SIgN Immunology Seminar

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MR1 presents conserved microbial vitamin B metabolites to MAIT cells

Host
Dr Lucia Mori
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Date
Monday,
14 January 2013

Time
11am – 12pm

Venue
SIgN Seminar Room,
Immunos Building
Level 4
Biopolis

Mucosal-associated invariant T (MAIT) cells are an abundant population of innate-like T cells in humans that are activated by an antigen(s) bound to the MHC class I-like molecule MR1. MAIT cells express a semi-invariant T cell receptor comprising human V-alpha7.2, J-alpha33, and a restricted repertoire of V-beta families. However, the molecular basis for MAIT TCR recognition by MR1 is unknown.

The crystal structure of a human V-alpha7.2, J-alpha33, V-beta2 MAIT TCR allowed rational mutagenesis of the receptor revealing highly conserved requirements for the MAIT TCR–MR1 interaction across different human MAIT TCRs stimulated by distinct microbial sources. Individual residues within the MAIT TCR beta chain were dispensable for the interaction with MR1, whereas the invariant MAIT TCR alpha chain controlled specificity through a small number of residues, conserved across species and located within the V-alpha-J-alpha regions. Mutagenesis of MR1 showed that only two residues, which were centrally positioned and on opposing sides of the antigen-binding cleft of MR1, were essential for MAIT cell activation. The mutagenesis data are consistent with a centrally located MAIT TCR–MR1 docking that was dominated by the alpha-chain of the MAIT TCR.

Although the identity of MR1-restricted antigen(s) was unclear at the time of these experiments, it was known to be present in numerous bacteria and yeast and we reasoned from our data that this was likely to be a highly conserved antigen(s) of limited variability. Biochemical characterization of MR1-bound ligands revealed that vitamin derivatives, originating from the bacterial riboflavin (vitamin B2) biosynthetic pathway, bound MR1 and specifically and potently activated MAIT cells. We also observed MR1-binding of the folate breakdown product 6-Formyl Pterin such that in X-ray crystalographic structures the pterin ring was sequestered within MR1 and hidden from solvent. Notably, the structure and chemistry within the antigen-binding cleft of MR1 is distinct from the MHC and CD1 families with MR1 being ideally suited to bind ligands originating from vitamin metabolites.

Accordingly, we show that metabolites of vitamin B represent a class of antigen that are presented by MR1 for MAIT-cell immunosurveillance. As many vitamin biosynthetic pathways are unique to bacteria and yeast, our data suggest that MAIT cells use these metabolites to detect microbial infection or overgrowth at mucosal surfaces.