SIGNALLING

Initiation of pro-IL-1β processing

The pro-inflammatory cytokine interleukin-1β (IL-1β) is generated from an inactive cytoplasmic precursor — pro-IL-1β — through cleavage by caspase-1, but the mechanism by which caspase-1 is activated is unknown. In a study published in *Molecular Cell*, Jürg Tschopp's group describe a caspase-activating complex — which they have named the 'inflammasome' — that consists of caspase-1, caspase-5, PYCARD (also known as ASC) and NALP1, which is structurally homologous to the NOD proteins.

NALP1 is a multi-domain protein that is expressed highly in cells of the immune system. It is a member of the NBS (nucleotide-binding site) family of molecules, which have important roles in caspase activation and apoptosis. APAF1, another member of this family, has been shown to be involved in the assembly of the apoptosome, an initiation complex for the activation of caspases in apoptosis. The multi-domain structure of APAF1 is crucial for its ability to form a large multi-component complex. In particular, the caspase-recruitment domain (CARD) of APAF1 is required for interaction with caspases. Because NALP1 also has a multi-domain structure — consisting of a pyrin domain (PYD), an NBS domain, leucine-rich repeats, a NALP-associated domain and a CARD domain — Tschopp's group decided to investigate the role of NALP1 in initiating caspase-1 activation.

First, they investigated whether the CARDs of NALP1 and PYCARD (an adaptor molecule containing a PYD and CARD that interacts with NALP1 through its PYD domain) can interact with caspases. The CARD of NALP1 binds to caspase-5, whereas the CARD of PYCARD binds to caspase-1. Both caspases were found to be required for optimal processing of pro-IL-1β to IL-1β. The role of NALP1 and PYCARD in caspase activation was then investigated in a cell-free system, in which THP1 cells were disrupted mechanically and the cytoplasmic fractions assessed for cleavage of pro-IL-1β. These experiments indicated that pro-IL-1β is cleaved after the assembly of NALP1, PYCARD, caspase-1 and caspase-5 into a multi-protein complex. This was confirmed in immunoprecipitation experiments and experiments in which extracts of THP1 cells were separated by gel filtration and the size of the complexes measured. In this system, a dominant-negative form of PYCARD (that can bind NALP1, but not caspases) blocked the maturation of IL-1β *in vivo*.

So, the inflammasome is an initiation complex for caspase activation and production of the mature form of IL-1β.

Elaine Bell

References and links

ORIGINAL RESEARCH PAPER Martinon, F., Burns, K. & Tschopp, J. The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-1β. *Mol. Cell* **10**, 417–426 (2002)

WEB SITE

Jürg Tschopp's lab: http://www.unil.ch/ib/GROUPS/TSCHOPP/gtschopp.htm

IN BRIEF

T CELLS

Expression of cutaneous lymphocyte-associated antigen by CD8⁺ T cells specific for a skin-tropic virus.

Koelle, D. M. *et al. J. Clin. Invest.* **110**, 537–548 (2002)

In this study, the trafficking of antigen-specific CD8⁺ T cells to the skin was investigated. Herpes simplex virus type 2 (HSV2) causes periodic lytic infection of the skin and genital mucosa. Cutaneous lymphocyte-associated antigen (CLA) is a carbohydrate moiety that decorates P-selectin glycoprotein ligand-1 on T cells. A CLA-like molecule can bind E-selectin, an adhesion molecule that is expressed by endothelial cells in inflamed skin and mucosa, leading to the rolling and adhesion of CLA-expressing cells on the vascular endothelium. Koelle *et al.* investigated the role of this CLA–E-selectin interaction in the trafficking of HSV2-specific T cells to the skin *in vivo*. This is the first report of the expression of tissue-homing molecules on virus-specific CD8⁺ T cells.

VACCINES

A pantothenate auxotroph of *Mycobacterium tuberculosis* is highly attenuated and protects mice against tuberculosis.

Sambandamurthy, V. K. *et al. Nature Med.* 9 September 2002 (DOI 10.1038/nm765)

The global incidence of tuberculosis is increasing, and although attenuated vaccines exist, there is a great need for improved vaccines. Here, Sambandamurthy *et al.* describe the development of an attenuated *Mycobacterium tuberculosis* vaccine. This candidate vaccine is an auxotrophic mutant of *M. tuberculosis* that cannot synthesize pantothenic acid (vitamin B5). Attenuation was assessed by infection of immunocompromised mice; mice infected with the pantothenate mutant survived longer than mice that were infected with either *Mycobacterium bovis* bacillus Calmette-Guerin (BCG) or virulent *M. tuberculosis*. Importantly, subcutaneous injection of the pantothenate mutant protected mice against challenge with virulent *M. tuberculosis*. These results indicate that this attenuated, persisting form of *M. tuberculosis* is a possible vaccine candidate for further development.

VIRAL IMMUNITY

Critical role for STAT4 activation by type 1 interferons in the interferon-γ response to viral infection.

Nguyen, K. B. *et al. Science* **297**, 2063–2066 (2002)

Type I (IFN-α and -β) and type II (IFN-γ) interferons are crucial for innate immunity and they have antiviral properties. The immunoregulatory functions of type I IFNs, particularly their ability to regulate IFN-γ production, are not well understood. Here, Nguyen *et al.* investigate this, and show that during viral infections in mice, type I IFNs activate signal transducer and activator of transcription 4 (STAT4) directly, which then binds to the proximal IFN-γ promoter, resulting in the increased production of IFN-γ.