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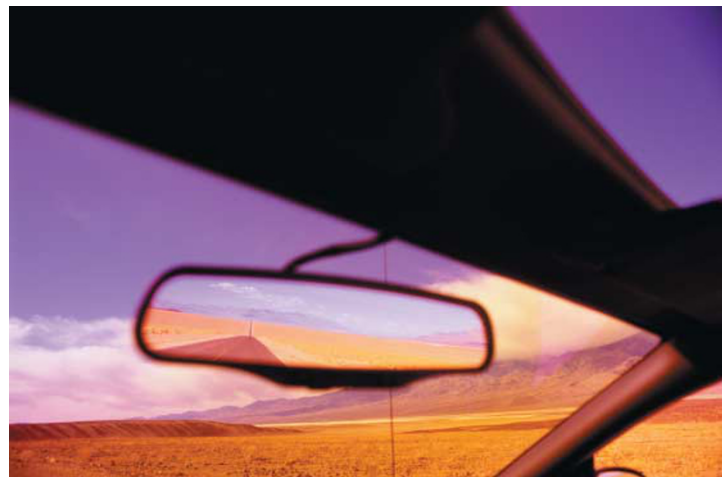
CYTOKINES

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.

Karen Honey

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).