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The Good, the Bad, or the Pretty: IL-17 Builds Lymphoid Tissues in the Brain

Burkhard Becher[1,*]
[1]Institute of Experimental Immunology, Inflammation Research, University of Zurich, 8057 Zurich, Switzerland
*Correspondence: becher@immunology.uzh.ch
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Lymph node development depends on well-orchestrated interactions between lymphoid tissue inducer cells and stromal cells. In this issue of *Immunity*, Pikor and colleagues (2015) find that signals from IL-17-producing T helper cells can alter the stromal microenvironment of the inflamed brain to generate a neo-lymphoid organ that drives further inflammation.

Secondary lymphoid tissues (SLTs), i.e., lymph nodes (LNs) and spleen, are highly organized organs with dedicated areas for the encounter between antigens (Ags) and Ag-presenting cells, as well as B and T cells, providing an ideal environment for the initiation of adaptive immune responses (Hofmann et al., 2010). SLTs arise during embryonic development at well-defined sites, usually between lymphatic ducts and blood vessels. The activity of lymphoid tissue inducer (LTi) cells, a subset of innate lymphoid cells (ILCs) that depend on the transcription factor RORγt, is crucial for initiating SLT formation. During embryonic development, LTi cells initiate the formation of SLT anlagen (site of SLT initiation) through interactions with stromal lymphoid tissue organizer (LTO) cells. Although lymphotoxin β receptor (LTβR) engagement is not absolutely necessary for the initial wave of LTi cell recruitment to the LN anlage, it seems to be required for the maturation and homeostasis of stromal cells (Chai et al., 2013). Activated LTOs then produce a number of factors including adhesion molecules and chemokines, which attract B and T lymphocytes. The stromal cells in these early LNs can then develop into either follicular dendritic cells (FDCs) or fibroblast reticular cells (FRCs), which provide the molecular and structural support for the attraction of B and T cells, respectively. The complex organization and genesis of SLTs highlight the interactions among hematopoietic cells, stromal cells, adhesion molecules, and cytokines.

In contrast to SLTs, tertiary lymphoid tissues (TLTs) can arise in chronically inflamed tissues, for instance, during autoimmune and/or inflammatory diseases (Neyt et al., 2012). The defining features of TLTs are juxtaposed B and T cell areas with FDC and FRC networks in each respective zone, along with high endothelial venules (HEVs) and germinal center activity in the B cell areas (i.e., class switching). There is evidence that TLTs can thus provide LN-like support for immune responses directly within the inflamed tissue microenvironment. In particular, in the inflamed CNS, during multiple sclerosis (MS), for instance, TLT formation is well described, but the functional impact on disease development is a matter of speculation. There are numerous open questions regarding the development and function of these structures: (1) what are the cellular players involved in the formation of TLTs in the adult, (2) what are the molecular underpinnings of this complex neo-organogenesis, and (3) what is the impact of TLTs on disease?

These questions most likely motivated Pikor and colleagues (2015) to delve deeper into studying the role of interleukin 17 (IL-17)-producing T helper (Th) cells in TLT formation. In agreement with an earlier report (Peters et al., 2011), they found that IL-17-secreting CNS-Ag-reactive, pathogenic Th cells were capable of inducing the formation of TLT-like structures in the inflamed brain of mice with experimental autoimmune encephalomyelitis (EAE), the animal model for MS. Extending this observation, Pikor et al. found that IL-17 and IL-22 were directly capable of engaging fibroblastic stromal cells and smooth muscle cells in the meninges (a three-layered membrane protecting the CNS) and that these cytokines were capable of inducing the transformation toward an FRC-like phenotype in these meningeal stromal cells (Figure 1). This also indicates that TLT formation in the brain is not dependent on adult LTi cells, whose biological functions are still poorly understood.

It has become clear that the expression of IL-17 in Th cells is not maintained in vivo and that these cells generally revert to secreting type I cytokines (Kurschus et al., 2010). Also, mice lacking the genes encoding IL-17A and IL-22 can still develop EAE and other autoimmune diseases. Lastly, whereas IL-17 has previously been implicated in the formation of TLTs, inducible bronchus-associated lymphoid tissues (iBALTs), which are canonical TLTs associated with the lung, can develop completely independently of IL-17A and IL-17F (Fleige et al., 2012), suggesting that these cytokines might be sufficient but not necessary for the generation of TLTs. Hence, it would have been an interesting addition to the report of Pikor et al. if they had determined whether the adoptive transfer of Th1-polarized encephalitogenic T cells could also trigger the remodeling of the meningeal microenvironment. Importantly, the report by Pikor et al. raises the question of whether tissue remodeling per se might be the primary function of IL-17 and IL-22 during neuro-inflammation. Are IL-17 and IL-22 essentially engaging with those CNS stromal cells, which, in contrast to most leukocytes, constitutively express IL-17 and IL-22 receptors?

Among the alterations observed in the inflamed meninges was the induction of extracellular matrix molecules (e.g., fibronectin), as well as the upregulation of chemokines (e.g., CXCL1) and adhesion molecules (e.g., ICAM1), which could potentially serve to trap leukocytes in the inflamed site. Interestingly, CXCL1 has

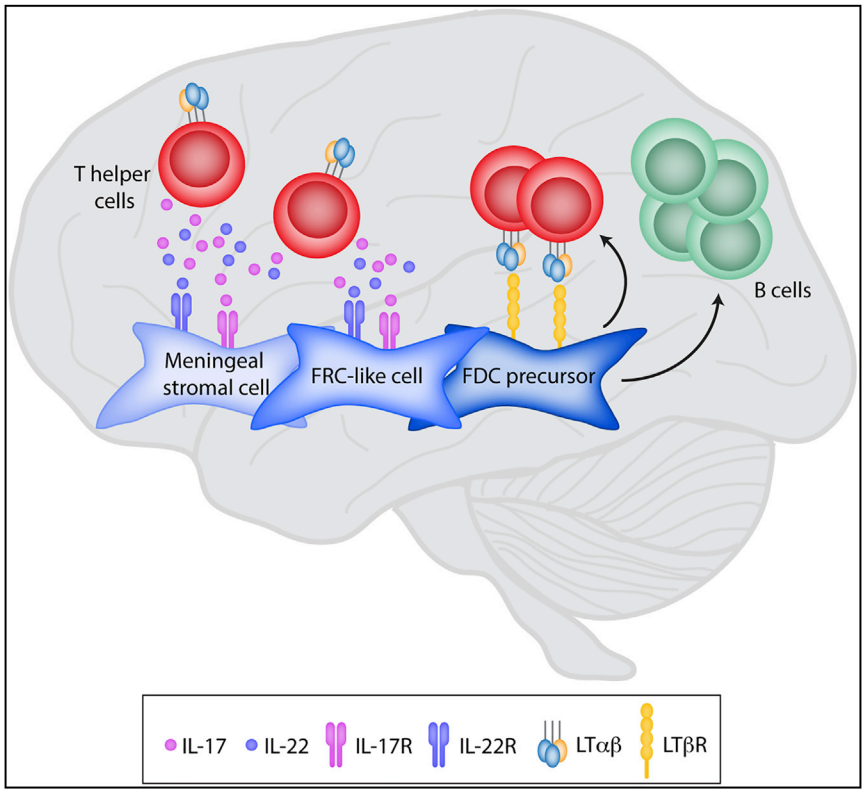

Figure 1. T-Helper-Cell-Induced Lymphoid Tissue Formation in the Brain
Accumulation of IL-17 and IL-22 in the meninges stimulates remodeling of meningeal stromal cells (fibroblasts and smooth muscle cells) so they develop into FRCs. LTβR engagement aids the development of FDC precursor cells, which supports B cell accumulation in the TLT. Activated FRCs in turn capture T cells and maintain their polarization and activation.

been implicated in the migration and positioning of oligodendrocyte precursor cells (Tsai et al., 2002) and wound healing. This raises the possibility that the transient production of IL-17 by CNS-invading Th cells could also serve to induce tissue remodeling and remyelination in general and not only in the attraction of leukocytes into the meningeal TLTs.

With respect to the molecular underpinnings of this neo-lymphoid organogenesis, the authors found that the FRC-like network could be induced independently of LTβR signaling and that IL-17 and/or IL-22 treatment of meningeal fibroblasts alone was sufficient to induce phenotypic changes akin to what would be observed in a bona fide TLT. Neutralization of this pathway primarily affected B cell zones in meningeal TLTs. Although the authors failed to detect mature FDCs in the meninges of mice with EAE, FDC formation (Krautler et al., 2012) seems more dependent than FRC formation (Chai et al., 2013) on LTβR signaling. The reliance of B cells on LTβR signaling in the tissue stroma confirms that mammalian B cell maturation requires the organized structures provided by mature SLTs or TLTs (whereas T cells are much more structure independent) and that productive T cell priming can occur outside of dedicated LNs or TLTs (Hofmann et al., 2010).

The major remaining question is whether emerging TLTs matter in the inflamed brain. In other words, will the targeted disruption of TLTs affect the overall inflammation or even clinical disease development? Alymphoplastic mutant mice, which are defective in LTβR signaling and thus devoid of all LNs, do develop EAE (Greter et al., 2009), indicating that (1) T cell priming against self-Ag can occur outside of dedicated lymphoid structures and (2) even if TLTs can emerge during inflammation, their function must be largely redundant. Pikor et al. propose that TLTs provide support for the maintenance of the IL-17 expression of Th cells locally by producing polarizing cytokines such as TGFβ and IL-6 (Figure 1). It is thus tempting to speculate that TLT formation in the meninges in chronic inflammatory disease serves primarily in the perpetuation of the inflammatory cascade and thus fuels the disease. However, the verdict on that is still outstanding. It is conversely possible that TLTs in the inflamed CNS serve to regulate and dampen an immune response akin to what is observed in tumor microenvironments, where regulatory T cells can gather to blunt T cell responses. Also, as mentioned earlier, TLT formation might be a sign of general tissue remodeling and wound healing. Although we have gained much better insights into the formation of TLTs in chronic inflammation, whether these are structures are good, bad, or merely pretty remains to be established.

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