Nanodynamics of MHC:Peptide Complexes: the key to understand function and disease association?

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Major Histocompatibility Complex (MHC) class I proteins are expressed on nearly all nucleated cells. They act on the cell surface presenting viral and self-peptides to the T-Cell receptors, thus permitting the recognition and the lysis of the infected cells. Understanding the structural and dynamical features of the MHC proteins is mandatory in order to elucidate the mechanism of the MHC recognition by the T-Cell receptors. In this work, we investigated by Molecular Dynamics simulations the dynamics of two MHC Class I subtypes: the HLA-B*2705 and the HLA-B*2709 subtype in complex with the viral peptide LMP2 and the self-peptides VIPR, pGR and TIS. Despite the two subtypes differing only at a single position at residue 116 (Asp116 in B*2705 and His116 in B*2709) they are differentially associated with the autoimmune disease ankylosing spondylitis (AS). Here, we report an increase in entropy for the viral-peptide LMP2 bound to the disease associated B*2705 subtype with respect to the non-disease associated B*2709. In contrast, the three self-peptides examined here displayed an increased entropy when bound to the non-disease associated B*2709 as shown before also for the case of the model peptide m9 [1]. Similarly, the peptide-binding groove revealed a both subtype- and peptide-dependent flexibility in a region crucial for binding to the T-Cell receptor [2]. Our results suggest a combination of both entropic control and conformational selection as the main driving force for antigen recognition by T-Cell receptor.

[1] T. Pöhlmann et al., *J.Biol.Chem.*, **2004**, *279*, 28197-28201
[2] H. Fabian et al., *J.Mol.Biol.*, **2008**, *376*, 798-810