Leukemia inhibitory factor tips the immune balance towards regulatory T cells in multiple sclerosis.

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Research question and background

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS), for which current treatments are unable to prevent disease progression. Based on its neuroprotective and neuroregenerating properties, leukemia inhibitory factor (LIF), a member of the interleukin-6 (IL-6) cytokine family, is proposed as a novel candidate for MS therapy. However, its effect on the autoimmune response remains unclear. In this study, we determined how LIF modulates T cell responses that play a crucial role in the pathogenesis of MS.

Methods and tissues used

Using flow cytometry, expression of the LIF receptor was identified on immune cells of MS patients and healthy donors. In vitro assays were performed to evaluate the effect of LIF on Treg induction. CNS-targeted overexpression of LIF was induced in vivo in a preclinical model of MS (EAE). Immunohistochemistry was performed on CNS tissue of 4 MS patients to determine the expression of the LIF receptor on monocytes/macrophages and CD4 cells in situ.

Results and conclusion

We demonstrate that expression of the LIF receptor was strongly increased on immune cells of MS patients. LIF treatment potently boosted the number of regulatory T cells (Tregs) in CD4+ T cells isolated from healthy controls and MS patients with low serum levels of IL-6. Moreover, IL-6 signaling was reduced in the donors that responded to LIF treatment in vitro. Our data together with previous findings revealing that IL-6 inhibits Treg development, suggest an opposing function of LIF and IL-6. In a preclinical animal model of MS we shifted the LIF/IL-6 balance in favor of LIF by CNS-targeted overexpression. This increased the number of Tregs in the CNS during active autoimmune responses and reduced disease symptoms. In conclusion, our data show that LIF downregulates the autoimmune response by enhancing Treg numbers, providing further impetus for the use of LIF as a novel treatment for MS and other autoimmune diseases.