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Survival of antigenic epitope requires class II MHC capture prior to lysosomal proteolysis

AeRyon Kim^{1,2}, Isamu Z. Hartman^{1,2}, and Scheherazade Sadegh-Nasseri^{2,3}

Abstract:

The paradigmatic model for the generation of peptide determinants for class II major histocompatibility complex molecules (MHC II) is that proteolytic fragmentation of antigen precedes the capture of the resulting peptides by MHC II (cut/trim first, bind later). However, circumstantial evidence exists to support an alternate model in which MHC II binding of antigenic epitope occurs prior to the proteolytic fragmentation of that antigen (bind first, cut/trim later). To distinguish between these two models, we analyzed the interaction of HLA-DR1 with influenza hemagglutinin. Here, using a novel cell-free antigen processing system composed solely of purified soluble protein components, HLA-DR1, two cathepsins, and HLA-DM, combined with mass spectrometric identification of the bound peptides, we demonstrate for both antigens that; i) the protein antigens bind MHC class II prior to digestion by lysosomal proteases, ii) the immunodominant epitope of the antigens are degraded by lysosomal proteases if not bound to MHC class II, and iii) the epitopes, when bound to MHCII, are protected from proteolytic degradation. These findings conclusively support the “bind first, cut/trim later” model and have important implications in understanding the sequence of events in antigen processing and the correlation between antigen structure and immunodominance.