Regulation and function of innate and adaptive interleukin-17-producing cells

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Interleukin-17 (IL-17)-mediated immune responses play a crucial role in the mucosal host defence against microbial and fungal pathogens. However, the chronic activation of IL-17-producing T helper cells can cause autoimmune disease. In addition, recent studies have highlighted key roles of innate cell-mediated IL-17 responses in various inflammatory settings. Besides inflammation, there have also been intriguing findings regarding the involvement of IL-17 responses in the pathogenesis of cardiovascular diseases and tumour formation. Here, we discuss the latest discoveries in regulation and function of innate and adaptive IL-17-producing cells.

Keywords: IL-17; T_H17 ; autoimmune; mucosal host defence; plasticity
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See Glossary for abbreviations used in this article.

Introduction

Interleukin-17 (IL-17) is a proinflammatory cytokine secreted by innate and adaptive immune cells (Cua & Tato, 2010; Hirota *et al*, 2010; Korn *et al*, 2009). Although the source of IL-17 is restricted to haematopoietic cells, the heterodimeric IL-17 receptor—consisting of IL-17 RA and IL-17 RC—is widely expressed by haematopoietic and non-haematopoietic cells, such as endothelial and epithelial cells. IL-17 downstream signalling is regulated by the complex IL-17R–Act1–TRAF6, which is antagonized by TRAF3 (Zhu *et al*, 2010). Therefore, potential target cell types, tissues and organs are also variable, depending on when and where an IL-17-mediated immune response occurs.

There are several types of haematopoietic cell known to produce IL-17, including $\alpha\beta T$, $\gamma\delta T$ and innate lymphocytes negative for lineage markers (Cupedo *et al*, 2009; Takatori *et al*, 2009). The predominant source of IL-17 depends on the inflammatory and physiological microenvironment, which provides the condition for a particular cell type to secrete IL-17. Analysis of an IL-17 Cre fate reporter mouse emphasized that, under steady-state conditions, most of the IL-17-producing cells are CD4 T cells found in the lamina propria of the small intestine, which also contains a population of innate lympho-

cytes, as previously determined with intracellular staining approaches (Hirota *et al*, 2011). Furthermore, there are $\gamma\delta T$ cells in the skin (dermal $\gamma\delta T$ cells) that express IL-17 (Gray *et al*, 2011), as well as a substantial population of a $\gamma\delta T$ -cell subset that expresses V γ 4 and IL-17 in the lung (Fig 1; J.H.D. & B.S., unpublished observations).

In line with the clear phenotypes of IL-17-deficient mice in various disease models, high levels of IL-17 are induced in response to a range of infections, as well as during the development of several autoimmune diseases.

To understand IL-17-mediated immune responses, several facets of this response have to be taken into account, as the IL-17 receptor is ubiquitously expressed throughout the body, resulting in pleiotropic actions of IL-17 on a wide range of cell types. One of the well-known biological outcomes of IL-17 signalling is the induction of proinflammatory cytokines and chemokines from target cells, such as fibroblasts and epithelial cells, leading to the recruitment of neutrophils (Fossiez *et al*, 1998). The primary function of activated neutrophils is to fight against invading pathogens, but this can damage the surrounding tissues.

Although the mechanisms that underlie the innate IL-17 response remain largely unknown, the differentiation, maintenance and effector function of IL-17-producing CD4 T cells have been extensively studied. Naive CD4 T helper cells can differentiate into IL-17-producing T cells, known as T_H17 cells. This particular subset of T helper cells can secrete not only the signature cytokine IL-17, but also TNF- α , GM-CSF, IL-2, IL-17F and IL-22, depending on inflammatory settings. IL-23 and environmental signals play a crucial role in the pathogenesis of T_H17 cells in autoimmune settings (Stockinger *et al*, 2011).

Here, we review the latest discoveries regarding the regulation and function of innate and adaptive IL-17-producing cells in the context of beneficial and adverse immune responses.

Transcriptional regulation of IL-17-positive cells

There have recently been major advances in our understanding of the transcriptional regulation of T_H17 cells. Although both innate and adaptive IL-17-producing cells express the master transcription factor Ror γ t, the differentiation and regulatory factors seem to differ between innate and adaptive cells. Most studies show a requirement for IL-6 signalling in T_H17 development, but notably IL-6 is irrelevant for the development and maintenance of IL-17-producing $\gamma\delta T$ cells as well as iNKT cells (Doisne *et al*, 2009; Martin *et al*, 2009). How the differentiation of IL-17-producing innate lymphocytes is regulated

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Fig 1 | Location of IL-17-producing cell types. There are characteristic populations of homeostatic IL-17-producing cell types in different mucosal tissues. Upon inflammation, these cells act in their resident tissue or migrate to other tissues to combat infection. For example, LN $CD4^+ T_H17$ cells can give rise to inflammatory $CD4^+ T_H17$ cells that migrate to many tissues in the body. ILC, innate lymphoid cell; iNKT, invariant natural killer T cell; LN, lymph node.

Sidebar A | In need of answers

- Which factors regulate the differentiation of IL-17-producing innate lymphoid cells? Where are they induced?
- Can Ror γ t antagonists limit IL-17-mediated tissue pathology in human diseases?
- Which factors and conditions drive T_H17 plasticity into different cytokine profiles?
- Can 'ex- T_H17 ' cells revert to their original state?
- Does T_H17 memory—in the absence of any triggering stimulus—exist?

is unknown (Sidebar A). Several papers have shown that TGF- β , in combination with IL-6, is required for the induction of Ror γ t and T_H17 development in mice and, in addition, the IL-21 and IL-23 signalling pathways amplify T_H17 differentiation (Hirota *et al*, 2010; Korn *et al*, 2009). In line with this, the development of IL-17-producing $\gamma\delta T$ cells is severely impaired in TGF- β -deficient mice, suggesting a crucial role of TGF- β signalling (Do *et al*, 2010). Nevertheless, this idea was challenged in a study suggesting that TGF- β -independent differentiation of T_H17 cells occurs through IL-23 in combination with IL-6 and IL-1 (Ghoreschi *et al*, 2010). However, it must be noted that, despite the use of neutralizing antibodies against TGF- β , it might be impossible to remove all sources of TGF- β , as a cell-associated form of TGF- β —produced by activated T cells—cannot be neutralized by the widely used TGF- β antibody (Clone:1D11; Oida & Weiner, 2011). Thus, it cannot be excluded that TGF- β generated in activated T cells and acting on bystander cells might have a role in T_H17 differentiation. Although TGF- β was initially reported in human studies to be redundant in generating T_H17 cells (Acosta-Rodriguez *et al*, 2007; Wilson *et al*, 2007), other groups demonstrated subsequently that TGF- β plays a crucial role in the induction of Ror γ t and differentiation of human T_H17 (Manel *et al*, 2008; O'Garra *et al*, 2008; Volpe *et al*, 2008). However, it has been suggested that TGF- β is required only to block the alternative T helper cell differentiation pathways, instead of directly affecting

T_H17 differentiation (Das *et al*, 2009). Indeed, TGF- β signalling suppresses the induction of T_H17 inhibitors such as SOCS3, a well-known negative regulator of STAT3, and blocks the induction of eomesodermin in a Smad-independent manner, indirectly promoting T_H17 differentiation (Ichiyama *et al*, 2011; Qin *et al*, 2009). Furthermore, the role of Smad2 and Smad3 signalling downstream from TGF- β during T_H17 development is not without controversy, as one study shows that both Smad2 and Smad3 are necessary for the optimal induction of T_H17 cells (Takimoto *et al*, 2010), whereas another indicates that Smad3 deficiency increases T_H17 differentiation (Martinez *et al*, 2009). Although there still remain unresolved issues, it is conceivable that TGF- β promotes T_H17 differentiation directly as well as indirectly.

A substantial amount of work has concentrated on the signalling and transcriptional events that occur during T_H17 development, influencing the induction and maintenance of their effector profile (Fig 2). The transcription factors Ror γ t, AhR and I κ B ζ are specifically induced during T_H17 -cell development and have key roles in their differentiation and function (Okamoto *et al*, 2010; Veldhoen *et al*, 2008). STAT3, IRF4, Runx1 and Batf, on the other hand, influence T_H17 development, but their expression is not restricted to T_H17 cells (Korn *et al*, 2009; Schraml *et al*, 2009). As anticipated, the transcriptional modulators that target these key transcription factors can either enhance or impair the differentiation of T_H17 cells. The positive and negative regulators of the key transcription factor IRF4—ROCK2 and IRF4 binding protein, respectively—were clearly shown to alter the activity of IRF4, thereby resulting in the spontaneous development of autoimmune disorders in mice with aberrantly activated ROCK2 and deficient in IRF4 binding protein (Biswas *et al*, 2010; Chen *et al*, 2008). The nuclear receptor LXR negatively regulates the IL-17 immune response by upregulating the transcription factor Srebp-1c, which interacts physically with AhR to interfere with its function in promoting T_H17 development (Cui *et al*, 2011). In addition, the nuclear receptor PPAR γ was shown to negatively regulate T_H17 differentiation by repressing the induction of Ror γ t.

Glossary

Act1	actin-related gene 1
AhR	aryl hydrocarbon receptor
apoE	apolipoprotein E
Batf	basic leucine zipper transcription factor, ATF-like
CARD	caspase recruitment domain family
CCL	chemokine (C-C motif) ligand
CCR	chemokine (C-C motif) receptor
CXCL	chemokine (C-X-C motif) ligand
CD161	killer cell lectin-like receptor subfamily B member 1C
eYFP	enhanced yellow fluorescent protein
FoxP3	forkhead box P3
GM-CSF	granulocyte monocyte colony stimulating factor
HIF-1 α	hypoxia-inducible factor 1 α
IFN- γ	interferon gamma
I κ B ζ	inhibitor of κ B ζ
IL	interleukin
IRF4	interferon regulatory factor 4
iNKT cell	invariant natural killer T cell
IKK- α	inhibitor of NF- κ B kinase alpha
LXR	liver X receptor
mTOR	mammalian target of rapamycin
NF- κ B	nuclear factor κ B
NK	natural killer
NKT	natural killer T
NOD	nucleotide-binding oligomerization domain
PdbU/ion	phorbol 12,13-dibutyrate/ionomycin
PPAR γ	peroxisome proliferator-activated receptor gamma
RAG	recombination activating gene
RelB	reticuloendotheliosis viral (v-rel) oncogene related B
Rheb	Ras homologue enriched in brain
ROCK2	Rho-associated protein kinase 2
RORC2	RAR-related orphan receptor C2
Roryt	RAR-related orphan receptor gamma t
Runx1	runt-related transcription factor 1
SOCS3	suppressor of cytokine signalling 3
Srebp-1c	sterol regulatory element binding transcription factor 1c
STAT	signal transducer and activator of transcription
T-bet	T-box 21
TGF- β	transforming growth factor beta
T _H	T helper
TNF	tumour necrosis factor
TRAF	TNF-receptor-associated factor

However, the precise mechanisms by which PPAR γ interferes with STAT3, IRF4 and Batf-mediated Roryt induction remain to be elucidated (Klotz *et al*, 2009). The transcription factor TCF1 inhibits transcription of IL-17 in a different manner, by directly binding to the regulatory region of the *IL-17* gene (Yu *et al*, 2011).

Similarly to the differential role of STAT4 and STAT6 for T_H1 and T_H2 differentiation, respectively, STAT3 downstream from IL-6 signalling has a central role in the initiation of T_H17 development. The negative effect of IL-2 signalling on T_H17 differentiation has been shown recently to be mediated by STAT5 activity. This activity competes with STAT3 for binding to multiple common sites of the IL-17 promoter region and directly antagonizes IL-17 transcription in part through an epigenetic modification (Yang *et al*, 2011).

The components of the NF- κ B signalling pathway regulate numerous immune responses, and their dysregulation is linked to inflammatory and autoimmune diseases, as well as cancer (Vallabhapurapu & Karin, 2009). Interestingly, several of these molecules regulate

Fig 2 | Transcriptional regulation of the IL-17 programme. Members of various transcription factor families are implicated in the regulation of *IL-17* transcription either directly (solid line) or indirectly (dashed line). Green indicates positive regulation and red negative regulation. AhR, aryl hydrocarbon receptor; Batf, basic leucine zipper transcription factor, ATF-like; HIF, hypoxia-inducible factor; I κ B, inhibitor of NF- κ B; IKK, inhibitor of NF- κ B kinase; IRF, interferon response factor; LXR, liver X receptor; mTORC, mammalian target of rapamycin complex; NF- κ B, nuclear factor κ B; PPAR, peroxisome proliferator-activated receptor; RelB, v-rel reticuloendotheliosis viral oncogene homologue B; ROR, retinoid-related orphan nuclear receptor; STAT, signal transducer and activator of transcription; TCF, T-cell-specific transcription factor.

Roryt and IL-17A expression. Thymic $\gamma\delta$ T cells express the surface lymphotoxin- β -receptor and, after its ligation, RelB mediates the induction of Roryt in $\gamma\delta$ T cells, but not $\alpha\beta$ T cells, which is required for the differentiation of IL-17-producing $\gamma\delta$ T cells and an innate IL-17 response to *Escherichia coli* infection (Powolny-Budnicka *et al*, 2011). This unique contribution of RelB to innate IL-17-producing cells suggests the different functional regulation of innate and adaptive IL-17 production. Besides NF- κ B, kinase inhibitors for NF- κ B signalling also play a role in T_H17 differentiation. Although IKK α was originally identified as an inhibitor of NF- κ B, IKK α can promote IL-17 transcription in T_H17 cells by binding to the IL-17 locus in a NF- κ B-independent way (Li *et al*, 2011). Furthermore, I κ B ζ is specifically induced during T_H17 differentiation and, in cooperation with Roryt, is essential for robust IL-17 transcription (Okamoto *et al*, 2010).

Several groups have demonstrated recently that the kinase mTOR and the transcription factor HIF1- α , which are cellular metabolic sensors, control T_H17 fate determination. The mTOR complex 1 (mTORC1), but not mTORC2, regulates the small GTPase Rheb signalling pathway, which promotes T_H1 and T_H17, but not T_H2, differentiation (Delgoffe *et al*, 2011). In addition, the detailed mechanisms by which HIF-1 α affects T_H17, but not T_H1, cell fate have been defined. HIF-1 α is upregulated during T_H17 differentiation, possibly in a STAT3- and mTOR-dependent manner, which in turn enhances Roryt expression. After this event, a molecular complex with STAT3, HIF-1 α , Roryt and P300 induces the robust expression of T_H17-associated genes (Dang *et al*, 2011; Shi *et al*, 2011).

Fig 3 | Defects and mutations resulting in mucocutaneous candidiasis. *Candida albicans* is recognized by dectin 1/2 in dendritic cells, which induces the CARD9-mediated transcription of IL-23. IL-23 is recognized by IL-23R, which is expressed by T_H17 , innate lymphocyte and $\gamma\delta T$ cells. This induces IL-17A and IL-17F expression, which modulate the immune response by inducing the expression of antimicrobial peptides and chemokines through binding to IL-17RA. T_H17 differentiation and IL-17 cytokine expression is positively regulated by STAT3, whereas STAT1 activation antagonizes T_H17 cell differentiation. Mucocutaneous candidiasis is caused by various defects in this immune response pathway, including (i) IL-17RA deficiency, (ii) autoantibodies for IL-17, (iii) lack of expression of IL-17F, (iv) mutations resulting in the dominant-negative form of STAT3, (v) expression of a hyperactivated (Act) form of STAT1, or (vi) CARD9 deficiency. CARD, caspase recruitment domain family; DC, dendritic cell; Dec, dectin; IL, interleukin; ILC, innate lymphocyte; STAT, signal transducer and activator of transcription; T_H , T helper.

Mucosal host defence

IL-17 is a potent proinflammatory cytokine that sets in motion the recruitment of neutrophils and monocytes in tissues and induces antimicrobial peptide production by epithelial barrier cells. In animal models of infection, IL-17-deficient mice are highly susceptible to bacterial and fungal infections. Coinciding with the discovery of IL-17 function in mouse models, two independent groups identified a crucial role for IL-17 in the defence against fungal and bacterial infections in humans (Fig 3). Dominant-negative mutations in human *STAT3* lead to the development of hyper-IgE syndrome, which compromises the generation of IL-17-producing cells. These patients suffer from repeated mucocutaneous candidiasis (CMCD) and pulmonary infections with *Staphylococcus aureus* (Holland *et al*, 2007; Minegishi *et al*, 2007). *STAT3* loss-of-function reduces the number of IL-17-producing cells, the differentiation of which *in vitro* is impaired due to the essential role of *STAT3* downstream from IL-6 in the development of T_H17 (de Beaucoudrey *et al*, 2008; Ma *et al*, 2008; Milner *et al*, 2008; Minegishi *et al*, 2009). In addition, IL-17F or IL-17 receptor A deficiency was linked to *Candida* infection (Puel *et al*, 2011). In other cases of CMCD, IL-17-producing cells were competent, but the patients generated neutralizing antibodies to IL-17 (Kisand *et al*, 2010). Furthermore, autosomal-recessive mutation of *CARD9* confers susceptibility to *Candida*

infection (Glocker *et al*, 2009). *CARD9* is an adaptor molecule that, in macrophages and dendritic cells, acts downstream from the pattern recognition receptors dectin 1 and dectin 2, which are activated by β -glucan—a component of the fungal cell wall—and drive IL-17 immunity (LeibundGut-Landmann *et al*, 2007; Robinson *et al*, 2009; Saijo *et al*, 2010). Finally, gain-of-function mutations in *STAT1*, which strongly inhibit the development of IL-17-producing cells, were found in patients with CMCD (Liu *et al*, 2011). Despite the fact that the phenotype of these genetic mutants clearly established the importance of IL-17 for defence against *Candida* infection, the cellular origin of the cytokine had not been identified. IL-17-producing $\gamma\delta T$ cells, but not $\alpha\beta T$ cells, have an important role in skin *S. aureus* infection (Cho *et al*, 2010). Thus, this $\gamma\delta T$ -cell subset acts as a first line of defence in the IL-17-mediated immune response and orchestrates the following inflammatory T_H17 response. To efficiently sense invading pathogens, IL-17-producing $\gamma\delta T$ cells highly express the Toll-like receptors TLR1 and TLR2, as well as dectin 1. Signalling from these molecules, together with environmental stimuli, regulate the magnitude of the IL-17 immune response and subsequent neutrophil activation (Martin *et al*, 2009).

The elucidation of the environmental signals that control the development and maintenance of mucosal T_H17 cells in the intestine remained an intriguing question. Recent studies have revealed

that colonization of the gut with T_H17 cells requires distinct commensal bacteria, such as segmented filamentous bacteria (Gaboriau-Routhiau *et al*, 2009; Ivanov *et al*, 2009). T_H17 colonization of the gut increases the level of antimicrobial defences and confers resistance to intestinal pathogens, such as *Citrobacter* and *Salmonella*, in a NOD1/NOD2-dependent manner (Geddes *et al*, 2011). The colonization of the intestine with T_H17 cells also has an impact on systemic immunity. In fact, germ-free conditions protected mice against the development of autoimmune arthritis in a model dependent on IL-17 production and germinal centre formation for autoantibody-secreting B cells. The introduction of segmented filamentous bacteria into such germ-free mice restored the intestinal T_H17 population and B cells causing autoantibody-mediated arthritis (Wu *et al*, 2010). Thus, the induction of T_H17 cells in the intestinal lamina propria might contribute not only to mucosal host defence, but also to the induction of autoimmunity in other tissues. Interestingly, intestinal T_H17 cells are entirely dependent on commensal flora, whereas germ-free mice contain numbers of IL-17-producing $\gamma\delta$ T cells in the skin and lung comparable with those in mice under specific pathogen-free conditions (J.H.D. & B.S., unpublished data). These findings suggest that, in addition to the distinct requirement of cytokines between innate and adaptive IL-17-producing cells, environmental factors strikingly affect their distribution and function.

Adverse effects of IL-17-mediated immune responses

In contrast to the beneficial effect of IL-17 on host defence, IL-17-mediated immune responses can have adverse effects resulting in tissue damage. Secondary tissue damage often occurs after infection. For example, although IL-17 signalling is not required for the function of cytotoxic CD8 T cells and viral clearance after flu infection, bystander IL-17-mediated neutrophil influx can cause lung damage (Crowe *et al*, 2009). Besides the infection-related pathology, unexpected adverse effects linked to IL-17 were discovered in cardiovascular diseases, ischaemic brain injury and tumorigenesis, which also involve immune cells and microinflammation. Both T_H1 and T_H17 cells infiltrate atherosclerotic plaques in human coronary arteries, and the combination of IFN- γ and IL-17 induces proinflammatory cytokines and chemokines that might recruit pathogenic monocytes and macrophages to atherosclerotic lesions (Eid *et al*, 2009). By using apoE-deficient mice—an animal model of atherosclerosis—IL-17, produced mainly by T_H17 and $\gamma\delta$ T cells, was shown to have a crucial role in the induction of IL-6, CCL5 and CXCL1 from aortic endothelial cells. This induction recruits other inflammatory cells and enlarges atherosclerotic lesions (Erbel *et al*, 2009; Smith *et al*, 2010). Furthermore, an upregulation of IL-17 was detected in human stable atherosclerotic lesions (Taleb *et al*, 2009). On the other hand, IL-17 seems to induce an immunosuppressive macrophage phenotype, which limits vascular inflammation and atherosclerosis lesion development. In addition to cardiovascular diseases, sterile inflammation is also observed due to danger signals released from necrotic cells after ischaemic brain injury. The recruitment and activation of immune cells sensing danger signals clearly cause secondary injury in the late phase. Activated $\gamma\delta$ T cells are a main source of IL-17 and a pathogenic effector in the late phase of ischaemic injury after the activation of infiltrating macrophages and production of IL-23 (Shichita *et al*, 2009).

Another type of microinflammation is tumour-associated immunity. Immune surveillance mediated by NK, T_H1 and cytotoxic CD8 T cells is essential to prevent and inhibit tumour formation.

Nonetheless, chronic inflammation is often related to the initiation of tumour formation. The enterotoxigenic *Bacteroides fragilis*—a common human commensal bacterium—induces chronic IL-17-mediated colonic inflammation through which colonic hyperplasia and carcinogenesis are initiated in a multiple intestinal neoplasia mouse model (Wu *et al*, 2009). IL-17 has also been associated with the formation of giant cells in Langerhans cell histiocytosis, which establishes dendritic cells as important targets for IL-17 in this disease (Coury *et al*, 2008).

Innate and adaptive IL-17 responses enable biological barriers against pathogens. Although innate IL-17 responses might suffice to eradicate most pathogens, excess innate immune reactions might lead to hyperinflammatory responses, resulting for example in allergy in the lung and inflammatory diseases. Adaptive IL-17 cells constitute the second stage of the immune reaction and might be recruited when the innate response fails to cope with invading pathogens. Pathogen-specific T_H17 cells raise a strong coordinated immune response, whereas IL-17-mediated autoimmune disorders can be initiated by autoreactive T_H17 cells, after tissue injury induces the release of self-antigen. Autoimmune diseases that are linked to IL-17 are invariably dependent on adaptive T cells, whereas innate IL-17 producers are either not involved or have merely accessory roles.

Several diseases that are considered to be of autoimmune origin are clearly associated with T_H17 cells, and deficiencies in T_H17 cytokines or transcription factors regulating the development and function of T_H17 cells often reduce pathology in various disease models (Hirota *et al*, 2010; Korn *et al*, 2009). Genome-wide association studies demonstrated that the T_H17 -related molecules IL-23 and chemokine receptor CCR6 are associated with inflammatory bowel disease, rheumatoid arthritis and psoriasis in humans (Duerr *et al*, 2006; Kochi *et al*, 2010; Nair *et al*, 2009). Nevertheless, the mechanisms that underlie pathogenicity against self are largely unknown. The primary immune response elicited by T_H17 cells is associated with preferential neutrophil infiltration, and innate immune cells activated by IL-17 could damage the surrounding tissue. Indeed, T_H17 cells directly cause the damage of axons, leading to neuronal dysfunction in a contact-dependent manner (Siffrin *et al*, 2010). Recent reports have revealed that not only T_H17 cells, but also IL-17-producing innate lymphocytes significantly contribute to the pathogenicity of autoimmune diseases. In experimental autoimmune encephalitis (EAE), $\gamma\delta$ T cells produce IL-17 early in response to IL-1 β and IL-23, which are secreted by macrophages and dendritic cells before the ensuing T_H17 response and amplified T_H17 -mediated autoimmunity (Sutton *et al*, 2009). Although not autoimmune in nature, other pathological states can be induced by, for example, IL-17-producing NKT cells in the lung. These cells initiate ozone-induced asthma, which is characterized by airway hypersensitivity and airway neutrophilia, but not eosinophilia (Pichavatt *et al*, 2008). Furthermore, pulmonary IL-17-producing $\gamma\delta$ T cells and T_H17 cells promote lung fibrosis through increased synthesis and secretion of collagen with neutrophilia in bleomycin-exposed mice (Mi *et al*, 2011; Wilson *et al*, 2010). In contrast to the cooperative action of innate cells with T_H17 cells, colonic-lineage negative innate lymphocytes that express Ror γ t and IL-23R produce IL-17 and IFN- γ , causing intestinal pathology in RAG-deficient mice independently of innate and adaptive T cells (Buonocore *et al*, 2010). IL-23 seems to be an essential cytokine to drive the pathogenicity of both innate and adaptive IL-17-producing cells, and an upstream mechanism underlying the induction of IL-1 β , IL-6 and IL-23 by macrophages and dendritic cells was reported. In synergy with pattern recognition receptor

signalling, the activation of serum complement pathways stimulates macrophages and dendritic cells to help initiate T_H17 differentiation and activation (Hashimoto *et al*, 2010; Lajoie *et al*, 2010).

Considering the adverse effects of dysregulated IL-17, controlling innate and adaptive IL-17-producing cells could be a key therapeutic target for the prevention and treatment of IL-17-associated tissue inflammation. The master transcription factor Ror γ universally marks innate as well as adaptive IL-17-producing cells. Therefore, the inhibition of Ror γ by small molecules might limit the sustainment of IL-17 immune reactions and the ensuing tissue damage. Three independent groups have shown that the natural cardiac glycoside digoxin and high-affinity synthetic ligands for Ror α and Ror γ inhibit the activity of these master regulators of IL-17 transcription and block the differentiation and effector function of T_H17 cells (Fujita-Sato *et al*, 2011; Huh *et al*, 2011; Solt *et al*, 2011). As the safety of digoxin is already established, it could be tested for its effect on the limitation of innate and adaptive IL-17-mediated tissue pathology.

Plasticity of T_H17 cells

Terminally differentiated effector CD4 T cells were thought to be stable, but numerous recent studies have identified factors that reinforce or destabilize effector-T-cell programmes (Murphy & Stockinger, 2010). T_H17 cells in particular seem to disobey the paradigm of irreversible commitment enunciated for T_H1 and T_H2 differentiation. Although *ex vivo* isolated T_H17 cells appear relatively stable, *in vitro*-generated T_H17 cells are substantially plastic and can turn into IFN- γ -producing, T_H1 -like, or IL-4-producing, T_H2 -like cells in response to IL-12 or IL-4, respectively (Lexberg *et al*, 2008). Furthermore, *in vitro*-generated T_H17 cells can cause IFN- γ -dependent type 1 diabetes and colitis after transfer into lymphopaenic recipient mice (Bending *et al*, 2009; Lee *et al*, 2009; Nurieva *et al*, 2009). Epigenetic analysis revealed that *in vitro*-generated T_H17 cells have DNA modifications accessible to T_H1 and T_H2 lineage transcription factors, whereas *in vitro*-generated T_H1 and T_H2 cells have epigenetic marks rendering IL-17A and Ror γ inaccessible (Mukasa *et al*, 2010). To investigate the plasticity of T_H17 cells *in vivo*, we generated a reporter mouse strain designed to fate-map cells that have activated IL-17. IL-17 fate reporter mice show that T_H17 cells developing during chronic inflammatory responses in the EAE model rapidly shut down expression of IL-17A and switch on alternative cytokines, whereas in a model of acute cutaneous *Candida* infection, T_H17 cells do not deviate to alternative cytokine production. During the development of EAE, T_H17 , rather than T_H1 , cells are the main source of IFN- γ and other pro-inflammatory cytokines in the spinal cord. Of note, T-bet $^+$ IFN- γ -producing 'ex- T_H17 ' cells driven by IL-23 retain specific markers of the T_H17 programme (Hirota *et al*, 2011). IL-23 was also shown to differentiate T cells into a pathogenic IL-17- and IFN- γ -producing subset in a colitis model (Ahern *et al*, 2010). Furthermore, T-bet-deficient T cells fail to develop into T_H1 -like cells from ex- T_H17 cells (Lazarevic *et al*, 2011). Our data suggest that the vast majority of proinflammatory cytokine-producing cells in EAE are originally T_H17 , suggesting that encephalitogenic T cells in EAE are primarily ex- T_H17 cells. This would change the interpretation of work reported by two independent groups showing that GM-CSF-producing T cells—instead of IFN- γ -producing or IL-17-producing T cells—are a pathogenic subset in EAE (Codarri *et al*, 2011; El-Behi *et al*, 2011). Intriguingly, it has been shown that, in human arthritis, a large population of synovial IL-17-negative IFN- γ -producing T_H1 cells express RORC2, CCR6 and CD161, which are markers of human T_H17 cells (Nistala *et al*,

2010). In contrast to the deviation of T_H17 cells to alternative pro-inflammatory cytokines in EAE, ex- T_H17 cells are not converted to a regulatory-T-cell phenotype that expresses FoxP3 or IL-10 in this setting, neither in the draining lymph node nor in the spinal cord. However, in a model of tolerance induced by CD3-specific antibody, activated CCR6 $^+$ T_H17 cells are intriguingly redirected to the small intestine by chemotaxis to CCL20, which is secreted by the intestinal epithelial cells. Once there, the proinflammatory T_H17 cells acquire a regulatory phenotype with *in vitro* and *in vivo* immune-suppressive properties (Esplugues *et al*, 2011).

Memory is a central feature of the adaptive immune system. Given that T_H17 cells easily switch off their signature cytokine and acquire alternative profiles in some immune responses, it is difficult to trace adaptive IL-17 producers through the assessment of intracellular cytokine profiles. Indeed, based on cytokine staining, it has been suggested that there are no memory phenotype cells expressing IL-17 (Pepper *et al*, 2010). The fate reporter system should allow a more detailed assessment of this issue. In agreement with our fate reporter study showing that a proportion of eYFP $^+$ T_H17 cells lacked IL-17 expression *ex vivo* even after PdbU/ion restimulation, a recent study in human subjects also suggested that a proportion of human CCR6 $^+$ memory T_H17 cells do not produce IL-17 *ex vivo* after restimulation. Intriguingly, recall responses resulting in IL-17 production were induced from IL-17 CCR6 $^+$, but not CCR6 $^-$ cells after *in vitro* culture with common γ -chain cytokines, such as IL-2, IL-7 and IL-15 (Wan *et al*, 2011). Further studies of memory formation and recall of distinct effector profiles are needed to understand the complexities of recalling memory cells into effector responses tailored to combat different types of pathogen that require specific cytokine responses (Sidebar A).

Concluding remarks

Accumulating evidence suggests that inborn errors of IL-17-mediated immune pathways precipitate CMCD and other infections in affected patients, emphasizing the crucial role of this cytokine for host defence against a range of pathogens. On the other hand, genome-wide association studies have identified T_H17 -related genes as contributors or initiators of autoimmune diseases such as multiple sclerosis, rheumatoid arthritis and psoriasis. These results clearly suggest that the activation and maintenance of IL-17-producing cells should be robust during infection and at the same time tightly regulated to avoid the risk of autoinflammatory disorders. Therefore, understanding the multiple steps of the IL-17-mediated immune response would help to develop future immunotherapy approaches for both infectious and autoimmune diseases. As the regulators of differentiation, maintenance and effector function between innate and adaptive IL-17-producing cells seem to be different, it is important to understand the distinct role and effector regulation of innate and adaptive IL-17-producing cell types in a variety of immune conditions. Lastly, epigenetic DNA modification and microRNAs are important factors in gene regulation, which can substantially modify the levels of target gene expression. Our understanding of IL-17 regulation by epigenetic mechanisms and microRNAs at a mechanistic level *in vivo* is still incomplete. Future research and integrated information will hopefully define improved targeted therapies based on transcriptional and post-transcriptional IL-17 gene regulation and an effective control of beneficial and adverse IL-17-mediated immune responses.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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João H. Duarte, Helena Ahlfors, Brigitta Stockinger & Keiji Hirota