MS04.15.07 STRUCTURAL ANALYSIS OF A PROTEIN COMPLEX IN THE IMMUNE SYSTEM. P.J. Bjorkman, W.P. Burmeister, M. Raghavan, D.E. Vaughn, California Institute of Technology, Pasadena, CA 91125

Maternal immunoglobulin G (IgG) in milk is transported to the bloodstream of newborn rodents via an Fc receptor (FcRn) expressed in the gut. FcRn binds IgG at the pH of milk in the intestine (pH 6.0 - 6.5) and releases IgG at the pH of blood (pH 7.5). The receptor shows a striking similarity to class I MHC molecules. Because the structures of MHC molecules appear uniquely adapted to their peptide binding function, it is surprising to find a molecule with a structural similarity, yet a completely different function in the immune system. The 2.2 Å crystal structure of soluble FcRn is similar to structures of class I MHC molecules. Although the two helices that form the sides of the MHC peptide binding groove on the tops of the alpha1 and alpha2 domains are present in FcRn, they are closer together than their MHC counterparts, rendering the FcRn groove incapable of binding peptides. Together with biochemical and structural data from an FcRn/Fc complex, the FcRn structure suggests a unique utilization of the MHC fold for immune recognition, differing substantially from modes of MHC interactions with peptides, T cell receptors or CD8. The co-crystal structure shows that FcRn binds to Fc at the interface between the Fc CH2 and CH3 domains, which contains several histidine residues that could account for the sharply pH dependent FcRn/IgG interaction. A dimer of FcRn heterodimers observed in the co-crystals and in the crystals of FcRn alone could be involved in binding Fc, correlating with the 2:1 binding stoichiometry between FcRn and IgG, and suggests an unusual orientation of FcRn on the membrane.

MS04.15.08 CRYSTAL STRUCTURE OF MURINE CD1d1. Ian A. Wilson[1], Zonghao Zeng[1], A. Raul Castaño[1], Brent Segelke[1], Enrico A. Stura[1], Per A. Peterson[2], [1]The Scripps Research Institute, Dept. of Molecular Biology, 10666 No. Torrey Pines Rd., La Jolla, CA 92037, [2]R. W. Johnson Pharmaceutical Research Institute, 3535 General Atomics Court, Suite 100, San Diego, CA 92121.

Murine CD1d1 is a member of a family of cell surface glycoproteins that are distantly related to MHC molecules.[1] CD1 molecules are encoded outside the MHC and have restricted tissue expression.[1,2] The precise function of CD1 molecules is as yet unknown but CD1 is believed to represent a novel class of antigen presenting molecules of the immune system. Like MHC class I presenting cells, CD1 presenting cells can illicit a cytolytic T-cell medicated immune response.[3,4] Two T-cell lines reactive to murine CD1d have been phenotyped; the first has a conventional MHC class I reactive phenotype α/β CD4-/CD8+ TCR+ and the second has phenotype α/β CD4-/CD8- TCR+.[5,6]

The crystal structure of a type II murine CD1 molecule, CD1d1, has been determined to 2.8Å by molecular replacement and refined to a crystallographic R value of 19%. Each of the four domains of the structure are structurally homologous with the corresponding domains of the known MHC and MHC-like molecules. With the exception of the small H1 helix of class I MHC antigens all of the secondary structural elements of the class I MHC are preserved, There are, however, substantial differences in the shape and chemical properties of the putative ligand binding groove suggesting a different mode of ligand binding.

[1]Calibi, F., Milsten, C., *Nature* (1986) 323:540.
[2]Calabi, F., Bradbury, A., *Tissue Antigens* (1991) 31:1.
[3]Porcelli, S., Brenner, M. B., Greenstein, J. L., Balk, S. P., Terhorst, C., and Bleicher, P. A., *Nature* (1989) 341:447.
[4]Porcelli, S., Morita, C. T., Brenner, M. B. *Nature* (1992) 360:593.
[5]Castaño, A. R., Tangari, S., Miller, J. E. W., Holocombe, H. R., Jackson, M. R., Huse, D. W., Kronenberg, M., Peterson, P. A. *Science* (1995) 269:223.
[6]Bendelac, A. *Science* (1995) 269:185.

MS04.15.09 STRUCTURE OF THE MHC CLASS II MOLECULE HLA-DR4/HA306-318 PEPTIDE/SUPERANTIGEN COMPLEX. W.C. Stallings, A.M. Stevens, R.A. Stegeman, M.L. Zacheis, D.A. Kirschmann, T. Witman, X-T. Fu, R.F. Karr, B.D. Schwartz, and S.L. Woulfe, Monsanto-Searle, 700 Chesterfield Village Parkway, St. Louis, MO 63198 USA

The crystal structure of a rheumatoid arthritis-associated human leukocyte antigen DR4 Dw4 complexed with the superantigen, S. aureus enterotoxin B, has been solved by molecular replacement techniques at 2.8 resolution (1). The peptide binding groove was loaded with a 13-residue antigenic peptide from hemagglutinin, HA306-318. Comparison of the DR1 (2) and DR4 peptide binding domains with bound HA306-318 revealed differences in the DR1 and DR4 backbones in the N-terminus of the a-chain helix beginning near residue 51 and continuing through residue 74 with maximal displacement between the two structures near the C-terminus of this region. In general, many of the DR1-HA peptide interactions were preserved in the DR4-HA structure. There were, however, significant differences in the orientation of peptide side chains at Lys 310, Gln 311, Asn 312, Lys 315, and Leu 316. Thus, the different class II major histocompatibility complex molecules recognize the same peptide in different ways. These findings provide support for the hypothesis that the orientation of peptide in the groove influences T cell recognition.

Crystals were grown from polyethylene glycol over a considerable pH range. The lattice parameters are a = 91.5, b =92.5, c =102.3 , space group $P2_12_12_1$ with a single superantigen and peptide-loaded MHC Class II molecule in the asymmetric unit; thus DR4 does not crystallize as a dimer. Data, 75% complete, were collected from a single crystal flashed cooled in a liquid nitrogen stream.

1. TS Jardetzky, JH Brown, JC Gorga, LJ Stern, RG Urban, Y-I Chi, C Stauffacher, JL Strominger & DC Wiley (1994) Nature 368, 711.
2. LJ Stern, JH Brown, TJ Jardetzky, JC Gorga, RG Urban, JL Stromeyer & DC Wiley (1993) Nature 368, 215.

MS04.15.10 STRUCTURE OF A T CELL RECEPTOR BOUND TO A CLASS I MHC-PEPTIDE COMPLEX. David N. Garboczi[1,5], Partho Ghosh[1,5], Ursula Utz[3], William E. Biddison[4], and Don C. Wiley[1,2], [1]Department of Molecular and Cellular Biology and [2]Howard Hughes Medical Institute, Harvard University, Cambridge, MA 02138, USA. [3]Laboratoire d'Immunologie, Institut de recherches cliniques de Montreal, Montreal, Canada H2W 1R7, [4]Molecular Immunology Section, Neuroimmunology Branch, National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA, [5]These authors contributed equally to the work presented

The central recognition event in the cellular immune response is between a T cell receptor (TCR) found on the surface of a T lymphocyte and an MHC-peptide complex found on the surface of a cell being inspected by the T lymphocyte. A TCR specific for HLA-A2 complexed with a peptide from the Tax protein of human T lymphotropic virus type 1 (HTLV-1) has been expressed in *E. coli* as inclusion bodies, refolded, and purified. This TCR binds specifically to its *in vivo* target, HLA-A2/Tax peptide, as seen by gelshift assays using HLA-A2 also expressed in *E. coli* as inclusion bodies and refolded. The ternary complex of TCR/peptide/MHC has been crystallized and Xray diffraction data to 2.7 Å have been collected at a synchrotron. The structure has been phased from two heavy atom derivatives and from partial molecular replacement solutions. Electron density maps from these phasing methods reveal the nature of interactions between TCR and MHC/peptide, elucidating at the atomic level the mechanism of immune surveillance.