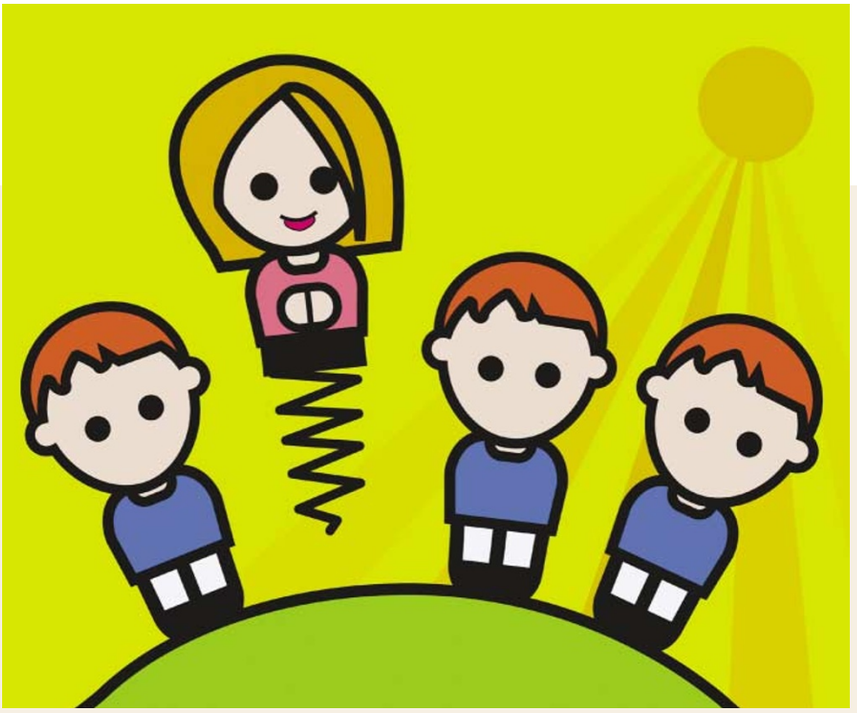
MUCOSAL IMMUNOLOGY

Oddball T cells



Although we typically think of T cells as expressing variant T-cell receptors (TCRs) that engage the classical MHC class I or II molecules, several other T-cell subsets exist, which are rather more odd in nature. For example, natural killer T (NKT) cells express an invariant Vα14 TCRα chain and are restricted by the MHC-like molecule CD1d. Other T cells that express invariant receptors are the human Vα7.2-Jα33 and mouse Vα19-Jα33 cells. A recent study now shows that these T cells preferentially localize in the gut and are restricted by an MHC class-I-like molecule known as MR1.

Initial studies showed that hVα7.2-Jα33 and mVα19-Jα33 T cells are enriched in the lamina propria region of the gut. These mucosal-associated T (MAIT) cells were more abundant in mice that lack the transporter for antigen processing (TAP) or invariant chain (in which the number of classical T cells is low because of the reduced expression of MHC class I and II molecules), but absent in mice that lack β_2-microglobulin (β_2m), indicating that β_2m is required for selection. To determine which cell type mediates the selection of these cells, various bone-marrow chimaeras were generated. These showed that β_2m-positive B cells were necessary for the selection of the MAIT cells. The MHC class-I-related molecule MR1 seemed to be a possible candidate ligand for MAIT cells. MR1 transfectants could stimulate cytokine release from MAIT cells and this interaction was inhibited using antibodies specific for the TCR. MR1-deficient mice had essentially no Vα19-Jα33-positive T cells. Furthermore, germ-free mice lacked MAIT cells, indicating that their selection is dependent on the presence of commensal gut flora.

The authors speculate that these MAIT cells are important for the regulation of immune responses at mucosal surfaces.

Elaine Bell

References and links

ORIGINAL RESEARCH PAPER Treiner, E. *et al.* Selection of evolutionarily conserved mucosal-associated invariant T cells by MR1. *Nature* **422**, 164–169 (2003)

CELL DEATH AND IMMUNITY

Turning up the heat

Identifying the gene behind an inherited disorder is always a triumphant moment, but this is when the real challenge — understanding how the gene causes disease — begins. Six years ago, familial Mediterranean fever (FMF), a recessive genetic disorder that is characterized by recurrent inflammation and fever, was shown to be caused by mutations in a gene encoding a new protein now known as pyrin. But the physiological function of pyrin and its role in FMF has not yet been resolved. Now, a new mouse model, reported in *Molecular Cell*, promises to provide some clarity.

Pyrin is an intracellular protein that contains a new protein–protein interaction module known as the pyrin domain (PYD), which has now been found in several molecules that regulate apoptosis and inflammation. One of these is the adaptor protein ASC (apoptosis-associated speck-like protein with a CARD), which can interact with pyrin through a PYD–PYD homotypic association. ASC is known to trigger autocatalysis of caspase-1, which cleaves the pro-inflammatory cytokine interleukin-1β (IL-1β) into its active form. On the basis of these observations, it was proposed that pyrin might control the production of IL-1β through ASC and that this regulation is disrupted in individuals with FMF. But *in vivo* evidence in support of this mechanism has been lacking.

To get a clearer picture of the physiological role of pyrin, Jae Jin Chae and colleagues generated mice that expressed a carboxy-terminal truncated form of pyrin that contains an intact PYD, similar to the mutant protein in FMF. These mice experienced episodes of fever and were hyper-responsive to lipopolysaccharide (LPS). LPS-induced IL-1β processing and caspase-1 activity was markedly increased in pyrin-mutant macrophages compared with controls, which supports the idea that pyrin regulates IL-1β processing. Retroviral transduction of macrophage cell lines with full-length pyrin completely inhibited IL-1β processing, providing further support for this hypothesis.

But this might not be the whole story. The pyrin-mutant macrophages also seemed to be less susceptible to apoptosis and this resistance was independent of IL-1β. As defective apoptosis has been associated with other inflammatory disorders, this could potentially be another mechanism that contributes to FMF.

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References and links

ORIGINAL RESEARCH PAPER
Chae, J. J. *et al.* Targeted disruption of pyrin, the FMF protein, causes heightened sensitivity to endotoxin and a defect in macrophage apoptosis. *Mol. Cell* **11**, 591-604 (2003).
WEB SITE
Daniel Kastner's homepage: http://www.irp.niams.nih.gov/NIAMS2/LabsBranches_member.jsp?memberId=135