A structural basis studies of HLA-cw*0801 allele associated Nevirapine (NVP) drug hypersensitivity syndromes

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ABSTRACT

Idiosyncratic adverse drug reaction (ADR's) are the common and a potentially life threatening problem in drug therapy. Patient's experience unnecessary morbidity and mortality while many effective drugs are withdrawn because of ADRs in patients. Recent studies have revealed that HLA alleles are the major genetic determinants of drug hypersensitivity but the insights of underlying molecular mechanism remains unclear. Nevirapine a non-nucleoside reverse transcriptase inhibitor (NNRTIs) used as a cornerstone for treatment of human immunodeficiency virus (HIV) in India. Human HLA-CW*08.01 allele has been significantly associated with nevirapine-induced hypersensitivity. Our aim was to identify the genetic relationship between Nevirapine hypersensitivity and HLA-Cw*08.01 allele. This would lay the groundwork for biochemical and structural studies that define binding in the antigen-binding cleft in a manner that alters the HLA-bound peptide repertoire. *In silico* docking studies was used to dissect the mechanism of NVP non-covalent binding within the antigen binding cleft of HLA- HLA-Cw*0801 alleles. We used the DS: Ligand fit module to dock NVP on the HLA into the Binding pocket, and we consistently observed NVP interaction with residues on the pocket. The binding is stronger without the presence of peptide. The HH12 atom and atom HH22 of ARG48 interacting with O_1 atom of Nevirapine by forming a hydrogen bond, with the bond distance of 2.05776 A^o and 2.79859 A^o respectively. There is an amide Pi stacked interaction between NVP and SER 52 of HLA-Cw*08.01 and Pi Alkyl interaction of PRO235 and NVP further accelerating stability of NVP and HLA allele interaction; thereby altering HLA allele's repertoire for self-peptides presentation to T cells. Thus self-peptides may bind at the termini pockets of the binding cleft of HLA allele and loop over NVP to interact with the TCR and causing alloreactive T cell response. This study not only provides new perspectives of the mechanisms of HLA-associated drug hypersensitivity but also a preclinical screening of the interaction between HLA and the NVP sheds insight on the improvement of drug safety.

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