Milestone 9

Surprising new TCR: the γδ T cells

The discovery of T cell antigen receptors (TCRs) in the 1980s was quickly followed by a period of characterization studies. During one of these studies aimed at identifying the chains of the heterodimeric TCR, the group of Susumu Tonegawa found a chain that did not match the properties of the previously described α- and β-chains.

This turned out to be the γ-chain of the γδ TCR. The δ-chain gene was subsequently identified a few years later by Mark Davis and colleagues. Research on the γδ TCR in mice showed that this receptor is found predominantly in T cells of epithelial organs such as the skin, reproductive organs or small intestine. Almost 40 years later, γδ T cells are still not as well characterized as other T cell subsets, but it has become clear that although they share some similarities with αβ T cells, they represent an atypical T cell subset, different in many ways, and they have unique roles in the immune system.

Like αβ T cells, γδ T cells originate in the thymus and are defined by the presence of TCRs on their cell surface. The two chains of the γδ TCR are formed by somatic variable-diversity-joining (V(D)J) recombination, similar to the segments of α- and β-chains in αβ TCRs (Milestone 8), which creates diversity among TCR.

Despite this potential for diversity, γδ TCRs of certain subpopulations of cells have only specific combinations of γ- and δ-chains. For example, intraepithelial lymphocytes (IELs) in both the skin and reproductive organs of mice have $V_\delta1$ δ-chains, whereas the γ-chains are invariably $V_\gamma5$ in skin IELs and $V_\gamma6$ in reproductive-organ IELs.

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Tonegawa's group noticed that these same $V_\gamma5V_\delta1$ and $V_\gamma6V_\delta1$ combinations of TCR γ- and δ-chains were invariable in mouse fetal thymocyte populations at different developmental stages, and they confirmed by PCR analysis that early fetal thymocytes are precursors of skin IELs, whereas fetal thymocytes at a later stage are precursors of reproductive-organ IELs.

Such lack of clonal diversity in γδ TCRs within the same cell type is different from the more diverse populations of αβ TCRs, but the differences do not end there. Although αβ TCRs need antigens to be presented as peptides by the major histocompatibility complex (MHC), this is not the case for γδ TCRs.

Several studies from the mid-1990s made it clear that γδ TCR antigens do not need the MHC and, crucially, are not necessarily peptides either. Knowing that human $V_\gamma9V_\delta2$ T lymphocytes responded to microbial infection, Jean-Jacques Fournié isolated a highly potent phosphorylated metabolite ('phosphoantigen') from Mycobacterium tuberculosis, the chemical structure of which was later identified as (E)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate. Further work by the groups of Michael Brenner and Barry Bloom confirmed that monoalkyl phosphates are able to mimic the stimulation of $V_\gamma9V_\delta2$ T cells with non-peptide antigens from mycobacteria independently of the MHC.

Since then, several other γδ TCR antigens have been identified, but the general mechanism of antigen recognition and the patterns that define γδ TCR antigens are still not fully understood.

Even though the full potential of γδ T cells is still being delineated, and understanding of this T cell subset remains in its relative infancy, these early studies have made it clear that these atypical T cells fulfil a unique role within the immune system with an equally unique position within the T cell family.

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Milestone study

Saito, H. et al. A third rearranged and expressed gene in a clone of cytotoxic T lymphocytes. *Nature* **312**, 36–40 (1984)

Further reading

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