T-CELL RESPONSES

Reversing exhaustion

Feeling the effects of a relentless and overloaded schedule? T cells also suffer from exhaustion and are less effective at doing their job when faced with persistent antigen, such as during chronic viral infection or cancer. Now, researchers reporting in *Nature* describe a mechanism that reverses the $CD8^+$ T-cell exhaustion seen in chronic infection of mice with lymphocytic choriomeningitis virus (LCMV) and restores the ability of T cells to control the virus.

LCMV is a natural pathogen of mice and, importantly for this study, strains are available that cause either acute (the Armstrong strain) or chronic (the clone 13 strain) infection. Therefore, infection with the Armstrong strain is cleared within a week and a stable pool of long-lived memory T cells is established. By contrast, the clone 13 strain establishes a persistent infection, which overwhelms the immune response and results in the generation of functionally impaired or exhausted virus-specific $CD8^+$ T cells.

To study T-cell dysfunction in chronic infection, Rafi Ahmed and colleagues first carried out gene-expression analysis of T cells that were generated following infection with each LCMV strain. Most notably, the exhausted virus-specific $CD8^+$ T cells contained more mRNA encoding the inhibitory receptor PD1 (programmed death 1; also known as PDCD1) than functional virus-specific $CD8^+$ T cells from Armstrong-strain-infected mice. Further analysis showed that although PD1 was transiently expressed by $CD8^+$ T cells after infection with the Armstrong strain, it was rapidly downregulated, whereas $CD8^+$ T cells responding to the clone 13 strain retained high PD1 expression throughout the chronic infection. Moreover, one of the ligands for PD1, PDL1, was shown to be highly expressed by persistently infected splenocytes, indicating that this inhibitory receptor–ligand interaction might regulate T-cell function during chronic LCMV infection.

To test this, the authors treated persistently infected mice with a blocking antibody specific for PDL1. Remarkably, compared with untreated mice, chronically infected mice that were treated with PDL1-specific antibody underwent a marked expansion of virus-specific $CD8^+$ T-cell populations, which had an increased ability to produce interferon-γ and tumour-necrosis factor, thereby reversing the exhausted phenotype. In addition, PDL1 blockade markedly reduced the viral load and resolved infection with the clone 13 strain.

The authors then showed that, even in mice that lack $CD4^+$ T cells and therefore suffer from a more severe form of chronic infection and T-cell exhaustion, PDL1 blockade could reverse the functional impairment of the exhausted T cells and reduce the viral load. This might be of particular relevance for HIV infection, which is characterized by a loss of $CD4^+$ T cells.

Although, on the basis of these results, blockade of the PD1–PDL1 pathway for the treatment of chronic viral infection or cancer is tantalizing, prolonged disruption of this regulatory pathway can result in autoimmunity, as exemplified by PDL1-deficient mice.

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ORIGINAL RESEARCH PAPER Barber, D. L. *et al.* Restoring function in exhausted CD8 T cells during chronic viral infection. *Nature* **439**, 682–687 (2006)
FURTHER READING Williams, M. A. & Bevan, M. J. Exhausted T cells perk up. *Nature* **439**, 669–670 (2006)