Journal of Autoimmunity xxx (2017) 1–15

Contents lists available at ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

Review article

# A cellular and molecular view of T helper 17 cell plasticity in autoimmunity

Ralph Stadhouders [a, b], Erik Lubberts [c], Rudi W. Hendriks [a, *]

[a] Department of Pulmonary Medicine, Erasmus MC Rotterdam, Rotterdam, The Netherlands
[b] Department of Cell Biology, Erasmus MC Rotterdam, Rotterdam, The Netherlands
[c] Department of Rheumatology, Erasmus MC Rotterdam, Rotterdam, The Netherlands

ARTICLE INFO

*Article history:*
Received 6 December 2017
Accepted 6 December 2017
Available online xxx

*Keywords:*
Autoimmune disease
Cytokine
Epigenetics
Plasticity
T helper cell
Th17
Transcription factor
Transdifferentiation

ABSTRACT

Since the original identification of the T helper 17 (Th17) subset in 2005, it has become evident that these cells do not only contribute to host defence against pathogens, such as bacteria and fungi, but that they are also critically involved in the pathogenesis of many autoimmune diseases. In contrast to the classic Th1 and Th2 cells, which represent rather stably polarized subsets, Th17 cells display remarkable heterogeneity and plasticity. This has been attributed to the characteristics of the key transcription factor that guides Th17 differentiation, retinoic acid receptor-related orphan nuclear receptor gamma (RORγ). Unlike the 'master regulators' T-bet and GATA3 that orchestrate Th1 and Th2 differentiation, respectively, RORγ controls transcription at relatively few loci in Th17 cells. Moreover, its expression is not stabilized by positive feedback loops but rather influenced by environmental cues, allowing for substantial functional plasticity. Importantly, a subset of IL-17/IFNγ double-producing Th17 cells was identified in both human and mouse models. Evidence is accumulating that these IL-17/IFNγ double-producing cells are pathogenic drivers in autoimmune diseases, including rheumatoid arthritis, multiple sclerosis and inflammatory bowel disease. In addition, IL-17/IFNγ double-producing cells have been identified in disorders in which the role of autoimmunity remains unclear, such as sarcoidosis. The observed plasticity of Th17 cells towards the Th1 phenotype can be explained by extensive epigenetic priming of the *IFNG* locus in Th17 cells. In fact, Th17 cells display an *IFNG* chromatin landscape that is remarkably similar to that of Th1 cells. On the other hand, pathogenic capabilities of Th17 cells can be restrained by stimulating IL-10 production and transdifferentiation into IL-10 producing T regulatory type 1 (Tr1) cells. In this review, we discuss recent advances in our knowledge on the cellular and molecular mechanisms involved in Th17 differentiation, heterogeneity and plasticity. We focus on transcriptional regulation of the Th17 expression program, the epigenetic dynamics involved, and how genetic variants associated with autoimmunity may affect immune responses through distal gene regulatory elements. Finally, the implications of Th17 cell plasticity for the pathogenesis and treatment of human autoimmune diseases will be discussed.



**Contents**



* Corresponding author. Department of Pulmonary Medicine, Erasmus MC Rotterdam, PO box 2040, 3000 CA Rotterdam, The Netherlands.
*E-mail address:* r.hendriks@erasmusmc.nl (R.W. Hendriks).

https://doi.org/10.1016/j.jaut.2017.12.007
0896-8411/

## 1. Introduction

$CD4^+$ T helper (Th) cells are central orchestrators of immune responses. They provide help to $CD8^+$ T cells and B cells and produce cytokines that activate or modulate innate immune cells, stromal cells and epithelial cells. Following the recognition of their cognate antigen on the surface of antigen presenting cells (APCs) by the T cell receptor (TCR), activated $CD4^+$ T cells are triggered to differentiate into effector Th cells, guided by specific co-stimulatory signals and the cytokine milieu.

In 1986 Mossmann, Coffman and colleagues first reported that upon antigenic stimulation naive $CD4^+$ T cells can differentiate into two functionally distinct subsets: Th1 or Th2 effector cells [1]. This division was based on cytokine production profiles and provided an explanation for the diverse responses of effector $CD4^+$ T cells in infection, allergy or autoimmunity. Th1 cells mainly produce IFNγ and TNF-α and are crucial for host defense against intracellular bacteria and viruses, but are also involved in the pathogenesis of autoimmune disorders. Th2 cells produce the signature cytokines IL-4, IL-5 and IL-13 to control helminth infections and are implicated in allergic immune responses. Differentiation into Th1 or Th2 cells is controlled by the key sequence-specific DNA-binding proteins (transcription factors, TFs) T-bet, encoded by the *TBX21* gene [2,3] and GATA3 [4,5] respectively, and involves epigenetic mechanisms that drive subset-specific differentiation and restriction of alternative fates. Since IL-12, IFNγ and T-bet have the capacity to repress Th2 polarization and, conversely, the IL-4-GATA3 axis represses Th1 differentiation, it appears that Th1 and Th2 cells represented mutually exclusive and stable, self-reinforcing, terminally differentiated subsets. This dichotomous Th1/Th2 division paradigm was challenged by the identification of highly stable T-$bet^+GATA3^+$ bifunctional Th1/Th1 hybrid cells that co-produced IFNγ and IL-4 at the single-cell level [6–8]. Moreover, to date Th cell differentiation has been extended to include various additional polarization states, including regulatory T cells (Tregs), Th9, Th17, Th22, follicular T helper cells (Tfh) and follicular Tregs (Tfr). Each of these subsets is characterized by a unique cytokine expression pattern and a lineage-associated TF network (Fig. 1).

The Th17 subset, identified in 2005 [9–12], resides mainly at mucosal sites such as in the gastrointestinal tract and the airways. These T cells secrete various cytokines including IL-17A, IL-17F, IL-21, IL-22 and granulocytes macrophage colony-stimulating factor (GM-CSF). Although Th17 cells were originally discovered in the context of autoimmune disease, they play a crucial role in the maintenance of mucosal homeostasis and contribute to the protection against bacterial and fungal pathogens, such as *Mycobacterium* and *Candida* [13]. The retinoic acid receptor-related orphan nuclear receptor gamma (RORγ) is the key TF that orchestrates the differentiation of the Th17 lineage and directly induces transcription of IL-17A/F [14]. However, in contrast to T-bet and GATA3 function in Th1 and Th2 cells, respectively, RORγ regulates transcription of remarkably few loci in Th17 cells and its expression is not stabilized by positive feedback loops [15]. Therefore, RORγ may not be regarded as a prototypical master regulator that functions to lock-in the Th17 differentiation program. Rather, expression of RORγ is influenced by environmental cues, making Th17 cells relatively unstable and allowing for substantial functional plasticity [15]. In particular, a subset of IL-17-producing cells that co-expresses IFNγ was identified in both human and mouse models and defined as non-classic Th1 cells, ex-Th17 cells or Th17.1 cells [16,17]. It is thought that following an IL-17/IFNγ double-producing phase, Th17 cells may lose IL-17 expression to become an $IFN\gamma^+$ Th1-like cells in which IL-17 expression is almost completely extinguished [17].

On the other hand, studies have shown that TGFβ and IL-6, which initially drive Th17 differentiation, can also restrain the pathogenic capabilities of Th17 cells by stimulating IL-10 production [18]. Indeed, fate-mapping studies provided evidence that Th17 cells may lose IL-17A expression and transdifferentiate into IL-10-producing Tr1 cells [19]. Given that Th17 cells have a beneficial role in barrier protection as well as a pathogenic pro-inflammatory role in many autoimmune diseases, their heterogeneity and plasticity is not only fundamentally interesting in the context of cell identity and reprogramming, but is also highly relevant for our understanding of autoimmunity and the development of novel therapeutic strategies. Recently, single-cell transcriptome analyses have shed light on the molecular basis of Th17 heterogeneity [20,21].

In this review, we summarize recent advances in our understanding of the molecular mechanisms involved in Th17 cell plasticity. We focus on gene expression programs in the Th17 subset that are regulated by TFs through changes in epigenetic modifications and chromatin structure. Finally, implications for the pathogenesis of human autoimmune diseases will be discussed.

## 2. T helper subset differentiation

Initially Th subset differentiation was thought to rely predominantly on single 'master' TFs that enforce lineage commitment and engage in positive auto-regulatory feedback loops and reciprocal

Please cite this article in press as: R. Stadhouders, et al., A cellular and molecular view of T helper 17 cell plasticity in autoimmunity, Journal of Autoimmunity (2017), https://doi.org/10.1016/j.jaut.2017.12.007