Nature Reviews Neurology **9**, 122 (2013); published online 19 February 2013; doi:10.1038/nrneurol.2013.30

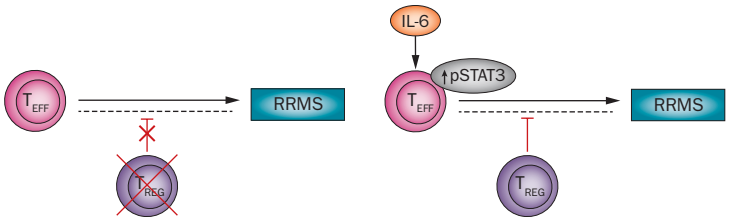
MULTIPLE SCLEROSIS

T-cell resistance to regulation in RRMS linked to IL-6 pathway

Multiple sclerosis (MS) is driven by neuroinflammation, but the mechanisms underlying failure to control the autoimmune response have been unclear. Now, researchers from the Benaroya Research Institute in Seattle, WA, USA, report that CD4$^+$ effector T (T_{EFF}) cells from patients with relapsing–remitting MS (RRMS) are resistant to suppression by T-regulatory (T_{REG}) cells, and that this mechanism is linked to the IL-6 pathway.

Previous studies suggested that a reduction in the number and function of T_{REG} cells caused the failure of immune regulation in RRMS. In other autoimmune diseases such as psoriasis and diabetes, however, resistance of T_{EFF} cells to T_{REG}-mediated suppression has been observed.

"The ability of IL-6 to cause T_{EFF} resistance has already been shown in other autoimmune diseases, and IL-6 is an important contributor to pathology in a mouse model of MS," says Jane Hoyt Buckner, who led the study. Signalling via the IL-6 receptor leads to phosphorylation of signal transducer and activator of transcription 3 (pSTAT3), and variants of the *STAT3* gene have been linked to MS risk, but this signalling pathway has not been extensively investigated in RRMS.



Failure of regulation in RRMS could result from inadequate numbers or function of T_{REG} cells (left) or from T_{EFF} resistance to suppression, mediated by IL-6 signalling and phosphorylation of STAT3 (right).

"We studied a group of RRMS patients who were not receiving immunological therapies at the time of blood draw, and performed *in vitro* suppression assays with T_{EFF} cells from these individuals while using T_{REG} cells from healthy controls," explains Buckner. "This approach enabled us to evaluate the T_{EFF} population specifically."

In two independent cohorts (total $n = 24$), suppression of T_{EFF} cells from patients with RRMS was significantly lower than that of T_{EFF} cells from healthy controls. After stimulation with IL-6, the percentage of pSTAT3-positive CD4$^+$ cells was higher in the RRMS cohort than in controls, suggesting that T_{EFF} cells from patients with RRMS are more responsive to IL-6.

In both groups, a negative correlation was observed between pSTAT3 expression and the level of T_{EFF} suppression, and resistance of T_{EFF} cells from three individuals with RRMS was reduced by a STAT3 inhibitor.

Collectively, these findings support a role for the IL-6 pathway in regulation of resistance in RRMS. "Furthermore, we found that alterations in T_{EFF} resistance were associated with more-aggressive and active disease," says Buckner.

The group now plans to assess IL-6 responses and T_{EFF} resistance over the course of disease in a larger RRMS cohort, and to establish whether these parameters change with therapy.

Katy Malpass

Original article Schneider, A. *et al.* In active relapsing–remitting multiple sclerosis, effector T cell resistance to adaptive T_{regs} involves IL-6 mediated signaling. *Sci. Transl. Med.* **5**, 170ra15 (2013)