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Perspective

# Friend or Foe? – The Role of $T_H17$ Immunity in Host Protection

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## Introduction

The discovery and characterisation of T-helper 17 (Th17) lymphocytes was first described in 2005 [1,2]. This new lymphocyte subset challenged immunologists' thinking of the day with respect to the immune system and the Th1/Th2 dogma described almost 30 years earlier by Mosmann and Coffman [3]. These Th17 cells were shown to have a potent pro-inflammatory effect important in protection of the host against bacterial or fungal infections [4]. A number of studies have since demonstrated that Th17 cells, in addition to Th1 cells, can also drive pathological responses in a number of inflammatory and autoimmune diseases such as multiple sclerosis, rheumatoid arthritis and psoriasis. However, the role of Th17 cells and its signature cytokine, IL-17A is also recognised to play a critical role in pathogen clearance. In humans, the mechanisms driving Th17 cell differentiation and its regulation in host protection are poorly understood. In this perspective article, we discuss the functional plasticity of Th17 cells in the context of autoimmunity and infection and how these responses may be targeted by new-generation therapies.

## $T_H17$ Differentiation Pathways

In mice, differentiation of naïve T cells into Th17 cells occurs mainly in the presence of IL-6 and TGFβ, resulting in IL-17 (or IL-17A) secretion and is characterised by the expression of the nuclear transcription factor RORγt [5] and STAT3 [6]. Although less well characterised in humans, this seems to require IL-1b and/or IL-23, the latter especially crucial for Th17 cell expansion, survival and stability [7]. In addition to IL-17A, Th17 cells also typically secrete IL-17F, IL-21and IL-22 under the transcriptional control of RORc (the human analog of RORγt) [8,9]. The function of Th17 cells is reciprocally regulated by another lymphocyte subset, the regulatory T cell (Treg) [10] which are either thymus-derived or induced in the periphery by TGFβ and express the transcription factor FoxP3 [11]. However, Th17 differentiation from naïve precursors is generally unstable compared to Treg and has been suggested to represent an intermediate phenotype that expresses both FoxP3 and IL-17 [12]. Moreover, conversion of Treg to Th17 cells *in vitro* is thought to be one mechanism that could explain their dual role in autoimmunity and pathogen clearance.

Two distinct Th17 cell populations are proposed to help explain the dual role of Th17 cells, those with a pathogenic role, termed Teff17, and those that are protective, termed Treg17 [12]. It is known that Teff17 cells require IL-23 as studies have shown that IL-23 and IL-23R knockout mice are not susceptible to autoimmunity [13] and also lack GM-CSF, another pathogenic cytokine [14]. In contrast, Treg17 development requires TGFβ, which can suppress GM-CSF as well as inducing IL-10 secretion to protect against tissue inflammation. In humans, Th17 skewing from Treg is less well understood, although one study has shown that Treg cells can also secrete IL-17 and express RORγt [15]. This information may be important in our understanding of the link between Th17 and Treg responses in health and disease.

## Pathogenic Role of Th17 Responses in Autoimmunity

Th17 cells were first documented to induce severe tissue inflammation in the context of autoimmunity. Many studies in mice have confirmed the pathogenic role of Th17 cells in experimental models of human diseases such as experimental autoimmune encephalitis (multiple sclerosis, MS) [16], collagen-induced arthritis (rheumatoid arthritis, RA) [17] and colitis (inflammatory bowel disease) [18]. In humans, the role of Th17 responses in autoimmunity has mostly been based on studies examining biomarker correlations with clinical disease. For example, MS patients were found to have elevated IL-17 levels in the serum and cerebrospinal fluid [19-21]. Recently, it was shown that the higher IL-17A levels in MS patients was correlated with neuronal glutamate excitotoxicity and associated downstream blood-brain barrier disruption [22]. This supports *in vitro* evidence that Th17 cells have a greater capacity to penetrate the blood brain barrier (BBB) and infiltrate the parenchyma of the central nervous system than Th1 cells [23]. Similarly for RA, Th17 cells were of higher frequency in patients compared to healthy controls [24,25] and the expression of IL-17, TNF and IL-1 predicted later joint destruction [26]. Furthermore, it was demonstrated that the activity of these Th17 cells was inhibited by Tregs from RA patients that were up regulated by anti-TNFα treatment [27]. Emerging data on the use of anti-Th17 based therapies such as secukinumab (anti-IL-17A) for psoriasis are promising [28] and larger clinical trials with these new-generation therapies will be of paramount importance.

## Protective Role of Th17 Immunity

Some pathogens, particularly fungi and bacteria, are known to stimulate the production of IL-17, which is necessary to limit the spread of the organism. A number of studies have demonstrated that specific microbial ligands are able to induce cytokines such as IL-23 that drive Th17 development. *Candida albicans, Klebsiella pneumoniae* and *Mycoplasma tuberculosis* all require Th17 responses




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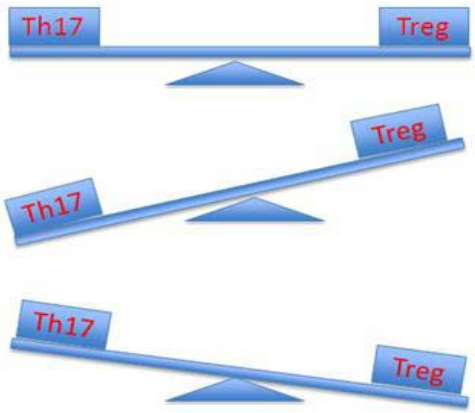


**Figure 1:** Schematic representation of the Th17-Treg axis in health and disease. Top panel: Under healthy immune homeostasis, the Th17 and Treg populations are counter-balanced; Middle panel: Protection against autoimmune and auto-inflammatory diseases is associated with skewing of the axis towards Treg cells ; Bottom panel: Th17 skewing is required for protection against bacterial and fungal infections, especially *Streptococcus pneumoniae.*

for their clearance, primarily through the upregulation of neutrophil function [29-31]. Recently, Th17 responses have been shown to protect mice against nasopharyngeal colonisation by *Streptococcus pneumoniae,* a major global pathogen responsible for the deaths of more than 1 million infants worldwide every year [32]. This is interesting as it suggests that antibody-independent mechanisms of protection are important in the mucosa in contrast to serotype-specific IgG, which is known to be the major correlate of protection against invasive pneumococcal disease.

The importance of IL-17-secreting Th17 cells in orchestrating the recruitment and activation of innate cells (neutrophils, monocytes and macrophages) in the upper respiratory tract and clearance of pneumococcal colonisation has been demonstrated [33,34]. This Th17 response was found to occur independently of antibodies and complement and was abrogated in the absence of the IL-17A receptor [35]. Importantly, high IL-17 expression was associated with low levels of pneumococcal nasopharyngeal carriage in both mice and young children [35-37] and stimulation of peripheral blood mononuclear cells *ex vivo* with pneumococcal pneumolysin generated substantial IL-17 [38,39]. In contrast, Tregs suppressed pneumococcal T cell responses in the mucosa, supporting the IL-17-Treg counter-regulatory developmental pathway and providing a possible mechanism by which carriage is sustained [40]. More recently, higher lung Tregs were detected in mice resistant to pneumococcal pneumonia, highlighting the importance of TGFβ signalling in these animals [41]. However, further studies in humans are needed to confirm the protective effects of Tregs in the context of pneumococcal disease.

The discovery that Th17 immunity protects against pneumococcal colonisation underpinned the development of a Whole Cell Vaccine (WCV) that protects mice against colonisation, pneumonia and sepsis [42]. This vaccine comprises a non-encapsulated strain of pneumococcus that expresses multiple conserved proteins across many serotypes with the ability to stimulate CD4+ Th17-derived IL-17 responses [43]. This is a major advance in pneumococcal vaccinology due to its perceived ability to overcome many of the limitations of current pneumococcal conjugate vaccines such as serotype replacement and cost of the vaccine. The WCV has already completed a Phase 1 clinical study in healthy adults, demonstrating immunogenicity and an acceptable safety profile, leading to early-stage clinical evaluation in Kenya and later Indonesia to provide evidence that this vaccine provides broad protection for children at greatest risk of the disease.

## Conclusion

Our understanding of Th17 biology has advanced substantially over the last 10 years. In particular, the balance between suppressive Treg cells and inflammatory Th17 cells has long been considered an important aspect to preventing chronic inflammatory diseases, providing the impetus for development of novel therapeutic strategies aimed at augmenting Treg responses or blocking Th17 immunity. However, Th17 cells also have protective roles and further studies to understand their differentiation from Treg precursors will be critical in this approach. Harnessing protective Th17 immunity without the risk of inducing chronic tissue inflammation is of paramount importance. New-generation vaccines such as WCV offer significant promise in the prevention of pneumococcal disease while development of various IL-17 inhibitors has shown some benefit against autoimmune diseases.

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