One for One Peptide Binding to MHC Molecules

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J Immunol 2005; 175:4161-4162; doi: 10.4049/jimmunol.175.7.4161
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B and T lymphocytes recognize Ag in very different contexts. Although B cells typically respond to native Ag, T lymphocytes are capable of recognizing both native and denatured Ag but only in the context of accessory cells. These latter cells, now known as APCs, are critical for T cell activation. Of key importance, APCs display on their surface polymorphic glycoproteins encoded within the MHC known as class I and class II molecules. Work at the turn of the 20th century suggested that genes within the MHC could control the engraftment or rejection of transplanted tissues, yet the cellular and molecular events responsible were at the time unclear. Years later, Zinkernagel and Doherty (1) revealed that specific MHC-encoded class I molecules restrict T cell responsiveness to viral Ag. Yet, understanding the role that APCs play in bringing MHC molecules together with Ag to promote T cell activation required further detective work and to this day continues to intrigue immunologists.

Investigations focusing on the mechanisms driving helper T cell activation offered important insights into the role of MHC molecules in conferring specificity during Ag recognition. Helper T cell responses are dependent upon APC expression of MHC-encoded class II molecules, I-A and I-E, in mouse or HLA-DR, DP, and DQ alleles in humans. Regardless of whether Ag is expressed by an infectious pathogen or delivered via immunization as a preparation of purified protein, metabolically active APCs are required for Ag-specific helper T cell activation. APCs internalize Ag, followed by Ag processing by proteases and denaturants within acidic lysosomes and endosomes (2). Treatment of APCs with aldehyde fixatives before incubation with Ag ablates the ability of these cells to display Ag to T cells. Yet, T cell responses to Ag can be detected using aldehyde-fixed APCs incubated with Ag, which has been previously cleaved into small peptides in vitro (3). These studies were among the first clues that peptides might be the true partners for MHC class II molecules.

Pursuing how Ag and MHC molecules might interact, Watts et al. (4) found that addition of a digested Ag, OVA, to purified murine class II I-A^d, which had been incorporated into a lipid bilayer, was sufficient to trigger the activation of OVA-specific, MHC-restricted T cells. Yet, as demonstrated in a study first published by Babitt et al. (5) in the journal Nature in 1985 and reprinted here, it would take classical biochemistry and a considerable number of APC to reveal that MHC molecules selectively bind peptides for T cell recognition. Allen et al. (6) had previously shown that a 10-residue peptide from the Ag hen egg lysozyme, when added to APCs, could trigger the activation of lysozyme-specific T cells. By labeling this synthetic peptide with a fluorescent probe, peptide-MHC complex formation could potentially be visualized. Using 10^{11} murine B hybridoma cells as a starting source, class II I-A molecules were purified from these APCs and incubated in vitro with the fluorescently tagged peptide followed by equilibrium dialysis. Saturation binding analysis revealed stable association of the fluorescent peptide with MHC class II I-A^d at a molar ratio approaching one. In vitro peptide binding was observed only with class II I-A^d and not the I-A^b allele, perfectly correlating with in vivo T cell responses to this peptide in the context of I-A^d but not I-A^b alleles. The authors also concluded that MHC class II-potential binding is sensitive to the peptide’s amino acid sequence, a first hint that prediction of peptide motifs for MHC alleles might be possible. The dissociation constant for these peptide-class II complexes was in the low micromolar range, an observation that was upheld in subsequent studies by Buus et al. (7), who demonstrated in vitro class II-peptide binding was a slow process. Shortly thereafter, evidence was also obtained that MHC class I molecules bind short peptides, leading to CD8 T cell activation (8). Thus, proof was finally in hand that MHC molecules can directly bind specific antigenic peptides analogous to receptor-ligand complexes.

The study of peptide-MHC molecule complex formation by Unanue, Grey, and others during these years offered a link between Ag processing and MHC-restricted presentation. Yet, could the high concentrations of peptide and MHC molecules required for peptide binding in vitro ever be duplicated inside APCs? And what of the observation by Buus et al. (7) that complex formation was slow in vitro? Subsequent studies have demonstrated the remarkable ability of different APCs to exploit intracellular pathways in the delivery of antigenic peptides to receptive MHC molecules. In the case of MHC class I molecules, chaperones and the peptide transporter TAP facilitate peptide loading by empty class I proteins in the endoplasmic reticulum. For class II molecules, the invariant chain chaperones class II proteins to endosomal compartments rich in antigenic peptides. There, MHC-encoded DM and DO molecules orchestrate peptide loading and exchange. Thus, we know now that APCs have evolved specific mechanisms to enhance intracellular peptide loading by MHC molecules.

Studies during the 1980s of TCR subunit structure were consistent with this idea of a 1:1 complex of peptide and MHC molecule serving as the restricting element for T cell activation. Only a few years later, Bjorkman et al. (9) would co-crystallize peptide and MHC molecules, providing a clear view of this complex, and the intricacies of the MHC protein ligand binding groove. Extending the studies of Unanue and colleagues,
several groups would perfect methods to elute and sequence the many thousands of peptides lodged within the groove of MHC class I and class II molecules. The importance of the groove within distinct MHC alleles in conferring specificity was quickly recognized, leading to the design of computer algorithms for predicting peptide motifs, which optimally bind MHC molecules. Analysis of peptide-MHC molecule binding remains key for vaccine design, as well as potentially useful for triggering the mobilization of immunomodulatory T cells. Multimeric complexes of purified peptide-MHC molecules are now used regularly as reagents to detect and quantitate Ag-specific T cells during host responses to pathogens and disease.

References