Trends in
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Spotlight

Th17 cells: from gut homeostasis to CNS pathogenesis

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Th17 cells play crucial roles in host–microbe interactions, but can also promote chronic inflammation and tissue pathology. Factors influencing Th17 cell heterogeneity and effector functions in different inflammatory contexts remain unclear. Schnell *et al*. demonstrate that intestinal Th17 cells form a reservoir from which pathogenic Th17 cells can be elicited during severe tissue inflammation.

During homeostasis, CD4$^+$ Th17 cells are enriched within barrier tissues, including the mammalian gastrointestinal (GI) tract, lung, and skin. Here, Th17 cells provide protection against pathogenic bacteria and fungi, while also regulating the composition and translocation of the commensal microbiota. By contrast, during severe tissue inflammation, Th17 cells adopt a distinct proinflammatory program that contributes to tissue and organ destruction. This program depends on IL-23 and coincides with IFN-γ and GM-CSF co-production. Pathogenic Th17 cells are also implicated in multiple autoimmune diseases. Therefore, targeting pathways central to pathogenic Th17 cell functions harbors significant therapeutic potential. However, this is complex, as highlighted by different therapeutic efficacies for anti-IL-17 and IL-23 targeted therapies in human disease [1]. While psoriasis and psoriatic arthritis respond to IL-17 and IL-23 blockade therapies, axial spondyloarthropathies demonstrate a superior anti-IL-17 antibody response relative to anti-IL-23-based approaches [1]. By contrast, for Crohn's disease, IL-23 blockade is therapeutic, whereas IL-17 blockade worsens disease [2]. These distinct outcomes suggest differences in Th17-driven pathology across disease and tissue types.

Extensive investigation of Th17 cell differentiation *in vitro* has identified several hallmarks of nonpathogenic and pathogenic Th17 cells. By directing naïve CD4$^+$ T cell polarization with distinct cytokine stimuli, early work identified TGF-β and IL-6 as promoting Th17 cell differentiation marked by elevated expression of *Maf*, *Ahr*, and *Il10*. By contrast, skewing naïve CD4$^+$ T cells with IL-1β, IL-6, and IL-23 drove the elevated expression of *Tbx21* (T-bet), *Ifng*, and *Csf2* (GM-CSF) [3,4]. *In vivo*, these *in vitro* signatures align with homeostatic and pathogenic Th17 cells, the latter requiring IL-23 to manifest autoimmune tissue pathologies. Fate-mapping using *Il17a*^{Cre} mice identified pathogenic Th17 cells *in vivo* [5]. These and other studies demonstrated the plasticity of Th17 cells during inflammation and their conversion to IFN-γ and GM-CSF producing 'ex-Th17' cells. Furthermore, IL-23 was deemed crucial for pathogenic Th17 cell function, in part, through the production of GM-CSF [5–7].

The complexities of Th17 cell contributions to homeostatic, protective, and pathogenic immune responses, and how these populations may be developmentally entwined, remains unclear. Understanding the developmental relationship between these cell types relative to the tissues they reside in may shed light on their role in immune homeostasis and disease. Also, an upswell in the use of single-cell RNA sequencing (scRNA-seq) analysis by immunologists has provided a new level of insight into previous descriptions of cellular heterogeneity and plasticity between CD4$^+$ T cell subsets, including Th17 cells [8,9]. However, the molecular mechanisms underlying acquisition of a pathogenic Th17 cell state *in vivo* are yet to be fully elucidated.

In an elegant study recently published in *Cell*, Schnell *et al*. advance our understanding of the relationship between homeostatic and pathogenic Th17 cells by using scRNA-seq, T cell receptor (TCR)-seq, and cytokine fate-mapping approaches to compare current and ex-Th17 cells elicited during homeostasis and tissue inflammation [10]. By using a combination of reporter alleles to isolate cells with current or previous *Il17a* expression (ex-Th17), the authors compared cell populations from naïve tissues (small and large intestinal lamina propria, Peyer's patches, mesenteric lymph nodes) with those from the inflamed central nervous system (CNS), inguinal lymph node, and spleen [9]. Immunization with MOG_{35-55} peptide in complete Freund's adjuvant (CFA) elicited the expansion of encephalitogenic CD4$^+$ T cells that trafficked to the CNS and drove tissue destruction. Direct comparison of homeostatic and pathogenic Th17 cell populations using scRNA-seq and TCR-seq enabled the authors to identify markers of homeostatic and pathogenic Th17 cells and also demonstrated that stem-like intestinal Th17 cells can contribute to the pathogenic Th17 cell pool, promoting CNS destruction.

Comparison of total Th17 cells from naïve and encephalitic mice identified distinct signatures of Th17 cells to be imprinted by the tissue of origin, which, for the most part, dominated over the cellular phenotype imposed by inflammation. As such, similar to Foxp3$^+$ regulatory T cells (Treg), or macrophages, tissue imprinting is a major mediator of Th17 cell heterogeneity [10]. To distinguish Th17 cell subsets *in vivo*, the authors identified SLAMF6 and CXCR6 as cell surface markers of homeostatic and pathogenic Th17 cells, respectively. Furthermore, by combining gene expression with TCR-seq, the authors further investigated this intra- and inter-tissue

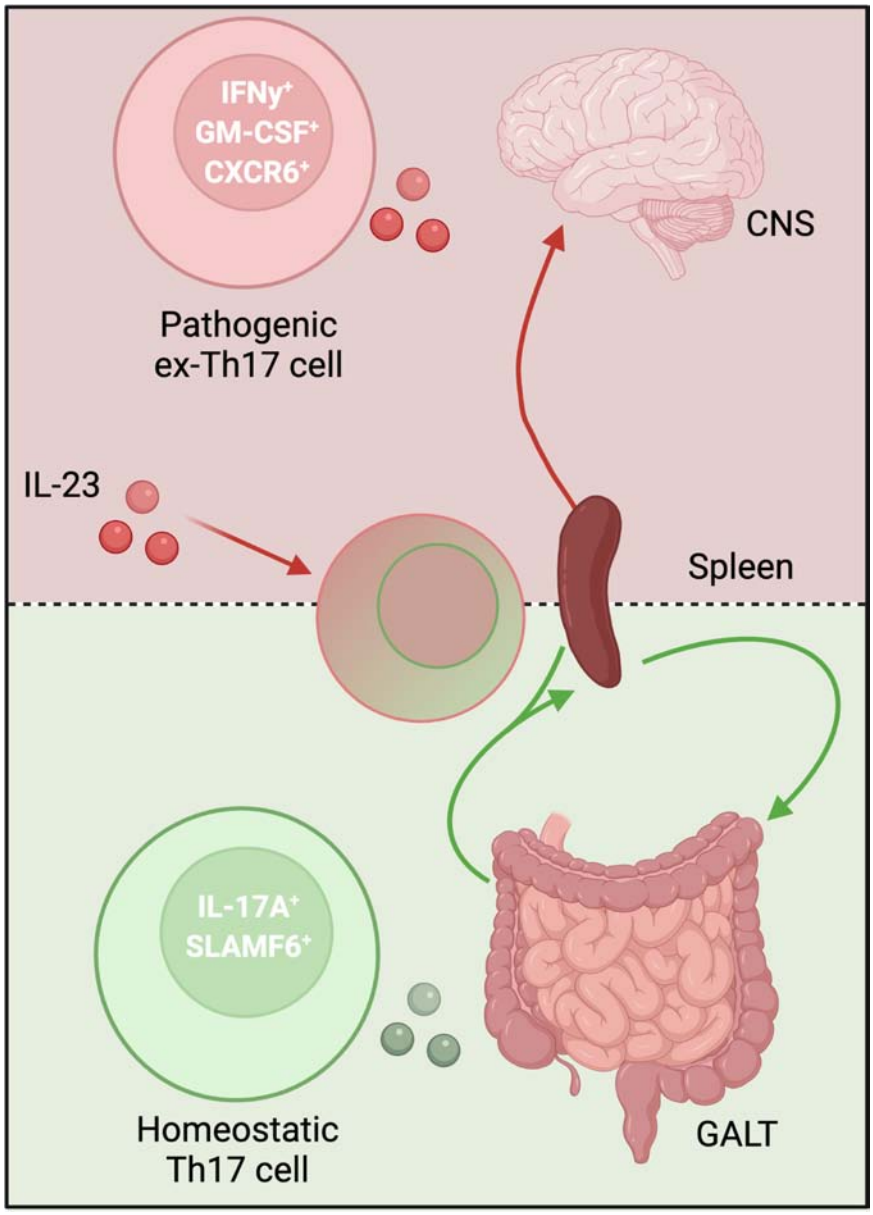

Figure 1. Intestinal Th17 cells contribute to the pathogenic Th17 cell pool during central nervous system (CNS) inflammation in mice. Homeostatic Th17 cells are enriched within intestinal tissues during homeostasis and recirculate through the spleen. During inflammation, IL-23 acts directly upon SLAMF6$^+$ Th17 cells to promote their conversion to pathogenic Th17 and ex-Th17 cells, which produce IFN-γ and GM-CSF, and to promote CNS tissue destruction. Abbreviation: GALT, gut-associated lymphoid tissues.

heterogeneity and inferred cellular hierarchy by linking these to clonotypic analyses. TCR clonotypes informed the expansion of distinct Th17 cell clusters, identifying distinct TCR usage by homeostatic Th17 cells derived from intestinal tissues and the spleen; by contrast, clonotypes elicited upon MOG/CFA immunization were enriched among pathogenic Th17 cells. Noteworthy, a small population of Th17 cells overlapping both homeostatic and pathogenic clonotypes was specifically identified in the spleen, suggesting a developmental relationship between a small reservoir of splenic homeostatic and pathogenic Th17 cells. By isolating SLAMF6$^+$ and CXCR6$^+$ Th17 cells, the authors formally demonstrated a developmental relationship between these subsets during the onset of experimental autoimmune encephalitis (EAE). Specifically, adoptive transfer of SLAMF6$^+$ Th17 cells into immunized mice demonstrated that SLAMF6$^+$ Th17 cells could give rise to CXCR6$^+$ Th17 cells; furthermore, this cell augmentation increased disease severity, directly implicating the adoption of a SLAMF6$^+$-to-CXCR6$^+$ Th17 cell pathogenic program in disease etiology [10] (see Figure 1).

Finally, the authors demonstrated that the transition from SLAMF6$^+$ to CXCR6$^+$ Th17 cells depended upon direct IL-23R signaling on Th17 cells, formally demonstrating previous descriptions of IL-23R-signaling as being key to Th17 pathogenicity. Moreover, these findings support previous studies detailing a role for encephalitogenic CXCR6$^+$ Th17 cells as primary producers of IFN-γ and GM-CSF during EAE. While CXCR6-mediated trafficking has been reported to be dispensable for the induction of EAE, depletion of CXCR6$^+$ cells, both prior and following disease onset, is sufficient to reduce CNS inflammation in EAE [11,12]. Overall, the study by Schnell and colleagues draws together multiple facets of Th17 cell and EAE biology, robustly demonstrating a developmental pathway that regulates pathogenic Th17 cell development and function in the murine CNS [10].

The findings from this study show the power of combining single-cell technologies to understand cell heterogeneity and fate but also raise additional questions that warrant further investigation. What are the specificities of TCRs shared by

SLAMF6$^+$ Th17 found in the gut and the CXCR6$^+$ Th17 cells found in the CNS? Answering this could shed light on putative pathogenic cell targets and inform on whether these might be crossreactive with the gut flora. Furthermore, what are the mechanisms through which CXCR6$^+$ Th17 cells are pathogenic? An in-depth assessment of CXCR6$^+$ Th17 cells found in the CNS has the potential to identify novel and targeted potential therapeutics. Are CXCR6$^+$ Th17 cells able to convert back to SLAMF6$^+$ Th17 cells upon cessation of inflammation? If so, can this be promoted to limit disease? Broadly, this study by Aviv Regev and Vijay Kuchroo's groups raises the question of whether this same developmental pathway might contribute to inducing pathogenic Th17 cells in other tissues, including the joint, skin, and GI tract. Furthermore, whether this developmental pathway is also shared by homeostatic and protective Th17 cell responses remains to be explored. Ultimately, might the described relationships be maintained in the human immune system and with disease? Answers to these questions may allow us to achieve the goal of targeting pathogenic Th17 cell differentiation, trafficking, and function, while sparing homeostatic Th17 cell function.

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Declaration of interests

No interests are declared.

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