IN BRIEF

NATURAL KILLER CELLS

Posttranslational regulation of the NKG2D ligand Mult1 in response to cell stress

Nice, T. J. *et al. J. Exp. Med.* 26 Jan 2009 (doi:10.1084/jem.20081335)

NKG2D (natural-killer group 2, member D) is a stimulatory receptor expressed by NK cells. NKG2D ligands are MHC class I-like molecules that are poorly expressed by normal cells, but their expression is upregulated by tumour cells and in response to some infections. High levels of ligand expression result in NK-cell-mediated killing of target cells, so it is important that ligand expression is tightly regulated. Nice and colleagues investigated how the expression of the NKG2D ligand MULT1 (murine ULBP-like transcript 1) is controlled; normal cells have abundant mRNA transcripts for MULT1 but no cell-surface expression. They describe a mechanism by which lysine residues in the cytoplasmic tail of MULT1 are ubiquitylated, which targets the protein for degradation in the lysosomes of normal cells. This process is downregulated in response to environmental stressors, such as heat shock and ultraviolet light.

NEUROIMMUNOLOGY

Immune cell-derived opioids protect against neuropathic pain in mice

Labuz, D. *et al. J. Clin. Invest.* **119**, 278–286 (2009)

This study shows that relief from shooting pains and from heightened sensitivity to normally innocuous stimuli (known as allodynia) following trauma to peripheral nerves could be provided by leukocyte-derived opioids. The authors used sciatic nerve constriction injury in mice to mimic neuropathic pain in humans and found that immune cells accumulated at the site of nerve injury. 30–40% of these immune cells expressed opioid peptides, such as β-endorphin, Met-enkephalin and dynophin A, and the receptor for corticotropin-releasing factor (CRF), which is known to stimulate the release of opioid peptides. Administration of CRF at the site of nerve injury fully reversed allodynia, an analgesic effect that depended on CRF-receptor-induced opioid production by local leukocytes. The expression of opioid receptors by injured nerves and the reversal of opioid-mediated analgesic effects by opioid receptor antagonists further supports the idea that leukocyte-derived opioids act on injured nerves to alleviate pain.

T-CELL RESPONSES

Human $CD4^+$ memory T cells are preferential targets for bystander activation and apoptosis

Bangs, S. C. *et al. J. Immunol.* **182**, 1962–1971 (2009)

The idea that T cells can be activated without encountering their specific antigen (known as bystander activation) is not new, but whether this actually occurs during an immune response is debated. To rule out the possibility of T-cell receptor (TCR) cross-reactivity, Bangs *et al.* cultured polyclonal human T cells with the superantigen staphylococcal enterotoxin B (SEB), which only activates $V\beta17^+$ T cells and not $V\beta13.1^+$ T cells. However, memory $V\beta13.1^+$ T cells did become activated in these cultures through a bystander mechanism that requires soluble mediators. Differently activated T-cell populations had distinct gene expression profiles; for example, genes involved in TCR downregulation were only induced following activation by SEB. Both means of activation led to increased apoptosis. The authors suggest that bystander activation and subsequent death of memory T cells might be a mechanism to create space for the proliferation of antigen-specific T cells.