CYTOKINES

Identifying how IL-23 drives disease

Studies using mice deficient in interleukin-23 (IL-23) have indicated a crucial role for this cytokine in the pathogenesis of autoimmune inflammation. Now, in a study published in *The Journal of Experimental Medicine*, IL-23 has been shown to mediate this effect by promoting the development of a pathogenic $CD4^+$ T-cell population that produces IL-6, IL-17 and tumour-necrosis factor (TNF).

IL-23 is a heterodimer that comprises a unique p19 subunit and the p40 subunit of IL-12 — a cytokine that is crucial for the development of interferon-γ (IFN-γ)-producing T helper 1 (T_H1) cells. Although IL-12 and IL-23 both contain the p40 subunit, they have distinct functions: for example, mice deficient in IL-12 are susceptible to inflammatory autoimmune diseases, whereas IL-23-deficient mice are resistant. So, Langrish *et al.* set out to investigate the cellular mechanism by which IL-23 elicits autoimmune inflammation. Surprisingly, although IL-23-deficient mice were resistant to experimental autoimmune encephalomyelitis (EAE), the number of immune cells infiltrating the central nervous system (CNS) and the proportion of the CNS-infiltrating $CD4^+$ T cells producing IFN-γ were the same as for EAE-susceptible wild-type control animals. By contrast, fewer $CD4^+$ T cells producing IL-6, IL-17 and TNF were found in the CNS of IL-23-deficient mice.

Consistent with a role for IL-23 in the development of IL-17-producing

$CD4^+$ T cells (T_HIL-17), but not IFN-γ-producing T_H1 cells, when *in vivo*-primed $CD4^+$ T cells were cultured *in vitro* in the presence of IL-23, T_HIL-17 cells clonally expanded, whereas T_H1 cells did not. By contrast, when cultured in the presence of IL-12, there was clonal expansion of T_H1 cells but not of T_HIL-17 cells. Gene-expression analysis further supported the idea that IL-12 and IL-23 induce distinct $CD4^+$ T-cell populations, with cells exposed to IL-23 being characterized by higher levels of mRNA encoding IL-6, IL-17 and TNF, as well as increased expression of other pro-inflammatory genes.

On a functional level, IL-23-expanded $CD4^+$ T cells specific for a CNS antigen induced severe EAE when transferred to naive recipients, whereas mice that received IL-12-expanded T_H1 cells showed no signs of disease. The severity of disease induced by the IL-23-expanded $CD4^+$ T cells correlated with the number of T_HIL-17 cells transferred, and the severity of actively induced disease was partially reduced by treatment with neutralizing antibodies specific for IL-17.

This study identifies a population of pathogenic IL-23-dependent $CD4^+$ T cells that produce IL-6, IL-17 and TNF. Future studies will focus on characterizing the molecular mechanisms by which IL-23 induces this highly pathogenic T-cell subset, and the authors suggest that this could provide new therapeutic targets for the treatment of inflammatory autoimmune diseases.

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References and links

ORIGINAL RESEARCH PAPER Langrish, C. L. *et al.* IL-23 drives a pathogenic T cell population which induces autoimmune inflammation. *J. Exp. Med.* **201**, 233–240 (2005).