IL-17A and Th17 cells as therapeutic targets for autoimmune diseases

Franco Di Padova

Novartis Institutes for Biomedical Research, WSJ 386-906, 4002 Basel, Switzerland

Abstract

The definition of the $CD3^+$ $CD4^+$ Th17 cell subset and the identification of the IL-23–Th17 axis have introduced new paradigms to explain the origin of autoimmune events in animal models, subverting the established Th1–Th2 paradigm. IL-17A has been pivotal for the discovery of the Th17 lineage, which probably evolved as an arm of the adaptive immune system for host protection against extracellular bacteria and fungi. IL-17A, is the founding member of the IL-17 family composed of six members. Th17 cells and IL-17A have been implicated in a variety of inflammatory and autoimmune diseases in rodents. In these models, Th17 cells are pivotal in the pathogenesis of the disease and IL-17A appears to be the main mediator, but the situation might be different in humans. In some human pathological conditions, in addition to Th17 cells, other IL-17A-producing cells have been described, including $CD8^+$ T cells, astrocytes, macrophages and Langerhans cells. The therapeutic effect of some new biologics can now, at least in part, be explained by their interference with mediators involved in the generation of Th17 cells, but more specific treatments would be valuable to dissect these intricate networks. An antibody neutralizing IL-17A is being evaluated under different autoimmune conditions. This approach might not only benefit patients, but, by neutralizing IL-17A selectively, might also help to define the role of this cytokine in autoimmune disorders and contribute to a new wave of selective and targeted therapies.

Introduction

The definition of the $CD3^+$ $CD4^+$ Th17 cell subset and the identification of the IL-23–Th17 axis have introduced new paradigms to explain the origin of autoimmune events in animal models, subverting the established Th1–Th2 paradigm [1]. IL-17A has been pivotal for the discovery of the Th17 lineage that probably evolved as an arm of the adaptive immune system for host protection against extracellular bacteria and fungi. Th17 cells and IL-17A are involved in the pathogenesis of several experimental autoimmune models of arthritis, colitis, psoriasis, uveitis, and encephalomyelitis. In these pathological conditions, Th17 cells are present and contribute

Th 17 Cells: Role in Inflammation and Autoimmune Disease,
edited by Valérie Quesniaux, Bernhard Ryffel and Franco Di Padova

to the inflammatory condition, neutralization of IL-17A ameliorates disease, and IL-17A-deficient animals are protected [2].

In mice, TGF-β and IL-6 appear to be involved in the commitment of naive T cells to the $CD4^+$ Th17 lineage. When IL-6 is lacking, as in knockout mice, IL-21 can step in and initiate an alternative pathway to induce pro-inflammatory Th17 cells [3]. Indeed, IL-21 is produced by Th17 cells and may be the main driver of an autocrine amplification loop. Once, IL-23R is expressed on the cell, IL-23 then drives Th17 cell survival. Still, several details of the process are missing. The Th17 cell population is probably regulated differently in man, where IL-1β in addition to IL-6 and IL-23 is required [4]. CCL20 is up-regulated in human Th17 cells and is a defining feature of the Th17 'signature', along with IL-17A, IL-17F and IL-22 [4].

Also in humans, several studies support a role for Th17 cells and IL-17A in autoimmune disorders. However, IL-17A can be produced by other cells including $CD8^+$ T cells, γδ T cells, a fraction of natural killer (NK) cells, neutrophils [1], macrophages [5], astrocytes and oligodendrocytes [6], and possibly Langerhans cells [7]. Therefore, it will be important to establish whether other $IL\text{-}17^+$ cells contribute to the pathogenesis of autoimmune disorders.

Differentiating between the role of Th17 cells and that of IL-17A is also relevant. While, in some instances, IL-17F and IL-22, cytokines released by Th-17 cells, might contribute to pathology, in other cases, the additional cell types able to produce IL-17A might participate. The introduction of more specific and targeted therapies, which might benefit patients reducing the risk of untoward side effects, remains an important goal.

IL-17A and IL-17F

IL-17A, previously called IL-17, is the founding member of the IL-17 family comprising at least six members [8, 9]. In the mouse, the IL-17 cytokine family consists of IL-17A (IL-17/CTLA-8), IL-17B (CX1/NERF), IL-17C (CX2), IL-17D , IL-17E (IL-25), and IL-17F (ML-1) [1]. IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (IL-25), and IL-17F are normally secreted as homodimers [10–12]. IL-17A and IL-17F can be secreted by the same cell, and share 55% identity [10, 13].

In most studies, IL-17A does not act as a growth factor, but as an inflammatory cytokine, like IL-1 and TNF. IL-17A has a major role in inflammation, PMN recruitment, inflammatory angiogenesis, formation of germinal centers and granulomas, and tissue remodeling and destruction. IL-17A exhibits pleiotrophic activities on various parenchymal cells, including the induction of IL-6, IL-8, G-CSF, leukemia inhibitory factor, PGE2, ICAM-1, and matrix metalloproteinase in fibroblasts and other stromal cells, induction of TNF-α and IL-1β in macrophages, production of NO, inducible NO synthase, and cyclooxygenase-2 by chondrocytes, and induction

of RANKL in osteoblasts, as well as stimulation of granulopoiesis, maturation of dendritic cells, and costimulation of T cell proliferation [1].

IL-17A has been implicated as an agent contributing to progression and pathology of a variety of inflammatory and autoimmune diseases in humans and in mouse models of human diseases [14, 15]. On the other hand, the role of IL-17F in human diseases is still uncertain. Recently, the analysis of animals deficient in either of the two genes has revealed distinct functions of IL-17A and IL-17F in inflammatory responses [16]. Additional studies with neutralizing antibodies selective for these two cytokines are required to clarify further the contribution of IL-17A and IL-17F under inflammatory conditions.

Moreover, it is not yet clear how the production of IL-17A and IL-17F is regulated at the single-cell level in Th17 cells. In mice, the genes encoding IL-17A and IL-17F are located on chromosome 1, and Th17 cell development seems to be accompanied by epigenetic changes at both the IL-17A and the IL-17F gene promoters [17]. However, at the single-cell level, IL-17A and IL-17F are not always coexpressed, as IL-17A and IL-17F single-positive cells are detected at relatively high frequencies [16, 18]. Moreover, in mice, $CD4^+$ IL-17A single-positive T cells seem to be prevalent in the lamina propria and intestinal intraepithelium [16]. It is not clear whether this differential expression results from the existence of different cell types, of various stages of maturation or of environmental factors.

More recently, an IL-17A/F heterodimer has been described both in man and in mice [18–20]. In a Th17 cell adoptive-transfer model characterized by increased neutrophilia in the airways, Liang et al. [18] were able to show that IL-17A homodimers are the most biologically active, with IL-17A/F heterodimers displaying a moderate activity and IL-17F homodimers showing the lowest activity. The role of the heterodimer in inflammatory diseases in mice and humans needs further investigations.

IL-17A and IL-17F receptors

The receptor for IL-17A, once cloned, was named IL-17RA [9]. Bioinformatic analysis led to identification of four additional IL-17 receptor-related molecules and these are now designated IL-17RB, IL-17RC, IL-17RD, and IL-17RE [10]. Despite the relatedness of the IL-17 and IL-17R family, the receptors for only three members of this cytokine family have been identified. In humans, hIL-17A binds to hIL-17RA and hIL-17RC, hIL-17F binds to hIL-17RC [21] and hIL-17E binds to hIL-17RB [22].

Kuestner et al. [21] have recently raised questions about the recognition of IL-17A and IL-17F by their receptors. They showed that, in humans, hIL-17A binds to hIL-17RA and to hIL-17RC with high affinity and that hIL-17F binds to hIL-17RC. Binding of IL-17F to hIL-17RA occurs with a 1000-fold lower affin-

ity, suggesting that, under physiological conditions, hIL-17F does not bind to this receptor. In addition, they reported that, while hIL-17RA is expressed ubiquitously, with higher levels observed in hemopoietic cells, hIL-17RC is expressed only in non-hemopoietic tissues. In summary, in humans, non-hemopoietic tissues should respond to both hIL-17A and -F, whereas hemopoietic cells should respond only to hIL-17A. In contrast, in mice, mIL-17RA binds both mIL-17A and -F, whereas mIL-17RC binds only mIL-17F. This implies that mouse cells expressing mIL-17RA respond to both mIL-17A and -F, whereas those expressing mIL-17RC respond only to mIL-17F. Therefore, the relative contributions of IL-17A and -F in inflammation could be different in humans and mice. If these data are confirmed, the role of hIL-17A could be more prevalent in human pathological conditions, as hIL-17A should be able to activate cells through both hIL-17RA and hIL-17RC. However, a formal proof of the function of the different receptors *in vivo* is still lacking. The presence in man and mice of spliced variants of IL-17RC, which are not functional, further complicates the picture, opening the question of the role of the non-functional receptors.

Different results were obtained by Zrioual et al. [23], who described the expression of IL-17RA and IL-17RC in peripheral whole blood from normal subjects and an overexpression in rheumatoid arthritis (RA) patients. In hemopoietic cells, protein and mRNA levels of IL-17RA were higher than those of IL-17RC. Both receptors were expressed in $CD14^+$ monocytes and $CD19^+$ B cells. In $CD3^+$ T cells, lower levels of IL-17RA were measured, while IL-17RC was almost completely absent [23]. In addition, both receptors were broadly expressed in whole synovium tissues from RA and osteoarthritic patients with stromal and infiltrating immune cells positively stained [23].

These data support the observation that hIL-17RA and hIL-17RC may function as a heterodimeric receptor complex for hIL-17A and perhaps also for hIL-17F [24]. The picture might be further complicated by the presence of IL-17A/F heterodimers [19]. At present, no information is available on the relative binding of IL-17A/F heterodimers to the IL-17RA and IL-17RC in humans and mice.

Cells that produce IL-17A in human pathological conditions

Increased levels of IL-17A are detected in several human pathological conditions but few studies have addressed the cells that produce IL-17A. The identification of the IL-17A-producing cells is essential to define their contribution to disease pathogenesis and to design targeted approaches. In the peripheral blood of healthy subjects, T cells can produce IL-17A. The $IL\text{-}17A^+$ T cells reside in more than one subpopulation and they are distinguished by the differential expression of specific chemokine receptors [25]. However, in pathological conditions, the situation might be more complex and different cell types may contribute to the production of IL-17A.

In RA, Kotake et al. [26] not only reported elevated IL-17A protein levels in synovial fluid but also identified a subset of $CD4^+$, $CD45RO^+$ memory T cells producing IL-17A in synovial tissue. T cells making IL-17A were also detected in synovial fluid from patients with Lyme arthritis [27]. Flow cytometry was used to analyze the phenotype, cytokine production and chemokine receptor expression of IL-17A-producing T cells in peripheral blood and synovial fluid of children with juvenile idiopathic arthritis (JIA) [28]. IL-17A-expressing T cells were highly enriched in the inflamed joints and their number directly correlated with the clinical phenotype. In the joint, IL-17A was produced by $CD4^+$ T cells. These cells were present at significantly higher numbers in the joint than in either the paired blood samples from JIA patients or the blood of healthy controls. The IL-$17A^+$ T cells had the characteristics of memory $CD4^+$, $CD45RO^+$ cells and included cells that also produced IL-22 and IFN-γ, but not IL-4. Moreover, while, in peripheral blood, IL-$17A^+$ T cells were clearly distinct from either Th1 cells (defined by IFN-γ production) or Th2 cells (defined by IL-4 production), in the joints, more than half of the cells producing IL-17A were also positive for IFN-γ production. In PBMCs, the expression of CCR4 on IL-$17A^+$ T cells mirrored that of CCR6, while the synovial IL-$17A^+$ T cells expressed CCR6, but showed variable expression of CCR4. Therefore, circulating IL-$17A^+$ T cells seem to have different characteristic from synovial IL-$17A^+$ T cells. Flow cytometric data from synovial fluid T cell analyses estimated that IL-17A is produced by about 1% of synovial tissue T cells. The authors also suggested that Th17 cell migration to the joint may set up a positive feedback loop for further recruitment through the autologous production of CCL20.

Page et al. [29] identified IL-17A-producing cells in activated lymph nodes, in RA synovium, and in the endomysium of patients with dermatomyositis. In this study, IL-17A-producing T cells had a plasma cell-like morphology, expressed the CD4 but not the CD3 and/or B/plasma cell markers, and some cells expressed both IL-17A and IFN-γ. Even though the authors showed that IL-17A and/or IFN-γ producing cells can down-regulate the expression of CD3 markers *in vitro* after activation, the absence *in vivo* of the CD3 marker is somehow intriguing as, in other studies, the CD3 marker was used to identify IL-17^+ T cells [6, 27]. In conclusion, even though there is compelling evidence from several studies that T cells are involved in the production of IL-17A in RA, additional analysis should be performed to confirm the origin of the IL-17^+ $CD4^+$ $CD3^-$ cells. It might be interesting here to bear in mind that plasmacytoid dendritic cells are $CD4^+$ and $CD3^-$, that they were initially described as plasmacytoid T cells/monocytes, and that they are localized in the T cell areas of human reactive lymph nodes [30]. Moreover, it has been shown that, under specific culture conditions, some dendritic cells can also produce IFN-γ [31] and more recently, that Langerhans cells, a specialized subset of dendritic cells, have been shown to produce IL-17A [7].

In psoriatic patients, IL-17 messenger RNA (mRNA) was identified within lesions [32, 33], but an increase in serum protein levels was not observed [34].

$CD45RO^+$ memory effector T cells, either $CD4^+$ or $CD8^+$, seem to play a role in the pathogenesis of psoriasis [35]. $CD4^+$ T cells are abundantly present in the upper lesional dermis, whereas in the lesional epidermis $CD8^+$ T cells are in the majority [36, 37]. More recently, IL-17-producing T cells were recovered at increased levels in the lesional epidermal and dermal samples of psoriatic patients [38]. However, no further characterization of the IL-17-secreting cells was reported.

In patients with active ulcerative colitis (UC) and Crohn's disease (CD), Fujino et al. [5] reported significantly elevated serum IL-17A levels, while Nielsen et al. [39] described an increased gene expression. In addition, Fujino et al. [5] described a marked increase in $IL\text{-}17^+$ cells in the inflamed regions of active UC and CD patients. In active UC patients, $IL\text{-}17^+$ cells were localized mainly within the lamina propria but, in active CD patients, they were scattered throughout the submucosa and muscularis propria. In this study, both T cells and monocytes/macrophages were identified as a source of IL-17. In this study an anti-CD68 antibody was used for the identification of monocytes/macrophages. Even though CD68 is considered a marker specific for monocytes/macrophages, other cell types can express it [40], and additional studies might be useful to confirm a consistent production of IL-17A by monocytes/macrophages in these diseases.

Another pathological condition, in which IL-17A seems to have a prominent pathogenic role, is multiple sclerosis (MS). Recently, Tzartos et al. [6] performed a systematic analysis of $IL\text{-}17A^+$ cells in the brains of MS patients. Using double immunofluorescence and *in situ* hybridization, they showed that IL-17A immunoreactivity was detected in T cells, astrocytes and oligodendrocytes. $CD8^+$ as well as $CD4^+$ T cells were equally immunostained for IL-17A. $IL\text{-}17A^+$ T cells were particularly prominent in perivascular spaces in acute and chronic active MS lesions, where they accounted for the majority of $CD3^+$ T cells. They proposed that the large numbers of $IL\text{-}17^+$ T cells, found in both active and chronic active lesions, implicate that IL-17A is involved not only in initiating the lesions but also in their persistence. Moreover, $CD8^+$ T cells were predominantly found in the central nervous system parenchyma, whereas $CD4^+$ T cells remained primarily in the perivascular regions, suggesting a prevalent role of $CD8^+$ T cells in actual tissue destruction. The linkage between CD8 T cells and IL-17A may also influence future strategies for the treatment of MS. A potential role of $CD8^+$ T cells in the pathogenesis of MS has recently emerged due to genetic association of MS with MHC class I alleles, the failure of therapies directed to $CD4^+$ T cells and the presence of clonally expanded $CD8^+$ T cells in inflammatory central nervous system plaques [41]. In addition, Tzartos et al. [6] reported IL-17A immunoreactivity in astrocytes and oligodendrocytes. IL-17A immunostaining was abundant in the highly activated astrocytes in acute lesions and in the borders of chronic active lesions, but was barely detectable in astrocytes in control brain. These findings suggest that in an inflammatory environment astrocytes and oligodendrocytes may also contribute to IL-17 production and confirm previous data showing that IL-17A is expressed by human astrocytes cultured in the

presence of TNF-α and IL-1β [42]. Therefore, it seems likely that astrocytes (and perhaps oligodendrocytes) can be induced to produce IL-17 under the influence of activating stimuli. These findings corroborate previous microarray analyses of MS lesions obtained at autopsy that demonstrated highly increased transcripts of IL-17A [43], and elevated IL-17A levels in the cerebrospinal fluid of patients with opticospinal MS [44].

The fact that other cells in addition to Th17 cells might produce IL-17A in pathological conditions is stressed by the findings in Langerhans cell histiocytosis (LCH), where large amounts of IL-17A are detected in serum, and Langerhans cells are the main producers of IL-17A [7]. In this study, intralesional IL-17A expression was analyzed by triple staining (Langerin, CD3 and IL-17A), and IL-17A$^+$ dendritic cells were detected in skin and bone lesions. Very few IL-17A$^+$ T cells were found. Moreover, multinucleated giant cells always expressed large quantities of IL-17A [7]. Interestingly, in this study monocyte-derived dendritic cells were positive for IL-17A and were able to spontaneously secrete this cytokine, implying that they were activated *in vivo*. The authors concluded that the main cellular source of IL-17A in LCH is a dendritic cell subpopulation. Expression of IL-17A mRNA in activated peripheral blood monocytes/macrophages was also detected by Fujino et al. [5]. As it is not yet clear whether LCH is a neoplastic or a reactive disease [45], it is not possible to infer whether the ability to secrete IL-17A is acquired and due to an oncogene that has transformed the cells or whether it is intrinsic and due to the response of a subset of dendritic cells to an altered environment.

Some studies have relied on the isolation or extraction of cells from physiological fluids or tissues and on the analysis of cultured and stimulated cell populations by FACS. These studies have almost uniformly identified CD4$^+$ T cells as the main source of IL-17A. On the other hand, studies that have used histochemistry have often come to the conclusion that different cell types contribute to the production of IL-17A. Both approaches are valuable, but they may provide different information. The first approach offers a more precise identification of the cells but selectively enriches the sample for cell populations that are more easily extracted or apt to culture conditions. The main limitation of the histochemical approach is linked to the difficulty to precisely identify cell surface markers and often to the lack of specificity of the reagents. In conclusion, additional studies are required to more precisely identify the cells contributing to the production of IL-17A. and to identify the cells that secrete IL-17F, IL-17AF heterodimer and IL-22. IL-17F and IL-22 are expressed at increased levels in several diseases [46, 47].

Targeting Th17 cells and IL-17A and IL-17F in humans

Biologics not only provide clinicians with a new armamentarium to treat autoimmune diseases but also represent tools to dissect pathogenic events and to define the

role of cells and cytokines involved in autoimmune disorders. Several new biologics are or will become soon available to treat patients with autoimmune disorders. Many of these principles have several mechanisms of action, target molecules involved in many biological events, and it is often impossible to define a critical step that explains their therapeutic effect. Some of them also show an activity on Th17 cells.

Etanercept is a recombinant TNF blocker made from the combination of two soluble human 75-kDa TNF receptors linked to the Fc portion of an IgG1. Etanercept has shown beneficial effect in many clinical conditions including RA, psoriasis and ankylosing spondilitis. Recently, Zaba et al. [48] have shown that, in psoriasis, one of the mechanisms of action of etanercept is to inhibit Th17 cells by reducing the production of IL-23 by dendritic cells. It will be interesting to verify whether this mechanism of action is shared by other anti-TNF approaches and whether it is effective in other clinical conditions that benefit from an anti-TNF treatment.

Abatacept (CTLA-4-Ig) is another promising approach for treatment of RA patients. It is a soluble fusion protein that consists of the extracellular domain of human cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) linked to the modified Fc (hinge, CH2, and CH3 domains) portion of human IgG1. The mechanism of action is to block costimulatory signals between antigen-presenting cells and T cells. The beneficial effect of an anti-CTLA4 approach in RA patients supports a role for T cell costimulation and might suggest a possible involvement of Th17 cells in the pathogenesis of this disease [49]. In fact, CD28 is not only a major costimulator for CD4 and CD8 naive T cells, it is also involved in the activation of memory Th17 cells [50].

Targeting IL-6 with a humanized anti-IL-6 receptor antibody is effective in several clinical studies in RA [51]. Several studies have shown that IL-6 is involved in the commitment of naive T cells to the Th17 cell lineage [1], and this mechanism of action may explain at least in part the therapeutic effect of this approach.

Ustekinumab, an antibody that neutralizes the effects of IL-12 and IL-23 by binding their shared p40 subunit, has shown dramatic effects in patients with psoriasis [52, 53]. IL-23 is directly involved in the survival of Th17 cells and this suggests that Th17 cells and their products might be involved in the pathogenesis of the disease. However, this antibody targets not only IL-23 but also IL-12, and it is not possible to differentiate the effects on Th17 cells *versus* those on Th1 cells. Therefore, to dissect further these cytokine networks, it would be important to develop even more specific tools and selectively block the effects of only one cytokine. Such targeted biologics might not only be of therapeutic value for the patients but also reduce further the risk of untoward side effects. With this goal in mind, we have generated a high-affinity fully human monoclonal anti-human IL-17A antibody of the IgG1/kappa isotype, which is now being developed for the potential treatment of several autoimmune disorders. This antibody is specific for IL-17A and does not recognize IL-17F. Therefore, it targets only one of the cytokines secreted by Th17

cells, and it will be important to assess its therapeutic effects in comparison with less selective approaches such as anti-p40 antibodies. On the other hand, in addition to Th17 cells, other cells may contribute to production of IL-17A in various pathological conditions. In conclusion, each therapy might have its own specific signature and it will be important to plan clinical trials able to highlight these differences, and to optimize treatment for the patients.

An additional approach is to use a soluble IL-17RC-Fc fusion protein [21]. This soluble fusion protein will probably consist of the extracellular domain of a human IL-17RA/RC-Fc fusion protein and will neutralize the biological effects of both hIL-17A and hIL-17F. By targeting IL-17F in addition to IL-17A, a different therapeutic profile might be expected.

In conclusion, through the development of new approaches targeting new cytokines and cell networks, not only will the patients have access to effective and more sophisticated therapies that might have a lower incidence of side effects, but the scientific community will acquire new knowledge about the role of cytokines and cells under different pathological conditions.

References

1 Weaver CT, Hatton RD, Mangan PR, Harrington LE (2007) IL-17 family cytokines and the expanding diversity of effector T cell lineages. *Annu Rev Immunol* 25: 821–852

2 Komiyama Y, Nakae S, Matsuki T, Nambu A, Ishigame H, Kakuta S, Sudo K, Iwakura Y (2006) IL-17 plays an important role in the development of experimental autoimmune encephalomyelitis. *J Immunol* 177: 566–573

3 Korn T, Bettelli E, Gao W, Awasthi A, Jager A, Strom TB, Oukka M, Kuchroo VK (2007) IL-21 initiates an alternative pathway to induce proinflammatory T(H)17 cells. *Nature* 448: 484–487

4 Wilson NJ, Boniface K, Chan JR, McKenzie BS, Blumenschein WM, Mattson JD, Basham B, Smith K, Chen T, Morel F et al (2007) Development, cytokine profile and function of human interleukin 17-producing helper T cells. *Nat Immunol* 8: 950–957

5 Fujino S, Andoh A, Bamba S, Ogawa A, Hata K, Araki Y, Bamba T, Fujiyama Y (2003) Increased expression of interleukin 17 in inflammatory bowel disease. *Gut* 52: 65–70

6 Tzartos JS, Friese MA, Craner M, Palace J, Newcombe J, Esiri MM, Fugger L (2007) Interleukin-17 production in CNS-infiltrating T-cells and glial cells is associated with active disease in multiple sclerosis. *Am J Pathol* 172: 146–155

7 Coury F, Annels N, Rivollier A, Olsson S, Santoro A, Speziani C, Azocar O, Flacher M, Djebali S, Tebib J et al (2008) Langerhans cell histiocytosis reveals a new IL-17A-dependent pathway of dendritic cell fusion. *Nat Med* 14: 81–87

8 Spriggs, MK (1997) Interleukin-17 and its receptor. J *Clin Immunol* 17: 366–369

9 Yao, Z, Fanslow WC, Seldin MF, Rousseau AM, Painter SL, Comeau MR, Cohen JI,

Spriggs MK (1995) Herpesvirus saimiri encodes a new cytokine, IL-17, which binds to a novel cytokine receptor. *Immunity* 3: 811–821

10 Moseley TA, Haudenschild DR, Rose L, Reddi AH (2003) Interleukin-17 family and IL-17 receptors. *Cytokine Growth Factor Rev* 14: 155–174

11 Kolls JK, Linden A (2004) Interleukin-17 family members and inflammation. *Immunity* 21: 467–476

12 Kawaguchi M, Adachi M, Oda N, Kokubu F, Huang SK (2004) IL-17 cytokine family. *J Allergy Clin Immunol* 114: 1265–1273

13 Starnes T, Robertson MJ, Sledge G, Kelich S, Nakshatri H, Broxmeyer HE, Hromas R (2001) Cutting edge: IL-17F, a novel cytokine selectively expressed in activated T cells and monocytes, regulates angiogenesis and endothelial cell cytokine production. *J Immunol* 167: 4137–4140

14 McAllister F, Henry A, Kreindler JL, Dubin PJ, Ulrich L, Steele C, Finder JD, Pilewski JM, Carreno BM, Goldman SJ et al (2005) Role of IL-17A, IL-17F, and the IL-17 receptor in regulating growth-related oncogene-α and granulocyte colony-stimulating factor in bronchial epithelium: Implications for airway inflammation in cystic fibrosis. *J Immunol* 175: 404–412

15 Lubberts E (2003) The role of IL-17 and family members in the pathogenesis of arthritis. *Curr Opin Investig Drugs* 4: 572–577

16 Yang XO, Chang SH, Park H, Nurieva R, Shah B, Acero L, Wang YH, Schluns KS, Broaddus RR, Zhu Z et al (2008) Regulation of inflammatory responses by IL-17F. *J Exp Med* 205: 1063–1075

17 Akimzhanov AM, Yang XO, Dong C (2007) Chromatin remodeling of interleukin-17 (IL-17)-IL-17F cytokine gene locus during inflammatory helper T cell differentiation. *J Biol Chem* 282: 5969–5972

18 Liang SC, Long AJ, Bennett F, Whitters MJ, Karim R, Collins M, Goldman SJ, Dunussi-Joannopoulos K, Williams CMM, Wright JF et al (2007) An IL-17F/A heterodimer protein is produced by mouse Th17 cells and induces airway neutrophil recruitment. *J Immunol* 179: 7791–7799

19 Wright JF, Guo Y, Quazi A, Luxenberg DP, Bennett F, Ross JF, Qiu Y, Whitters MJ, Tomkinson KN, Dunussi-Joannopoulos K et al (2007) Identification of an interleukin 17F/17A heterodimer in activated human $CD4^+$ T cells. *J Biol Chem* 282: 13447–13455

20 Chang SH, Dong C (2007) A novel heterodimeric cytokine consisting of IL-17 and IL-17F regulates inflammatory responses. *Cell Res* 17: 435–440

21 Kuestner RE, Taft DW, Haran A, Brandt CS, Brender T, Lum K, Harder B, Okada S, Ostrander CD, Kreindler JL et al (2007) Identification of the IL-17 receptor related molecule IL-17RC as the receptor for IL-17F. *J Immunol* 179: 5462–5473

22 Lee J, Ho WH, Maruoka M, Corpuz RT, Baldwin DT, Foster JS, Goddard AD, Yansura DG, Vandlen RL, Wood WI et al (2001). IL-17E, a novel proinflammatory ligand for the IL-17 receptor homolog IL-17Rh1. *J Biol Chem* 276: 1660–1664

23 Zrioual S, Toh ML, Tournadre A, Zhou Y, Cazalis MA, Pachot A, Miossec V, Miossec

P (2008) IL-17RA and IL-17RC receptors are essential for IL-17A-induced ELR$^+$ CXC chemokine. expression in synoviocytes and are overexpressed in rheumatoid blood. *J Immunol* 180: 655–663

24 Toy D, Kugler D, Wolfson M, Vanden Bos T, Gurgel J, Derry J, Tocker J, Peschon J (2006) Cutting edge: Interleukin 17 signals through a heteromeric receptor complex. *J Immunol* 177: 36–39

25 Acosta-Rodriguez EV, Rivino L, Geginat J, Jarrossay D, Gattorno M, Lanzavecchia A, Sallusto F, Napolitani G (2007) Surface phenotype and antigenic specificity of human interleukin 17-producing T helper memory cells. *Nat Immunol* 8: 639–646

26 Kotake S, Udagawa N, Takahashi N, Matsuzaki K, Itoh K, Ishiyama S, Saito S, Inoue K, Kamatani N, Gillespie MT et al (1999) IL-17 in synovial fluids from patients with rheumatoid arthritis is a potent stimulator of osteoclastogenesis. *J Clin Invest* 103: 1345–1352

27 Infante-Duarte C, Horton HF, Byrne MC, Kamradt T (2000) Microbial lipopeptides induce the production of IL-17 in Th cells. *J Immunol* 165: 6107–6115

28 Nistala K, Moncrieffe H, Newton KR, Varsani H, Hunter P, Wedderburn LR (2008) Interleukin-17-producing T cells are enriched in the joints of children with arthritis, but have a reciprocal relationship to regulatory T cell numbers. *Arthritis Rheum* 58: 875–887

29 Page G, Sattler A, Kersten S, Thiel A, Radbruch A, Miossec P (2004) Plasma cell-like morphology of Th1–cytokine-producing cells associated with the loss of CD3 expression. *Am J Pathol* 164: 409–417

30 Liu Y (2002) Uncover the mystery of plasmacytoid dendritic cell precursors or type 1 interferon producing cells by serendipity. Hum Immunol 63: 1067–1071

31 Fricke I, Mitchell D, Mittelsta J, Lehan N, Heine H, Goldmann T, Bohle A, Brandau S (2006) Mycobacteria induce IFN-γ production in human dendritic cells *via* triggering of TLR2. *J Immunol* 176: 5173–5182

32 Teunissen MB, Koomen CW, de Waal Malefyt R, Wierenga EA, Bos JD. (1998) Interleukin-17 and interferon-gamma synergize in the enhancement of proinflammatory cytokine production by human keratinocytes. *J Invest Dermatol* 111:645–649

33 Li J, Li D, Tan Z (2004) The expression of interleukin-17, interferon-gamma, and macrophage inflammatory protein-3 alpha mRNA in patients with psoriasis vulgaris. *J Huazhong Univ Sci Technol Med Sci* 24: 294–296

34 Arican O, Aral M, Sasmaz S, Ciragil P (2005) Serum levels of TNF-alpha, IFN-gamma, IL-6, IL-8, IL-12, IL-17, and IL-18 in patients with active psoriasis and correlation with disease severity. *Mediators Inflamm* 2005: 273–279

35 Bos JD, Hagenaars C, Das PK Krieg SR, Voorn WJ, Kapsenberg ML (1989) Predominance of 'memory' T cells (CD4$^+$, CDw29$^+$) over 'naive' T cells (CD4$^+$, CD45R$^+$) in both normal and diseased human skin. *Arch Dermatol Res* 281: 24–30

36 Bos JD, Zonneveld I, Das PK Krieg SR, van der Loos CM, Kapsenberg ML (1987) The skin immune system (SIS): distribution and immunophenotype of lymphocyte subpopulations in normal human skin. *J Invest Dermatol* 88: 569–573

37 Bovenschen HJ, Seyger MMB, Van De Kerkhof PCM. (2005) Plaque psoriasis vs. atopic dermatitis and lichen planus: A comparison for lesional T-cell subsets, epidermal proliferation and differentiation. *Br J Dermatol* 153: 72–78
38 Lowes MA, Kikuchi T, Fuentes-Duculan J, Cardinale I, Zaba LC, Haider AS, Bowman EP, Krueger JG (2008) Psoriasis vulgaris lesions contain discrete populations of Th1 and Th17 T cells. *J Invest Dermatol* 128:1207–1211
39 Nielsen OH, Kirman I, Rudiger N, Hendel J, Vainer B (2003) Upregulation of interleukin-12 and -17 in active inflammatory bowel disease. *Scand J Gastroenterol* 38: 180–185
40 Gottfried E, Kunz-Schughart LA, Weber A, Rehli M, Peuker A, Muller A, Kastenberger M, Brockhoff G, Andreesen R, Kreutz M (2008) Expression of CD68 in non-myeloid cell types. *Scand J Immunol* 67:453–463
41 Friese MA, Fugger L (2005) Autoreactive CD8(+) T cells in multiple sclerosis: A new target for therapy? *Brain* 128: 1747–1763
42 Meeuwsen S, Persoon-Deen C, Bsibsi M, Ravid R, van Noort JM (2003) Cytokine, chemokine and growth factor gene profiling of cultured human astrocytes after exposure to proinflammatory stimuli. *Glia* 43: 243–253
43 Lock C, Hermans G, Pedotti R, Brendolan A, Schadt E, Garren H, Langer-Gould A, Strober S, Cannella B, Allard J et al (2002) Gene-microarray analysis of multiple sclerosis lesions yields new targets validated in autoimmune encephalomyelitis. *Nat Med* 8: 500–508
44 Ishizu T, Osoegawa M, Mei FJ, Kikuchi H, Tanaka M, Takakura Y, Minohara M, Murai H, Mihara F, Taniwaki T et al (2005) Intrathecal activation of the IL-17/IL-8 axis in opticospinal multiple sclerosis. *Brain* 128: 988–1002
45 Laman JD, Leenen PJM, Annels NE, Hogendoorn PCW, Egeler RM (2003) Langerhans-cell histiocytosis 'insight into DC biology'. *Trends Immunol* 24: 190–196
46 Hizawa N, Kawaguchi M, Huang SK, Nishimura M (2006) Role of interleukin-17F in chronic inflammatory and allergic lung disease. *Clin Exp Allergy* 36: 1109–1114
47 Andoh A, Zhang Z, Inatomi O, Fujino S, Deguchi Y, Araki Y, Tsujikawa T, Kitoh K, Kim–Mitsuyama S, Takayanagi A et al (2005) Interleukin-22, a member of the IL-10 subfamily, induces inflammatory responses in colonic subepithelial myofibroblasts. *Gastroenterol* 129: 969–984
48 Zaba LC, Cardinale I, Gilleaudeau P, Sullivan-Whalen M, Fariñas MS, Fuentes-Duculan J, Novitskaya I, Khatcherian A, Bluth MJ, Lowes MA et al (2007) Amelioration of epidermal hyperplasia by TNF inhibition is associated with reduced Th17 responses. *J Exp Med* 204: 3183–3194
49 Massarotti EM (2008) Clinical and patient-reported outcomes in clinical trials of Abatacept in the treatment of rheumatoid arthritis. *Clin Therapeutics* 30: 429–442
50 Chen Z, Tato CM, Muul L, Laurence A, O'Shea JJ (2007) Distinct regulation of interleukin-17 in human T helper lymphocytes. *Arthritis Rheum* 56: 2936–2946
51 Ohsugi Y, Kishimoto T (2008) The recombinant humanized anti-IL-6 receptor antibody

tocilizumab, an innovative drug for the treatment of rheumatoid arthritis. *Expert Opin Biol Ther* 8: 669–681

52 Leonardi CL, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y, Li S, Dooley LT, Gordon KB (2008) Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet* 371: 1665–1674

53 Papp KA, Langley RG, Lebwohl M, Krueger GG, Szapary P, Yeilding N, Guzzo C, Hsu MC, Wang Y, Li S et al (2008) Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet* 371: 1675–1684