The IL-23–IL-17 immune axis: from mechanisms to therapeutic testing

Sarah L. Gaffen[1], Renu Jain[2], Abhishek V. Garg[1] and Daniel J. Cua[2]

Abstract | Following the discovery of T helper 17 (T_H17) cells, the past decade has witnessed a major revision of the T_H subset paradigm and substantial progress has been made in deciphering the molecular mechanisms of T cell lineage commitment and function. In this Review, we focus on the recent advances that have been made regarding the transcriptional control of T_H17 cell plasticity and stability, as well as the effector functions of T_H17 cells, and we highlight the mechanisms of IL-17 signalling in mesenchymal and barrier epithelial tissues. We also discuss the emerging clinical data showing that IL-17-specific and IL-23-specific antibody treatments are remarkably effective for treating many immune-mediated inflammatory diseases.

Crohn's disease
A type of inflammatory bowel disease that affects any part of the gastrointestinal tract from the mouth to the anus. Symptoms include abdominal pain, bloody diarrhoea, fever and weight loss. Other complications may occur outside the gastrointestinal tract and include anaemia, skin rashes, arthritis, inflammation of the eye and an increased risk of bowel cancer.

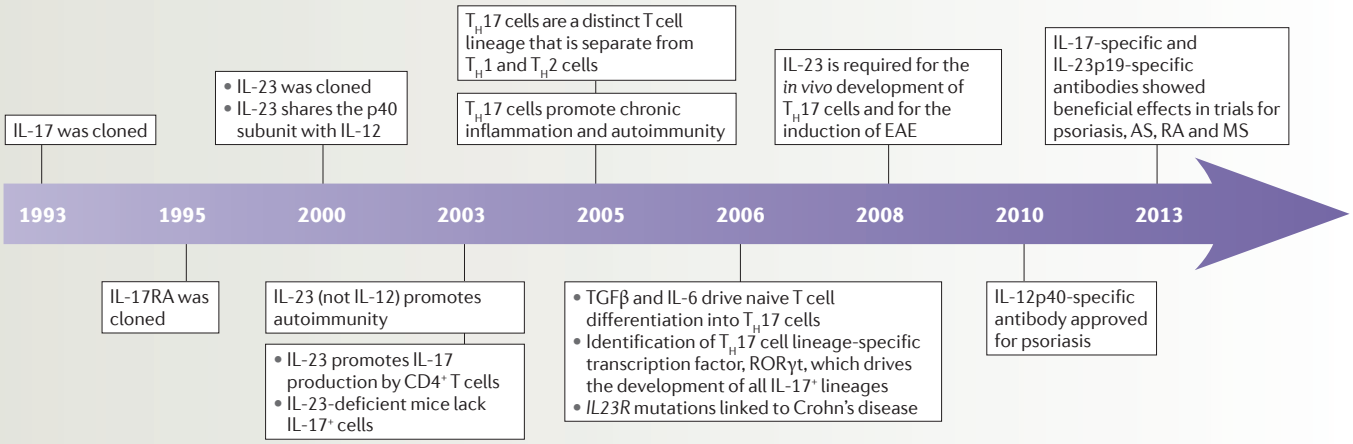
[1]Division of Rheumatology and Clinical Immunology, S702 BST, 3500 Terrace Street, Pittsburgh, Pennsylvania 15261, USA.
[2]Merck Research Laboratories, Palo Alto, 901 California Avenue, Palo Alto, California 94304, USA.
Correspondence to D.J.C.
e-mail: daniel.cua@merck.com
doi:10.1038/nri3707

The discovery of interleukin-23 (IL-23) and the elucidation of the biology governed by this cytokine has led to important new insights within immunology[1–3]. IL-23 has crucial roles in the pathogenesis of autoimmunity as it induces a cell population with a unique inflammatory gene signature that includes *Il17a* (which encodes IL-17A), *Il17f*, *Il6*, *Csf2* (which encodes colony-stimulating factor 2; also known as GM-CSF), *Tnf* (which encodes tumour necrosis factor (TNF)), *Ccl20* (which encodes CC-chemokine ligand 20 (CCL20)), *Ccl22*, *Il1r1* (which encodes IL-1 receptor type 1 (IL-1R1)), and *Il23r* (which encodes IL-23 receptor (IL-23R))[4,5]. On the basis of this distinct gene expression profile and unique Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway, a novel subset of T helper (T_H) cells was discovered and designated '$Th_{IL\text{-}17}$' or 'T_H17' (REFS 4,6,7). The discovery of the IL-23–T_H17 pathway has led to fundamental changes in our understanding of cellular immunity (FIG. 1 (TIMELINE)). In 1989, Mossman and Coffman proposed to divide $CD4^+$ T_H cells into interferon-γ (IFNγ)-producing T_H1 cells (which are dependent on STAT1) and IL-4-producing T_H2 cells (which are dependent on STAT6) to explain the tendency of T cells to diverge into mediators of either a cellular or humoral immune response, respectively[8,9]. At that time, it was predicted that additional $CD4^+$ T cell subsets may exist that drive the full spectrum of immune responses. Indeed, the T_H1–T_H2 hypothesis does not adequately explain the regulation of STAT3-dependent $CD4^+$ T cells during autoimmunity and infection[3]. In 2003, the recognition that IL-23 is indispensable for promoting autoimmunity led to a re-evaluation of the established paradigm[1,3,4,10,11].

In addition to T_H17 cells, many innate immune cells respond to IL-23 and are also important in both resistance to infection and in mediating autoimmune pathology. These cells are characterized by expression of the transcription factor retinoic acid receptor-related orphan receptor-γt (RORγt; which is encoded by *Rorc*)[12] and include subsets of γδ T cells, natural killer T (NKT) cells, 'natural' T_H17 cells and innate lymphoid cells (ILCs) — collectively, these subsets are termed 'type 17' cells[13–17] (BOX 1). These innate immune cells are located in non-lymphoid tissues where they are poised to respond immediately to tissue injury or pathogenic insults. Stimulation of T_H17 cells and type 17 cells with IL-1β and IL-23 induces local tissue inflammation, which is mainly mediated by type 17 signature cytokines such as IL-17, IL-22 and GM-CSF[4,18–20].

The exploration of type 17 immunity has led to the identification of previously unrecognized immune cell subsets and to the development of new paradigms stating that disease localization is dependent on the distribution of cell populations that express IL-23R and RORγt. These concepts are at the core of novel therapeutic strategies that aim to neutralize IL-17 or IL-23, which have shown encouraging results for the treatment of psoriasis, multiple sclerosis, Crohn's disease and ankylosing spondylitis. In this Review, we highlight the roles of cytokines that promote the development and stabilization of T_H17 cells via complex transcriptional networks. We discuss how the IL-17 signalling pathway is unique compared with that of other cytokine receptor families and we highlight recent studies that reveal the mechanisms by which IL-17 signalling is

Figure 1 | **Timeline of the discovery and elucidation of IL-17 and IL-23 biology**



AS, ankylosing spondylitis; EAE, experimental autoimmune encephalomyelitis; IL, interleukin; IL-12p40, p40 subunit of IL-12 and IL-23 (also known as IL-12β); IL-17RA, IL-17 receptor A; IL-23p19, p19 subunit of IL-23 (also known as IL-23A); *IL23R*, IL-23 receptor; MS, multiple sclerosis; RA, rheumatoid arthritis; RORγt, retinoic acid receptor-related orphan receptor-γt; TGFβ, transforming growth factor-β; T_H, T helper.

regulated. Finally, we discuss disease settings in which IL-17-specific and IL-23-specific therapeutic agents have worked as predicted, and where they have shown unexpected effects.

Cytokines that promote T_H17 cell development

RORγt$^+$ T_H17 cells can be broadly divided into two groups: first, host protective cells that express both IL-17 and IL-10 (REFS 21–23) and, second, a highly inflammatory population that expresses IL-17, IL-22, IFNγ and GM-CSF[4,18]. The ultimate outcome of T_H17 cell activity is determined by the balance of these effector functions. T_H17 cells activated by transforming growth factor-β (TGFβ) and IL-6 promote mucosal defence and barrier tissue integrity, and curtail immunopathogenic responses[21–23], whereas IL-23-activated T_H17 cells promote chronic tissue inflammation during infection, granuloma formation and autoimmunity[24–26].

Initiating cytokines. Studies in 2003 and 2005 showed that IL-23 promotes the development and expansion of a pathogenic T cell population that has a unique inflammatory gene signature[1,4,6,7]. However, IL-23 alone cannot drive the differentiation of T_H17 cells from naive CD4$^+$ T cell precursors[4,27], indicating that additional factors are required for their lineage fate determination. Shortly thereafter, the laboratories of Stockinger, Weaver and Kuchroo simultaneously showed that the addition of TGFβ and IL-6 during initial T cell recognition of cognate antigen promotes T_H17 cell differentation[27–29]. IL-6 has an essential role in this process by activating STAT3 (REF. 30), which directly drives the transcription of T_H17 lineage-specific genes, including *Rorc*, *Il17* and *Il23r*[31]. STAT3 also suppresses TGFβ-induced forkhead box P3 (FOXP3) expression, and thereby inhibits the generation of regulatory T (T_{Reg}) cells[27]. Consequently, *Il6*$^{-/-}$ mice are unable to generate T_H17 cells and they are protected from developing experimental autoimmune encephalomyelitis (EAE)[32] and collagen-induced arthritis (CIA)[33]. Although IL-6 was identified as a therapeutic target long before the discovery of T_H17 cells, recent advances have validated IL-6 as a target for the treatment of rheumatoid arthritis and other inflammatory conditions. Whereas IL-6 and TGFβ regulate the initial lineage specification of T_H17 cells, IL-21 is an important autocrine growth factor. IL-21 is produced by a number of NK cell and T cell subsets, and is a homologue of IL-2, IL-4, IL-7, IL-9 and IL-15 that signals via a receptor complex composed of a unique IL-21R chain and the shared common γ-chain (also known as γc and IL-2Rγ). It is interesting that this JAK–STAT activating cytokine can replace IL-2 as an autocrine growth factor for the expansion of T_H17 cells[34–36].

IL-1β signalling also has a crucial role during the initial stages of T_H17 cell differentiation. *Il1r1*$^{-/-}$ mice fail to develop antigen-specific T_H17 cells and are resistant to EAE[37]. The expression of IL-1R1 by T_H17 cells is induced by IL-6, and signalling through the IL-1R promotes the transcription factor interferon-regulatory factor 4 (IRF4), which reinforces the expression of RORγt[38]. Mechanistically, IL-1β induces phosphorylation of mammalian target of rapamycin (mTOR) and thereby enhances the metabolic fitness of rapidly dividing T_H17 cells during inflammation. Indeed, rapamycin treatment or mTOR deficiency completely abolishes IL-1β-induced T_H17 cell proliferation[39]. These results suggest that IL-6 directs the differentiation of T_H17 cells, whereas IL-1β enhances the expansion of these cells when they are in competition with other T cell subsets in the context of a resource-limited tissue environment.

In contrast to IL-1β and IL-6, the role of TGFβ in T_H17 cell differentiation is more complex. Genetic approaches such as the expression of a dominant-negative TGFβ receptor II (which inhibits the formation of a functional TGFβ signalling complex) and a T cell-specific deletion of the gene encoding TGFβ have confirmed that endogenous TGFβ induces T_H17 cell development *in vivo*[40–42]. However, deletion of the gene encoding TGFβ also led to the excessive production of

Box 1 | **Type 17 immune cells**

Type 17 cells ubiquitously express retinoic acid receptor-related orphan receptor-γt (RORγt) and interleukin-23 receptor (IL-23R), and they develop in the thymus, with the exception of group 3 innate lymphoid cells (ILCs), which develop in the bone marrow. Adaptive $CD4^+$ IL-17-producing cells require IL-6 signalling during initial activation of the T cell receptor (TCR), whereas all other subsets respond to IL-1β and IL-23 signalling upon emigration from the thymus and do not require IL-6. These 'innate' immune cells are poised to produce IL-17 upon sensing inflammatory cytokines, as well as in response to stress and injury signals. Whereas the adaptive T_H17 cells primarily reside in secondary lymphoid organs, the innate type 17 cells are situated in a broad range of peripheral tissues where they directly survey the interface between the host and the environment.

Cell type	TCR usage	Developmental timing of RORγt and IL-23R expression	Requirements for IL-17 expression	Primary tissue location (in the steady state)	Refs
Adaptive T_H17 cells	Diverse TCR	Expression induced during thymic development from adolescence to adulthood	Antigen-specific TCR activation in the presence of IL-6, TGFβ, IL-1 and IL-23	Lymphoid organs	12
Natural T_H17 cells	• Diverse TCR • Self-reactivity?	Expression induced during thymic development from adolescence to adulthood	IL-1 and IL-23	Skin and mucosal tissues	17
IL-17-producing γδ T cells	Invariant TCR (Vγ6, Vγ4 or Vγ1)	Expression induced during fetal and neonatal thymic development	Dectins, TLRs, IL-1 and IL-23	Mucosal and peripheral tissues	13
	Variable TCR	Expression induced during thymic development from adolescence to adulthood	TCR, IL-1 and IL-23	Lymphoid organs	177
iNKT cells	Oligoclonal	Expression induced during thymic development from adolescence to adulthood	CD1 and glycolipids	Liver	178
Group 3 ILCs	None	Expressed throughout life	Dectins, TLRs, IL-1 and IL-23	Gut and skin	151, 179

iNKT cell, invariant natural killer cell; TCR, T cell receptor; TGFβ, transforming growth factor-β; TLR, Toll-like receptor.

IFNγ and IL-4, which inhibited T_H17 cell development and population expansion[40,41]. Thus, TGFβ can either function as a direct T_H17 cell-inducing factor or could indirectly suppress alternative cell fates. Notably, in the absence of TGFβ, IL-6 alone can promote the development of T_H17 cells from T cells that lack the transcription factors T-bet (which is encoded by *Tbx21*) and STAT6 (REF. 43), which suggests that TGFβ suppresses T_H17 cell differentiation indirectly by repressing T-bet and GATA-binding protein 3 (GATA3). This complexity is further highlighted by human studies, as three separate research groups have shown that TGFβ is required for *in vitro* T_H17 cell development, whereas two other groups found that a cocktail of IL-1β, IL-6 and IL-23 is sufficient to drive T_H17 cell differentiation[44–48]. These discrepancies could be owing to the different sources of the human T cells that were used in these studies (for example, peripheral blood versus umbilical cord blood), which may influence their developmental status and, hence, the requirement for TGFβ. However, under *in vivo* inflammatory conditions, the presence of TGFβ is probably necessary for optimal T_H17 cell differentiation.

Although the combination of TGFβ and IL-6 efficiently generates T_H17 cells *in vitro*, the cells generated by this cocktail are only weakly pathogenic and subsequent exposure to IL-23 is essential to drive pathogenicity[21,49–53]. A recent study has further supported the notion that TGFβ is not always required for *in vitro* T_H17 cell differentiation, as T_H17 cells could be generated in response to IL-1β, IL-6 and IL-23 in a TGFβ-independent manner[53]. Interestingly, these TGFβ-independent IL-23R$^+$RORγt$^+$ T_H17 cells are also T-bet$^+$, and they co-express IFNγ and GM-CSF[4,19,20,53]. Such 'hybrid' T cells with diverse functional plasticity (see below) are frequently detected in lesions from patients with multiple sclerosis and mice with EAE[54,55].

The studies mentioned above specifically examined TGFβ1. In a recent report, it was proposed that TGFβ3 promotes the development of pathogenic T_H17 cells by upregulating IL-23R expression[56]. Interestingly, TGFβ3 was induced by IL-23 and acted in a feedforward loop to enhance IL-23R expression, thereby amplifying IL-23 signalling[56]. Taken together, these studies indicate that isoforms of TGFβ, together with IL-6, can drive the development of IL-17- and IL-10-producing cells that are important for mucosal defence; however, subsequent exposure to IL-23 is required for the development of pathogenic T_H17 cells.

Differentiating and stabilizing cytokines. TGFβ- and IL-6-driven T_H17 cells have limited inherent pathogenicity, and exposure to IL-23 is essential for the maturation of inflammatory T_H17 cells[1,4]. This is supported by genetic studies that link *IL23R* polymorphisms with susceptibility to autoimmune diseases such as psoriasis, psoriatic arthritis, ankylosing spondylitis, multiple

sclerosis and Crohn's disease[57–61]. Accumulating data clearly indicate that IL-23 promotes the pathogenicity of mature T_H17 cells by several mechanisms, including through the maintenance of T_H17 signature gene expression (*Rorc* and *Il17*); the induction of effector genes (*Il22, Csf2* and *Ifng*); the downregulation of repressive factors (*Il2*, *Il27* and *Il12*); and the amplification of its own signalling by upregulating *Il23r* expression.

By using an approach that restricts IL-23R deficiency to T cells, we have shown that in the absence of IL-23 signalling, T_H17 cells are arrested at an early activation stage and are unable to mediate encephalitogenicity in EAE[51]. Subsequent studies have revealed that IL-23R is needed for co-expression of GM-CSF, as GM-CSF-deficient mice are resistant to EAE and GM-CSF-deficient T_H17 cells cannot transfer EAE to naive recipients[19,20]. IL-23 also induces IFNγ expression in T_H17 cells, and the pathogenicity of $IFN\gamma^+IL\text{-}17^+$ cells was demonstrated by the transfer of an $IL\text{-}23R^+$ memory-activated T cell population (co-expressing T-bet, IFNγ, RORγt and IL-17) that promoted severe EAE[52,55,62]. To gain inflammatory function, T_H17 cells must overcome the effects of inhibitory cytokines such as IL-27 and IL-2 (REFS 63,64). Indeed, committed $IL\text{-}23R^+$ T_H17 cells are highly resistant to IL-27- and IL-2-mediated suppression[65]. This phenomenon could be owing to the downregulation of IL-27R in mature T_H17 cells[63,65]. Pathogenic T_H17 cells induced by IL-23 in the absence of TGFβ also express reduced levels of aryl hydrocarbon receptor (AHR), C-MAF (also known as MAF) and IL-10 compared with TGFβ-driven T_H17 cells[56,62]. AHR and C-MAF are induced under TGFβ- and IL-6-driven T_H17 differentiation conditions, and they transactivate *Il10* expression[66–68]. However, it is unclear whether IL-23 directly suppresses these factors to drive pathogenicity. The upregulation of IL-23R expression is important for IL-23 to drive the differentiation and stabilization of pathogenic T_H17 cells, which depends on STAT3 (REFS 10,62). Taken together, these studies establish that TGFβ, IL-6 and IL-1β are essential elements that initiate T_H17 cell development, whereas IL-23 serves as a pivotal factor that drives both the differentiation and inflammatory functions of pathogenic T_H17 cells.

Transcriptional control of T_H17 cells

The knowledge of transcriptional control of T_H17 differentiation is mainly based on studies of non-pathogenic T_H17 cells. $CD4^+$ T_H cell populations are considered as unique lineages on the basis of their characteristic expression of transcriptional regulators and signature cytokines. RORγt serves as the master regulator for T_H17 cells, and $Rorc^{-/-}$ mice lack T_H17 cells and exhibit reduced autoimmune disease severity[12]. By contrast, enhanced expression of RORγt in naive $CD4^+$ T cells induces key genes that are essential for T_H17 cell differentiation[12]. RORγt cooperates with a network of transcription factors — most notably, STAT3, IRF4 and basic leucine zipper transcription factor ATF-like (BATF) — to initiate the complete differentiation programme. The activation of STAT3 by IL-6 and IL-23 is a key event in T_H17 lineage specification. Chromatin immunoprecipitation followed by sequencing (ChIP–seq) analysis has demonstrated that STAT3 directly regulates the T_H17-type cytokine and cytokine receptor genes (such as *Il17*, *Il17f* and *Il23r*), and that it also controls expression of the T_H17 cell-specific transcription factors *Rorc, Batf and Irf4* (REF. 31). In addition, STAT3 binds both the promoter regions of *Il17a* and *Il17f*, and their intergenic regions, which contain enhancer elements that undergo histone modifications during differentiation[31]. These findings are also relevant to humans, as patients with *STAT3* mutations suffer from autosomal dominant hyper-IgE syndrome (AD-HIES; also known as Job's syndrome) and are susceptible to recurrent pulmonary infections and chronic mucocutaneous candidiasis (CMC) owing to a reduced frequency of IL-17-producing T cells[69,70] (see below).

BATF is a member of the activator protein 1 (AP-1) family of transcription factors, which is upregulated in T_H cells following T cell receptor (TCR) activation[71,72]. In 2009, a study showed that BATF is essential for T_H17 cell differentiation and that mice lacking BATF are resistant to EAE[72]. $Batf^{-/-}$ mice have normal TGFβ and IL-6 signalling, and can upregulate RORγt early on during T cell development, but they fail to maintain RORγt expression[72]. However, the overexpression of RORγt could only partially rescue the T_H17 cell defects observed in $Batf^{-/-}$ cells, and the expression of both BATF and RORγt is required to drive IL-17 expression, which suggests that BATF and RORγt cooperatively control T_H17 cell differentiation. Furthermore, BATF forms a dimer with JUNB that directly binds to the promoters of *Il17*, *Il21* and *Il22* in T_H17 cells[72]. IRF4 was originally reported to be essential for T_H2 cell differentiation[73] and has now also been implicated in T_H17 cell differentiation[74]. IRF4-deficient mice are protected from EAE and exhibit a defect in T_H17 cell differentiation that stems from impaired RORγt expression[74]. However, similarly to BATF, the overexpression of RORγt in $Irf4^{-/-}$ T cells could only partially restore IL-17 production, which indicates that both RORγt and IRF4 are required to establish the T_H17 lineage.

Two recent studies show that BATF and IRF4 are 'pioneer factors' that cooperatively bind and govern the accessibility of chromatin, which enables RORγt recruitment and binding to T_H17 signature genes[75,76]. A comprehensive ChIP–seq analysis revealed a striking overlap between BATF and IRF4 promoter occupancy in T_H17 cells[76]. Furthermore, these transcription factors form a complex and regulate the DNA-binding activities of each other. As the binding of BATF and IRF4 promotes strong association and co-occupancy by T_H17 cell-defining transcription factors (STAT3 and RORγt), BATF and IRF4 seem to serve as the initiating factors that regulate chromatin accessibility in T_H17 cells. Surprisingly, co-occupancy by these transcription factors was also observed in TCR-activated but non-polarized T_H0 cells. Thus, BATF and IRF4 are bona fide pioneer factors that remodel chromatin to enable access of lineage-specifying transcription factors induced by certain environmental signals.

The transcription of a gene is regulated by sequence-specific binding of proteins to the promoter region and to distant regulatory enhancer sites. Enhancer activity is modified by histone-modifying enzymes — such as the

Chromatin immunoprecipitation followed by sequencing (ChIP–seq). A technique used to analyse the interactions between transcription factors and their target DNA. ChIP–seq combines chromatin immunoprecipitation (ChIP) with massively parallel DNA sequencing to identify the specific sequences bound by regulatory proteins.

Hyper-IgE syndrome
An inherited immune deficiency that is usually caused by mutations in signal transducer and activator of transcription 3 (*STAT3*) and is associated with reduced T helper 17 (T_H17) cell frequency. The disease is characterized by elevated levels of serum IgE, eosinophilia, 'cold' staphylococcal abscesses, eczema, pulmonary infections and chronic mucocutaneous candidiasis.

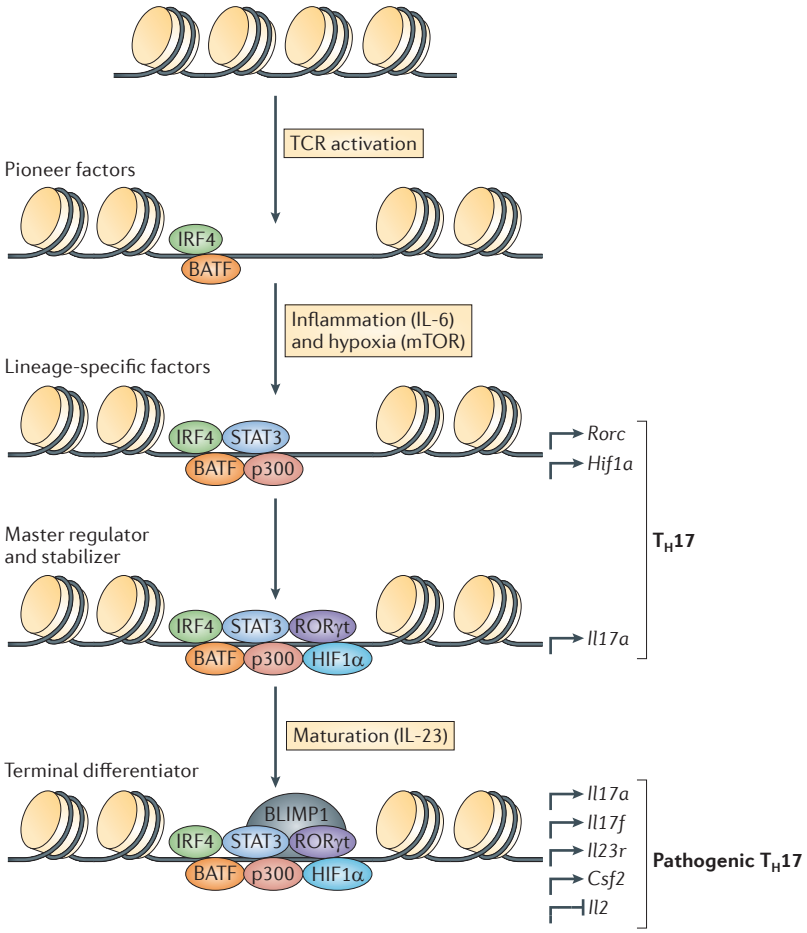


Figure 2 | **Schematics of transcription factor regulation for T_H17 cell lineage specification and function.** T cell receptor (TCR) signalling activates pioneering transcription factors — basic leucine zipper transcription factor ATF-like (BATF) and interferon-regulatory factor 4 (IRF4) — to engage with and open up target gene structures, which enables the recruitment of inflammation-associated transcription factor signal transducer and activator of transcription 3 (STAT3). STAT3 acts in complex with BATF, IRF4 and the co-activator histone acetyltransferase p300 to promote the expression of the genes encoding retinoic acid receptor-related orphan receptor-γt (RORγt; the master transcriptional regulator; encoded by *Rorc*) and hypoxia-inducible factor 1α (HIF1α; a lineage-stabilizer; encoded by *Hif1a*) leading to lineage specification of T helper 17 (T_H17) cells. Further exposure to interleukin-23 (IL-23) activates and recruits B lymphocyte-induced maturation protein 1 (BLIMP1) to the RORγt–STAT3 transcriptional complex to enhance the expression T_H17 cell signature genes, while repressing genes that promote alternative T cell fate. *Csf2*, colony-stimulating factor 2 (also known as GM-CSF); mTOR, mammalian target of rapamycin.

histone acetyltransferase p300 (also known as EP300) — which are recruited by lineage-specifying signals, and the presence of p300-induced histone modification marks indicates a transcriptionally active regulatory domain. Strikingly, BATF, IRF4 or STAT3 deficiency substantially reduces p300 binding, but a lack of RORγt has almost no effect on the enhancer landscape[76]. Although RORγt is referred to as a master transcription factor, in fact only a few T_H17 cell-specific genes — *Il17*, *Il17f* and *Il23r* — are exclusively dependent on RORγt[76]. Instead, RORγt acts as a modulator that finetunes a pre-established T_H17 lineage programme. RORγt positively regulates the T_H17 cell-specific genes while simultaneously repressing alternate lineage fates, by exploiting the altered enhancer landscape that is initially created by BATF and IRF4 (induced by TCR signalling), and STAT3 (induced by cytokines)[76] (FIG. 2). These new insights argue against the notion that a single factor governs lineage specificity, and instead indicate that a transcription factor complex regulates fate commitment[77]. Furthermore, these results are consistent with studies that have identified other transcriptional regulators — such as T-bet (for T_H1 cells) and FOXP3 (for T_{Reg} cells) — as factors that take advantage of an enhancer landscape that is already established by STAT proteins[78,79].

Another key transcription factor in T_H17 cell fate determination is hypoxia-inducible factor 1α (HIF1α), which is a key sensor of hypoxia (FIG. 2). HIF1α is induced upon TCR activation, and its expression is further enhanced by the hypoxic conditions associated with tissue inflammation, as well as by IL-6- and STAT3-dependent differentiation signals[80]. Mechanistically, HIF1α directly binds and drives transcription of *Rorc*, and forms a complex with RORγt and p300 to drive *Il17* expression[80]. HIF1α can also form a complex with FOXP3 and targets it for proteasomal degradation[80]. In this way, pro-inflammatory environmental cues, such as hypoxia, stabilize the T_H17 lineage. Two recent studies further demonstrate that a pro-inflammatory environment can also simultaneously destabilize the T_{Reg} cell lineage through the regulation of FOXP3 at the post-translational level by enhanced recruitment of an E3 ubiquitin-protein ligase STUB1 (also known as CHIP) that mediates FOXP3 ubiquitylation or by decreased expression of deubiquitylase ubiquitin carboxy-terminal hydrolase 7 (USP7)[81,82].

Despite advances in deciphering the T_H17 transcriptional network, we still lack a clear understanding of IL-23-dependent mechanisms that coordinate the differentiation of pathogenic T_H17 cells. STAT3 activation alone cannot explain the unique requirement for IL-23 in pathogenic T_H17 cell commitment, as IL-6 is an even more potent activator of STAT3. Additional IL-23-induced transcriptional regulators or signalling pathways must operate to promote inflammatory T_H17 cell effector function. Furthermore, it will be important to assess the T_H17 cell enhancer landscape that is created by IL-6 compared with IL-23 to determine whether divergence at an epigenetic level influences functional outcomes.

T_H17 cell plasticity versus stability

T_H17 cell plasticity refers to the ability of T_H17 cells to acquire divergent functional capabilities while maintaining the fundamental T_H17 programme that is defined by the expression of RORγt and IL-17. Recently published data indicate that T_H17 cells retain a high degree of plasticity that enables them to co-express alternative lineage-specifying transcription factors and effector cytokines[23,53,55,56,83]. Such functional heterogeneity endows T_H17 cells with an enhanced ability to traffic to a broad range of anatomical sites and to efficiently promote diverse functions, including host defence, barrier tissue integrity and wound-healing responses.

Defining the factors that regulate T_H17 cell plasticity is an area of intensive investigation. Although RORγt is essential for the development of T_H17 cells, it is not sufficient to promote all functional capabilities. As mentioned above, IL-23 might be a pivotal factor dictating the functional diversity of T_H17 cells through the induction of alternate lineage-specific transcription factors (such as *Tbx21*) and effector genes (such as *Il22, Csf2* and *Ifng*), while still maintaining the core T_H17 programme (which entails expression of *Rorc* and *Il17*)[4,25]. We have recently shown that the transcription factor B lymphocyte-induced maturation protein 1 (BLIMP1; which is encoded by *Prdm1*) is induced by IL-23 and acts both as a gene activator and repressor to induce T_H17 cell maturation (R.J. and D.J.C., unpublished observations). BLIMP1 coordinates with RORγt to enhance the expression of *Il23r* and *Csf2*, while simultaneously repressing *Il2* and alternate fate-determining factors (such as *Bcl2*, *Foxp3* and *Gata3*). Interestingly, BLIMP1 directly engages with the *Il23r, Il17f* and *Csf2* loci in close proximity to RORγt, p300 and STAT3, which suggests that BLIMP1 is part of a complex that regulates the pathogenic function of T_H17 cells (R.J. and D.J.C., unpublished observations).

T_H17 cell plasticity could be explained by epigenetic modifications. Recent advances in the genome-wide analysis of histone modifications enables examination of the permissive and repressive histone marks, H3K4 trimethylation (H3K4me3) and H3K27me3, respectively, on lineage-specifying genes. Interestingly, T_H17 cells display both active and repressive histone marks on *Tbx21* and *Gata3,* whereas T_H1 and T_H2 cells show only repressive marks on the *Rorc* and *Il17* loci[84]. In other words, T_H17 cells seem to be highly poised to acquire other T_H cell functions under appropriate environmental stimuli[84]. Interestingly, T_{Reg} cells are the only other cell type with such dual modifications at the gene loci encoding T_H cell master transcription factors, which gives them the advantage of functional diversity and plasticity.

The extent to which the T_H17 cell phenotype shows stability is more than a question of functional malleability. Stability is defined by whether RORγt-expressing T_H17 cells can lose their core transcriptional and functional characteristics and become RORγt$^-$ "ex-T_H17" cells[55]. The concept of T_H17 stability has been explored in studies using both *in vitro* and *in vivo* approaches. The *in vitro* polarization approach, in which the inducing signals are constantly present, has been unable to demonstrate that T_H17 cells are unstable[85]. However, *in vivo* systems such as mouse strains expressing Cre recombinase under the control of the *Il17a* promoter have greatly enhanced our understanding of this important issue[22,55,85]. Crossing the *Il17a*^{Cre} mice with *Rosa26*-enhanced yellow fluorescence protein (YFP)-reporter mice generated a fate-mapping system in which *Il17a*-expressing cells are permanently marked with YFP. This cell-tagging system has demonstrated that bona fide T_H17 cells can be destabilized and converted into T_H1 cells when exposed to appropriate environmental stimuli[55]. Histone modification analysis of IL-17$^+$ cells isolated using cytokine capture beads from the inflamed intestine has confirmed these results[86]. However, epigenomic analysis of ex-T_H17 cells at a single-cell level is required to gain a deeper molecular understanding of T_H17 cell stability and to avoid any variations caused by heterogeneity within the cell population. For example, it would be revealing to analyse epigenetic changes in T_H17 cells that acquire T_H1-type functions. Do they undergo complete epigenetic remodelling of T_H17 cell-associated genes or do they retain epigenetic evidence of their T_H17 cell origins? Are former T_H17 cells capable of reacquiring the original T_H17 cell programme upon TCR stimulation because they retain a core epigenetic status? Understanding the plasticity of T_H17 cells at the epigenetic level may have important advantages. First, it could enable us to predict the developmental stages at which T_H17 cells would be susceptible to reprogramming towards the T_{Reg} cell phenotype. This cellular reprogramming could have added anti-inflammatory benefits, in addition to depleting T_H17 cells. Second, it is vital to understand the durability of the T_H17 effector cell suppression and/or reprogramming. It is crucial to determine whether ex-T_H17 cells can revert back to their original pathogenic phenotype after reprogramming in patients.

IL-17 signal transduction

As outlined above, much effort has been devoted to defining the cellular sources of IL-17 and understanding the subsequent regulation of its expression. This section describes the current understanding of the IL-17-induced signalling pathways that link receptor ligation to the downstream biological effects of this cytokine. Cells that respond to IL-17 are mainly, though not exclusively, non-haematopoietic, and the effects of IL-17 are most similar to other innate inflammatory effectors, especially those that belong to the IL-1 family of cytokines and Toll-like receptor (TLR) ligands[87]. In particular, IL-17 is a potent regulator of neutrophils and this effect is mediated by IL-17-induced genes such as those that encode granulocyte colony-stimulating factor (G-CSF; also known as CSF3) and the CXC chemokines[88]. The IL-17R has many unique and unexpected properties in terms of its structure and signalling, and a detailed understanding of these events may reveal novel drug targets or potential avenues for therapeutic intervention.

Activation of IL-17R signalling. When IL-17R (now known as IL-17RA) was cloned in 1995, it was noteworthy for its striking lack of similarity to known receptor families[89]. Subsequently, it became clear that IL-17RA was the founding member of a new subclass of cytokine receptors, which comprises five receptor subunits — IL-17RA–IL-17RE — that have homology to one another but not to other receptor families[87] (FIG. 3). All subunits of the IL-17R family have a broad expression pattern, with IL-17RA being most highly expressed in haematopoietic cell types and IL-17RC in non-haematopoietic cells[90]. Most of the homology within the IL-17R family is found in the conserved cytoplasmic SEF/IL-17R (SEFIR) motif, which

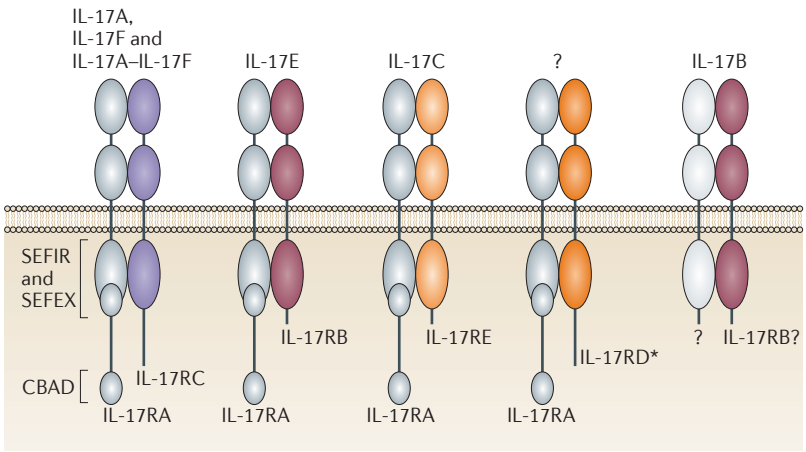


Figure 3 | **IL-17 ligand and receptor family members.** Interleukin-17 receptor A (IL-17RA) has been shown to serve as a common receptor chain for all IL-17 ligand members except for IL-17B. Whereas IL-17A and IL-17F are T helper 17 (T_H17) cell signature genes, IL-17E (also known as IL-25) is a T_H2-type cytokine that is involved in anti-helminth immunity and allergic responses. IL-17C is an autocrine factor that is primarily produced by and activates signalling in skin and gut epithelial cells. Currently, there is limited knowledge of IL-17B and IL-17D biology. CBAD, C/EBPβ activation domain; SEFEX, SEFIR extension; SEFIR, SEF/IL-17R. *IL-17RD is also known as SEF.

suggests a common mode of signalling that is probably distinct from other cytokine receptors. A landmark bioinformatic study demonstrated that this domain is related to the Toll/IL-1R (TIR) domain[91]. Recent studies have revealed that the IL-17RA subunit is shared by the receptors for several members of the IL-17 cytokine family (FIG. 3). IL-17RA is essential for IL-17E (also known as IL-25) signalling when partnered with IL-17RB, and for IL-17C signalling when partnered with IL-17RE[92,93]. The only other identified protein that has been shown to have a SEFIR domain is the adaptor protein ACT1 (also known as CIKS)[91]; indeed, ACT1 is essential for signal transduction by all of the known IL-17R family members[87,94,95].

Despite the similarity between the SEFIR domain of the IL-17R and the TIR domains of TLRs and IL-1R, studies of IL-17 have shown that these receptors operate differently. For example, ACT1 only positively regulates signalling by the IL-17R family and it is not involved in any other cytokine signalling pathways[96]. ACT1 serves both as a signalling adaptor — to recruit TNFR-associated factor (TRAF) proteins and direct the activation of several downstream signalling cascades[94] — and as an E3 ligase to mediate the ubiquitylation of TRAF6 (REF. 97). The recruitment and ubiquitylation of TRAF6 leads to activation of the canonical nuclear factor-κB (NF-κB) pathway and mitogen-activated protein kinase (MAPK) pathways, which include extracellular signal-regulated kinase (ERK), p38 and JUN N-terminal kinase (JNK). Consequently, the activation of these pathways by IL-17 is impaired in the absence of either ACT1 or TRAF6 (REFS 94,95,98). Alternatively, ACT1 can recruit TRAF2 and TRAF5, which promote the activation of an mRNA stability pathway by sequestering ASF/SF2 (also known as SRSF1) and recruiting the stabilizing factor HuR (also known as ELAVL1)[99,100]. These alternative pathways are regulated by ACT1 phosphorylation, which is mediated by inducible IκB kinase (IKKi; also known as IκBKε) and serine/threonine-protein kinase TBK1 (REFS 101,102) (FIG. 4). ACT1 function and stability is in turn regulated by the chaperone heat shock protein 90 (HSP90). The inhibition of HSP90 results in proteasomal degradation of ACT1, which suppresses IL-17 signalling[103]. ACT1 seems to be required for most, if not all, IL-17-dependent signalling events[104] and the majority of phenotypes seen in *Act1*$^{-/-}$ mice are similar to *Il17ra*$^{-/-}$ mice. Notably, a single nucleotide polymorphism (SNP) in *ACT1* has been associated with psoriasis[105]. Thus, for the IL-17R family, all known signalling pathways emanate from ACT1, which leads to an activation of pro-inflammatory signalling cascades.

IL-17 mainly induces signalling in cells of non-haematopoietic origin, including epithelial and mesenchymal cell types. The genes that are induced by IL-17 largely explain its pro-inflammatory activities — for example, IL-17 induces the expression of chemokines such as CXC-chemokine ligand 1 (CXCL1), CXCL2 and CXCL5, which promote neutrophil chemotaxis[106]. IL-17 also induces the expression of CCL20, which promotes the trafficking of mucosa-associated cells that express CC-chemokine receptor 6 (CCR6) — notably, CCR6 is a characteristic receptor on IL-17-expressing cells such as T_H17 cells and ILC3s[107]. Other cytokines induced by IL-17, such as IL-6 and G-CSF, regulate myeloid cell lineages and especially neutrophils. Additionally, IL-17 is a strong inducer of antimicrobial peptides, particularly β-defensins, which can prevent infection at mucosal surfaces and in the skin, and that may also exert chemotactic activity[108]. Lipocalin 2 (LCN2; also known as 24p3) is another IL-17-induced antimicrobial protein that controls bacterial growth by restricting access to dietary iron[109].

The CCAAT/enhancer-binding protein (C/EBP) family of transcription factors is also activated by IL-17 signal transduction, and is often just as important as NF-κB in the regulation of target genes. For example, the *Il6* and *Lcn2* promoters require both NF-κB and C/EBP elements, as deletion of either element renders their promoters insensitive to IL-17-mediated signals[110,111]. IL-17 induces the expression of C/EBPδ at the mRNA and protein level and, to a lesser extent, that of C/EBPβ[110,112]. The latter is regulated extensively by post-transcriptional and post-translational modifications, including alternative translation and phosphorylation[113]. The phosphorylation of C/EBPβ depends on a glycogen synthase kinase 3β (GSK3β)- and ERK-dependent pathway, which dampens IL-17-dependent signalling (see below)[114].

On their own, IL-17A (and IL-17F) are modest activators of signalling, but they function cooperatively with other pro-inflammatory molecules, particularly TNF, but also IFNγ, IL-22, lymphotoxin, IL-1β and lipopolysaccharide[88]. The molecular basis for this synergy is not completely understood and probably involves multiple mechanisms. In synovial tissue, IL-17 upregulates TNFR2 expression, and thereby enhances responsiveness to TNF[115]. For some genes, cooperativity between IL-17 and TNF occurs at the level of the

Antimicrobial peptides
Short peptides (typically 12–50 amino acids) with bactericidal and fungicidal activities. Some may also exhibit chemotactic activities.

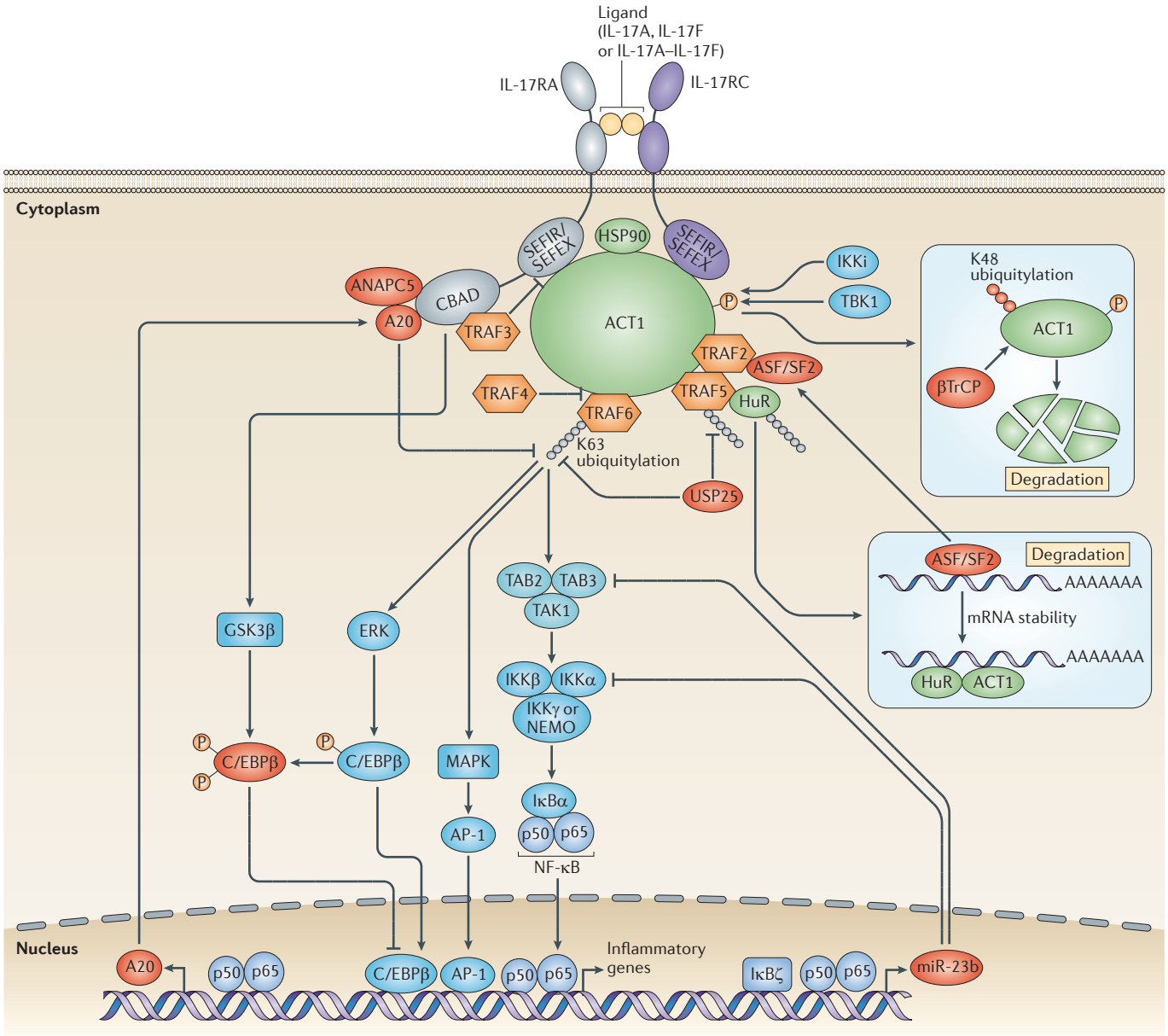


Figure 4 | **IL-17 receptor signal transduction.** Interleukin-17 (IL-17) signalling is activated upon binding of IL-17 to a dimeric receptor complex that is composed of IL-17 receptor A (IL-17RA) and IL-17RC. Positive regulators of signalling are shown in blue and green. Tumour necrosis factor receptor-associated factors (TRAFs) are shown in orange, and they have both positive and negative regulatory effects. Structure–function analyses of both IL-17RA and IL-17RC has demonstrated that the conserved SEF/IL-17R (SEFIR) domain, as well as non-conserved downstream residues (known as the 'SEFIR extension' (SEFEX) domain), are essential for the activation of signalling. Both IL-17R subunits recruit the adaptor protein ACT1, which serves as an adaptor and an E3 ubiquitin ligase. ACT1 mediates the K63-linked ubiquitylation of TRAF6, which results in the downstream activation of TAK1, the inhibitor of nuclear factor (NF)-κB (IKK) complex and canonical NF-κB. IL-17 also activates components of mitogen-activated protein kinase (MAPK) pathways, including JUN N-terminal kinase (JNK), p38 and extracellular signal-regulated kinase (ERK). In addition, IL-17 signalling induces the phosphorylation of the CCAAT/enhancer-binding protein-β (C/EBPβ) transcription factor by ERK- and glycogen synthase kinase 3β (GSK3β)-mediated pathways. In an alternative signalling pathway, ACT1 is phosphorylated by inducible IκB kinase (IKKi; also known as IκBKε) and serine/threonine-protein kinase TBK1. Phosphorylated ACT1, together with TRAF2 and TRAF5, sequesters the RNA-binding protein ASF/SF2 and recruits HuR to stabilize target mRNA transcripts. The chaperone heat shock protein 90 (HSP90) controls stability of ACT1, promoting signal transduction. Negative regulators of signalling are shown in red. The deubiquitylating enzyme A20 is induced by IL-17 and mediates negative feedback by targeting TRAF6 to negatively regulate NF-κB and MAPK signalling. Similarly, ubiquitin C-terminal hydrolase 25 (USP25) targets both TRAF5 and TRAF6 to inhibit IL-17-mediated signalling. The microRNA miR-23b also acts as an inhibitor of IL-17 signalling by targeting TGFβ-activated kinase 2 (TAB2), TAB3 and IKKα. The E3 ubiquitin-protein ligase complex βTrCP facilitates proteasomal degradation of ACT1 via K48-linked ubiquitylation. TRAF3 and TRAF4 inhibit IL-17 by competing with ACT1 for binding to IL-17RA and TRAF6, respectively. The distal C/EBPβ activation domain (CBAD) of IL-17RA coordinates the inhibition of IL-17 signalling by several mechanisms. GSK3β-mediated inhibitory phosphorylation of C/EBPβ is dependent on the CBAD. The inhibitors A20, TRAF3 and anaphase-promoting complex subunit 5 (ANAPC5) also associate with IL-17RA through the CBAD. AP-1, activator protein 1; IκBζ, NF-κB inhibitor-ζ; NEMO, NF-κB essential modulator.

promoter (for example, *Il6* and *Lcn2*) and/or mRNA stability (for example, mRNA encoding chemokines such as CXCL1)[116]. IL-17 also upregulates the expression of NF-κB inhibitor-ζ (IκBζ) — which, despite its name, has both positive and negative regulatory effects on the NF-κB family — that in turn promotes the expression of at least some target genes[117]. The ability of IL-17 to signal cooperatively with other cytokines is probably an important aspect of its biology, as inflammatory environments contain multiple cytokines that can act in concert.

Negative regulation of IL-17 signalling. Dysregulated IL-17 production and signalling is associated with the development of several autoimmune diseases and, thus, it is not surprising that IL-17-mediated inflammatory signalling is regulated at multiple levels. As outlined below, a variety of inhibitory mechanisms that restrict signal transduction have been identified (FIG. 4).

Deubiquitylating enzymes (DUBs) can reduce IL-17-mediated signal transduction by targeting TRAFs — for example, ubiquitin C-terminal hydrolase 25 (USP25) removes K63-linked ubiquitin chains on both TRAF5 and TRAF6, which inhibits the transcription of IL-17 target genes, as well as IL-17-induced mRNA stability[99]. USP25 deficiency is associated with enhanced IL-17-dependent pulmonary inflammation and an increased susceptibility to EAE[118].

We recently identified A20 (which is encoded by *TNFAIP3*) as a vital feedback inhibitor of IL-17 signalling[119]. SNPs in *TNFAIP3* are associated with numerous autoimmune and lymphoproliferative diseases, including psoriasis, rheumatoid arthritis and certain B cell malignancies[120]. IL-17 induces the expression of *Tnfaip3* mRNA and increases A20 protein levels, which triggers the deubiquitylation of TRAF6 and downregulates the activation of NF-κB and MAPK (particularly JNK)[119]. Notably, A20 directly associates with IL-17RA through the C-terminal C/EBPβ activation domain (CBAD) of the receptor[119]. The CBAD is also an interaction site for TRAF3, which is another negative regulator of IL-17 signalling[121], and several years ago, a structure–function analysis of IL-17RA showed that deletion of the CBAD enhances IL-17 signalling[122]. Intriguingly, A20 seems to inhibit IL-17 in a non-canonical manner. In other systems, A20 needs to interact with accessory factors — such as TAX1-binding protein 1 (TAX1BP1) and E3 ubiquitin-protein ligase ITCH — in order to hydrolyse K63-linked substrates efficiently[123], and deletion of the gene encoding TAX1BP1 or ITCH results in a phenotype that is similar to (albeit less severe than) that caused by the lack of A20 (REFS 124,125). However, knockdown of either TAX1BP1 or ITCH does not inhibit IL-17 signalling, which suggests that A20 might use alternative adaptors[127]. Indeed, we found that A20 associates with anaphase-promoting complex subunit 5 (ANAPC5)[126,127], which is best known as a subunit of a multiprotein E3 ubiquitin ligase complex that regulates cell cycle progression. Together, these data show that the reversal of K63 ubiquitylation on TRAF6 via A20 is an important downregulatory strategy for restricting IL-17-mediated inflammation.

K48-linked ubiquitylation and proteasomal degradation of adaptor proteins is another means of regulating inflammatory signalling. IL-17R signalling is inhibited by the E3 ubiquitin-protein ligase complex βTrCP, which induces the K48 ubiquitylation of phosphorylated forms of ACT1 that in turn leads to its proteasomal degradation[128]. TRAF proteins also have negative roles in regulating IL-17-induced inflammatory signalling pathways[129]. For example, TRAF3 associates with IL-17RA through a consensus TRAF binding site in the CBAD of the receptor, thereby competing with ACT1 for binding to IL-17RA and dampening IL-17-dependent signalling[121]. Similarly, TRAF4 directly binds ACT1 upon IL-17 stimulation and competes for its association with TRAF6. Consistent with this, TRAF3 and TRAF4 limit IL-17-mediated development of EAE[121,130].

Some data implicate microRNAs (miRNAs) in regulating both T_H17 cell development and IL-17 signalling. The miRNA miR-155 is expressed in $CD4^+$ T cells and positively regulates T_H17 cell differentiation[131], which may be due to blockade of suppressor of cytokine signalling 1 (SOCS1), a negative regulator of JAK–STAT signalling[132]. Consequently, miR-155-deficient mice or mice in which this miRNA is silenced are resistant to EAE[131,133]. In terms of signalling, miR-23b keeps IL-17-induced NF-κB activation in check by targeting TGFβ-activated kinase 2 (TAB2), TAB3 and IKKα for degradation[134]. Consistent with a role for enhanced IL-17 signalling in disease, patients with rheumatoid arthritis and systemic lupus erythematosus show reduced expression of miR-23b[134].

As noted above, C/EBPs regulate IL-17-induced gene expression. Interestingly, C/EBPβ is both a positive and negative regulator of the IL-17 pathway. Although C/EBPβ can positively transactivate IL-17 target genes[110], phosphorylation of C/EBPβ by the kinases ERK and GSK3β correlates with a decrease in IL-17-induced gene expression[114]. Notably, phosphorylation of C/EBPβ by GSK3β is dependent on the CBAD, representing another negative regulatory event mediated by the IL-17RA distal domain[114].

Effector cytokines of T_H17 cells

T_H17 cells in the steady state. T_H17 cells did not evolve to cause autoimmunity but to provide effective host defence against pathogens. Experiments have shown that IL-17- and IL-17R-knockout mice have an increased susceptibility to infection by a wide variety of microorganisms, including bacteria, parasites, fungi and viruses[135]. However, examination of families or individuals with specific mutations in the T_H17 pathway has indicated a surprisingly limited role for T_H17 cells and IL-17 in immunity to infection, with susceptibility to commensal fungi (mainly *Candida albicans*) being by far the most dominant cause of disease seen in these settings (TABLE 1). Although the reasons for the dichotomy between mice and humans are still unclear, this is similar to findings in myeloid differentiation primary response protein 88 (MYD88)-deficient humans, who show a relative restricted susceptibility to pyogenic bacteria, in contrast to the broadly susceptible MYD88-knockout mice[136].

A20
The product of the tumour necrosis factor-α-induced protein 3 (*TNFAIP3*) gene. This is a zinc finger-containing protein with E3 ligase and deubiquitylase activity that downregulates signalling by multiple inflammatory effectors.

microRNAs
(miRNAs). Single-stranded RNA molecules of approximately 21–23 nucleotides in length that regulate gene expression.

Autoimmune polyendocrinopathy syndrome 1
(APS1; also known as autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED) syndrome). An inherited autoimmune disorder that affects multiple endocrine tissues and is caused by mutations in the autoimmune regulator (*AIRE*) gene. The disease is associated with a high incidence of mucocutaneous candidiasis, which is thought to be owing to neutralizing autoantibodies against interleukin-17A (IL-17A), IL-17F and/or IL-22.

As noted above, patients with AD-HIES have dominant-negative mutations in *STAT3* that are associated with a reduced frequency of T_H17 cells and susceptibility to CMC, *Staphylococcus aureus* and pulmonary infections[69,137]. The reduced frequency of T_H17 cells in CMC is associated with mutations that impair fungal sensing, inhibit IL-23 signalling or enhance negative regulation of T_H17 differentiation[138–140] (TABLE 1). Similarly, patients with autoimmune polyendocrinopathy syndrome 1 (APS1; also known as autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED) syndrome) suffer from CMC (but no other infections), which is apparently owing to naturally occurring neutralizing antibodies against T_H17-type cytokines[141,142]. Null mutations in *IL17RA* or *ACT1* and dominant-negative mutations in *IL17F* also promote CMC and some staphylococcal infections[143,144]. Thus, deficiencies in T_H17 cells and/or IL-17 are strongly linked to defects in fungal immunity and these association studies support data from mouse studies[145].

T_H17 cells in disease states. Although T_H17 cells did not evolve to cause disease, they are programmed to provide formidable host protective responses, which are often associated with the rapid recruitment and activation of granulocytes and macrophages that are capable of producing tissue-damaging reactive oxygen species[146]. During prolonged and dysregulated exposure to IL-1 and IL-23, T_H17 cells recruit inflammatory myeloid cells that cause severe local tissue injury[38,147]. Experiments using IL-17-, IL-22-, IL23A- or IL-23RA-deficient mice, as well as antibody-mediated inhibition, have demonstrated a requirement for these cytokines in EAE, collagen antibody-induced arthritis, and CIA, and models of inflammatory bowel disease (IBD), ankylosing spondylitis and psoriasis[4,5,25,147,148]. On the basis of these preclinical models, as well as human genome-wide association studies (GWASs) and pharmacogenomic disease association analyses, psoriasis, IBD and ankylosing spondylitis have emerged as the leading disease indications for IL-17-specific and IL-23-specific antibody treatments[57–61,149].

Psoriasis is an immune-mediated inflammatory disorder that is characterized by the activation of both adaptive and innate type 17 responses[150]. The pathogenic involvement of IL-23 in psoriasis is supported by the increased expression of IL-23 in psoriatic lesional skin and its ability to induce psoriasiform characteristics in a preclinical model of intradermal IL-23 administration[148]. The injection of IL-23 promoted dermal acanthosis, neutrophil recruitment, and the infiltration of IL-17- and IL-22-producing T cells. In addition, inhibition of

Table 1 | **Human mutations that affect the T_H17 pathway**

Gene	Syndrome and/or disease features	Connection to T_H17 pathway	Refs
STAT3	Autosomal dominant hyper-IgE syndrome (Job's syndrome), mucocutaneous candidiasis, *S. aureus*-induced cold abscesses and increased susceptibility to viruses	Reduced T_H17 cell frequency, and defects in IL-6, IL-23 and IL-22 signal transduction	70,180
TYK2	Autosomal recessive hyper-IgE syndrome (Job's syndrome), mucocutaneous candidiasis and *S. aureus*-induced cold abscesses	Reputed loss of IL-23 signalling	181
IL12B	Autosomal recessive susceptibilty to mycobacteria, salmonellae and mucocutaneous candidiasis	Reduced T_H17 (and T_H1) cell frequency	182
IL12RB1	Autosomal recessive susceptibilty to mycobacteria, salmonellae and mucocutaneous candidiasis	Reduced T_H17 (and T_H1) cell frequency	183,184
IL17F	Mucocutaneous candidiasis and increased susceptibility to *S. aureus* infection	Dominant-negative mutation in IL-17F that blocks IL-17F and IL-17A–IL-17F-mediated signalling	143
IL17RA	Mucocutaneous candidiasis and increased susceptibility to *S. aureus* infection	Loss of function in IL-17RA	143
DECTIN1	Mucocutaneous candidiasis	Induces T_H17 cell differentiation in response to β-glucans	180
CARD9	Mucocutaneous and disseminated candidiasis	Induces T_H17 cell differentation in response to fungal PAMPs via CLRs	138
STAT1	Mucocutaneous candidiasis	Gain-of-function mutaton in *STAT1* leads to reduced T_H17 cell frequency, and increased IL-27 and type I IFN signalling	139,140
AIRE	APS1 and mucocutaneous candidiasis	Patients produce neutralizing antibodies against T_H17-type cytokines (IL-17A, IL-17F and/or IL-22)	141,142
ACT1	Mucocutaneous candidiasis	Loss of IL-17R family signal transduction	144
IL17RC	Mucocutaneous candidiasis	Loss of function in IL-17RC	J.-L. Casanova and A. Puel, personal communication

AIRE, autoimmune regulator; APS1, autoimmune polyendocrinopathy syndrome 1 (also known as autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED) syndrome); *CARD9*, caspase recruitment domain-containing protein 9; CLR, C-type lectin receptor; IFN, interferon; IL, interleukin; *IL12B*, gene encoding IL-12p40; *IL12RB1*, IL-12 receptor β1; *IL17RA*, IL-17 receptor A; PAMP, pathogen-associated molecular pattern; *S. aureus*, *Staphylococcus aureus*; *STAT*, signal transducer and activator of transcription; T_H, T helper; *TYK2*, tyrosine kinase 2.

IL-23 led to a significant reduction of IL-17 and IL-22 levels in psoriatic lesional skin, which supports the role of these cytokines as key regulatory factors in this disease. IL-17-producing $CD4^+$ T cells, $CD8^+$ T cells, γδ T cells and ILCs can all be found in psoriatic skin[151]. Additional skin-resident cells — such as keratinocytes, fibroblasts and endothelial cells — respond to IL-17 and produce autocrine factors that promote rapid cell division and neo-angiogenesis, which strongly contribute to the disease process. The inappropriate secretion of antimicrobial peptides (such as β-defensins, lipocalins, LL-37 (also known as cathelicidin) and S100A7) and chemokines (CXCL1, CXCL2, CXCL3, CXCL5, IL-18 and CCL20) by keratinocytes further recruits and activates mast cells, neutrophils and inflammatory macrophages[152]. This interaction between type 17 lymphoid cells and tissue-resident keratinocytes and fibroblasts creates amplification loops that drive epidermal hyperplasia and pro-inflammatory conditions, which are hallmarks of psoriasis.

The seronegative spondyloarthropathies are a heterogeneous group of immunological diseases that follow specific types of viral and bacterial infections and include ankylosing spondylitis, psoriatic arthritis and reactive arthritis[153]. In contrast to rheumatoid arthritis, in which inflammation is accompanied by bone erosion and destruction, spondyloarthropathy is characterized by new bone formation at sites where ligaments attach onto bone, which are known as the entheseal organ. Using a mouse model of spondyloarthropathy, we have recently demonstrated the presence of $ROR\gamma t^+IL\text{-}23R^+CD3^+CD4^-CD8^-SCA1^+$ entheseal-resident cells and shown that their production of IL-17 and IL-22 is the major cause of STAT3-dependent osteoblast-mediated bone remodelling[147]. The new bone appears as inappropriate bony outgrowths from spinal vertebrae, which can fuse and immobilize the spine, causing the ultimate morbidity for this disease[154]. This condition is commonly associated with uveitis, aortic valve inflammation, psoriasis and IBD. Indeed, uveitis is a significant comorbidity in ankylosing spondylitis, affecting 40% of patients[155]. In addition, up to 70% of patients with ankylosing spondylitis have microscopically evident bowel inflammation[155]. These observations suggest that there is a fundamental underlying pathology linking these immune disorders. Recently, GWASs have identified multiple SNPs in *IL23R* that are associated with either susceptibility to or protection from ankylosing spondylitis, psoriasis and IBD, or increased susceptibility to these autoimmune conditions[57–61].

The same *IL23R* SNPs that are found in individuals with ankylosing spondylitis and psoriasis were present in patients with Crohn's disease, along with SNPs in *NOD2* (nucleotide-binding oligomerization domain-containing protein 2; also known as *CARD15*), which encodes a sensor of bacterial cell wall components[57,156,157]. This is consistent with the immune system having an elevated T_H17 cell response in the intestinal mucosa, which is possibly directed against commensal bacterial antigens. Preclinical animal studies have also identified IL-23 as a key inflammatory mediator that promotes chronic tissue injury responses. In Crohn's disease, increased expression of IL-17A (at both the mRNA and protein level) has been reported in the intestinal mucosa[158]. Elevated faecal IL-17A levels were also described in active Crohn's disease[159]. Taken together, these observations implicate the IL-23–IL-17 immune axis in the pathogenesis for Crohn's disease and related immune disorders — such as psoriasis and spondyloarthropathies — and provide a rationale for developing therapies that target these cytokines.

Targeting the T_H17 pathway in disease

IL-17 and IL-23 are emerging as essential factors in the pathogenesis of many autoimmune diseases. Currently, a number of pharmaceutical companies are testing antibodies that target IL-17A, IL-17RA, IL-17A/IL-17F (that is, an antibody recognizing common motifs of the two related cytokines), IL-17A/TNF (a bi-specific antibody with one complementarity-determining region that recognizes IL-17A and the other that recognizes TNF), the p40 subunit of IL-23 and IL-12 (IL-12p40; also known as IL-12β), as well as the p19 subunit of IL-23 (IL-23p19; also known as IL-23A). These antibodies are being trialled in patients with psoriasis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, autoimmune uveitis, asthma and multiple sclerosis (TABLE 2). To date, the antibodies that specifically neutralize IL-23 or IL-17A have shown remarkable effectiveness for the treatment of psoriasis. These agents are also showing promising initial results in ankylosing spondylitis and multiple sclerosis.

Currently, four companies are in the final stages of clinical testing of IL-23-specific and IL-17-specific antibodies for psoriasis (TABLE 2) (also see Supplementary information S1 (table)). The Phase II proof-of-concept studies for ixekizumab (an IL-17A-specific antibody), secukinumab (an IL-17A-specific antibody), brodalumab (an IL-17RA-specific antibody), and tildrakizumab (an IL-23p19-specific antibody)[160–163] showed that the inhibition of IL-17, IL-17RA or IL-23p19 had similar safety profiles and therapeutic efficacy (see Supplementary information S1 (table)), which were comparable or better than current standard-of-care drugs, such as ustekinumab (an IL-12p40-specific antibody) and etanercept (a TNF-specific antibody)[164]. All agents showed impressive efficacy, with 70–80% of the patients achieving Psoriasis Activity and Severity Index 75 (PASI-75) — which is defined as having >75% disease clearance — and nearly half reaching PASI-100, a remarkable 100% disease clearance (see Supplementary Information S1 (table)). Currently, all four compounds have advanced to Phase III trials. These clinical data support the concept that IL-17 and IL-23 are key 'checkpoints' for the psoriatic inflammatory skin conditions.

Conventional treatment for Crohn's disease includes immunosuppression with corticosteroids, methotrexate and TNF-specific antibodies. Many patients cannot be treated with these therapies in the long term owing to

Table 2 | **Targeting of the IL-17–IL-23 immune axis to treat human diseases**

Agent (alternative name or names)	Target	Companies running trials	Indications	Clinical trial stage	Clinical trial identifier*
Ixekizumab (LY-2439821)	IL-17A	Eli Lilly	Psoriasis	Phase III	NCT01597245
			Rheumatoid arthritis	Phase II completed	NCT00966875
Secukinumab (AIN457)	IL-17A	Novartis	Psoriasis	Phase III	NCT01544595
			Rheumatoid arthritis	Phase III	NCT01770379
			Ankylosing spondylitis	Phase III	NCT01358175
			Psoriatic arthritis	Phase III	NCT01892436
			Asthma	Phase II	NCT01478360
			Multiple sclerosis	Phase II	NCT01874340
			Type 1 diabetes	Phase II terminated	NCT02044848
			Crohn's disease	Phase II terminated	NCT01009281
Brodalumab (AMG-827)	IL-17RA	Amgen and MedImmune	Psoriasis	Phase III	NCT01708590
			Psoriatic arthritis	Phase III	NCT02024646
			Asthma	Phase II	NCT01902290
			Crohn's disease	Phase II terminated	NCT01150890
ABT-122	IL-17A and TNF	Abbott and AbbVie	Rheumatoid arthritis	Phase I	NCT01853033
Ustekinumab (CNTO-1275; Stelara)	p40 subunit of IL-12 and IL-23	Johnson & Johnson and Janssen Biotech	Psoriasis	Approved 2009	NA
			Crohn's disease	Phase III completed	NCT01369329
			Ankylosing spondylitis	Phase II completed	NCT01330901
			Rheumatoid arthritis	Phase II completed	NCT01645280
			Psoriatic arthritis	Phase II completed	NCT01009086
			Multiple sclerosis	Phase II completed	NCT00207727
			Graft-versus-host disease	Phase II	NCT01713400
			Atopic dermatitis	Phase II	NCT01945086
Briakinumab (ABT-874)	p40 subunit of IL-12 and IL-23	Abbott	Crohn's disease	Phase II terminated	NCT00562887
			Psoriasis	Phase III completed	NCT00626002
			Multiple sclerosis	Phase II completed	NCT00086671
Tildrakizumab (MK-3222; SCH-900222)	IL-23p19	Merck	Psoriasis	Phase III	NCT01729754
Guselkumab (CNTO-1959)	IL-23p19	Johnson & Johnson and Janssen Biotech	Psoriasis	Phase II completed	NCT01483599
			Rheumatoid arthritis	Phase II completed	NCT01645280
AMG-139	IL-23p19	Amgen and MedImmune	Psoriasis	Phase I completed	NCT01094093
			Crohn's disease	Phase I	NCT01258205
LY-3074828	IL-23p19	Eli Lilly	Psoriasis	Phase I	NCT01947933
BI-655066	IL-23p19	Boehringer Ingelheim	Ankylosing spondylitis	Phase II	NCT02047110
			Crohn's disease	Phase II	NCT02031276
			Psoriasis (single rising dose)	Phase II	NCT02054481

IL-17A, interleukin-17A; IL-17RA, IL-17 receptor A; IL-23p19, p19 subunit of IL-23; NA, not applicable; TNF, tumour necrosis factor. *Clinical trial identifiers are provided for reference; please see the ClinicalTrials.gov website for further details. Data are accurate as of July 2014.

drug intolerance or loss of initial response (for example, owing to the development of antibodies against the drug). Ustekinumab has been tested in patients with moderate to severe Crohn's disease[165]. The study found that patients who showed elevated C-reactive protein (CRP) levels, colonic inflammation and a failure to respond to TNF-targeted therapies had better overall treatment response rates. These results are consistent with the concept that targeting the IL-23–IL-17 immune axis may reduce the disease burden in patients with Crohn's disease and suggest that targeting additional check points along this pathway may be effective.

On the basis of preclinical studies of IL-17 blockade in models of IBD and the encouraging ustekinumab study, two groups have evaluated IL-17-specific antibodies in patients with IBD. Unexpectedly, trials of brodalumab and secukinumab for Crohn's disease were terminated owing to a lack of efficacy and/or disease exacerbation[166,167]. None of the treatment groups receiving IL-17RA-specific antibody showed improvement in Crohn's Disease Activity Index scores compared with patients receiving placebo. Moreover, these trials showed a disproportionate worsening of disease in patients who were treated with IL-17RA-specific antibodies. A higher frequency of fungal infections was observed in patients on secukinumab (9%) compared with placebo (0%), consistent with the possibility that inhibition of IL-17 may increase susceptibility to CMC (see above). However, it is unclear why this condition occurred during secukinumab treatment in patients with Crohn's disease but not in those with psoriasis. To compound the situation, post hoc analysis revealed that the subgroup of patients who were treated with IL-17RA-specific antibodies and showed disease exacerbation had elevated inflammatory markers, including serum CRP and faecal calprotectin (also known as S100A8–S100A9)[166], which are known targets of IL-23 and IL-22. It is intriguing that the blockade of IL-17 results in mucosal tissue damage that is associated with upregulation of IL-23 and RORγt-dependent inflammatory signals. One plausible explanation is that the basal levels of IL-17 may be gut-protective. Indeed, *Il17*$^{-/-}$ mice have increased gut mucosal permeability, predisposing them to higher incidence and severity of IBD[168], which is perhaps owing to impaired tight junction integrity (C. M. Tato and D.J.C., unpublished observations). These findings may explain the differences between targeting IL-12p40 and IL-23p19 — which leave tonic levels of IL-17 intact — compared with complete ablation of IL-17.

Conclusions and perspectives

Since the discovery of the IL-23–T_H17 immune pathway a decade ago, immunologists and clinicians have diligently worked to bring novel therapeutic strategies targeting the IL-23–IL-17 axis to the clinic. Such therapies are now showing encouraging results for psoriasis, Crohn's disease, rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis[165,169]. However, this treatment strategy is complex. It was initially assumed that IL-23 controls the production of pathogenic IL-17 and that these cytokines are 'duplicate' targets. Recent clinical results suggest that is not the case at all. We are now beginning to appreciate that IL-23p19-specific versus IL-17-specific antibody treatments each have their own beneficial effects, as well as each presenting unique challenges in different disease settings. For example, IL-17-specific antibodies showed good therapeutic efficacy for the treatment of psoriasis — even surpassing TNF-specific antibody therapy[164,170] — but have failed to treat Crohn's disease. The search for better clinical efficacy biomarkers is crucially needed to improve patient stratification and the selection of particular disease indications. In addition, a better understanding of T_H17 cell biology and cellular mechanisms would allow the discovery of additional targets for inflammatory diseases.

Research in deciphering IL-17R-mediated signal transduction cascades has advanced considerably in recent years. Data indicate that although these signalling pathways overlap with IL-1R- and TLR-mediated pathways in many respects, there are also distinct processes that seem to be IL-17 specific. Understanding these events, particularly those that are unique to the IL-17 pathway, may reveal novel treatment strategies. Similarly, new insights into the epigenetic and transcriptional control of T_H17 cells have revealed new treatment paradigms. A novel approach could be to destabilize the T_H17 cell lineage by inducing reprogramming or functional suppression, which could have immense therapeutic potential. Indeed, the suppression of JAK- and tyrosine kinase 2 (TYK2)-dependent STAT3 activation[171,172], as well as the direct inhibition of RORγt — using small-molecule pharmacologic agents — have demonstrated impressive efficacy in preclinical disease models[173–176]. It is only a matter of time before these new therapeutic approaches will begin to make a difference in the clinic. Thus, the discovery of the IL-23–IL-17 immune axis has brought about fundamental changes in our understanding of cellular immunology and, more importantly, improved the quality of life for many patients.

1. Cua, D. J. *et al.* Interleukin-23 rather than interleukin-12 is the critical cytokine for autoimmune inflammation of the brain. *Nature* **421**, 744–748 (2003).
This study shows that IL-23 controls a key checkpoint for the induction of autoimmune inflammation.
2. Oppmann, B. *et al.* Novel p19 protein engages IL-12p40 to form a cytokine, IL-23, with biological activities similar as well as distinct from IL-12. *Immunity* **13**, 715–725 (2000).
3. Kastelein, R. A., Hunter, C. A. & Cua, D. J. Discovery and biology of IL-23 and IL-27: related but functionally distinct regulators of inflammation. *Annu. Rev. Immunol.* **25**, 221–242 (2007).
4. Langrish, C. L. *et al.* IL-23 drives a pathogenic T cell population that induces autoimmune inflammation. *J. Exp. Med.* **201**, 233–240 (2005).
This is the first study to suggest that IL-17-producing cells are crucial mediators of autoimmunity, and it led to the proposal of the T_H17 hypothesis.
5. Murphy, C. A. *et al.* Divergent pro- and antiinflammatory roles for IL-23 and IL-12 in joint autoimmune inflammation. *J. Exp. Med.* **198**, 1951–1957 (2003).
6. Harrington, L. E. *et al.* Interleukin 17-producing CD4$^+$ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages. *Nature Immunol.* **6**, 1123–1132 (2005).
This study coined the term 'T_H17' cells to describe a unique lineage that is STAT3 dependent, rather than STAT4- and STAT6-independent.
7. Park, H. *et al.* A distinct lineage of CD4 T cells regulates tissue inflammation by producing interleukin 17. *Nature Immunol.* **6**, 1133–1141 (2005).
This is one of the first papers suggesting the existence of IL-17-producing inflammatory T cells.
8. Mosmann, T. R., Cherwinski, H., Bond, M. W., Giedlin, M. A. & Coffman, R. L. Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. *J. Immunol.* **136**, 2348–2357 (1986).
This is the landmark paper proposing the T_H1 – T_H2 hypothesis.
9. Mosmann, T. R. & Coffman, R. L. TH1 and TH2 cells: different patterns of lymphokine secretion lead to different functional properties. *Annu. Rev. Immunol.* **7**, 145–173 (1989).
10. Parham, C. *et al.* A receptor for the heterodimeric cytokine IL-23 is composed of IL-12Rβ1 and a novel cytokine receptor subunit, IL-23R. *J. Immunol.* **168**, 5699–5708 (2002).
11. Weaver, C. T., Hatton, R. D., Mangan, P. R. & Harrington, L. E. IL-17 family cytokines and the expanding diversity of effector T cell lineages. *Annu. Rev. Immunol.* **25**, 821–852 (2007).
12. Ivanov, I. I. *et al.* The orphan nuclear receptor RORγt directs the differentiation program of proinflammatory IL-17$^+$ T helper cells. *Cell* **126**, 1121–1133 (2006).
This study describes the discovery of a novel transcriptional regulator that controls *Il17a* expression and provides the definitive proof that T_H17 cells belong to a new lineage of CD4$^+$ T_H cells.
13. Cua, D. J. & Tato, C. M. Innate IL-17-producing cells: the sentinels of the immune system. *Nature Rev. Immunol.* **10**, 479–489 (2010).

14. Annunziato, F., Cosmi, L., Liotta, F., Maggi, E. & Romagnani, S. Type 17 T helper cells—origins, features and possible roles in rheumatic disease. *Nature Rev. Rheumatol.* **5**, 325–331 (2009).
15. Zuniga, L. A., Jain, R., Haines, C. & Cua, D. J. Th17 cell development: from the cradle to the grave. *Immunol. Rev.* **252**, 78–88 (2013).
16. Kim, J. S. *et al.* Natural and inducible T_H17 cells are regulated differently by Akt and mTOR pathways. *Nature Immunol.* **14**, 611–618 (2013).
17. Marks, B. R. *et al.* Thymic self-reactivity selects natural interleukin 17-producing T cells that can regulate peripheral inflammation. *Nature Immunol.* **10**, 1125–1132 (2009).
18. Zheng, Y. *et al.* Interleukin-22, a T_H17 cytokine, mediates IL-23-induced dermal inflammation and acanthosis. *Nature* **445**, 648–651 (2007).
19. El-Behi, M. *et al.* The encephalitogenicity of T_H17 cells is dependent on IL-1- and IL-23-induced production of the cytokine GM-CSF. *Nature Immunol.* **12**, 568–575 (2011).
20. Codarri, L. *et al.* RORγt drives production of the cytokine GM-CSF in helper T cells, which is essential for the effector phase of autoimmune neuroinflammation. *Nature Immunol.* **12**, 560–567 (2011).
21. McGeachy, M. J. *et al.* TGF-β and IL-6 drive the production of IL-17 and IL-10 by T cells and restrain T_H-17 cell-mediated pathology. *Nature Immunol.* **8**, 1390–1397 (2007).
22. Hirota, K. *et al.* Plasticity of Th17 cells in Peyer's patches is responsible for the induction of T cell-dependent IgA responses. *Nature Immunol.* **14**, 372–379 (2013).
23. Esplugues, E. *et al.* Control of T_H17 cells occurs in the small intestine. *Nature* **475**, 514–518 (2011).
24. Chackerian, A. A. *et al.* Neutralization or absence of the interleukin-23 pathway does not compromise immunity to mycobacterial infection. *Infect. Immun.* **74**, 6092–6099 (2006).
25. Chen, Y. *et al.* Anti-IL-23 therapy inhibits multiple inflammatory pathways and ameliorates autoimmune encephalomyelitis. *J. Clin. Invest.* **116**, 1317–1326 (2006).
26. Lieberman, L. A. *et al.* IL-23 provides a limited mechanism of resistance to acute toxoplasmosis in the absence of IL-12. *J. Immunol.* **173**, 1887–1893 (2004).
27. Bettelli, E. *et al.* Reciprocal developmental pathways for the generation of pathogenic effector T_H17 and regulatory T cells. *Nature* **441**, 235–238 (2006).
28. Mangan, P. R. *et al.* Transforming growth factor-β induces development of the T_H17 lineage. *Nature* **441**, 231–234 (2006).
29. Veldhoen, M., Hocking, R. J., Atkins, C. J., Locksley, R. M. & Stockinger, B. TGFβ in the context of an inflammatory cytokine milieu supports *de novo* differentiation of IL-17-producing T cells. *Immunity* **24**, 179–189 (2006).
References 27–29 show the importance of TGFβ plus IL-6 in the lineage specification of T_H17 cells.
30. Yang, X. O. *et al.* STAT3 regulates cytokine-mediated generation of inflammatory helper T cells. *J. Biol. Chem.* **282**, 9358–9363 (2007).
31. Durant, L. *et al.* Diverse targets of the transcription factor STAT3 contribute to T cell pathogenicity and homeostasis. *Immunity* **32**, 605–615 (2010).
32. Samoilova, E. B., Horton, J. L., Hilliard, B., Liu, T. S. & Chen, Y. IL-6-deficient mice are resistant to experimental autoimmune encephalomyelitis: roles of IL-6 in the activation and differentiation of autoreactive T cells. *J. Immunol.* **161**, 6480–6486 (1998).
33. Alonzi, T. *et al.* Interleukin 6 is required for the development of collagen-induced arthritis. *J. Exp. Med.* **187**, 461–468 (1998).
34. Korn, T. *et al.* IL-21 initiates an alternative pathway to induce proinflammatory T_H17 cells. *Nature* **448**, 484–487 (2007).
35. Nurieva, R. *et al.* Essential autocrine regulation by IL-21 in the generation of inflammatory T cells. *Nature* **448**, 480–483 (2007).
36. Spolski, R. & Leonard, W. J. The Yin and Yang of interleukin-21 in allergy, autoimmunity and cancer. *Curr. Opin. Immunol.* **20**, 295–301 (2008).
37. Sutton, C., Brereton, C., Keogh, B., Mills, K. H. & Lavelle, E. C. A crucial role for interleukin (IL)-1 in the induction of IL-17-producing T cells that mediate autoimmune encephalomyelitis. *J. Exp. Med.* **203**, 1685–1691 (2006).
38. Chung, Y. *et al.* Critical regulation of early Th17 cell differentiation by interleukin-1 signaling. *Immunity* **30**, 576–587 (2009).
39. Gulen, M. F. *et al.* The receptor SIGIRR suppresses Th17 cell proliferation via inhibition of the interleukin-1 receptor pathway and mTOR kinase activation. *Immunity* **32**, 54–66 (2010).
This paper shows that IL-1 is a key factor that provides a key competitive advantage for *in vivo* T_H17 cell expansion and survival during inflammatory conditions by inducing catabolic energy pathways.
40. Veldhoen, M., Hocking, R. J., Flavell, R. A. & Stockinger, B. Signals mediated by transforming growth factor-β initiate autoimmune encephalomyelitis, but chronic inflammation is needed to sustain disease. *Nature Immunol.* **7**, 1151–1156 (2006).
41. Li, M. O., Wan, Y. Y. & Flavell, R. A. T cell-produced transforming growth factor-β1 controls T cell tolerance and regulates Th1- and Th17-cell differentiation. *Immunity* **26**, 579–591 (2007).
42. Gutcher, I. *et al.* Autocrine transforming growth factor-β1 promotes *in vivo* Th17 cell differentiation. *Immunity* **34**, 396–408.
43. Das, J. *et al.* Transforming growth factor β is dispensable for the molecular orchestration of Th17 cell differentiation. *J. Exp. Med.* **206**, 2407–2416 (2009).
44. Volpe, E. *et al.* A critical function for transforming growth factor-β, interleukin 23 and proinflammatory cytokines in driving and modulating human T_H-17 responses. *Nature Immunol.* **9**, 650–657 (2008).
45. Manel, N., Unutmaz, D. & Littman, D. R. The differentiation of human T_H-17 cells requires transforming growth factor-β and induction of the nuclear receptor RORγt. *Nature Immunol.* **9**, 641–649 (2008).
46. Acosta-Rodriguez, E. V., Napolitani, G., Lanzavecchia, A. & Sallusto, F. Interleukins 1β and 6 but not transforming growth factor-β are essential for the differentiation of interleukin 17-producing human T helper cells. *Nature Immunol.* **8**, 942–949 (2007).
47. Wilson, N. J. *et al.* Development, cytokine profile and function of human interleukin 17-producing helper T cells. *Nature Immunol.* **8**, 950–957 (2007).
48. Chen, Z., Tato, C. M., Muul, L., Laurence, A. & O'Shea, J. J. Distinct regulation of interleukin-17 in human T helper lymphocytes. *Arthritis Rheum.* **56**, 2936–2946 (2007).
49. Yang, Y. *et al.* T-bet is essential for encephalitogenicity of both Th1 and Th17 cells. *J. Exp. Med.* **206**, 1549–1564 (2009).
50. Jager, A., Dardalhon, V., Sobel, R. A., Bettelli, E. & Kuchroo, V. K. Th1, Th17, and Th9 effector cells induce experimental autoimmune encephalomyelitis with different pathological phenotypes. *J. Immunol.* **183**, 7169–7177 (2009).
51. McGeachy, M. J. *et al.* The interleukin 23 receptor is essential for the terminal differentiation of interleukin 17-producing effector T helper cells *in vivo*. *Nature Immunol.* **10**, 314–324 (2009).
This paper describes the crucial roles of IL-23 for the *in vivo* expansion and function of T_H17 cells during inflammation.
52. Haines, C. J. *et al.* Autoimmune memory T helper 17 cell function and expansion are dependent on interleukin-23. *Cell Rep.* **3**, 1378–1388 (2013).
53. Ghoreschi, K. *et al.* Generation of pathogenic T_H17 cells in the absence of TGF-β signalling. *Nature* **467**, 967–971 (2010).
54. Kebir, H. *et al.* Preferential recruitment of interferon-γ-expressing T_H17 cells in multiple sclerosis. *Ann. Neurol.* **66**, 390–402 (2009).
55. Hirota, K. *et al.* Fate mapping of IL-17-producing T cells in inflammatory responses. *Nature Immunol.* **12**, 255–263 (2011).
This elegant study used an *Il17a* fate-mapping strategy to demonstrate the existence of "ex-T_H17" cells driving autoimmune pathology.
56. Lee, Y. *et al.* Induction and molecular signature of pathogenic T_H17 cells. *Nature Immunol.* **13**, 991–999 (2012).
57. Duerr, R. H. *et al.* A genome-wide association study identifies *IL23R* as an inflammatory bowel disease gene. *Science* **314**, 1461–1463 (2006).
58. Liu, Y. *et al.* A genome-wide association study of psoriasis and psoriatic arthritis identifies new disease loci. *PLoS Genet.* **4**, e1000041 (2008).
59. Reveille, J. D. *et al.* Genome-wide association study of ankylosing spondylitis identifies non-MHC susceptibility loci. *Nature Genet.* **42**, 123–127 (2010).
60. Lock, C. *et al.* Gene-microarray analysis of multiple sclerosis lesions yields new targets validated in autoimmune encephalomyelitis. *Nature Med.* **8**, 500–508 (2002).
61. Burton, P. R. *et al.* Association scan of 14,500 nonsynonymous SNPs in four diseases identifies autoimmunity variants. *Nature Genet.* **39**, 1329–1337 (2007).
62. Ghoreschi, K. *et al.* Generation of pathogenic T_H17 cells in the absence of TGF-β signalling. *Nature* **467**, 967–971 (2010).
63. Diveu, C. *et al.* IL-27 blocks RORc expression to inhibit lineage commitment of Th17 cells. *J. Immunol.* **182**, 5748–5756 (2009).
This study shows that IL-27 is an inhibitor of the T_H17 immune pathway and explores the mechanisms underlying IL-27-mediated regulation of inflammation.
64. Laurence, A. *et al.* Interleukin-2 signaling via STAT5 constrains T helper 17 cell generation. *Immunity* **26**, 371–381 (2007).
65. El-behi, M. *et al.* Differential effect of IL-27 on developing versus committed Th17 cells. *J. Immunol.* **183**, 4957–4967 (2009).
66. Veldhoen, M. *et al.* The aryl hydrocarbon receptor links T_H17-cell-mediated autoimmunity to environmental toxins. *Nature* **453**, 106–109 (2008).
67. Quintana, F. J. *et al.* Control of T_{reg} and T_H17 cell differentiation by the aryl hydrocarbon receptor. *Nature* **453**, 65–71 (2008).
68. Apetoh, L. *et al.* The aryl hydrocarbon receptor interacts with c-Maf to promote the differentiation of type 1 regulatory T cells induced by IL-27. *Nature Immunol.* **11**, 854–861 (2010).
69. Milner, J. D. *et al.* Impaired T_H17 cell differentiation in subjects with autosomal dominant hyper-IgE syndrome. *Nature* **452**, 773–776 (2008).
70. Minegishi, Y. *et al.* Dominant-negative mutations in the DNA-binding domain of STAT3 cause hyper-IgE syndrome. *Nature* **448**, 1058–1062 (2007).
71. Ise, W. *et al.* The transcription factor BATF controls the global regulators of class-switch recombination in both B cells and T cells. *Nature Immunol.* **12**, 536–543 (2011).
72. Schraml, B. U. *et al.* The AP-1 transcription factor *Batf* controls T_H17 differentiation. *Nature* **460**, 405–409 (2009).
73. Lohoff, M. *et al.* Dysregulated T helper cell differentiation in the absence of interferon regulatory factor 4. *Proc. Natl Acad. Sci. USA* **99**, 11808–11812 (2002).
74. Brustle, A. *et al.* The development of inflammatory T_H-17 cells requires interferon-regulatory factor 4. *Nature Immunol.* **8**, 958–966 (2007).
75. Li, P. *et al.* BATF–JUN is critical for IRF4-mediated transcription in T cells. *Nature* **490**, 543–546 (2012).
76. Ciofani, M. *et al.* A validated regulatory network for Th17 cell specification. *Cell* **151**, 289–303 (2012).
This study argues against the hypothesis that RORγt is the only factor that regulates the specification of the T_H17 lineage.
77. Oestreich, K. J. & Weinmann, A. S. Master regulators or lineage-specifying? Changing views on $CD4^+$ T cell transcription factors. *Nature Rev. Immunol.* **12**, 799–804 (2012).
78. Vahedi, G. *et al.* STATs shape the active enhancer landscape of T cell populations. *Cell* **151**, 981–993 (2012).
79. Samstein, R. M. *et al.* Foxp3 exploits a pre-existent enhancer landscape for regulatory T cell lineage specification. *Cell* **151**, 153–166 (2012).
80. Dang, E. V. *et al.* Control of T_H17/T_{reg} balance by hypoxia-inducible factor 1. *Cell* **146**, 772–784 (2011).
81. Chen, Z. *et al.* The ubiquitin ligase Stub1 negatively modulates regulatory T cell suppressive activity by promoting degradation of the transcription factor Foxp3. *Immunity* **39**, 272–285 (2013).
82. van Loosdregt, J. *et al.* Stabilization of the transcription factor Foxp3 by the deubiquitinase USP7 increases Treg-cell-suppressive capacity. *Immunity* **39**, 259–271 (2013).
83. Yang, X. O. *et al.* Molecular antagonism and plasticity of regulatory and inflammatory T cell programs. *Immunity* **29**, 44–56 (2008).
84. Wei, G. *et al.* Global mapping of H3K4me3 and H3K27me3 reveals specificity and plasticity in lineage fate determination of differentiating $CD4^+$ T cells. *Immunity* **30**, 155–167 (2009).
85. Lee, Y. K. *et al.* Late developmental plasticity in the T helper 17 lineage. *Immunity* **30**, 92–107 (2009).
86. Morrison, P. J. *et al.* Th17-cell plasticity in Helicobacter hepaticus-induced intestinal inflammation. *Mucosal Immunol.* **6**, 1143–1156 (2013).

87. Iwakura, Y., Ishigame, H., Saijo, S. & Nakae, S. Functional specialization of interleukin-17 family members. *Immunity* **34**, 149–162 (2011).
88. Onishi, R. & Gaffen, S. L. IL-17 and its target genes: mechanisms of IL-17 function in disease. *Immunology* **129**, 311–321 (2010).
89. Yao, Z. *et al.* Herpesvirus Saimiri encodes a new cytokine, IL-17, which binds to a novel cytokine receptor. *Immunity* **3**, 811–821 (1995).
90. Ishigame, H. *et al.* Differential roles of interleukin-17A and -17F in host defense against mucoepithelial bacterial infection and allergic responses. *Immunity* **30**, 108–119 (2009).
91. Novatchkova, M., Leibbrandt, A., Werzowa, J., Neubuser, A. & Eisenhaber, F. The STIR-domain superfamily in signal transduction, development and immunity. *Trends Biochem. Sci.* **28**, 226–229 (2003).
92. Rickel, E. A. *et al.* Identification of functional roles for both IL-17RB and IL-17RA in mediating IL-25-induced activities. *J. Immunol.* **181**, 4299–4310 (2008).
93. Bordon, Y. Cytokines: IL-17C joins the family firm. *Nature Rev. Immunol.* **11**, 805 (2011).
94. Qian, Y. *et al.* The adaptor Act1 is required for interleukin 17-dependent signaling associated with autoimmune and inflammatory disease. *Nature Immunol.* **8**, 247–256 (2007).
95. Chang, S. H., Park, H. & Dong, C. Act1 adaptor protein is an immediate and essential signaling component of interleukin-17 receptor. *J. Biol. Chem.* **281**, 35603–35607 (2006).
96. Li, X. Act1 modulates autoimmunity through its dual functions in CD40L/BAFF and IL-17 signaling. *Cytokine* **41**, 105–113 (2008).
97. Liu, C. *et al.* Act1, a U-box E3 ubiquitin ligase for IL-17 signaling. *Sci. Signal.* **2**, ra63 (2009).
98. Schwandner, R., Yamaguchi, K. & Cao, Z. Requirement of tumor necrosis factor-associated factor (TRAF)6 in interleukin 17 signal transduction. *J. Exp. Med.* **191**, 1233–1239 (2000).
99. Sun, D. *et al.* Treatment with IL-17 prolongs the half-life of chemokine CXCL1 mRNA via the adaptor TRAF5 and the splicing-regulatory factor SF2 (ASF). *Nature Immunol.* **12**, 853–860 (2011).
100. Herjan, T. *et al.* HuR is required for IL-17-induced Act1-mediated CXCL1 and CXCL5 mRNA stabilization. *J. Immunol.* **191**, 640–649 (2013).
101. Bulek, K. *et al.* The inducible kinase IKKi is required for IL-17-dependent signaling associated with neutrophilia and pulmonary inflammation. *Nature Immunol.* **12**, 844–852 (2011).
102. Qu, F. *et al.* TRAF6-dependent Act1 phosphorylation by the IκB kinase-related kinases suppresses interleukin-17-induced NF-κB activation. *Mol. Cell. Biol.* **32**, 3925–3937 (2012).
103. Wang, C. *et al.* The psoriasis-associated D10N variant of the adaptor Act1 with impaired regulation by the molecular chaperone hsp90. *Nature Immunol.* **14**, 72–81 (2013).
104. Sonder, S. U. *et al.* IL-17-induced NF-κB activation via CIKS/Act1: physiologic significance and signaling mechanisms. *J. Biol. Chem.* **286**, 12881–12890 (2011).
105. Huffmeier, U. *et al.* Common variants at *TRAF3IP2* are associated with susceptibility to psoriatic arthritis and psoriasis. *Nature Genet.* **42**, 996–999 (2010).
106. Shen, F., Ruddy, M. J., Plamondon, P. & Gaffen, S. L. Cytokines link osteoblasts and inflammation: microarray analysis of interleukin-17- and TNF-α-induced genes in bone cells. *J. Leukoc. Biol.* **77**, 388–399 (2005).
107. Acosta-Rodriguez, E. V. *et al.* Surface phenotype and antigenic specificity of human interleukin 17-producing T helper memory cells. *Nature Immunol.* **8**, 639–646 (2007).
108. Yang, D. *et al.* β-Defensins: Linking innate immunity and adaptive immunity through dendritic and T cell CCR6. *Science* **286**, 525–528 (1999).
109. Goetz, D. H. *et al.* The neutrophil lipocalin NGAL is a bacteriostatic agent that interferes with siderophore-mediated iron acquisition. *Mol. Cell* **10**, 1033–1043 (2002).
110. Ruddy, M. J. *et al.* Functional cooperation between interleukin-17 and tumor necrosis factor-a is mediated by CCAAT/enhancer binding protein family members. *J. Biol. Chem.* **279**, 2559–2567 (2004).
111. Shen, F., Hu, Z., Goswami, J. & Gaffen, S. L. Identification of common transcriptional regulatory elements in interleukin-17 target genes. *J. Biol. Chem.* **281**, 24138–24148 (2006).
112. Patel, D. N. *et al.* Interleukin-17 stimulates C-reactive protein expression in hepatocytes and smooth muscle cells via p38 MAPK and ERK1/2-dependent NF-κB and C/EBPβ activation. *J. Biol. Chem.* **282**, 27229–27238 (2007).
113. Ramji, D. P. & Foka, P. CCAAT/enhancer-binding proteins: structure, function and regulation. *Biochem. J.* **365**, 561–575 (2002).
114. Shen, F. *et al.* IL-17 receptor signaling inhibits C/EBPβ by sequential phosphorylation of the regulatory 2 domain. *Sci. Signal.* **2**, ra8 (2009).
115. Zrioual, S. *et al.* Genome-wide comparison between IL-17A- and IL-17F-induced effects in human rheumatoid arthritis synoviocytes. *J. Immunol.* **182**, 3112–3120 (2009).
116. Shen, F. & Gaffen, S. L. Structure–function relationships in the IL-17 receptor: Implications for signal transduction and therapy. *Cytokine* **41**, 92–104 (2008).
117. Karlsen, J. R., Borregaard, N. & Cowland, J. B. Induction of neutrophil gelatinase-associated lipocalin expression by co-stimulation with interleukin-17 and tumor necrosis factor-α is controlled by IκB-ζ but neither by C/EBP-β nor C/EBP-δ. *J. Biol. Chem.* **285**, 14088–14100 (2010).
118. Zhong, B. *et al.* Negative regulation of IL-17-mediated signaling and inflammation by the ubiquitin-specific protease USP25. *Nature Immunol.* **13**, 1110–1117 (2012).
119. Garg, A. V., Ahmed, M., Vallejo, A. N., Ma, A. & Gaffen, S. L. The deubiquitinase A20 mediates feedback inhibition of interleukin-17 receptor signaling. *Sci. Signal.* **6**, ra44 (2013).
References 118 and 119 show that IL-17R signalling is restrained by multiple deubiquitylating enzymes that target TRAF6.
120. Ma, A. & Malynn, B. A. A20: linking a complex regulator of ubiquitylation to immunity and human disease. *Nature Rev. Immunol.* **12**, 774–785 (2012).
121. Zhu, S. *et al.* Modulation of experimental autoimmune encephalomyelitis through TRAF3-mediated suppression of interleukin 17 receptor signaling. *J. Exp. Med.* **207**, 2647–2662 (2010).
122. Maitra, A. *et al.* Distinct functional motifs within the IL-17 receptor regulate signal transduction and target gene expression. *Proc. Natl Acad. Sci, USA* **104**, 7506–7511 (2007).
123. Shembade, N. & Harhaj, E. W. Regulation of NF-κB signaling by the A20 deubiquitinase. *Cell. Mol. Immunol.* **9**, 123–130 (2012).
124. Iha, H. *et al.* Inflammatory cardiac valvulitis in TAX1BP1-deficient mice through selective NF-κB activation. *EMBO J.* **27**, 629–641 (2008).
125. Shembade, N. *et al.* The E3 ligase Itch negatively regulates inflammatory signaling pathways by controlling the function of the ubiquitin-editing enzyme A20. *Nature Immunol.* **9**, 254–262 (2008).
126. Garg, A. V. & Gaffen, S. L. IL-17 signaling and A20: a balancing act. *Cell Cycle* **12**, 3459–3460 (2013).
127. Ho, A. W. *et al.* The anaphase-promoting complex protein 5 (AnapC5) associates with A20 and inhibits IL-17-mediated signal transduction. *PLoS ONE* **8**, e70168 (2013).
128. Shi, P. *et al.* Persistent stimulation with interleukin-17 desensitizes cells through $SCF^{\beta\text{-}TrCP}$-mediated degradation of Act1. *Sci. Signal.* **4**, ra73 (2011).
129. Xie, P. TRAF molecules in cell signaling and in human diseases. *J. Mol. Signal* **8**, 1–31 (2013).
130. Zepp, J. A. *et al.* Cutting edge: TNF receptor-associated factor 4 restricts IL-17-mediated pathology and signaling processes. *J. Immunol.* **189**, 33–37 (2012).
131. O'Connell, R. M. *et al.* MicroRNA-155 promotes autoimmune inflammation by enhancing inflammatory T cell development. *Immunity* **33**, 607–619 (2010).
132. Yao, R. *et al.* MicroRNA-155 modulates Treg and Th17 cells differentiation and Th17 cell function by targeting SOCS1. *PLoS ONE* **7**, e46082 (2012).
133. Murugaiyan, G., Beynon, V., Mittal, A., Joller, N. & Weiner, H. L. Silencing microRNA-155 ameliorates experimental autoimmune encephalomyelitis. *J. Immunol.* **187**, 2213–2221 (2011).
134. Zhu, S. *et al.* The microRNA miR-23b suppresses IL-17-associated autoimmune inflammation by targeting TAB2, TAB3 and IKK-α. *Nature Med.* **18**, 1077–1086 (2012).
This is the first identification of an miRNA feedback loop in the IL-17R signalling pathway.
135. Milner, J. D. & Holland, S. M. The cup runneth over: lessons from the ever-expanding pool of primary immunodeficiency diseases. *Nature Rev. Immunol.* **13**, 635–648 (2013).
136. von Bernuth, H. *et al.* Pyogenic bacterial infections in humans with MyD88 deficiency. *Science* **321**, 691–696 (2008).
137. Ma, C. S. *et al.* Deficiency of Th17 cells in hyper IgE syndrome due to mutations in *STAT3*. *J. Exp. Med.* **205**, 1551–1557 (2008).
138. Glocker, E. O. *et al.* A homozygous *CARD9* mutation in a family with susceptibility to fungal infections. *N. Engl. J. Med.* **361**, 1727–1735 (2009).
139. Liu, L. *et al.* Gain-of-function human *STAT1* mutations impair IL-17 immunity and underlie chronic mucocutaneous candidiasis. *J. Exp. Med.* **208**, 1635–1648 (2011).
140. van de Veerdonk, F. L. *et al. STAT1* mutations in autosomal dominant chronic mucocutaneous candidiasis. *N. Engl. J. Med.* **365**, 54–61 (2011).
141. Puel, A. *et al.* Autoantibodies against IL-17A, IL-17F, and IL-22 in patients with chronic mucocutaneous candidiasis and autoimmune polyendocrine syndrome type I. *J. Exp. Med.* **207**, 291–297 (2010).
142. Kisand, K. *et al.* Chronic mucocutaneous candidiasis in APECED or thymoma patients correlates with autoimmunity to Th17-associated cytokines. *J. Exp. Med.* **207**, 299–308 (2010).
143. Puel, A. *et al.* Chronic mucocutaneous candidiasis in humans with inborn errors of interleukin-17 immunity. *Science* **332**, 65–68 (2011).
144. Boisson, B. *et al.* A biallelic *ACT1* mutation selectively abolishes interleukin-17 responses in humans with chronic mucocutaneous candidiasis. *Immunity* **39**, 676–686 (2013).
References 143 and 144 directly link mucosal *C. albicans* infections with the IL-17R-mediated signalling axis.
145. Hernández-Santos, N. & Gaffen, S. L. Th17 cells in immunity to *Candida albicans*. *Cell Host Microbe* **11**, 425–435 (2012).
146. Stark, M. A. *et al.* Phagocytosis of apoptotic neutrophils regulates granulopoiesis via IL-23 and IL-17. *Immunity* **22**, 285–294 (2005).
147. Sherlock, J. P. *et al.* IL-23 induces spondyloarthropathy by acting on ROR-γt$^+$ CD3$^+$CD4$^-$ CD8$^-$ entheseal resident T cells. *Nature Med.* **18**, 1069–1076 (2012).
148. Chan, J. R. *et al.* IL-23 stimulates epidermal hyperplasia via TNF and IL-20R2-dependent mechanisms with implications for psoriasis pathogenesis. *J. Exp. Med.* **203**, 2577–2587 (2006).
149. Tonel, G. *et al.* Cutting edge: A critical functional role for IL-23 in psoriasis. *J. Immunol.* **185**, 5688–5691 (2010).
150. Perera, G. K., Di Meglio, P. & Nestle, F. O. Psoriasis. *Annu. Rev. Pathol.* **7**, 385–422 (2012).
151. Villanova, F. *et al.* Characterization of innate lymphoid cells in human skin and blood demonstrates increase of NKp44 + ILC3 in psoriasis. *J. Invest. Dermatol.* **134**, 984–991 (2014).
152. Guttman-Yassky, E. *et al.* Low expression of the IL-23/Th17 pathway in atopic dermatitis compared to psoriasis. *J. Immunol.* **181**, 7420–7427 (2008).
153. Rudwaleit, M. *et al.* The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. *Ann. Rheum. Dis.* **70**, 25–31 (2011).
154. van Echteld, I. *et al.* Identification of the most common problems by patients with ankylosing spondylitis using the international classification of functioning, disability and health. *J. Rheumatol* **33**, 2475–2483 (2006).
155. Mielants, H. *et al.* The evolution of spondyloarthropathies in relation to gut histology. II. Histological aspects. *J. Rheumatol* **22**, 2273–2278 (1995).
156. Cotterill, L. *et al.* Replication and meta-analysis of 13,000 cases defines the risk for interleukin-23 receptor and autophagy-related 16-like 1 variants in Crohn's disease. *Can. J. Gastroenterol.* **24**, 297–302 (2010).
157. Lesage, S. *et al. CARD15/NOD2* mutational analysis and genotype-phenotype correlation in 612 patients with inflammatory bowel disease. *Am. J. Hum. Genet.* **70**, 845–857 (2002).
158. Fujino, S. *et al.* Increased expression of interleukin 17 in inflammatory bowel disease. *Gut* **52**, 65–70 (2003).
159. Dige, A. *et al.* Increased levels of circulating Th17 cells in quiescent versus active Crohn's disease. *J. Crohns Colitis* **7**, 248–255 (2013).

160. Leonardi, C. *et al.* Anti-interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. *N. Engl. J. Med.* **366**, 1190–1199 (2012).
161. Rich, P. *et al.* Secukinumab induction and maintenance therapy in moderate-to-severe plaque psoriasis: a randomized, double-blind, placebo-controlled, phase II regimen-finding study. *Br. J. Dermatol.* **168**, 402–411 (2013).
162. Papp, K. A. *et al.* Brodalumab, an anti-interleukin-17-receptor antibody for psoriasis. *N. Engl. J. Med.* **366**, 1181–1189 (2012).
References 160–162 report clinical trials that reveal the remarkable efficacy of IL-17- or IL-17RA-specific antibody therapy for the treatment of psoriasis.
163. Papp, K. A. *et al.* Dose-dependent improvement in chronic plaque psoriasis following treatment with anti-IL-23p19 humanized monoclonal antibody (MK-3222). *Late-breaking Research Symposium. 71st Annual Meeting of the American Academy of Dermatology* (2013).
164. Chiricozzi, A. & Krueger, J. G. IL-17 targeted therapies for psoriasis. *Expert Opin. Investig. Drugs* **22**, 993–1005 (2013).
165. Sandborn, W. J. *et al.* Ustekinumab induction and maintenance therapy in refractory Crohn's disease. *N. Engl. J. Med.* **367**, 1519–1528 (2012).
166. Hueber, W. *et al.* Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn's disease: unexpected results of a randomised, double-blind placebo-controlled trial. *Gut* **61**, 1693–1700 (2012).
167. Targan, S. R. *et al.* A randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and efficacy of AMG 827 in subjects with moderate to severe Crohn's disease. **143**, e26 (2012).
168. Ogawa, A., Andoh, A., Araki, Y., Bamba, T. & Fujiyama, Y. Neutralization of interleukin-17 aggravates dextran sulfate sodium-induced colitis in mice. *Clin. Immunol.* **110**, 55–62 (2004).
169. Patel, D. D., Lee, D. M., Kolbinger, F. & Antoni, C. Effect of IL-17A blockade with secukinumab in autoimmune diseases. *Ann. Rheum. Dis.* **72**, Suppl. 2, iii116–iii123 (2013).
170. Garber, K. Anti-IL-17 mAbs herald new options in psoriasis. *Nature Biotech.* **30**, 475–477 (2012).
171. Nakamura, R. *et al.* Tyk2-signaling plays an important role in host defense against *Escherichia coli* through IL-23-induced IL-17 production by γδ T cells. *J. Immunol.* **181**, 2071–2075 (2008).
172. Ishizaki, M. *et al.* Tyk2 is a therapeutic target for psoriasis-like skin inflammation. *Int. Immunol.* **26**, 257–267 (2013).
173. Solt, L. A. *et al.* Suppression of T_H17 differentiation and autoimmunity by a synthetic ROR ligand. *Nature* **472**, 491–494 (2011).
174. Huh, J. R. *et al.* Digoxin and its derivatives suppress T_H17 cell differentiation by antagonizing RORγt activity. *Nature* **472**, 486–490 (2011).
175. Xiao, S. *et al.* Small-molecule RORγt antagonists inhibit T helper 17 Cell transcriptional network by divergent mechanisms. *Immunity* **40**, 477–489 (2014).
176. Lee, J. S. & Cua, D. J. The emerging landscape of RORγt biology. *Immunity* **40**, 451–452 (2014).
177. Stritesky, G. L., Jameson, S. C. & Hogquist, K. A. Selection of self-reactive T cells in the thymus. *Annu. Rev. Immunol.* **30**, 95–114 (2012).
178. Kronenberg, M. Toward an understanding of NKT cell biology: progress and paradoxes. *Annu. Rev. Immunol.* **23**, 877–900 (2005).
179. Spits, H. *et al.* Innate lymphoid cells—a proposal for uniform nomenclature. *Nature Rev. Immunol.* **13**, 145–149 (2013).
180. Plantinga, T. S. *et al.* Early stop polymorphism in human DECTIN-1 is associated with increased *Candida* colonization in hematopoietic stem cell transplant recipients. *Clin. Infect. Dis.* **49**, 724–732 (2009).
181. Minegishi, Y. *et al.* Human tyrosine kinase 2 deficiency reveals its requisite roles in multiple cytokine signals involved in innate and acquired immunity. *Immunity* **25**, 745–755 (2006).
182. Prando, C. *et al.* Inherited IL-12p40 deficiency: genetic, immunologic, and clinical features of 49 patients from 30 kindreds. *Medicine* **92**, 109–122 (2013).
183. de Beaucoudrey, L. *et al.* Revisiting human IL-12Rβ1 deficiency: a survey of 141 patients from 30 countries. *Medicine* **89**, 381–402 (2010).
184. Ouederni, M. *et al.* Clinical features of Candidiasis in patients with inherited interleukin 12 receptor β1 deficiency. *Clin. Infect. Dis.* **58**, 204–213 (2014).

Acknowledgements
S.L.G. was supported by US National Institutes of Health (NIH) grants AI107825 and DE022550. The content of this review is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Competing interests statement
The authors declare competing interests: see Web version for details.

FURTHER INFORMATION
ClinicalTrials.gov: https://clinicaltrials.gov/

SUPPLEMENTARY INFORMATION
See online article: S1 (table)

ALL LINKS ARE ACTIVE IN THE ONLINE PDF