

PROBING THE IMMUNE PROTEOME: BIOCHEMICAL AND STRUCTURAL BASIS OF THE LIGAND SPECIFICITY OF CLOSELY RELATED HLA ALLELES

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Mass spectrometry is now the technique of choice for studies of the proteome as it related to the functioning of the immune system and immune responses to pathogenic stimuli. The HLA B44 family of alleles is an important family of HLA molecules that are found at high frequency in all populations (e.g. in around 24% of Caucasians). Given the prevalence of this allele it is not surprising that it participates in important anti-viral and tumoricidal responses as well as being implicated in transplant rejection and autoimmune disorders. We have examined in detail the implications of naturally occurring polymorphism between three important HLA B44 family members (HLA B*4402, B*4403 and B*4405). These alleles differ from each other by 1-2 amino acids yet they display very different behavior in terms of antigen presentation. Compared to HLA B*4402 and B*4403 (the two most prevalent alleles of this family) HLA B*4405 is able to present antigen more rapidly and exhibits independence on the chaperone tapasin for antigen loading and surface expression. This does not appear to be due to the acquisition of higher affinity ligands or enhanced thermostability of the complex. We present a proteomics based analysis of the peptides naturally presented by these three alleles when introduced into the same parental cell line, we demonstrate that despite a high level of shared repertoire, important differences are observed in ligand selection by each allele. We present X-ray crystallographic structures of HLA B4402, 03 and 05 each bound to the same naturally selected peptide ligand and demonstrate structural basis of ligand specificity and results of receptor polymorphism on the conformation of the complex. Finally we demonstrate that these differences have profound biological outcomes in terms of induction of alloresponses and intracellular behavior of the complexes during their maturation and egress to the cell surface.
