region, and are structurally more variable. One of the flanking regions divides Ly49s into those that recognize both H-2D and H-2K versus only H-2D ligands, whereas the other discriminates among H-2D or H-2K alleles. The modular design of Ly49 binding sites provides a framework for predicting the MHC-binding specificity of Ly49s that have not been characterized experimentally.

Keywords: natural killer cell, crystal structure, immune system

P04.11.272

Acta Cryst. (2008). A**64**, C316

Structure of the subdominant TCR in complex with HLA-B8FLRGRAYGL

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The cytotoxic T cell response towards viruses is directed towards class I Major Histocompatibility Complex (MHC-I) molecules complexed to peptide antigens (pMHC-I). These pMHC-I complexes are expressed on the surface of infected cells and are recognized by clonally distributed ab T cell receptors (TCR) on CD8+ T-cells. Appropriately armed and activated CD8+ T-cells can eliminate infected cells and prevent viral replication. The CD8+ T-cell response towards many viruses can be extremely focused with viral eradication occurring through the recognition of only one or two immunodominant epitopes. Epstein Barr virus (EBV) is a ubiquitous human pathogen with around 90% of the population persistently infected. EBV infection, although typically asymptomatic in immuno-competent individuals, is the causative agent of infections mononucleosis and has been linked to the development of cancers. Viral infection and persistence is achieved through a balance of lytic and latent infections controlled by a series of lytic or latent proteins respectively. The immunodominant HLA-B8 restricted epitope, FLRGRAYGL (FLR), is from EBNA 3A (latent protein). We have previously studied the biased TCR usage of the B8+ individuals infected by EBV, and solved the structure of the public TCR named LC13 in complex with B8-FLR. Interestingly the public LC13 TCR displays alloreactivity towards HLA-B44. Accordingly, in HLA B8+/B44+ individuals, the CTL responses towards FLR express different TCRs that exhibit altered specificity. We present recent findings in this area that allows us to compare how two different TCRs can interact with the same pMHC-I. These results are important, as well as EBV is the best know and most widely studied herpes virus due to its clinical and oncogenic importance.

Keywords: T cell receptor, HLA, Epstein Barr virus

P04.11.273

Acta Cryst. (2008). A**64**, C316

Crossreactive T cells spotlight the germline rules for TCR interactions with MHC molecules

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To test whether highly crossreactive alpha/beta T cell receptors (TCRs) produced during limited negative selection best illustrate evolutionarily conserved interactions between TCR and major histocompatibility complex (MHC) molecules, we solved the structures of three TCRs bound to the same MHC II peptide (IAb-3K). The TCRs had similar affinities for IAb-3K but varied from noncrossreactive to extremely crossreactive with other peptides and MHCs. Crossreactivity correlated with a shrinking, increasingly hydrophobic TCR-ligand interface, involving fewer TCR amino acids. A few CDR1 and CDR2 amino acids dominated the most crossreactive TCR interface with MHC, including Vbeta8 48Y and 54E and Valpha4 29Y, arranged to impose the familiar diagonal orientation of TCR on MHC. These interactions contribute to MHC binding by other TCRs using related V regions, but not usually so dominantly. These data show that crossreactive TCRs can spotlight the evolutionarily conserved features of TCR-MHC interactions and that these interactions impose the diagonal docking of TCRs on MHC.

Keywords: T cell receptors, MHC complexes, immune system

P04.11.274

Acta Cryst. (2008). A**64**, C316

Ligand binding to pentraxins

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The human pentraxin proteins, serum amyloid P component (SAP) and C-reactive protein (CRP) have emerged as potentially important targets in the treatment of amyloidosis and cardiovascular diseases respectively, although their normal physiological functions are unclear. Structurally highly conserved homologous proteins are present in common experimental animals such as the rat, mouse, rabbit and hamster but there are major differences from the human pentraxins in their normal behaviour as acute phase proteins, fine ligand specificity and capacity to activate the complement system. SAP binds to amyloid fibrils of all types and may contribute to their formation, stabilisation and persistence. Since important biological functions of proteins are often conserved among species, the structural differences between the rat and human pentraxins were investigated. Here we report the X-ray crystal structure of rat SAP in complex with phosphocholine (PC) to 2.2 Å resolution. The structure reveals the pentraxin fold and a bound PC in a pocket on each subunit indicating that rat SAP is also a PC-binding protein. This pentameric structure displayed subtle differences in the electrostatic properties. It remains to be determined whether this has an effect on avid binding of SAP to deoxyribonucleic acid (DNA), a functional property of human SAP still poorly understood.

Keywords: pentraxin, serum amyloid P component, phosphocholine