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T cell recognition: few more tricks up their sleeves

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Our immune system comprises an army of diverse cell types designed to defend our body against infections. These immune cells specifically recognise invaders (pathogens) and, once activated, elicit a targeted attack to eliminate the infection. Within the army of immune cells are cytotoxic T cells equipped with receptors (TCRs). TCRs recognise a fragment of a pathogen (i.e., bits of peptides, lipids, or small molecules) that are presented by a host-specific major histocompatibility complex (MHC) molecule found on the surface of antigen-presenting cells (APCs). This interaction between a TCR and an antigen (i.e., a pathogen fragment) bound to an MHC molecule is critical, as it is the first event in the process of T cell activation that will, in turn, dictate the fate of an infection.

Over the last 20 years, the field of T cell immunology has greatly benefited from structural biology. The first structure of a TCR recognising an antigen bound by an MHC molecule was solved in 1996. Since then, numerous co-crystal structures of TCRs in complex with different MHC molecules bearing diverse antigens have been reported, providing us with a snapshot of this critical interaction. Studies linking structural and functional information about T cell recognition have also been highly informative. From the structures available, some common features of the molecular basis of antigen recognition by T cells have emerged. In particular, we have observed conserved docking modes and interactions across diverse TCRs and pathogens. However, new T cells have recently been discovered as a result of advances in isolating rare T cell populations and the development of targeted mass-spectrometry techniques to identify novel antigens. Surprisingly, these newly identified T cells do not follow the previous dogma, and have made us rethink the molecular basis of TCR recognition.

Using X-ray crystallography to determine the specific interaction between the TCR and the antigens-MHC complexes, my group's work has revealed some novel modes of antigen recognition by T cells. Those discoveries have opened up new avenues in the field of T cell immunology. Here I will present examples of those unusual TCR-antigen-MHC structures, and show that T cells still have a few more tricks up their sleeves in the fight against infection.

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