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HLA-DM mediates peptide exchange by a hit-and-run mechanism

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Abstract

The peptide editor HLA-DM (DM) mediates the exchange of peptides bound to MHC class II molecules in the low pH compartments of APCs by catalyzing both peptide association and dissociation from these molecules. We have defined conformational differences between peptide-MHC II complexes as a dominant factor for recognition by HLA-DM. We have further demonstrated that DM dissociates the peptide-MHC II complexes that it recognizes by perturbing a critical H-bond between MHC II and the peptide backbone. Here, we show that DM induces a short lived peptide-receptive conformation in MHC II but does not maintain this conformation in the absence of peptides. Also, independent of pre-incubation, DM-mediated peptide association is inhibited by increasing solvent viscosity. Hence a single action can be assigned to DM: the generation of a peptide-receptive conformation of MHC class II via transient and repeated "hit-and-run" interactions that result in the opening of the peptide binding groove of the MHC class II molecule. The continuous presence of peptide and DM in the milieu is thus crucial for the efficient generation of specific peptide-MHC class II complexes. Supported by R01AI063764 and R01GM53549 to SS-N.