Point mutations in or near the antigen-binding groove of HLA-DR3 implicate class II-associated invariant chain peptide affinity as a constraint on MHC class II polymorphism.

Abstract:

During maturation of MHC II molecules, newly synthesized and assembled complexes of MHC II alphabeta dimers with invariant chain (Ii) are targeted to endosomes, where Ii is proteolysed, leaving remnant class II-associated Ii peptides (CLIP) in the MHC II peptide binding groove. CLIP must be released, usually with assistance from the endosomal MHC II peptide exchange factor, HLA-DM, before MHC II molecules can bind endosomal peptides. Structural factors that control rates of CLIP release remain poorly understood, although peptide side chain-MHC II specificity pocket interactions and MHC II polymorphism are important. Here we report that mutations betaS11F, betaS13Y, betaQ70R, betaK71E, betaK71N, and betaR74Q, which map to the P4 and P6 pockets of the groove of HLA-DR3 molecules, as well as alphaG20E adjacent to the groove, are associated with elevated CLIP in cells. Most of these mutations increase the resistance of CLIP-DR3 complexes to dissociation by SDS. In vitro, the groove mutations increase the stability of CLIP-DR3 complexes to dissociation. Dissociation rates in the presence of DM, as well as coimmunoprecipitation of some mutant DR3 molecules with DM, are also diminished. The profound phenotypes associated with some of these point mutations suggest that the need to maintain efficient CLIP
release represents a constraint on naturally occurring MHC II polymorphism.