VACCINES

Smallpox vaccine dogma challenged

The widely held belief that the smallpox vaccine only provides protection against smallpox for 3–5 years is untrue, according to a new study in *Nature Medicine*.

The vaccine, which was routinely administered in the United States until 1972, comprises live vaccinia virus, an orthopoxvirus that is closely related to variola, the causative agent of smallpox. In the largest study of its kind so far, a team of researchers at Oregon Health and Science University, United States analysed the antiviral immune response in 306 volunteers who had been vaccinated against smallpox at least once in their lifetime. The timing of the vaccinations varied from between one month before testing to 75 years before testing.

The cell-mediated immune response was quantified using an *ex vivo* assay that detects the production of interferon-γ (IFN-γ) and tumour-necrosis factor (TNF) by peripheral-blood mononuclear cells following direct challenge with vaccinia. The smallpox vaccine stimulates a strong virus-specific $CD4^+$ and $CD8^+$ T-cell response, which declines slowly with an average half-life of 8–15 years.

Image courtesy of CDC/James Gathany

Hammarlund *et al.* then used a vaccinia-specific enzyme-linked immunosorbent assay and a neutralization assay to detect vaccinia-specific antibodies. In contrast to the cell-mediated response, the humoral immune response was shown to remain steady for as long as 75 years and could therefore have a greater role in smallpox immunity than was previously thought.

It has long been maintained that repeated vaccination against smallpox is required for maximal protection against the disease. However, analysis of the immune response of volunteers who had been immunized more than once revealed that although repeated vaccination resulted in a short-term boost in immune responses, it did not markedly increase the levels of long-term cell-mediated or humoral immunity.

These results indicate that the prevailing immunity to smallpox in the general population in the United States is greater than was previously thought. More than 90% of the participants in the study showed measurable cell-mediated or humoral immunity to smallpox. Given that more than 90% of Americans over the age of 35 — some 140–150 million individuals — have been vaccinated against smallpox, this could provide at least some degree of herd immunity in the event of an outbreak.

Sheilagh Clarkson, Associate Editor,
Nature Reviews Microbiology

References and links

ORIGINAL RESEARCH PAPER Hammarlund, E. *et al*. Duration of antiviral immunity after smallpox vaccination. *Nature Med.* **9**, 1131–1137 (2003)

FURTHER READING Smith, G. L. & McFadden, G. Smallpox: anything to declare? *Nature Rev. Immunol*. **2**, 521–527 (2002).

WEB SITE

Mark Slifka's lab: http://www.ohsu.edu/vgti/slifka.htm

IN BRIEF

ANTIGEN PRESENTATION

Characterization of the MHC class I crosspresentation pathway for cell associated antigens by human dendritic cells.

Fonteneau, J. F. *et al*. *Blood* 21 August 2003 (DOI: 10.1182/blood-2003-06-1801)

This study is the first to characterize fully the MHC class I cross-presentation pathway in human dendritic cells (DCs) using a physiologically relevant system. The authors used apoptotic or necrotic monocytes infected with recombinant vaccinia virus expressing influenza A virus matrix protein 1 (MP). These were co-cultured with immature DCs, and the ability of the DCs to stimulate interferon-γ production by a MP-specific $CD8^+$ T-cell clone was measured. By pre-incubating the DCs with various inhibitors that block the normal MHC class I presentation pathway, Fonteneau *et al.* showed that MP from apoptotic/necrotic cells is actively internalized by phagocytosis or macropinocytosis, pre-processed in endosomes by cathepsin D then enters the cytosol for processing by the proteasome and TAP-dependent entry into the endoplasmic reticulum and loading on to MHC class I molecules.

IMMUNOGENETICS

Parasite selection for immunogenetic optimality.

Wegner, K. M. *et al*. *Science* **301**, 1343 (2003)

Theoretical models have predicted that MHC diversity is a balance between evolutionary pressure to increase diversity for recognition of a greater number of potential pathogens and evolutionary pressure to decrease diversity to reduce the number of T cells that are deleted during negative selection. Wegner *et al.* have now provided experimental evidence for this theory. They infected groups of sticklebacks with common parasites and then measured the mean infection rate. The groups differed in terms of MHC diversity (number of MHC alleles), and the authors found that those fish with an intermediate number of alleles had the lowest infection rate and, therefore, the highest level of fitness.

HIV

Directed expression of the HIV-1 accessory protein Vpu in *Drosophila* fat-body cells inhibits Toll-dependent immune responses.

Leulier, F. *et al*. EMBO reports 12 September 2003 (DOI: 10.1038/sj.embor.embor936)

HIV-1 expresses various accessory proteins that interfere with host processes to optimize replication and viral pathogenesis. One of these is viral protein U (Vpu) — *in vitro* experiments have shown that Vpu can inhibit the nuclear factor-κB (NF-κB) signalling pathway. As the NF-κB signalling pathways that regulate innate responses in vertebrates and antimicrobial responses in *Drosophila melanogaster* are highly conserved, Leulier *et al.* investigated the function of Vpu in *D. melanogaster*. Overexpression of Vpu by fat-body cells specifically affected the Toll pathway and antimicrobial responses were disrupted. Because of the conservation of this pathway in flies and mammals, this indicates that Vpu might function to disrupt NF-κB-mediated innate responses.