Nature Reviews Immunology | AOP, published online 10 July 2015; doi:10.1038/nri3890

Tristan Ben Mahjoub/Alamy

AUTOIMMUNITY

Benefits of exhaustion

T cell exhaustion promotes viral persistence and is associated with a poor outcome in viral infections, but whether T cell exhaustion has a role in the clinical outcome of autoimmunity remains unknown. McKinney *et al.* now show that a transcriptional signature of CD8$^+$ T cell exhaustion, which is inversely linked with a CD4$^+$ T cell co-stimulation signature, predicts a low relapse rate in multiple autoimmune and inflammatory diseases.

In order to investigate the mechanisms driving relapsing autoimmunity, the authors analysed the transcriptome of purified CD4$^+$ and CD8$^+$ T cells isolated from 44 patients with active, untreated anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV) disease or from 23 patients with active, untreated systemic lupus erythematosus (SLE). Using several different analysis methods, they found that a gene expression signature in CD4$^+$ T cells that is associated with co-stimulation correlated with disease relapse, whereas a signature of exhaustion in CD8$^+$ T cells correlated with a low risk of relapse and thus, a better prognosis. This suggests that a transcriptional signature of CD8$^+$ T cell exhaustion, in conjunction with a signature of low CD4$^+$ T cell co-stimulation, may be associated with a favourable long-term outcome in autoimmune diseases. Indeed, CD8$^+$ T cells from patients with a good disease prognosis were characterized by the expression of a distinct subset of exhaustion-associated co-inhibitory receptors. Furthermore, a subgroup of patients with both early and recurrent relapses could be identified from independent cohorts of patients with SLE, AAV or inflammatory bowel disease based on the absence of a CD8$^+$ T cell exhaustion signature.

> “a signature of exhaustion in CD8$^+$ T cells correlated with a low risk of relapse”

Persistent T cell receptor stimulation is known to promote T cell exhaustion, and the authors showed that co-stimulation via CD2 prevents the development of this phenotype in human CD8$^+$ T cells *in vitro*. This inhibitory effect of CD2 signalling on exhaustion could be reversed by stimulation of the co-inhibitory receptor programmed cell death protein 1 (PD1). Therefore, the induction of exhaustion can be manipulated, at least *in vitro*, through PD1 and CD2.

Because most published datasets profile unseparated peripheral blood mononuclear cells, the authors identified a surrogate marker of the CD4$^+$ T cell co-stimulation module that could be used in the datasets to independently validate these observations. They found that the presence of this surrogate marker correlated with a good response to combined interferon and ribavirin therapy in patients with chronic hepatitis C virus infection and to vaccination for malaria, flu or yellow fever. By contrast, the presence of this surrogate marker of CD4$^+$ T cell co-stimulation was associated with poor outcome in autoimmune and inflammatory diseases, such as idiopathic pulmonary fibrosis and type 1 diabetes.

Together, this study shows that, unlike in chronic viral infections, CD8$^+$ T cell exhaustion is associated with a good outcome in autoimmune and inflammatory diseases. Therefore, manipulation of exhaustion may be a possible therapeutic mechanism to suppress autoreactivity.

Olive Leavy

ORIGINAL RESEARCH PAPER
McKinney, E. F. *et al.* T-cell exhaustion, co-stimulation and clinical outcome in autoimmunity and infection. *Nature* http://dx.doi.org/10.1038/nature14468 (2015)
FURTHER READING Wherry, E. J. & Kurachi, M. Molecular and cellular insights into T cell exhaustion. *Nat. Rev. Immunol.* (in the press)