

Structural and physical underpinnings of specificity in cellular immunity

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The immune system is tasked with recognizing targets from pathogens and diseased cells. Specific recognition of targets is a hallmark of the immune system. However, key receptors of the immune system are characterized by a high degree of degeneracy or cross-reactivity. One example is T cell receptors (TCRs), molecules similar to antibodies found on white blood cells. TCRs recognize small peptides bound and “presented” by MHC proteins. Although T cell immune responses are specific, any one TCR can recognize millions of different peptide/MHC complexes. The presence of both specificity and cross-reactivity in this component of the immune system is often described as an enigma or paradox. Here we demonstrate that the structural and physical rules of protein molecular recognition can fully explain these seemingly paradoxical properties. Consideration of these rules should permit an improved understanding of T cell mediated immune responses, including our ability to predict TCR targets and generate new T cell-based therapeutics using engineered TCRs.