Experimental Autoimmune Encephalomyelitis
Identification of the Antigen Presenting Cell Responsible for Priming Th17 Lymphocytes in EAE

Popular Scientific Summary

Genetic studies indicate a cell-mediated mechanism in Multiple Sclerosis where a subtype of helper T lymphocytes called T_h17 lymphocytes are assumed to be the responsible type and that their de-novo differentiation is supported by a cytokine called TGF-β1 and IL-6 that is derived from dendritic cells. The differentiation of T_h17 is further amplified by the cytokines IL-1β and TNF-α. The survival and expansion of these IL-17 producing T_h17 lymphocytes is maintained by IL-23 which is produced predominantly by macrophages and dendritic cells (DCs) and shows activity on memory T cells.

Depending on MyD88, T_h17 cells secrete IL-17 molecules that are IL-17A, IL-17B, IL-17C, IL-17D, IL-17F and IL-17E. MyD88 mediates proinflammatory cytokine expression inducing Experimental Autoimmune Encephalomyelitis (EAE). However, T_h17 also secrete GM-CSF, a crucial cytokine for the functioning of T_h17 and which renders them highly pathogenic. GM-CSF production is driven by ROR-γt; is essential for the effector phase of autoimmune inflammation; and is upregulated by IL-1β and IL-23.

EAE is induced by the presentation of an antigen of the MOG protein on MHC class II molecules by antigen presenting cells (APCs) to T_h17 lymphocytes. We are interested in identifying the APC that primes T_h17. For this purpose we used four transgenic mouse strains with the Cre-*Lox*P system cloned into their genome. Three strains carry the gene encoding the Cre recombinase under an APC-specific promoter. Cre is an enzyme that, depending on the orientation of the *Lox*P sites, induces changes in the DNA sequence such as inversion, deletion or insertion. The strains are: CD11c-Cre, encodes Cre under the relatively DC-specific promoter CD11c; CD19-Cre, encodes Cre under the B cell-specific promoter CD19; and Lyz2-Cre, encodes Cre under the macrophage-specific murine promoter LyzM. These three strains are crossed with a fourth strain that has our gene of interest being flanked with directly oriented *Lox*P sites. Crossing these strains results in offspring with our gene of interest knocked out in the respective cell type.

Mice with such genotypes are immunized with MOG emulsified in complete Fruend's adjuvant (CFA) to induce EAE. The clinical scores of the disease are to be compared in an attempt to correlate the disease severity, mitigated scores or the resistant state observed in the three strains to identify the APC that primes T_h17 lymphocytes.

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