

## **Interleukin-15 amplifies the pathogenic properties of CD4+CD28- T cells in multiple sclerosis.**

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### Research question and background

CD4+CD28- T cells arise through repeated antigenic stimulation and are present in diseased tissues of patients with various autoimmune disorders, including multiple sclerosis (MS). These cells are believed to have cytotoxic properties that contribute to the pathogenic damaging of the target organ. Endogenous cues that are increased in the diseased tissue may amplify the activity of CD4+CD28- T cells. In this study, we focused on IL-15, a cytotoxicity-promoting cytokine that is increased in the serum and cerebrospinal fluid of MS patients.

### Methods and tissues used

Immunohistochemistry for IL-15, astrocytes and infiltrating cells was performed on central nervous system (CNS) of two MS patients and two non-demented controls. Flow cytometry was performed on PBMC from MS patients and healthy donors to determine the phenotype of CD4+CD28+ and CD4+CD28- T cells. In vitro migration assays, TEER and flow cytometry was performed to identify the effect of IL-15 on endothelial cells and migration of CD4+CD28- T cells.

### Results and conclusion

We demonstrate that IL-15 is mainly produced by astrocytes and infiltrating macrophages in inflammatory lesions of MS patients. Moreover, in vitro transmigration studies reveal that IL-15 selectively attracts CD4+CD28- T cells of MS patients, but not of healthy individuals. IL-15 further induces the expression of chemokine receptors and adhesion molecules on CD4+CD28- T cells, resulting in enhanced migration over a monolayer of human brain endothelial cells. Finally, flow cytometric analyses revealed that IL-15 increases the proliferation and production of GM-CSF, expression of cytotoxic molecules (NKG2D, perforin, and granzyme B), and degranulation capacity of CD4+CD28- T cells. Taken together, these findings indicate that increased peripheral and local levels of IL-15 amplify the pathogenic potential of CD4+CD28- T cells, thus contributing to tissue damage in MS brain lesions.