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Dynamic characterization of HLA-B*44 Alleles: A comparative molecular dynamics simulation study

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ABSTRACT

Human Leukocyte Antigens (HLA) are highly polymorphic proteins that play a key role in the immune system. HLA molecule is present on the cell membrane of antigen-presenting cells of the immune system and presents short peptides, originating from the proteins of invading pathogens or self-proteins, to the T-cell Receptor (TCR) molecule of the T-cells. In this study, peptide-binding characteristics of HLA-B*44:02, 44:03, 44:05 alleles bound to three nonameric peptides were studied using molecular dynamics simulations. Polymorphisms among these alleles (Asp116Tyr and Asp156Leu) result in major differences in the allele characteristics. While HLA-B*44:02 (Asp116, Asp156) and HLA-B*44:03 (Asp116, Leu156) depend on tapasin for efficient peptide loading, HLA-B*44:05 (Tyr116, Asp156) is tapasin independent. On the other hand, HLA-B*44:02 and HLA-B*44:03 mismatch is closely related to transplant rejection and acute-graft-versus-host disease. In order to understand the dynamic characteristics, the simulation trajectories were analyzed by applying Root Mean Square Deviation (RMSD) and Root Mean Square Fluctuation (RMSF) calculations and hydrogen bonding analysis. Binding dynamics of the three HLA-B*44 alleles and peptide sequences are comparatively discussed. In general, peptide binding stability is found to depend on the peptide rather than the allele type for HLA-B*44 alleles.

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1. Introduction

Major histocompatibility complex (MHC) class I molecules are heterodimer cell membrane proteins consisting of a highly polymorphic heavy chain (α-chain), a light chain, β2-microglobulin and a peptide. Forming highly stable complexes with the peptides, they have roles in the recognition of the peptides by T cells. Peptides are generally between 8 and 11 amino acids in length and have allele-specific anchor residues at certain positions (Falk et al., 1991). Due to the large number of available peptide binders leading to tremendous number of possible peptide-MHC complexes, the immune system is challenged to respond to a wide variety of complexes (Madden, 1995). Studies on MHC molecule have been accomplished from past to present due to the importance of MHC molecule in the immune response to foreign antigens (Ostermeir et al., 2015).

HLA encoded genes are the most polymorphic genes in the whole genome, while polymorphisms affect the specific region for peptide binding region. Polymorphism occurring in the peptide binding region of the HLA molecule is important for antigen presentation and recognition of antigens by T cells. Additionally, polymorphisms for HLA class I molecules are also known to affect the Tapasin dependency (Macdonald et al., 2002), which is a transmembrane glycoprotein that plays an important role in the stabilization of peptide receptive state of HLA class I molecules (Badrinath et al., 2014). Tapasin exerts an optimizing influence and is correlated with the rate of peptide dissociation from class I molecules. The dependence to Tapasin is still an unsolved issue, and it is still not known why some alleles depend on tapasin while the others don't (Garstka et al., 2011). In this respect, HLA-B44 family has been under investigation (Garstka et al., 2011; Ostermeir et al., 2015; Ostermeir and Zacharias, 2014; Sieker et al., 2007, 2008) since they display varying Tapasin dependencies. Among HLA-B*44:02/03/05, there are two polymorphic positions, 116 and 156 (HLA-B*44:02; Asp116, Asp156; HLA-B*44:03; Asp116, Leu156; HLA-B*44:05; Tyr116, Asp156). Residue 116 is buried at the bottom of the F-pocket (formed by residues 95, 97, 116, 118) on the floor of the antigen binding cleft contributing to the peptide binding, away from the tapasin binding region (residues 134, 229 and 229 (Suh et al., 1999; Zernich et al., 2004)) and 156 is located on the α2 helix forming part of the D/E pocket (Ostermeir et al., 2015) (Fig. 1). HLA-B*44:02 and HLA-B*44:03 mismatch is closely related to transplant rejection and acute-graft-versus-host disease (GvHD). The polymorphic position 156 is known to be one of the most non-permissive transplantation mismatches

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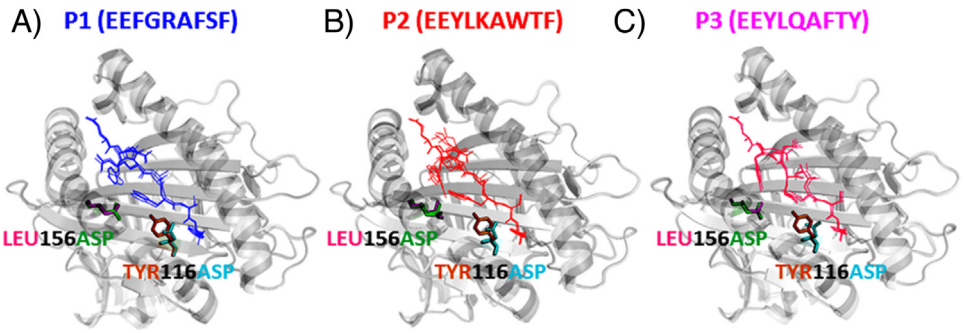

Fig. 1. The superposition of the peptides on different alleles are shown on the structures of A) HLA-B*44:02, B) HLA-B*44:03 and C) HLA-B*44:05. The polymorphic residues (Leu156Asp and Tyr116Asp) are also shown in sticks. The structures are drawn using Pymol (The PyMOL Molecular Graphics System).

(Badrinath et al., 2012). Additionally, HLA-B*44:02 and HLA-B*44:03 show tapasin dependence during peptide loading (Thammavongsa et al., 2006), while HLA-B*44:05 is tapasin independent (Zernich et al., 2004).

In this study, the dynamics of peptide binding on HLA-B*44:02/03/05 alleles bound to three different peptides was examined via 20 ns molecular dynamics simulations. Root mean square deviation (RMSD), root mean square fluctuation (RMSF) profiles as well as hydrogen bonding were investigated for the polymorphic HLA molecules bound to the same peptide.

2. Materials and methods

2.1. Structures

HLA-B*44 alleles are the most commonly processed alleles for antigen presentation because of their polymorphic properties related to varying tapasin dependency and transplant rejection. Table 1 lists the molecules examined in this study along with their respective polymorphic residues. The structures of the complexes were retrieved from protein data bank (PDB) (Berman et al., 2000). Although binding to the same peptide, the conformations of the peptides show small variations among the alleles as well. Structures are displayed in Fig. 1.

2.2. Molecular dynamics simulations

20 ns molecular dynamics simulations were conducted on the 9 structures given in Table 1. A total of 18 simulations were employed together with the parallel runs. MD simulations were performed with NAMD 2.9 (Phillips et al., 2005) using CHARMM 27 force field. An integration time step of 2 fs was used. Langevin Dynamics was used to keep temperature and pressure stable at 310 K and 101.3 kPa. The structure was surrounded by water molecules with a solvent area shaped as a rectangular box with 10 Å padding. The system was ionized with Na and Cl ions. Periodic boundary conditions were applied and Particle Mesh Ewald summation (Darden et al., 1993) with 12 Å cutoff distance for non-bonded interaction energies was used during the simulations.

For the determination of the overall stability of simulations, time evolution of the root-mean square deviation (RMSD) of backbone atoms with respect to the initial structure was monitored. Further detailed analysis (RMSF and hydrogen bonding between the peptide and the binding groove residues) was employed on the simulations after the determination of the equilibrium time step. Details of the calculations are given in Supplementary Material. The analyses were conducted using VMD program (Humphrey et al., 1996) packages. For hydrogen analysis, a distance of 3 Å and an angle cut-off of 20° is used.

3. Results and discussion

3.1. Root mean square deviation (RMSD) and root mean square fluctuation (RMSF) profiles

Average RMSD results for HLA-B*44:02, HLA-B*44:03 and HLA-B*44:05 bound to three different peptides are shown in Fig. 2.

In all the simulations, structures are observed to reach equilibrium after approximately 5 ns with respect to the starting structure. The rest of the calculations were based on the equilibrium parts of the simulations. Comparisons of peptide RMSF (Cα atoms) results based on the same peptide bound to different alleles are shown in Fig. 3 together with the parallel simulation results.

Peptide P1 (EEFGRAFSF) demonstrates the highest conformational fluctuations when bound to HLA-B*44:02 (1M6O) in both simulations, when compared with other HLA-peptide complexes (Fig. 3, A). This is similar to a previous finding by (Sieker et al., 2008), where B*44:02 was observed to display higher flexibility when compared to B*44:05. For the structures bound to peptide P2 (EEYLKAWTF), all the RMSF profiles display a stable behavior without much fluctuation. On the other hand, peptide P3 (EEYLQAFTY) demonstrates slightly higher conformational fluctuations in the mid-section of the peptide when bound to HLA-B*44:03 (3KPN).

RMSF analysis of the Cα atoms on the binding groove residues (1–180) suggest that the same residues (16, 41, 56, 90, 105, 128–148 and 177) display larger fluctuating behavior in all the

Table 1
PDB accession codes for crystal structures of HLA-B*44 proteins with different bound peptides selected for the study. Related polymorphic residues are also given.

PEPTIDE	P1 EEFGRAFSF (Macdonald et al., 2002; Zernich et al., 2004)	P2 EEYLKAWTF (Macdonald et al., 2009)	P3 EEYLQAFTY (Macdonald et al., 2009)	Polymorphic residues	
ALLELE				116	156
HLA-B*44:02	1M6O	3KPM	3KPL	Asp	Asp
HLA-B*44:03	1N2R	3KPO	3KPN	Asp	Leu
HLA-B*44:05	1SYV	3KPQ	3KPP	Tyr	Asp

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