EVOLUTION

A common solution to an age-old problem

A study of adaptive immunity in sea lampreys — a type of jawless vertebrate from which jawed vertebrates diverged around 500 million years ago — has shown the evolution of a common solution to the problem of preventing autoimmunity, according to Max Cooper and colleagues.

The ability to recall previous encounters with a nearly unlimited variety of antigens, which is the hallmark of adaptive immunity, requires the generation of clonally diverse receptors. This is achieved by V(D)J recombination of B cell receptor (BCR) and T cell receptor (TCR) genes in jawed vertebrates, whereas jawless vertebrates insert variable leucine-rich repeat segments into incomplete germline variable lymphocyte receptor *VLRA* and *VLRB* genes. But the development of a randomly generated receptor repertoire creates a risk of autoimmunity. In jawed vertebrates, part of the solution to this problem has been the evolution of separate but interacting lymphocyte populations — CD4⁺ T cells recognise antigen and help B cells respond to antigen — with a mechanism for selection against

self-reactive T cells. Max Cooper and colleagues now show that dual recognition and response arms of the adaptive immune system have evolved independently in jawless vertebrates.

Using monoclonal antibodies specific for *VLRA* or *VLRB*, they identified discrete *VLRA*⁺ and *VLRB*⁺ lymphocyte-like cell populations in the peripheral lymphoid tissues of lamprey larvae. *VLRA*⁺ cells were shown to have assembled mature *VLRA* gene configurations and to express *VLRA* transcripts exclusively, and the same relationship held for *VLRB* gene assembly and expression by *VLRB*⁺ cells. Mature and germline *VLRA* configurations were found in equal proportions in *VLRA*⁺ cells, which shows that there is monoallelic *VLRA* gene assembly (similar to the TCR and BCR genes and as has been previously shown for *VLRB*).

VLRA⁺ and *VLRB*⁺ cell populations had different gene expression profiles. Notably, many of the genes that were selectively expressed by *VLRA*⁺ cells are orthologous to genes that are typically expressed by T cells and are required for precursor cell

homing to the thymus and T cell lineage commitment and function, such as *CCR9*, *Notch1*, *CD45*, *CXCR2* (the receptor for interleukin-8 (IL-8)), *IL17* and *MIF*. In line with earlier studies showing that *VLRB*⁺ cells resemble B cells in terms of the production of soluble *VLRB* 'antibody' in response to antigen, the *VLRB*⁺ cells in this study had a gene expression profile that was similar to that of B cells. The expression of IL-8 and IL-17 receptor by *VLRB*⁺ cells indicates the potential for reciprocal interactions between *VLRA*⁺ and *VLRB*⁺ cells.

Following the immunization of lamprey with *Bacillus anthracis*, *VLRA*⁺ and *VLRB*⁺ cells proliferated to a similar extent, but *VLRA*⁺ cells that bind *B. anthracis* spores could not be found before or after immunization. This suggests that *VLRA*⁺ cells might recognize processed rather than native antigens in a manner analogous to T cells. In contrast to *VLRB*⁺ cells, *VLRA*⁺ cells did not secrete *B. anthracis*-specific antibodies, which indicates that *VLRA* proteins, similarly to TCR proteins, are expressed exclusively as transmembrane molecules. In support of the analogy between *VLRA*⁺ cells in jawless vertebrates and T cells in jawed vertebrates, *VLRA*⁺ cells responded more vigorously than *VLRB*⁺ cells to a classical T cell mitogen.

So, the discovery of independently evolved lymphocyte populations in lamprey that are analogous to B cells and T cells shows the importance of this division of labour in adaptive immunity. However, researchers have so far failed to find an equivalent of the thymus in lamprey and it is unclear whether *VLRA*⁺ cells undergo repertoire selection to avoid autoimmunity.

Kirsty Minton

ORIGINAL RESEARCH PAPER Guo, P. et al. Dual nature of the adaptive immune system in lampreys. *Nature* 27 May 2009 (doi:10.1038/nature08068)