Summary
Franco Di Padova, Bernhard Ryffel and Valerie Quesniaux

Introduction

The identification of IL-17A and Th17 cells have modified the established Th1, Th2 paradigm, led to the definition of a new the CD3⁺CD4⁺ Th17 cell subset and introduced a new paradigm to explain the origin of several autoimmune events. However, this paradigm shift tended also to identify the effects of IL-17A with those of Th17 cells and *vice versa*. This view might be insufficient to explain the role of IL-17 in several infection and autoimmune models. IL-17A is in fact produced by several other cell types involved in host defense, autoimmunity and inflammation. Overall, we favor the hypothesis that in an early phase of the immune response γδ T cells are directly involved in the production of IL-17A. This is followed by the involvement of αβ Th17 cells. We cannot exclude that, in some human chronic diseases, other cell types like macrophages or astrocytes may also acquire the capacity to produce IL-17A and be involved in pathology.

Keywords: CD4⁺ T cell, Th17 cell, γδ T cells, iNKT cells, IL-17A, IL-10, IL-23

Summary
Robert Sabat, Katrin Witte, and Kerstin Wolk

IL-22 and IL-17: Common and different properties

Many studies over the last few years have shown that a subpopulation of T helper cells called Th17 cells play a major role in both the defense against certain microbes and the development and maintenance of chronic inflammatory diseases. IL-22, IL-17A, and IL-17F may be the most important effector mediators of this novel cell population. This chapter illuminates the common and differing properties of IL-22, IL-17A, and IL-17F with respect to their genes, protein structure, cellular sources, receptors, target cells, and biological effects. Surprisingly, with the exception of a few similarities (in part identical producing cell types and responding cells), most basic aspects of IL-22 and IL-17A/IL-17F are different.

Summary
Marie-Laure Michel and Maria C. Leite-de-Moraes

Other sources of IL-17: Invariant natural killer T cells

Interleukin-17 (IL-17) plays a major role in various models of immune-mediated tissue injury, including organ-specific autoimmunity, allergic disorders and microbial infections. Th17 cells are currently the most thoroughly characterized source of IL-17 credited for causing and sustaining the tissue damage mediated by this cytokine. Similarly to their Th1 and Th2 counterpart, Th17 cells depend on specific factors for their differentiation from naïve T cell precursors, before acquiring their typical cytokine profile. However, this is not the case for all IL-17-producing cells, particularly for a subset of invariant natural killer T cells, termed iNKT17, which are ready to produce this cytokine immediately upon stimulation, in keeping with their capacity to intervene during early stages of the inflammatory response.

Keywords: iNKT cells, IL-17, NK1.1, CD1d, inflammation, autoimmunity, asthma
Summary
Jean-Christophe Renaud and Laure Dumoutier
Contributions of IL-22 to Th17 responses: Repairing and protecting peripheral tissues

IL-22 is a cytokine mainly produced by Th17 cells under the control of IL-23. Although this cytokine is structurally related to IL-10, it does not share any activity with IL-10 and is, so far, completely devoid of activity on immune and hematopoietic cells. IL-22 responsive cells are mainly found in peripheral tissues and include keratinocytes, lung and intestinal epithelial cells as well as hepatocytes. *In vivo*, IL-22 expression fits with the spectrum of inflammatory processes related to Th17 activation, including multiple sclerosis, inflammatory bowel disease and psoriasis in human. However, its pathophysiological significance varies in each of these diseases. IL-22 does not seem to play any major role in multiple sclerosis, at least based on the classical mouse model for this disease. By contrast, this cytokine appears to play a protective role in mucosal inflammation both in lungs and colon. Finally, IL-22 turns out to be one of the main proinflammatory mediators responsible for inappropriate activation of keratinocytes in psoriasis lesions, raising some promising perspectives for future clinical applications.

**Keywords:** IL-22, keratinocytes, psoriasis, Crohn’s disease, Inflammatory Bowel Disease, epithelial cells, hepatitis, multiple sclerosis, acute phase response

Summary
Daniel Mucida and Hilde Cheroutre
Retinoic acid in mucosal immune-regulation

The vitamin A metabolite, retinoic acid (RA), and transforming growth factor-β (TGF-β) are both abundantly produced in the gut and are known to play significant roles in a variety of developmental processes, including the differentiation of lymphocyte lineages. TGF-β mediates the direct inhibition of Th1 and Th2 cytokine polarization concomitant with the generation of regulatory T cells (Tregs). Paradoxically, along with inflammatory cytokines such as IL-6, it also induces the differentiation of pro-inflammatory IL-17-producing CD4 helper T cells (Th17). RA, in contrast, is able under certain conditions to stimulate Th2 differentiation and it is a profound inhibitor of IFN-γ synthesis. Additionally, RA has been shown to efficiently promote gut tropism. We recently described RA as a key modulator of TGF-β-driven immune deviation capable of suppressing Th17 differentiation while promoting Foxp3^+^Treg generation. Here we discuss how RA can affect mucosal immune regulation.

**Keywords:** TGF-β, retinoic acid, Foxp3, T\textsubscript{H}17, IL-6, mucosal immune regulation, oral tolerance, nuclear receptors

Summary
Pornpimon Angkasekwinai and Chen Dong
IL-25, another promoter of allergy

Although there have been significant insights into the mechanism underlying the initiation of type 1 immune response, how type 2-mediated pathology especially allergic diseases is developed remains unclear. Cytokine environment is important in shaping and initiating Th2 responses. IL-25, also called IL-17E, belongs to the IL-17 family but, unlike other IL-17 cytokine members, possesses a unique function in regulating type 2 immune responses. Here we summarize recent work demonstrating the role of this cytokine in promoting allergy, and
discuss its potential producer and responder cells during allergic inflammation. IL-25 thus serves as a novel target for pharmaceutical intervention of allergic asthma disease.

Keywords: IL-25, IL-17E, allergic inflammation, Th2, type 2 immune responses

Summary
Marije I. Koender and Wim B. van den Berg
Critical role of IL-17 in experimental arthritis

Since the discovery of IL-17 expression in synovial fluid and biopsies in rheumatoid arthritis patients, the role of this pro-inflammatory T cell cytokine in arthritis has been extensively studied using animal models of arthritis. In this chapter, an overview is given of the most important publications elucidating the role of IL-17 in the onset and the progression of experimental arthritis. IL-17 is essential for normal T and B cell development, but is also locally involved in the arthritic process, enhancing the expression of pro-inflammatory cytokines and chemokines. IL-17 also contributes to joint destruction directly by up-regulation of matrix metalloproteinases and stimulating osteoclastogenesis through RANKL induction. The recently discovered Th17 cell is regarded as the main source of IL-17, and the influence of IL-12/IL-23 and other mediators in experimental arthritis is discussed.

Keywords: IL-17, animal models, experimental arthritis

Summary
Bruno Schnyder and Silvia Schnyder-Candrian
Dual role of IL-17 in allergic asthma

A proinflammatory role of IL-17 in autoimmune disorders has been favored, although there is evidence that IL-17 has a dual role as negative regulator. Here we review the concept of dual IL-17 functions in the light of recent strategies to use IL-17 neutralization as potential alternative to neutralizing TNF and IL-1 treatments in chronic inflammatory disorders. Expectedly, in allergic lung inflammation, neutralization of IL-17 inhibited neutrophil recruitment. However, this IL-17 antibody treatment concomitantly increased eosinophil recruitment by neutralizing IL-17’s dual role as negative regulator. IL-17 negatively regulated dendritic cell function and activation of T helper cell (Th)2 cytokine production. Furthermore, IL-17 inhibited Th2-characteristic chemokine and adhesion molecule expression. On a mechanistic level, IL-17 acted on IκB-β by preventing degradation and in turn leading to reduced NF-κB activation or IL-17 inhibited transcription factor IRF-1. Therefore, anti-IL-17 therapy, although presenting a promising lead in chronic inflammatory disorders, bears a potential risk of exacerbating allergic asthma.

Keywords: Asthma, allergy, inflammation, chemokines

Summary
Isabelle Couillin, Pamela Gasse, Francois Huaux, Silvia Schnyder-Candrian, Bruno Schnyder, Francois Erard, René Moser and Bernhard Ryffel
Contribution of IL-17 to the pulmonary inflammatory response

Airway exposure to endotoxin and other microbial Toll-like receptor (TLR) agonists induces a rapid production of mediators including IL-1, neutrophil recruitment and bronchoconstriction, which are abrogated in mice deficient for distinct TLRs or the common adaptor molecule myeloid differentiation factor 88 (MyD88). Intranasal IL-17 administration
causes acute neutrophilic lung inflammation in a proinflammatory environment. Recent investigations revealed that IL-17 is up-regulated upon endotoxin aerosol exposure and neutralization of IL-17 diminished endotoxin-induced inflammation, suggesting a role of endogenous IL-17 in endotoxin-induced lung inflammation. Furthermore, administration of IL-1β mobilizes neutrophils and induces IL-17 production in the lung. Therefore, IL-17 might participates in IL-1β-induced lung inflammation. Importantly, lung injury leads to NALP3 inflammasome activation, leading to IL-1β-dependent acute inflammation. The participation of IL-17 in this response is discussed. In conclusion, TLR-agonist and injury-induced lung inflammation depend in part on IL-1β and IL-17. The role of inflammasome activation cleaving pro-IL-1β leading to mature IL-1β and IL-1β-dependent IL-17 production and inflammation need to be explored further.

Summary
Alan Valaperti and Urs Eriksson
The role of IL-17 in experimental autoimmune myocarditis

Experimental autoimmune myocarditis (EAM) represents a CD4\(^+\) T cell-mediated mouse model of inflammatory heart disease. Induction of autoreactive, heart-specific CD4\(^+\) T cells depends on Toll-like receptor-mediated activation of self-antigen-loaded antigen-presenting cells beyond a genetically determined threshold. Recent findings suggest that the expansion of a specific subset of heart-pathogenic CD4\(^+\) cells characterized by IL-17 production is required for disease development. Accordingly, cytokines promoting Th17 CD4\(^+\) expansion, such as IL-6, IL-23, and IL-1 are key players in EAM. Understanding the specific role of distinct cytokines during induction and progression of EAM expands our knowledge on the mechanisms of inflammatory heart diseases and contributes to the development of novel treatment strategies in the future.

Keywords: autoimmunity, mouse model, myocarditis, T helper cells, Interleukin-1, Interleukin-6, Interleukin-17, Interleukin-23, Interferon gamma, dendritic cells, monocytes/macrophages, Toll-like receptors, nitric oxide, innate immunity

Summary
Ye Chen and Kathryn J. Wood
Th17 cells in organ transplantation

A newly discovered subset of T helper cells, Th17 cells, has been implicated in a number of models of autoimmunity. However, their role in transplantation remains undefined. This is despite studies showing a link between IL-17, a cytokine secreted by Th17 cells, and acute allograft rejection. This chapter summarises current evidence for a role of Th17 cells in transplant rejection, tolerance and ischaemia reperfusion injury.

Summary
Andrea M. Cooper
Is IL-17 required to control tuberculosis?

We review the state of knowledge regarding the role of IL-17 in tuberculosis (TB). IL-17 is clearly induced following exposure to mycobacteria in mice and humans and therefore its role in both protection and the immunopathological consequences of infection must be fully defined. IL-17-producing T cells can be seen in both mice and humans and these cytokine-producing cells are dependent to a large degree upon IL-23. Based on what we know of the
function of IL-17 and the nature of TB, it would be surprising if this were a disease where IL-17 would have a dramatic impact; indeed the experimental data suggests that it is not required for control of bacterial growth. However, while it is clear that IL-17 is present during TB, its function(s) is not yet known. Key questions that will help elucidate function include – the role the mycobacteria plays in induction and regulation of the IL-17 response and the role IL-17 plays in modulating the inflammatory response during chronic disease.

Keywords: tuberculosis, inflammation, T cell activation, Th17, Th1, T cells, human, mouse, immunity, IL-17, IL-23, IFN-γ, IL-12

Summary
Shabaana A. Khader and Jay K. Kolls
IL-17 and mucosal host defense

IL-17, a cytokine initially cloned from memory CD4^+ T cells is produced by Th17 cells, a new lineage of T cells that are controlled by the transcription factor RORγt, as well as γδ T cells and NK T cells. IL-17A and IL-17F use both IL-17RA and IL-17RC for signaling. IL-17RA is widely expressed in myeloid cells, fibroblasts, and epithelium. IL-17RA signaling is critical for mucosal immunity in the lung against extracellular bacterial infection through the regulation of granulopoietic growth factors and CXC chemokines required for neutrophil recruitment, as well as anti-microbial protein expression in epithelium. IL-17RA has a limited role in controlling the primary response to intracellular pathogens such as Listeria monocytogenes or Mycobacterium tuberculosis, which require Th1 immunity. However, in the setting of vaccine-induced immunity, IL-17 regulates the recruitment of Th1 cells and is required for optimal vaccine responses for both extracellular and intracellular pathogens.

Summary
Martin Öft
IL-23 orchestrates the switch from tumor immune surveillance to tumor-promoting inflammation

Human tumor cells acquire and accumulate mutations and transcriptional changes that provide growth and survival signals and a tumor-promoting microenvironment. Over the last few decades it has become clear that the mammalian immune system is able to recognize these genetic and epigenetic changes, and that T cells specific to oncogenes and oncofetal antigens are present in human cancer patients and their tumors. Immune-mediated inflammation, however, increases tumor incidence and progression. Epidemiologically, inflammatory disease-inducing cytokines have also been linked to tumor progression. However, the nature of the pro-inflammatory T cells that control the chronic inflammatory response, and their regulation by cytokines like IL-23, only became known recently. This review attempts to summarize our knowledge of pro-inflammatory T cells in cancer, and the cytokines that contribute to the deregulation of tumor-promoting inflammation and its inhibitory consequences on the tumor cell elimination by cytotoxic T cells.

Summary
Pierre Miossec
IL-17 and Th17 cells in rheumatoid arthritis

IL-17 was identified in 1995/96 as a T cell-derived cytokine with effects on inflammation and neutrophil activation. Rheumatoid arthritis has emerged as the most studied situation to justify the selection of IL-17 as a therapeutic target. By interacting with other proinflammatory
Cytokines, IL-17 was found to induce bone and cartilage destruction. In 2006, the precise cell source of IL-17 was identified in the mouse. These cells were named Th17 and their key role was demonstrated in various situations associated with inflammation and matrix destruction. These new findings confirmed and extended the results previously obtained following the identification of IL-17 as a T cell-derived cytokine. At the same time, additional information was obtained on the other members of the IL-17 family and on the structure of the IL-17 receptor complex. Such knowledge has further extended the choice of possible modalities to control IL-17.

**Keywords:** IL-17, cytokines, inflammation, destruction, TNFα, IL-1

**Summary**

**Aaron J. Martin and Stephen D. Miller**

**Targeting Th17 cells in CNS immune pathology**

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system (CNS) mediated by autoreactive T lymphocytes. A new class of CD4+ T cells, the Th17 lineage, has recently been described and has been implicated in initiating immune responses against CNS autoantigens. Findings in experimental autoimmune encephalomyelitis (EAE, the animal model for MS) suggest that targeting Th17 cells may have a beneficial outcome for patients suffering from MS. Several existing and emerging therapeutic strategies are discussed based on the manner in which they target Th17-mediated autoimmunity: lymphocyte depletion, prevention of Th17 development, and prevention of Th17 function. T cell-ablating agents are not Th17 specific and are associated with toxicity and opportunistic infections. The prevention of Th17 differentiation can be achieved experimentally by neutralizing cytokines required for Th17 development and by the administration of cytokines or other chemicals that interfere with differentiation; however, these strategies may also lead to disease. Prevention of functional Th17 responses can be accomplished by inhibiting leukocyte trafficking or by neutralizing IL-17. While several promising therapeutic candidates have been identified using EAE and clinical experimentation, both the risks of immunomodulation as well as the efficacy of such candidates in human patients needs to be completely characterized and carefully considered.

**Keywords:** Multiple sclerosis, experimental autoimmune encephalomyelitis, Th17, autoimmunity

**Summaries**

**Anders Lindén**

**IL-17 cytokines in asthma**

The current chapter scrutinizes the published evidence from humans that IL-17, as well as more recently discovered members of the IL-17 cytokine family, may be involved in the pathogenesis of asthma by contributing to the mobilization of granulocytes. Whereas there is indicative published evidence from patients with asthma arguing for IL-17 and, to lesser degree, for IL-17F, involvement, the current case for the other IL-17 cytokines remains weak in terms of clinical evidence. For the future, there is a need for more studies on human patients with well-characterized phenotypes and consistent medication, to more firmly establish the pathogenic role of IL-17 cytokines in asthma and the pharmacotherapeutic potential of targeting these intriguing molecules.

**Keywords:** Interleukin-17A, IL-17E, IL-17F, IL-25, neutrophil, T cell, macrophage
Summary
Isabelle Wolowczuk, Matthieu Allez and Mathias Chamaillard
IL-17/23, potential targets for Crohn’s disease

Biological agents have profoundly changed the therapeutical management of Crohn’s disease and ulcerative colitis, the major clinical subentities of inflammatory bowel disease (IBD). In the gut mucosa, the interleukin (IL)-23 drives the development of the effector Th17 lineage, which plays an essential role in maintaining tissue homeostasis and in repelling enteropathogenic infections. Conversely, aberrant IL-17- and IL-23-dependent signaling have been recently linked to the predisposition of IBD, prioritizing IL-17 and/or IL-23 signaling as potential therapeutical targets in such common immunopathologies. Clinical trials are currently evaluating the safety and efficacy of fully human recombinant immunoglobulins neutralizing IL-12p40 or IL-17. Consistent with a physiopathological role of IL-17 and IL-23 in Crohn’s disease, preliminary data showed encouraging results in regards to tolerability and beneficial effects. Long-term follow-up monitoring is now eagerly awaited to provide evidence of a durable protective role of IL-12/IFN-γ in host defense against pathogens, as well as additional clinical trials to assess the efficacy of anti-IL-23p19 treatment.

Keywords: innate immunity, Crohn’s disease, IL-17, IL-23

Summary
Franco Di Padova
IL-17A and Th-17 cells as therapeutic targets for autoimmune diseases

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, Th-17 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.

Keywords: CD4+ T cell, Th17 cell, Langerhans cell, astrocyte, IL-17A, IL-17F, IL-22, IL-17RA, IL-17RC, Interleukins, anti-IL-17 antibodies
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