arthritis research&therapy

COMMENTARY

Diversity and flexibility of Th17 effector functions

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Abstract

IL-17-producing CD4+ T-helper cells (Th17 cells) have been recognised as important drivers of pathogenesis in a multitude of inflammatory diseases, including arthritis. The cytokines and transcription factors that instruct and execute Th17 lineage differentiation have been identified. This has induced hopes that targeting Th17 cells might yield a magic bullet against autoimmune diseases. A new wave of published reports shows that matters are more complicated: Th cells can coexpress IL-17 with a variety of other cytokines, including IFNγ, IL-4, or IL-10, with different functional consequences. Moreover, IL-17 memory is not stable – Th17 cells can be instructed to express other lineage-defining cytokines and to halt IL-17 expression. Finally, Th17 cells may exert tissue-protective effects, even in the context of some inflammatory diseases. Manipulating Th17 cells or IL-17 effects may be more difficult than initially appreciated. Notwithstanding these facts, IL-17 remains a valuable and even more interesting therapeutic target.

Cytokines produced by CD4+ T-helper (Th) lymphocytes are critical for protective and pathogenic immune responses. According to their cytokine production, Th cells can be categorised into at least four functionally distinct lineages, called Th1, Th2, Th17, and Treg. Differentiation of naive Th cells is induced upon antigen recognition in the presence of instructive cytokines, resulting in the upregulation of so-called master transcription factors – that is, T-bet, GATA-3, retinoic acid-related orphan receptor γt (RORγt), or FoxP3 for Th1, Th2, Th17, or Treg cells, respectively – and imprinting of functionally relevant genes, such as genes encoding for cytokines and chemokine receptors [1,2].

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Th17 cells were originally characterised by their co-expression of IL-17 (also called IL-17A) together with IL-17F, TNFα, granulocyte–macrophage colony-stimulating factor, and lymphotactin, but not Th1 or Th2 cytokines [3,4]. Over the past several years it has become clear that Th17 cells do not represent a homogeneous lineage. IL-17 can be coexpressed with a variety of other cytokines including IL-21, IL-22, IFNγ, IL-10, and IL-4, with consequences for the cells' functionality [1,2,5-7]. Moreover, IL-17 is not exclusively produced by CD4+ cells but also by CD8+ T cells, γδ T cells, natural killer T cells, natural killer cells, and perhaps also neutrophils, mast cells, and others [2]. Not all IL-17 producers therefore are Th17 cells. One possible current definition of Th17 cells would be CD4+ Th cells that express IL-17A, the IL-23 receptor, and CCR6, and have high levels of expression of the transcription factor RORγt in the absence of significant expression of other lineage-specific transcription factors and cytokines. In humans, CD161 expression has been described as a surface marker for Th17 cells [7].

IL-17A and IL-17F are highly homologous (50% amino acid identity) and share the same receptor. Yet they perform distinct functions. IL-17A seems to be more relevant for the development of autoimmunity and inflammation than IL-17F, and also plays important roles in the host defence against bacterial and fungal infections, whereas IL-17F is mainly involved in mucosal host defence mechanisms [8].

The main physiological function of IL-17 is the recruitment, activation, and migration of neutrophils. Consequently, IL-17 is critically involved in defence against extracellular pathogens, including fungi [9]. Lack of Th17 differentiation or function results in increased susceptibility to extracellular bacterial and fungal infections in humans [10,11].

Th17 cells are central for the pathogenesis in many murine models of inflammatory diseases. These cells contribute to inflammation through the recruitment of neutrophils and the induction of secretion of proinflammatory mediators such as IL-6, IL-8, TNFα, IL-1β, CXCL1, CXCL10, and matrix metalloproteinases from tissue cells [4,9]. In particular, IL-17 is pathogenetically relevant in most murine models of arthritis with the notable exception of proteoglycan-induced arthritis,

which is IFNγ dependent [4,12]. Injection of IL-17 into a mouse knee joint induces cartilage degradation, and IL-17 overexpression induces bone erosion and cartilage degradation [12]. In man, acting synergistically with IL-1 and TNFα, IL-17 was originally shown to induce massive IL-6 production in synovial fibroblasts [4]. The frequency of IL-17-producing cells in the synovium correlates with disease severity in juvenile idiopathic arthritis, rheumatoid arthritis, and psoriatic arthritis [13,14]. In addition, there is a wealth of data demonstrating the presence of IL-17 in inflammatory lesions in other diseases.

While the prevailing view holds Th17 cells responsible for pathology in most inflammatory diseases, recent data also support a tissue-protective function of IL-17 in models of graft versus host disease, colitis, and bronchial hyperreactivity [2]. Whether IL-17-producing Th cells exert pathogenic or protective effects depends partly on coexpressed cytokines, tissue-specific factors, and the pathogenesis stage. Th cells that coexpress IL-17 and IL-22 together with Th2 cytokines contribute to the pathogenesis of human asthma and a murine model thereof [6], whereas IL-17 alone suppresses bronchial hypersensitivity in the effector phase of the disease.

In a murine model for multiple sclerosis (experimental autoimmune encephalitis), Th cells that recognise a myelin autoantigen and produce IL-17, IL-22, CXCL10, CCL2, and CCL5 induce disease upon adoptive transfer into recipients. In contrast, IL-17-producing Th cells recognising the same myelin autoantigen, which produce IL-17 together with IL-10, IL-22, and CCL20, are unable to cause disease and even protect recipient mice from the pathogenic effect of the aforementioned IL-17 producers [5]. In humans, IL-17-producing RORγt$^+$Foxp3$^+$T cells that retain their ability to suppress effector lymphocytes have been described [9,15]. It is noteworthy in this context that transforming growth factor beta is an important instructive signal for the development of both Th17 and iTregs. In response to IL-6, the transcription factor IRF-4 suppresses FoxP3 expression while increasing RORγt expression, resulting in the development of Th17 cells rather than iTregs [16].

Th17 cells can be converted into other Th subtypes or nonclassical Th17 cells that coexpress other lineage-defining cytokines [1,2,7,9,15,17]. It has become obvious that the expression of cytokines and master transcription factors is flexible in Th cells [1,2,9,15,17], breaking the dogma of fixed Th lineages. A thorough appreciation of the flexibility inherent in Th-cell cytokine production will probably halt the currently popular tendency to label every Th cell that produces a particular combination of cytokines as a distinct T-cell lineage. For example, Th17 cells can be converted into Th1/Th17 cells expressing both IFNγ and IL-17 by combined IFNγ and IL-12 signalling. IFNγ is required to upregulate expression of the IL-12Rβ2 chain, and IL-12 is required for Th1 polarisation. These Th1/Th17 cells stably coexpress RORγt and T-bet [17]. Such flexibility is pathogenetically relevant. Diabetes induction by adoptive transfer of highly purified Th17 cells expressing the diabetogenic BDC2.5 T-cell receptor could surprisingly be prevented with antibodies against IFNγ but not with anti-IL-17 antibodies. Isolation and re-analysis of the transferred Th17 cells showed that they had downregulated RORγt and IL-17 expression and had upregulated T-bet and IFNγ [18]. Jenkins and coworkers demonstrated that Th17 cells elicited in response to *Listeria monocytogenes* declined faster after the infection than did Th1 cells [19]. Their results suggest that Th17 cells are less likely to give rise to long-lived memory Th cells, although it is not clear whether the Th17 cells have lost their IL-17 expression or have died.

In conclusion, given the highly complex mechanisms of differentiation, cytokine coexpression, and pathogenic or protective effector functions of Th17 cells, the specific modulation of Th17 effector functions is a major therapeutic challenge. Current treatment options for autoimmune diseases include the blockade of IL-1, IL-6, and IL-23 (p40). Since these cytokines are relevant for the induction or maintenance of Th17 cells, the therapeutic efficacy may partly be due to reduced IL-17 production. Two humanised antibodies against IL-17A are currently in clinical trial for rheumatoid arthritis, psoriasis, and uveitis, and the first results look promising [20,21]. The effects of blocking IL-17F alone or together with IL-17A or other IL-17 family members in patients are not yet known. One can safely assume that much will be learned about the relevance of IL-17 family members for human diseases once the data from large clinical trials are publicly available.

Abbreviations

CCL, CC chemokine ligand; CXCL, CXC chemokine ligand; FoxP3, Forkhead box protein 3; IFN, interferon; IL, interleukin; iTreg, inducible regulatory T cell; RORγt, retinoic acid-related orphan receptor γt; Th, T helper; TNF, tumour necrosis factor; Treg, regulatory T cell.

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Competing interests

The authors declare that they have no competing interests.

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