

Tuesday, November 3, 2009
2:00 PM - 3:30 PM

Abstract Session 1: HLA Peptides and Disease

2-OR

CYNOMOLGUS MACAQUE MHC CLASS I MOLECULES PRESENT HLA-A AND HLA-B LIKE PEPTIDES. Runying Tian,¹ Daryl Cox,² Danijela Mojsicovic,¹ Oriana Hawkins,¹ David Watkins,³ William Hildebrand.¹ ¹Department of Microbiology and Immunology, University of Oklahoma Health Science Center, Oklahoma City, OK, USA; ²Department of Chemistry, Southern Nazarene University, Bethany, OK, USA; ³Wisconsin Regional Primate Center, University of Wisconsin, Madison, WI, USA.

Aim: Cynomolgus macaque (*Macaca fascicularis*) is used as an alternative nonhuman primate model for studying HIV, transplantation and Vaccines due to the increasing demand and limiting number of Rhesus macaques. Understanding the nature of cynomolgus macaque MHC class I peptide-binding would shed light on Cynomolgus macaque related research.

Methods: In this study, peptide-binding motifs and endogenous peptides from eight Mafa class I molecules (Mafa-A*25, A*29, B*43, B*44, B*45, B*46, B*51 and I*10) were characterized.

Results: These data revealed that Mafa class I molecules present peptides resembling those presented by human MHC class I molecules. Four of eight mafa molecules share similar peptide-binding motifs with seven HLA-A class I molecules, whereas, the other four Mafa molecules have an overlapping peptide-binding motif with nine HLA-B molecules. Of the 149 Mafa endogenous peptide ligands sequenced by Mass Spectroscopy, 17 have been reported for HLA class I molecules.

Conclusions: It is of interest to note that Mafa class I molecules show HLA-A and HLA-B like cross-species peptide-presentation. Mafa and human class I molecules which share similar or identical peptide-binding motifs show a total polymorphism of 16-24% within $\alpha 1$ and $\alpha 2$ domain, whereas 31%-60% of those polymorphism were located in the specificity pockets. Thus, the characterization of endogenously loaded Mafa MHC class I peptides indicates that Mafa class I molecules are functionally equivalent to HLA-A and HLA-B at the individual peptide level.

3-OR

HLA AND PHARMACOGENETICS: DISSECTING THE FUNCTIONAL MECHANISM BEHIND STRONG ASSOCIATION OF HLA-B*5701 WITH ABACAVIR HYPERSENSITIVITY. Faisal Khan,^{1,2} John Gill,² Tineke Schollaardt,² Carrillo Christina,² Nouredine Berka.^{1,2} ¹Calgary Laboratory Services; ²University of Calgary, Calgary, AB, Canada.

Aim: The susceptibility to Abacavir hypersensitivity (ABH) in HIV-1 positive patients is strongly linked to the carriage of HLA-B*5701 but the precise mechanism is still been contested. Here we assess the association of HLA-B*5701 with ABH and its functional basis in a multi ethnic cohort of 404 HIV-1 positive patients.

Methods: Genotyping of HLA B*5701 allele was performed by PCR-SSP method. PBMCs from HLA-B*5701^{pos} and HLA-B*5701^{neg} individuals were stimulated with Abacavir. Multicolor flow cytometry was done to assess the cytokine (IFN γ) production and degranulation (CD107a expression) after 6-18 hrs culture and to enumerate proliferating CD4/CD8 T cells by culturing CFSE-loaded PBMCs for 7 days.

Results: HLA-B*5701 was found strongly associated with the ABH ($p < 0.0001$; OR=73.78). CD8+ T cells from HLA-B*5701+ABH+ individuals were multifunctional- proliferating, IFN γ producing, degranulating (CD107a+) and both IFN γ producing and degranulating (CD107a+) whereas CD4+ T cells were not activated when stimulated with Abacavir. Percentage of Abacavir specific proliferating, IFN γ +, CD107a+ and IFN γ +CD107a+ CD8 T cells were 10-, 5-, 8- and 15-fold higher respectively in HLA-B*5701^{pos} than HLA-B*5701^{neg} individual. All functional responses were partially blocked by addition of HLA-B*5701- reactive Bw4 mAb, but not by non-HLA-B*5701-reactive Bw6 mAb.

Conclusions: The study is the first evidence that CD8 T cell restricted multiple immune response (proliferation, cytokine production, degranulation, both degranulation and cytokine production) against Abacavir in individuals carrying HLA-B*5701 is the basis of the strong association of HLA-B*5701 with ABH.