suggesting that this cytokine does not play a major role in the context of neuron-specific autoimmune inflammation. IL-22 also participates in epithelial barrier immunosurveillance. Two groups recently showed an important role for IL-22 in host defense against mucosal infections [58, 59]. In lung infections with *Klebsiella pneumoniae*, IL-23 was required for IL-22 expression from T cells, and although IL-22 and IL-17 both contributed to the production of cytokines and anti-microbial products from epithelial cells, IL-22 was ultimately more important than IL-17 for defense against the bacteria [58]. In an infection model of the intestinal mucosa, blocking IL-22 resulted in increased susceptibility to the enteric pathogen *Citrobacter rodentium* [59], supporting the notion that IL-22 is an important cytokine for bacterial defense at mucosal surfaces. IL-22 also participates in protection by inducing expression of β-defensins and anti-microbial proteins, including the Reg family of anti-microbial proteins (RegIIIβ and RegIIIγ), at epithelial barrier surfaces [59]. Although these studies have delineated a protective role for this cytokine, other studies have shown that skin inflammation in a mouse model of psoriasis is dependent on IL-22 [60], indicating that IL-22 also contributes to pathologic inflammatory processes. Thus, as noted, IL-22, either from T_H17 cells or otherwise, can have divergent effects depending on the situation. Two recent papers have identified a newly described population of $CD4^+$ T cells that express IL-22 in the absence of IL-17, and that are distinct from the T_H1, T_H2, and T_H17 subsets [61, 62]. These cells were, like T_H17 cells, also induced by AhR agonists, and, consistent with the known roles of IL-22 from T_H17 cells, seem to be important in maintenance of skin homeostasis and wound healing.

Another IL-10 family cytokine, IL-10 itself, is expressed by some but not all T_H17 cell subsets. IL-10 is an anti-inflammatory cytokine that helps to control T_H1- and T_H17-mediated inflammatory processes [42], and will be discussed more completely below.

Reciprocal relationship between T_H17 and T_{reg}

Polarization of naïve T cells towards the T_H17 lineage requires a combination of TCR stimulation as well as the cytokines TGF-β and IL-6. TGF-β is a cytokine produced by various cell types including T_{reg} cells and innate immune cells, with broad inhibitory effects on various elements of the immune system. TGF-β has been thought of primarily as an anti-inflammatory cytokine, partly because it induces the T_{reg}-specific transcription factor forkhead box P3 (FOXP3) and thus in vitro differentiation of FOXP3-expressing T_{reg} [63]. Thus, TGF-β can induce either anti-inflammatory T_{reg} or pro-inflammatory T_H17 cells, depending on the presence or absence of IL-6. The common requirement for TGF-β in generation of T_H17 and T_{reg} cells was established by Betelli et al. [31], who demonstrated the presence of a reciprocal relationship between the developmental pathways for generation of T_H17 effector cells and T_{reg} cells. This reciprocal relationship was further elucidated by Littman and colleagues, who showed that the T_H17-specific and T_{reg}-specific transcription factors, RORγt and FOXP3, respectively, are co-expressed in naïve $CD4^+$ T cells exposed to TGF-β, and that the balance between generation of T_H17 or T_{reg} cells depends on cytokine-induced interactions between these transcription factors [64]. IL-6, by tipping the balance from FOXP3 towards RORγt expression, acts as the "switch factor" controlling the preferential differentiation of T_H17 cells over T_{reg} [64]. Consistent with this concept is the observation that conditional deletion of FOXP3 in adult mice results in the increase of both IL-17 and RORγt expression [65]. TGF-β is actually required for expression of both FOXP3 and RORγt transcription factors [64], although the downstream signaling requirements after TGF-β receptor engagement are likely to differ in each case.

More recent work, also from the Littman group in collaboration with others, has demonstrated that TGF-β-induced FOXP3 inhibits T_H17 cell differentiation by directly antagonizing RORγt function, via a mechanism requiring both exon 2 of FOXP3, which binds directly to RORγt, and the FOXP3 Forkhead (FKH) domain, which mediates FOXP3 DNA-binding activity [64]. This work suggests that T cells that encounter TGF-β cytokine have the potential to develop into either the T_{reg} or the T_H17 lineage. In the absence of pro-inflammatory cytokines, FOXP3 inhibits the activity of RORγt, and cells do not differentiate into pro-inflammatory T_H17 cells. In the presence of pro-inflammatory cytokines, FOXP3 is repressed, and RORγt is concurrently stabilized or upregulated, allowing for differentiation of T_H17 cells [64]. The transcription factor Runx1, which is required both for differentiation of T_H17 cells as well as for FOXP3 function

[18, 66], also participates in the interplay between FOXP3 and RORγt. Binding of Runx1 and RORγt together to the *Il17a* locus leads to increased expression of IL-17, while FOXP3 can bind to both Runx1 and RORγt to inhibit activity [18]. Runx1, therefore, may be able to bind differentially to RORγt and FOXP3 to mediate activating or repressing activities depending on the cytokine environment.

Plasticity in T_H17 and T_{reg} development

It is clear that there are many connections in the development of T_H17 and T_{reg} cells, from the shared requirement of TGF-β to the reciprocal properties and interactions of RORγt and FOXP3. There are even some studies that have described populations of cells that express both transcription factors in vitro and in vivo [64, 67], although the function of these dual-expressors remains unclear. Contrastingly, T_H17 cells are thought to develop relatively independently from the factors that promote T_H1 and T_H2 differentiation [11]. However, a notable similarity in pathways does exist. T_H1 and T_H17 cells differ in their dependence on IL-12 family cytokines IL-12 and IL-23. During differentiation, T_H1 cells upregulate IL-12R and not IL-23R downstream of the T_H1-specific transcription factor T-bet to enhance responsiveness to IL-12 [68]. Meanwhile, developing T_H17 cells upregulate both IL-23R and IL-12R, enabling responsiveness to both IL-23 and IL-12 [69]. The upshot of this nonspecificity of T_H17 cells still needs to be elucidated, but this observation helps to explain a curious finding: cells that co-express both IFN-γ and IL-17, especially in inflammatory settings [69]. This raised the idea that $CD4^+$ T cells may not differentiate into rigidly defined T_H1, T_H2, T_H17, and T_{reg} categories as had originally been thought. Subsequently, the potential for reversibility of function in T_H cells was addressed experimentally, showing that so-called "master regulator" transcription factors such as T-bet exhibit a broad range of epigenetic states, allowing for activation and plasticity in already differentiated $CD4^+$ cells [70]. Furthermore, a recent study by Lexberg et al. reported that IL-17A-producing cells could be repolarized to either a T_H1 or a T_H2 phenotype in the presence of IL-12 or IL-4 [71]. However, IL-17^+ memory T cells retained T_H17 characteristics despite culture with IL-12 or IL-4, indicating that some T_H17 cells do maintain phenotypic stability [71]. Other studies have shown T_H17 cells to transition to an IFN-γ-producing population in in vivo models. Transfer of T_H17-polarized islet-reactive TCR transgenic T cells induced diabetes associated with the transition of the transferred T cells to T_H1-type cells, where islet injury was dependent on IFN-γ [72, 73]. Similarly, transfer of ex vivo polarized T_H17 cells into immunodeficient hosts induced colitis that was associated with a decrease in IL-17A and IL-17F production, and an induction of IFN-γ in the transferred T cells [69]. Along with T_H17 cells, T_{reg} cells also exhibit considerable plasticity of phenotype, especially in the context of inflammatory cytokine production. T_{reg} cells stimulated with IL-6 can downregulate FOXP3 and induce expression of IL-17, suggesting that mature T_{reg} cells can be subverted into the T_H17 differentiation programme [74]. This idea is corroborated by the finding that T_{reg} cells can be converted into IL-17-producing cells by DC activated with dectin-1 [75].

These studies illustrating the capability of T_H17 and T_{reg} cell subsets to undergo phenotype conversions are very compelling. Importantly, however, the finding of specific roles for both of these subsets in mediating immune tolerance, in host defense, and in autoimmunity indicate that while there may be some plasticity, T_H17 and T_{reg} as such are still necessary. It remains possible that these subsets are particularly adept at responding to changing environmental conditions in order to maintain appropriate immune control depending on the presence of microbes, signals from innate immune cells, and the cytokine microenvironment.

T_{reg} cells and controlling the immune response

Regulatory $CD4^+$ T cells, or T_{reg} cells, actively suppress the immune system, maintaining immune system homeostasis and tolerance to self-antigens, and thereby preventing pathological self-reactive inflammation and autoimmunity [76]. There has been interest in a so-called 'suppressor' population of T cells that limit inflammation and prevent autoimmunity for at least the last 30 years [77], but the modern field of regulatory T cell biology really began with the identification by Sakaguchi et al. [78] of a population of $CD4^+$ T cells constitutively expressing the interleukin 2 receptor-α (IL-2Rα) chain (CD25) that could prevent autoimmune disease via suppressor activity. These $CD4^+CD25^+$ T_{reg} cells thus became prime candidates for a T cell population mediating dominant tolerance to self. Other markers on T_{reg} cells were identified, including: CD5 and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), two negative regulators of TCR signaling and T cell activation; TNF receptor family member GITR; neuropilin-1 (Nrp-1), a neuronal guidance protein; and lymphocyte activation gene 3 [79–83]. However, the presence of these markers on some activated nonregulatory T cells precluded their use as functionally definitive molecules for the T_{reg} population. The need for a specific T_{reg} marker was fulfilled with the identification of the transcription factor FOXP3 [84, 85], a discovery that revolutionized the field and led to many subsequent studies that later

conclusively showed the essential role of FOXP3 in both the development and function of T_{reg} cells [86]. There are two types of T_{reg} cells: the naturally occurring T_{reg} cells that originate in the thymus from a dedicated lineage, and the 'induced' T_{reg} cells that differentiate de novo in secondary lymphoid tissues from naïve $CD4^+$ T cell precursors in the presence of TGF-β [63]. These 'induced' T_{reg} cells produce TGF-β, express FOXP3, and have suppressive activity indistinguishable from that of 'natural' T_{reg} cells [87].

Mechanisms by which T_{reg} cells mediate immune suppression are not fully resolved. Expression of IL-10 and TGF-β have been linked to suppression mediated by T_{reg} in in vivo experimental models [88, 89], although blockade of these cytokines does not abrogate suppressive ability in vitro [90]. T_{reg} cells can directly suppress activity via reverse signaling through crosslinking of B7 (CD80 and CD86) on APC or activated T cells with CTLA-4 [91]. The role of CTLA-4 in T_{reg} cells has been recently confirmed in a study where selective ablation of this marker resulted in spontaneous lymphoproliferation and fatal T cell-mediated autoimmune disease due to a loss of function in the T_{reg} cells, particularly in their ability to downregulate CD80 and CD86 on DC [92]. This suggested that T_{reg} may critically require CTLA-4 to suppress immune responses by modulating potency of APC. Other surface molecules on T_{reg} cells can also affect DC activity: recently, a novel Ig family member, TIGIT, which is expressed at high levels on T_{reg} cells, was shown to induce DC to produce immunosuppressive cytokines IL-10 and TGF-β when T_{reg} interacted physically with the DC [93]. Long-lasting physical T_{reg} cell interactions with DC do occur [94], and these interactions are facilitated by Nrp-1, as blockade of Nrp-1 interferes with T_{reg} cell-mediated suppression [95].

Several secreted proteins identified in gene expression studies, including granzyme B, IL-9, IL-10, and IL-35, have also been implicated in T_{reg} cell-mediated suppressor function. Expression of ectoenzymes CD73 and CD39 on the surface of T_{reg} cells can also contribute to immune suppression via a mechanism involving hydrolysis of ATP [96, 97]. Another mechanism by which T_{reg} cells may suppress inflammation is by "soaking up" T cell growth factors such as IL-2 [98].

As many of these suppression mechanisms seem to be at least somewhat redundant, the likelihood is that specific mechanisms of T_{reg} suppression activity may vary depending on the tissue and type of inflammation. For example, in an experimental skin transplantation model, T_{reg}-derived granzyme B and IL-9 contribute to tolerance and long-lived graft survival [99], while controlling inflammation in the colon seems to be largely independent of granzyme B, instead requiring IL-10 and IL-35 secretion by T_{reg} cells [100, 101].

T_H17 cells in autoimmunity

Findings over many years of study in the field of experimental autoimmunity pointed to IL-12 and T_H1 cells with specificity for self-antigens as autopathogenic and required for induction of organ-specific autoimmunity. However, the concept of autoimmunity as a T_H1-driven condition was challenged when it became clear that IFN-γ- and IFN-γ receptor-deficient mice, as well as mice lacking other molecules involved in T_H1 differentiation including IL-12p35, were not protected from EAE, but rather developed more severe disease [102, 103]. This suggested that another subset of T cells, distinct from the T_H1 lineage, might be required for induction of EAE and other organ-specific autoimmune diseases.

From a computational sequence screen looking for homologs of the IL-6 cytokine family, a novel cytokine chain, termed p19, was discovered and found to form heterodimers with the p40 chain of IL-12 [104]. The cytokine formed by this heterodimeric pairing was called IL-23. Early experiments on p19 where the cytokine subunit was transgenically expressed in mice showed that expression of p19 resulted in widespread multiorgan inflammation and early death [105]. Because of the participation of the IL-12p40 chain in IL-23, the specificity to IL-12 of many of the experiments that had been performed using polyclonal antibodies to block IL-12 were called into question, as any approaches that targeted IL-12p40 would also have affected IL-23. The studies that needed to be re-examined included ones pointing to the importance of IL-12 in the development of EAE and collagen-induced arthritis (CIA), essentially implicating IL-12 and T_H1 cells as being critical for organ-specific autoimmune pathology [106]. In a set of seminal experiments to settle this problem, Cua and colleagues created IL-23p19 knockout mice and compared them with mice deficient in IL-12p35. In this way, they demonstrated that IL-23 and not IL-12 was crucial for the development of EAE [107]. Furthermore, IL-23 expanded an IL-17-producing T_H cell population that was effective at induction of EAE when adoptively transferred into naïve mice, and these IL-17-producing T cells were reduced in the central nervous system of IL-23-p19-deficient mice [9].

Since these initial studies, the importance of T_H17 cells in the pathogenesis of organ-specific autoimmune inflammation has now been well established, and demonstrated in many different animal models. IL-17 is directly involved in cartilage and bone erosion as observed in an experimental model of autoimmune arthritis [108], and blocking IL-17A prior to disease onset attenuates antigen-induced arthritis in mice [109]. Consistent with these findings, IL-17A-deficient mice develop reduced CIA [110], as well as developing EAE with delayed onset and reduced severity

[111]. IL-17 has also been demonstrated to participate in regulation of germinal center formation as well as autoantibody production in autoimmune mice [112]. Consistent with these studies, the loss of a proximal regulator of IL-17, IL-23, is protective in autoimmune arthritis in mouse models, while loss of IL-12 correlates with increased severity of disease as well as increased numbers of IL-17-expressing lymphocytes [8].

Reports describing the presence of T_H17 cells in various human autoimmune conditions have also been compelling, and they help to validate mouse studies indicating the importance of the IL-23-IL-17 axis in autoimmune disorders. IL-17A is upregulated in central nervous system lesions of patients with multiple sclerosis (MS) [113]. Also, IL-17-expressing perivascular lymphocytes have been described in brain lesions of patients with active MS, while these IL-17^+ cells were reduced in patients with quiescent MS [114]. IL-17 has also been observed in psoriatic skin lesions [115], and has been shown to induce intracellular adhesion molecule-1 (ICAM-1), IL-6, and IL-8 in human keratinocytes [115]. More recent studies have shown that IL-17-expressing cells in human psoriatic skin are in fact T_H17 cells, and that these cells express IL-17A and IL-17F, IL-23R, and CCL20 as well as the T_H17 transcription factor, RORγt [16]. Transcripts of IL-1β, an important factor for human T_H17 differentiation, were also observed to be upregulated in psoriatic skin [16].

T_H17 cells are also associated with chronic inflammatory diseases. Patients with the inflammatory bowel diseases, ulcerative colitis and Crohn's disease, have elevated IL-17 mRNA in the colonic mucosa as compared to corresponding samples from either normal controls or patients with infectious or ischemic colitis [116]. IL-17-producing cells in gut mucosa of humans with Crohn's disease have been observed. Along with IL-17, these cells also produce IFN-γ and express IL-23R and CCR6 [117]. IL-17 is also implicated in mouse models of inflammatory bowel disease. Blocking IL-23 is sufficient to prevent onset of colitis in IL-10-deficient mice, by a mechanism involving inhibition of IL-17. Also, in a TNBS-induced colitis model, an animal model of inflammatory bowel disease employing the use of 2,4,6-trinitrobenzenesulfonic acid (TNBS) which, when administered intrarectally to SJL/J mice, induces colonic inflammation in these mice that resembles features of human Crohn's disease, IL-17R-deficient mice show reduced emigration of polymorphonuclear cells into the colon and reduced severity of disease [118].

Overall, the IL-17 pathway plays an essential pathological role in many autoimmune diseases. Phase II studies for the efficacy and safety of a monoclonal anti-IL-17 antibody, AIN457, are presently underway for Crohn's disease and psoriasis patients that are refractory to current therapies [144]. The results of these trials will likely advance our understanding of the contributions of IL-17 and the IL-17 pathway to these diseases. Specifically, it will be important to elucidate whether anti-IL-17 antibody therapies will have increased benefits as compared to or combined with anti-TNF and anti-IL-23 therapies, especially given the cooperative nature and related aspects of these pathways.

T_H17 cells in host defense

The first studies demonstrating a role for IL-17 in host defense against microbial pathogens were performed by Kolls and colleagues comparing susceptibility of IL-17 receptor (IL-17R)-deficient and control mice to infection with experimental *Klebsiella pneumoniae* pulmonary infection. After intranasal infection, IL-17R-deficient mice had increased numbers of bacteria in the lung, increased dissemination of bacteria into the spleen, and reduced overall survival [119]. This enhanced susceptibility was associated with delayed neutrophil recruitment and defective granulocyte colony stimulating factor (G-CSF) and CXCL-1 expression in the lung in response to the infection [119, 120]. Treatment with exogenous G-CSF does not restore neutrophil recruitment to the pulmonary compartment. This is likely due to the fact that IL-17R-deficient mice, as well as mice treated with IL-17 blocking antibodies, are defective in production of CXC chemokines [120, 121]. IL-23 plays an important role in amplifying the IL-17 response in protection against this pathogen. Similar to IL-17R-deficient mice, IL-23p19-deficient mice are highly susceptible to infection with *K. pneumoniae* and, importantly, do not show the characteristic upregulation of IL-17 in response to infection seen in resistant control mice [122]. Furthermore, IL-23p19-deficient mice treated with recombinant IL-17 show reduced bacterial burdens and restored chemokine responses [122]. IL-17A-deficient mice are also susceptible to *K. pneumoniae* infection and show reduced G-CSF and CXC chemokines in the lung following infection [58]. Taken together, these studies demonstrate that IL-23p19 and IL-17 together play an important role in recruitment of neutrophils and other inflammatory cells to provide protective immunity from *K. pneumoniae* infection.

Since these initial studies, important roles for IL-23 and IL-17 in host defense against many other pathogens have been established. IL-17 released by $CD4^+$ T cells plays a critical role in the orchestration of the formation of intra-abdominal abscesses and neutrophil recruitment in in vivo responses to infection with the gram-negative bacteria *Bacteroides fragilis* [13]. IL-17R-deficient mice are also highly susceptible to parasitic infection with

Toxoplasmosis gondii [123], as well as fungal infection with *Candida albicans* [124]. IL-17-expressing $CD4^+$ T cells have been shown to be actively induced in response to infection with the mouse enteric pathogen *Citrobacter rodentium* [32], and early phase defense against this pathogen requires IL-22 as well as IL-23, both T_H17-related cytokines [59]. T_H17 cytokines also seem to be important in immune responses to infection with *Mycoplasma*: neutralization of IL-23p19 before *Mycoplasma pneumoniae* infection impairs IL-17 expression but also impairs effective bacterial clearance [125].

Although IL-17 is generally thought to be more salient for host defense against extracellular rather than intracellular bacterial pathogens, there is some evidence that IL-17 can also enhance responses to intracellular micro-organisms. In these cases, however, T_H17 cells do not seem to be necessary; rather, IL-17 derived from non-$CD4^+$ T cell sources (such as gammadelta- ($\gamma\delta$-) T cells) is playing an important role. For example, although IL-17-deficient mice survive sublethal infections with *Salmonella enterica* equally as well as control mice, there are consistently higher bacterial burdens in the spleen and liver of mice lacking IL-17 [126]. Similarly, increased bacterial burdens and defects in formation of organized granulomas are found in IL-17-deficient mice infected with *Listeria monocytogenes* [127].

It is not yet clear what elements of these infections elicit specifically a T_H17 versus a T_H1 or other immune response in vivo. One thing that many of these pathogens have in common is that infection can result in induction of host cell apoptosis. Some pathogens induce apoptosis in infected or neighboring host cells directly, such as *B. fragilis* [128] and *C. rodentium* [129], whereas infection with others, like *C. albicans*, can cause host cells to initiate apoptosis intrinsically [130]. Similarly, upon infection with *L. monocytogenes*, macrophages activate caspase-1 and undergo apoptotic or pyroptotic cell death as a mechanism of defense against the infection [131]. Be that as it may, these studies overall suggest that IL-17 and IL-23 expressed by $CD4^+$ T cells are critical for generation of effective, appropriate host immune responses to infection, particularly infections with extracellular and/or gram-negative bacteria.

Self-regulation of T_H17 cell pathology

Regulation of robust T cell responses is necessary for preventing host tissue damage and bystander pathology during clearance of infectious pathogens. Unregulated T cell activity can lead to autoimmunity in various ways. The immunoregulatory cytokine IL-10 has long been thought of as important for regulation of T_H1 responses, but only more recently has it been described to be produced by T_H1 cells themselves, along with their typical production of IFN-γ, as a self-regulatory mechanism [132]. A similar process has been described for T_H17 cells. When T_H17 cells are generated in the presence of TGF-β + IL-6, the resultant population includes a subset of cells that produce IL-10 along with IL-17 [42]. Continued exposure of T_H17 cells to TGF-β and IL-6 results in increased production of regulatory IL-10 cytokine, while restimulation of T_H17 cells generated in this manner with IL-23 results in an overall gain of pathogenic function by promoting T_H17 cells that do not co-produce IL-10 [42]. IL-23 does not specifically maintain IL-10 production induced by TGF-β + IL-6 but does not directly inhibit its expression. These $IL\text{-}17^+IL\text{-}10^+$ co-producing cells are not thought of as a separate subset; rather, the production of IL-10 by T_H17 cells is considered to be a mechanism of self-regulation to limit an otherwise potentially dangerous T_H17 immune response. T_H17 cells have also been associated with tissue repair functions through their production of the cytokine IL-22 along with IL-10 [133]. The protective roles of IL-22 in infections [59], as well as acute and chronic inflammatory conditions [55, 134], are associated with its functions in maintaining the integrity of epithelial barriers.

Stimuli that promote T_H17 cell-inducing dendritic cells

Several studies have been performed delineating the microbial factors and pathways that stimulate the T_H17 cell-inducing phenotype in DC. As noted above, IL-17 is important in the control or clearance of various pathogens [12]. These include the extracellular bacteria *K. pneumoniae* [119] and *C. rodentium* [32], as well as systemic infection with the fungal pathogen *C. albicans* [124].

Several adjuvants including bacterial lipopolysaccharide (LPS) and bacterial CpG DNA products promote synthesis of some T_H17-promoting cytokines, such as IL-23 and IL-6 by DC, but these also strongly induce IL-12 and therefore promote T_H1 cell responses preferentially over IL-17-expressing cells. However, the *Saccharomyces cerevisiae* cell wall component, zymosan, promotes strong T_H17 cell responses in murine cell cultures and in vivo [135]. β-glucan components in zymosan signal through TLR-independent pathways to promote induction of T_H17 cells [136]. Fungal β-glucans, including curdlan, bind to dectin-1, a C-type lectin on DC, and trigger IL-23 production. Dectin-1-activated DC also synthesize pro-inflammatory cytokines such as IL-6 and TNFα and upregulate co-stimulatory molecules. These dectin-1-activated DC can preferentially induce T_H17 over T_H1 cell responses, but only when in the presence of TGF-β-producing T_{reg} cells or exogenous TGF-β [136]. *Mycobacterium tuberculosis*, a

key component in complete freund's adjuvant (CFA), can promote T_H17 responses in murine cell culture and in vivo. CFA is a widely used adjuvant for murine immunization protocols, and while it was long thought to initiate T_H1 responses, it is now clear that CFA can also induce T_H17 responses. This is likely due to the ability of CFA to induce not only IL-6 and IL-23 but also TGF-β, allowing for differentiation of naïve $CD4^+$ T cells into T_H17 without the addition of exogenous TGF-β, as is required for LPS-activated APC-induced T_H17 cells [30]. Although APC activated with LPS can induce T_H17 in the presence of TGF-β, those activated with TLR3 ligand poly(I:C) preferentially produce IL-12 and IL-27 over IL-6 and TGF-β [137], thereby specifically blocking T_H17 differentiation via inhibition of RORγt.

Signaling innate immune cells to drive T_H17 differentiation

A question remained as to the nature of a specific, physiological innate immune stimulus that could elicit both TGF-β and IL-6 together from APC in order to promote T_H17 differentiation. This was a confounding problem because of the seemingly disparate actions of the two cytokines. TGF-β is an important tolerogenic cytokine. It has been known for some time that phagocytosis of apoptotic cells by macrophages induces synthesis of TGF-β [138, 139], presumably in order to maintain a state of tolerance towards self-antigens present in dead and dying cells that are cleared by phagocytes. Contrastingly, IL-6 is a prototypical pro-inflammatory cytokine synthesized by APC as a direct result of TLR activation by microbial structures [140–142].

We hypothesized that DC recognition of apoptotic cells dying as a result of infection might induce not only pathways necessary for synthesis of TGF-β, but would also, because of the presence of TLR ligands from the infection, promote synthesis of IL-6. When we investigated our hypothesis, we found that this was in fact the case, and that the TGF-β and IL-6 from DC that recognized apoptotic cells carrying TLR ligands were able to drive differentiation of naïve $CD4^+$ T cells to the T_H17 lineage [143]. Furthermore, phagocytosis of apoptotic cells in the absence of TLR ligands induced TGF-β alone, causing DC to direct naïve $CD4^+$ T cells towards the reciprocal T_{reg} lineage [143]. In other words, the presence or absence of TLR ligands in apoptotic cells dictates whether DC that phagocytose those cells instruct generation of T_H17 or T_{reg} cells (Fig. 2).

Using *C. rodentium* as a model of infection that has been shown to induce T_H17 immunity [32], we also found that *C. rodentium* induction of host cell apoptosis was necessary to induce this response. Thus, phagocytosis of apoptotic

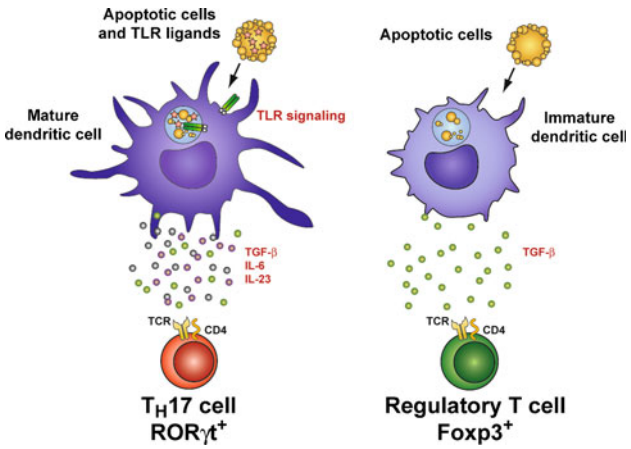

Fig. 2 Innate immune recognition of infected apoptotic cells instructs T_H17 cell differentiation. When dendritic cells phagocytose apoptotic cells carrying TLR ligands, pathogen associated molecular patterns (PAMPs) associated with the infection engage Toll-like receptors, allowing for DC maturation and production of pro-inflammatory cytokines such as IL-6 and IL-23. The apoptotic cell element of the phagocytic cargo induces DC synthesis of the immunoregulatory cytokine TGF-β through recognition of apoptotic cell-specific molecules such as phosphatidyl serine (not shown in figure). Thus, phagocytosis of apoptotic cells by DC during an infection by DC preferentially induces differentiation of naïve $CD4^+$ T cells into T_H17 cells. When DC phagocytose apoptotic cells in the absence of infection or TLR ligands, they synthesize TGF-β without pro-inflammatory cytokines, thereby promoting differentiation of tolerogenic $FOXP3^+$ T_{reg} cells

cells contributes signals which, in combination with TLR engagement, induce tailored immunity to bacterial infection through development of T_H17 cells. Many pathogens that are potent inducers of host cell apoptosis have been implicated as requiring T_H17 immunity for host defense as discussed above, including not only *C. rodentium* but also *B. fragilis*, *C. albicans*, and *L. monocytogenes*. T_H17 cells are also associated with tissue repair processes besides inflammatory IL-17 production [59, 133], and thus may be uniquely suited to aid in host response against pathogens that cause significant apoptosis and tissue damage.

Conclusions

Over the last few years since its identification as a distinct lineage of T helper cells, the T_H17 subset has been implicated in many immune processes. Much progress has been made in understanding the kinds of immunity mediated by IL-17 and T_H17 cells, as well as the mechanisms behind cell differentiation to the subset. T_H17 responses are induced by specific pathogens, and effective T_H17 responses as well as T_H17-related cytokines are necessary for clearance of many infections. Naïve $CD4^+$ T cells need signals from the innate immune system to differentiate into T_H17 as well as T_H1 and T_H2 cells, but it was

surprising that T_H17 lineage commitment required a combination of pro-inflammatory and anti-inflammatory cytokines for differentiation to occur. The role of TGF-β in the differentiation of both induced T_{reg} cells as well as T_H17 cells, along with the documented interactions between RORγt and FoxP3 that influence the two subsets, suggest a system that balances inflammation with tolerance. The finding that apoptotic cells dying during infection can provide the stimulus to innate immune cells to synthesize TGF-β and IL-6 and drive differentiation of T_H17 cells supports this notion, further indicating that T_H17 cells have a singular role in providing specific, tailored immunity to bacterial infection.

Many questions remain regarding the T_H17 subset and its roles in vivo. T_H17 cytokines can have varied effects depending on location and context, and T_H17 responses clearly play key roles not only in the defense against certain pathogens but also in driving inflammation and autoimmunity. The link of apoptotic cells dying during infection with T_H17 differentiation can provide a new direction when considering how to minimize T_H17-driven immunopathology while retaining important host defense and tissue repair functions of the subset.

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