

## Th17 Cells in Inflammatory Conditions

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### ■ Abstract

CD4<sup>+</sup> T cells have been subdivided into different subsets, largely on the basis of the cytokines they produce. These subsets include Th1, Th2 and regulatory T cells. Recently, another population of T cells have been described, namely Th17, which are characterized by their production of IL-17. Two other important cytokines, which are related to each other, are associated with the development of Th cells, namely IL-12 and IL-23. While IL-12 plays a key role in the differentiation of naïve T cells to Th1 cells, IL-23 promotes the expansion of Th17 cells. IL-12 and IL-23 are heterodimers with a shared subunit, p40. They furthermore

bind to receptors which have unique and shared subunits. Several previous studies have evaluated the role of IL-12 in inflammatory diseases on the basis of p40. Therefore a re-evaluation of the role of IL-12 and Th1 cells in a range of inflammatory conditions has been carried out. This new wave of studies has resulted in the recognition of the role of IL-23 and Th17 cells in inflammatory conditions, such as arthritis and inflammatory bowel disease. There is also the speculation about a possible role in type 1 diabetes.

**Keywords:** inflammatory disease · Th cell · regulatory T cell · Th17 cell · IL-17 · IL-23 · type 1 diabetes

### Introduction

CD4<sup>+</sup> T cells have been subdivided into a range of different subsets on the basis of the cytokines they produce and the functions they perform. Th1, Th2 and regulatory T cells (Tregs) have been well characterized with respect to factors influencing their development, the cytokines they produce and their respective roles in response to pathogens, tumors and self-antigens [1-7]. Another population of Th cells, Th17, characterized by their production of the cytokine IL-17, has been described [8], and it is only recently that factors determining their generation have been identified [9, 10]. The role of Th17 cells in mediating autoimmune pathology is also now becoming recognized, interestingly in events that were previously thought to be Th1-mediated. As type 1 diabetes is

thought to be a Th1-mediated disease it would be appropriate to examine the involvement of Th17 in beta cell destruction. The role of these cells, however, in type 1 diabetes remains to be clarified.

### The IL-17 cytokine family

The IL-17 produced by Th17 cells is IL-17A and is one of the six family members of related cytokines [11]. Of the other family members, IL-17B, C, D, E and F only IL-17E and F are known to also be made by CD4<sup>+</sup> T cells. IL-17E, which is also known as IL-25, is associated with Th2 responses and the immune response against helminths [12, 13]. IL-17A is regarded as a pro-inflammatory cytokine capable of eliciting the production of other inflammatory cytokines and chemokines such as IL-6, IL-8, GM-CSF and MCP-1

by fibroblasts, endothelial and epithelial cells [14-19]. Elevated levels of IL-17 have been detected in rheumatoid synovium and have been associated with multiple sclerosis, psoriasis and systemic lupus erythematosus.

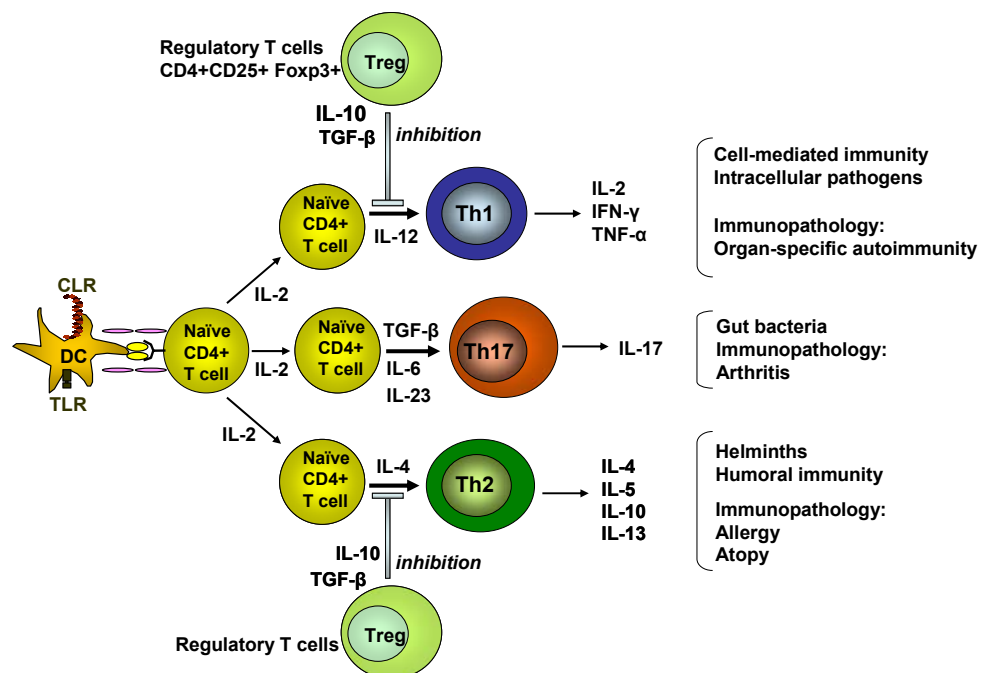
### Factors influencing Th17 development and differentiation

It is well known that IL-12 regulates Th1 while IL-4 regulates Th2 differentiation [7]. Recent studies have clarified the cytokine-related requirements for Th17 differentiation. These elegant studies show that TGF- $\beta$  and IL-6 are required for naïve CD4<sup>+</sup> T cells to differentiate into Th17 cells [9, 10]. This differentiation is facilitated by the absence of IFN- $\gamma$  and IL-4. As TGF- $\beta$  has usually been associated with the development of Treg cells [20] and the inhibition of Th1 and Th2 cell differentiation [21], it is interesting to note that in the presence of an inflammatory cytokine, such as IL-6, the inhibition of Treg cell development and differentiation of naïve CD4<sup>+</sup> T cells into Th17 could be observed [9]. This data confirms the view that Th17 cells are a completely separate lineage of CD4<sup>+</sup> T cells (Figure 1).

It is known that the signal transducer and activator of transcription (STAT)-4 and the transcription factor T-bet are essential for development of Th1 while STAT-6 and GATA-3 are needed for Th2 development. However, only recently it could be shown that STAT-3 is also involved in Th17 development together with the suppression of cytokine signaling (Socs) 3, which acts as a regulator of IL-23-induced STAT-3 phosphorylation and Th17 development.

IL-23 has also been shown to regulate IL-17 production and to promote the expansion of Th17 cells [22, 23]. It is a

heterodimeric cytokine comprised of p40 and p19 subunits. The p40 subunit is also found in IL-12. The receptors for IL-23 and IL-12 share a subunit, IL-12R $\beta$ 1. The IL-12R $\beta$ 1 subunit combines with IL-23R to give the functional IL-23 receptor and, together with IL-12R $\beta$ 2, to give a functional IL-12R. It can be seen that this subunit sharing by these cytokines and their receptors could have been a source of confusion in assigning a role for IL-12 and Th1 cells in certain pathological conditions. Early studies suggested that effects on inflammatory responses can be observed following the blockade of p40 with antibody or its targeted mutation. These results were interpreted as demonstrating an involvement of IL-12 and correspondingly Th1 cells in the pathogenesis of inflammatory conditions. However, subsequent studies showed that the specific targeting of IL-23 resulted in the alleviation of several inflammatory conditions [24-26], while the lack of IL-12 in some situations actually exacerbated inflammation [24]. In summary, these studies emphasized the potential importance of Th17 cells in inflammatory responses.



**Figure 1. Functional development and activity of Th cell subpopulations.** Activation of dendritic cells (DC) follows interaction of pattern recognition receptors such as C type lectin receptors (CLR) or toll like receptors (TLR) with molecules on the surface of microorganisms. Antigen presentation to naïve T cells results in the development of Th1, Th2 or Th17 cells depending on the cytokine milieu. Cells of the innate immune system, e.g. DC and NKT cells, are the source of promoting cytokines, IL-4, IL-6, TGF- $\beta$  and IL-12. IL-23 promotes the expansion rather than the development of Th17 cells. The cytokines which are made would depend on the antigenic stimulus. The activity of Th cell subpopulations can be regulated by Tregs which may include naturally arising Foxp3-expressing Tregs.

## Th17 cells and autoimmune disease

IL-17 levels are elevated in a range of inflammatory conditions including systemic sclerosis, psoriasis and rheumatoid arthritis synovium [27-31]. Collagen induced arthritis (CIA) and experimental induced encephalomyelitis (EAE) were thought to be Th1-mediated autoimmune diseases. As discussed above, this assumption arose in part from experiments that did not distinguish between effects on IL-12 or IL-23. More recently it has been shown that these two experimentally induced autoimmune conditions as well as some others are mediated by Th17 cells. The absence of IL-6, which is needed for Th17 development, protected mice against both EAE and CIA [32-35]. Neutralization of IL-17 by specific antibody treatments *in vivo* has been shown to prevent the induction of EAE and the deficiency in IL-23 has been shown to protect mice against both EAE and CIA. The involvement of Th17 cells in mediating pathology in EAE has recently been beautifully demonstrated by the work of Kuchroo and colleagues [9].

There is little information, as yet, regarding the role of IL-17 and Th17 cells in type 1 diabetes. The ability of IL-17 to induce inducible nitric oxide synthase (iNOS) in chondrocytes [36] could be observed to occur in mouse islets exposed to this cytokine [37]. A potential role for Th17 cells in the exacerbation of diabetes is suggested by the observation that IL-23 induces

diabetes in mice if co-administered with sub diabetogenic multiple low doses of streptozotocin [38]. Whether Th17 cells and cytokines IL-23 and IL-17 play a role in the spontaneous onset of diabetes remains to be clarified.

## Conclusion

There has been recent interest in the role of a distinct lineage of Th cells, Th17 cells, in autoimmune pathology. Several autoimmune conditions, previously assumed to be Th1-mediated, have now been shown to involve Th17 cells. The different subpopulations of Th cells have distinct functions and have evolved to combat infections of historical importance. Figure 1 shows that Th17 cells may have a specific role in combating certain bacterial gut infections, thus complementing the activities of Th1 and Th2 cells in their responses against intracellular pathogens and helminths, respectively. The other side of the coin is that the same cell populations are associated with inflammatory responses that can be damaging to the host. In the presence of tight regulatory networks, host pathology should be controlled. There is increasing interest in the ways in which infections may influence the establishment of such regulatory networks.

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