INSECT IMMUNITY

Insect immune receptor shows variety

A recent report in *Science* indicates that immune-receptor diversity is evolutionarily conserved as far back as insects: in the immunocompetent cells of insects, alternative splicing of the mRNA encoding immunoglobulin-superfamily receptor Down's syndrome cell-adhesion molecule (DSCAM) has the potential to generate more than 18,000 distinct protein isoforms.

The presence of highly diverse immune receptors generated by recombination-activating-gene-mediated somatic gene rearrangement is restricted to a subset of jawed vertebrates. However, it has previously been shown that the gene encoding *Drosophila melanogaster* DSCAM — which is essential for neuronal wiring — contains both constant and variable exons and that alternative splicing could allow for the generation of more than 19,000 distinct DSCAM extracellular domains. So, Watson *et al.* set out to analyse DSCAM expression in immunocompetent cells in *D. melanogaster*. It was shown that haemocytes and fat-body cells — cells of the insect immune system — expressed multiple *Dscam* mRNAs, most of which contained unique combinations of the variable exons, although some splice variants were more common than others. Consistent with this, proteins with amino-acid sequences corresponding to alternatively spliced mRNA transcripts were secreted by the haemocyte-like S2 cell line. Because soluble DSCAM proteins were also found in haemolymph serum, the authors suggest that thousands of DSCAM isoforms might circulate in the haemolymph of *D. melanogaster*.

An immune function for DSCAM isoforms was indicated by the observation that phagocytosis of heat-killed, fluorescently labelled *Escherichia coli* was impaired if haemocytes were isolated from *D. melanogaster* larvae expressing markedly reduced levels of DSCAM or if S2 cells were cultured for a short period in the presence of DSCAM-specific antibodies. Furthermore, two DSCAM isoforms were found to bind live *E. coli*, although a third did not. Binding was dependent on the ten amino-terminal domains, which include the region encoded by the three variable exons, indicating that exon usage might determine the binding properties of an individual DSCAM isoform.

Importantly, other insect species (*Tribolium castaneum* and *Bombyx mori*) also expressed alternatively spliced *Dscam* mRNAs, indicating that DSCAM diversity is conserved across insect species. These studies lead the authors to suggest that immune-receptor diversity in species as evolutionarily diverse as insects and jawed vertebrates is indicative of convergent evolution, although the altered splicing of *Dscam* mRNA provides a new mechanism by which immune-receptor diversity is generated.

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References and links

ORIGINAL RESEARCH PAPER Watson, F. L. *et al.* Extensive diversity of Ig-superfamily proteins in the immune system of insects. *Science* 18 Aug 2005 (doi:10.1126/science.1116887)

IN BRIEF

TECHNIQUE

Production of human monoclonal antibody in eggs of chimeric chickens.

Zhu, L. *et al*. *Nature Biotech.* **23**, 1159–1169 (2005)

This study outlines a new method for the production of human monoclonal antibodies in chickens, rather than by traditional mammalian cell-culture protocols, to meet the increasing demand for therapeutic use. An expression vector encoding a monoclonal antibody under the control of the upstream and downstream regulatory DNA sequences from the gene encoding chicken ovalbumin, which is expressed specifically in egg white, was used to stably transfect chicken embryonic stem cells (ESCs). When the chicken ESCs were used to generate female chicken chimeras, the monoclonal antibody was expressed specifically by the oviduct and was deposited in egg white. Antibody purified from egg white had a higher activity in terms of antibody-dependent cellular cytotoxicity than antibody produced by mammalian cell culture.

MACROPHAGES

Inflammation-induced lymphangiogenesis in the cornea arises from CD11b-positive macrophages.

Maruyama, K. *et al*. *J. Clin. Invest.* **115**, 2363–2372 (2005)

Wayne Streilein and colleagues have shown that $CD11b^+$ macrophages can physically contribute to the formation of lymphatic vessels in the corneal stroma that occurs during inflammatory conditions of the eye. This new insight into lymphangiogenesis has implications for both tumour metastasis and antigen presentation in lymph nodes during the response to infection. After the induction of corneal inflammation, new lymphatic vessels arose *de novo* from clusters of bone-marrow-derived macrophages expressing the lymphatic markers LYVE1 and PROX1, and these cells were shown to form tube-like structures *in vitro*. Furthermore, systemic administration of clodronate liposomes to deplete $CD11b^+$ macrophages suppressed corneal lymphangiogenesis. The authors suggest that inflammatory macrophages might also have a role in the development of lymphatic vessels in other tissues and organs.

VACCINES

Vaccine-induced tumor-specific immunity despite severe B-cell depletion in mantle cell lymphoma.

Neelapu, S. S. *et al*. *Nature Med.* **11**, 986–991 (2005)

Neelapu *et al.* tested the effects of B-cell depletion on the induction of immune responses to a therapeutic vaccine in humans with mantle-cell lymphoma. The vaccine consisted of the unique variable regions of the lymphoma B-cell receptor (the idiotype) conjugated to a carrier protein. After chemotherapy and B-cell depletion using rituximab, several doses of vaccine were administered. Despite the absence of B cells, $CD4^+$ and $CD8^+$ T-cell responses to the idiotype and carrier protein were rapidly induced in most individuals, and these contributed to marked type I cytokine production. By contrast, tumour-specific antibody responses were delayed, and they correlated with the recovery of B cells. So, despite the increasing use of B-cell depletion in patients with lymphoma, vaccines remain a viable treatment option.