Nature Reviews Immunology | AOP, published online 18 February 2011; doi:10.1038/nri2949

IMMUNE RESPONSES

IL-7 goes antiviral

It is well appreciated that interleukin-7 (IL-7) has essential roles in lymphocyte development and homeostasis. A new study in *Cell* shows that IL-7 also has potent pro-immune functions during viral infection.

Many chronic viral infections, such as those established in individuals infected with HIV or hepatitis C virus (HCV), are characterized by an upregulation of inhibitory immune pathways. Pellegrini *et al.* hypothesized that IL-7, which overcomes inhibitory mechanisms to promote homeostatic immune cell expansion, might also have the ability to overcome the inhibitory networks that develop during chronic viral infection. To explore this, they therapeutically administered IL-7 to mice with established chronic lymphocytic choriomeningitis virus (LCMV) clone 13 infection. Although control animals that received PBS were unable to clear LCMV clone 13 even several months after the initial infection, mice that received IL-7 therapy cleared LCMV clone 13 from the spleen, liver and other chronic viral reservoirs shortly after the completion of 3 weeks of treatment.

IL-7 seemed to promote antiviral immunity by increasing the numbers of LCMV-specific $CD8^+$ T cells, as well as by enhancing the effector functions of these cells. Treatment with IL-7 also led to a marked expansion of B cells and non-LCMV-specific T cells, but cell depletion experiments showed that only $CD4^+$ and $CD8^+$ T cells were essential for the promotion of viral clearance in mice in response to IL-7 therapy. Using transgenic reporter mice, the authors showed that IL-7 expanded non-virus-specific naive T cell populations during LCMV infection by promoting increased export of T cells from the thymus. Interestingly, although the total number of regulatory T (T_{Reg}) cells also increased in response to IL-7 treatment, the proportion of T_{Reg} cells within the total T cell population was reduced in IL-7-treated mice. However, conditional depletion of T_{Reg} cells did not affect viral loads or lead to greater immunopathology in either of the treatment groups.

The authors next investigated cytokine responses and found that the levels of several inflammatory cytokines, including IL-6, IL-17 and interferon-γ, were dramatically increased in the serum of IL-7-treated mice. Notably, this elevated pro-inflammatory cytokine response appeared to promote antiviral immunity without inducing increased immunopathology in infected tissues. This seemed to be due to IL-7-mediated upregulation of the cytoprotective cytokine IL-22; indeed, antibody-mediated blockade of IL-22 in LCMV-infected IL-7-treated mice caused significant hepatitis in these animals.

Finally, having observed such a marked increase in inflammatory cytokine production, the authors asked whether IL-7 might repress inhibitors of cytokine signalling. In support of this, they showed that T cells aberrantly upregulate suppressor of cytokine signalling 3 (SOCS3) during chronic LCMV infection, but IL-7 treatment led to reduced expression of SOCS3 by T cells. Further experiments suggested that IL-7 may repress SOCS3 indirectly by downregulating forkhead box O (FOXO) transcription factors and, strikingly, when mice with a T cell-specific deletion of *Socs3* were infected with LCMV, they were able to clear infection without any notable immunopathology, in a similar manner to the IL-7-treated mice.

These findings indicate that IL-7 promotes antiviral immunity by suppressing T cell expression of inhibitory molecules, such as SOCS3. The efficacy of therapeutic IL-7 in this study is particularly exciting, as it suggests that IL-7 therapy could be used for managing HIV or HCV infections in humans.

Yvonne Bordon

ORIGINAL RESEARCH PAPER Pellegrini, M. *et al.* IL-7 engages multiple mechanisms to overcome chronic viral infection and limit organ pathology. *Cell* 3 Feb 2011 (doi:10.1016/j.cell.2011.01.011)