

Getting to the crux of the matter: IL-23 and Th17 cell accumulation in the CNS

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IL-23 plays a critical role in EAE induced by the active immunization of C57BL/6 mice with an immunodominant epitope of myelin oligodendrocyte glycoprotein (MOG_{35–55}). It was initially assumed that the pathogenic effects of IL-23 were directly related to the generation, expansion and/or stabilization of autoreactive CD4⁺ Th17 cells. However, a number of recent studies have uncovered discrepancies between the requirement for IL-23, as opposed to Th17 cells or their products (IL-17A, IL-17F and IL-22), in the development of EAE. In this issue of the *European Journal of Immunology*, it is demonstrated that impairment of IL-23 signaling does not impede the expansion of myelin-specific CD4⁺ T cells in peripheral lymphoid tissues but inhibits their accumulation in the CNS. This paper contributes to a growing body of data that implicates IL-23 in the acquisition of CNS homing properties by autoreactive effector cells.

Key words: EAE · IL-23 · Th subsets



See accompanying article by Gyölvézi *et al.*

In 1989 Mosmann and Coffman introduced the concept that CD4⁺ effector T cells could be categorized into functionally distinct Th subsets based on the production of polarized panels of effector cytokines [1]. Shortly thereafter, the Th1 subset was implicated in the pathogenesis of organ-specific autoimmunity. It was proposed that CNS tissue injury in EAE and MS was initiated by IL-12p70-stimulated, IFN- γ -producing myelin-specific T cells [2, 3]. This hypothesis was reinforced by the observations that C57BL/6 mice deficient in IL-12p40 (one of the two component chains of IL-12p70) or IL-12 receptor β 1 chain (IL-12R β 1, required for IL-12p70 signaling) were resistant to induction of EAE by active immunization against an immunodominant peptide of myelin oligodendrocyte glycoprotein (MOG_{35–55}) [4, 5].

In contrast, subsequent studies in EAE were inconsistent with a Th1-based mechanism of autoimmune pathogenesis. Hence, C57BL/6 mice deficient in the IL-12p35 or IL-12R β 2 chains (the unique components of IL-12p70 and the IL-12

receptor, respectively), as well as mice deficient in the effector cytokine, IFN- γ , remained susceptible to MOG_{35–55}-induced disease [4, 6–10]. In fact, each of those genetically deficient mice experienced a more severe clinical course than their WT counterparts.

The discovery of IL-23 in 2000 appeared to reconcile these paradoxes [11]. IL-23 is a heterodimeric cytokine produced by activated myeloid cells. It is composed of the common IL-12p40 chain (shared with IL-12p70) and a unique chain, termed IL-23p19. Its receptor, expressed on activated CD4⁺ T cells and NK cells, is a heterodimer of IL-12R β 1 (shared with IL-12 receptor) complexed to IL-23R (a unique subunit). Numerous studies published between 2005 and the present have demonstrated that genetic deficiency or *in vivo* neutralization of the IL-23p19 chain confers resistance against EAE [12–15]. Furthermore, several groups found that reactivation of myelin-reactive T cells in the presence of recombinant IL-23 enhances their pathogenicity [16, 17]. Based on these lines of evidence, it was concluded that IL-23, rather than IL-12p70, is critical for the manifestation of EAE, at least in MOG_{35–55}-immunized C57BL/6 mice.

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The mechanism underlying the disease promoting effects of IL-23 proved to be elusive. IL-23-deficient mice are compromised in the generation of IL-17A-producing CD4⁺ T-cell populations (*i.e.* Th17 cells) in response to antigenic challenge *in vivo* [13]. This initially led to the assumption that the role of IL-23 in autoimmunity is to promote the differentiation, expansion, survival and/or stability of autoreactive Th17 effector cells. However, the importance of the IL-23/IL-17 axis has been challenged by recent studies showing that deficiency of IL-17A, either alone or in combination with the related cytokine IL-17F, does not completely abrogate EAE [18–20]. Similarly, IL-22, which is secreted by Th17 cells, is dispensable for the development of EAE [21].

The article by Gyölvézi *et al.* [22], published in this issue of the *European Journal of Immunology*, proposes an alternative modus operandi of IL-23, namely that of bestowing autoimmune effector cells with CNS homing properties. The authors found that MOG-specific CD4⁺ T cells parked in syngeneic hosts expanded to a similar extent in peripheral lymphoid tissues following challenge with MOG_{35–55} in CFA, irrespective of their ability to respond to IL-23. However, only T cells defective in IL-23 signaling failed to accumulate in the CNS during peak disease.

Gyölvézi *et al.*'s findings [22] are consistent with the report by Prat and colleagues that IL-23-stimulated human peripheral blood CD4⁺ lymphocytes are particularly efficient at penetrating brain-derived microvascular endothelial monolayers *in vitro* [23]. This could be secondary to IL-23-driven upregulation of adhesion molecules on CD4⁺ T cells that enhance their interactions with the endothelium. By analogy, IL-12 stimulates CD4⁺ Th1 cells to express P-selectin ligand, thereby enabling them to access sites of inflammation from which Th2 cells are excluded [24, 25]. IL-23 could also stimulate CD4⁺ T cells to secrete soluble factors and/or upregulate cell surface molecules that induce adhesion molecule expression on endothelial cells, or disrupt junctions between endothelial cells, in their vicinity. Alternatively, IL-23 could influence T-cell trafficking by modulation of chemokine receptor profiles. Of potential relevance, Th17 cells are enriched in CCR6⁺, as opposed to CCR6⁻, CD45RO human peripheral CD4⁺ T lymphocytes [26–28]. Recently, Reboli and colleagues demonstrated that CCR6 is selectively expressed on MOG_{35–55}-primed murine Th17, but not Th1 or Th2, cells. Furthermore, CCR6 expression is critical for the early entry of Th17 effector cells into the CNS during the preclinical stage of EAE [29]. The authors also found that CCR6⁺CD25⁻CD4⁺ T cells were enriched in the cerebrospinal fluid of patients with a first clinical demyelinating event and in the inflamed brain parenchyma from patients with established MS. Despite these intriguing observations, a direct link between IL-23 and CCR6 has yet to be definitively demonstrated.

While there remains much to learn, the finding by Gyölvézi *et al.* that IL-23 influences CNS homing of myelin-reactive T cells and/or their survival/expansion in the CNS microenvironment [22] represents a significant advance in our understanding of the factors that control autoimmune demyelinating disease. Future investigations will likely lead to the discovery of new biomarkers and therapeutic targets based on trafficking molecules that are

more specific to the interface between autoimmune effector cells and the blood–brain barrier.

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