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Poster presentation

P09-03. HLA class I alleles impact on HIV-1 disease progression by interacting with immunoregulatory HLA receptors on dendritic cells

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Background

HLA-B*35-Px subtypes are associated with accelerated HIV-1 disease courses, in contrast to HLA-B*35-PY subtypes which do not have any detectable impact on HIV-1 disease, although they differ in as few as one amino acid. The mechanisms accounting for the differential influence of HLA-B*35 subtypes on HIV-1 disease progression remain unclear. ILT4 is an inhibitory HLA class I receptor that is upregulated during HIV-1 infection and can critically regulate the functional profile of DCs.

Methods

To test whether HIV-1 CTL epitopes presented by alternative HLA-B*35 subtypes are differentially recognized by ILT4, we used recombinant HLA-B*3501 (PY) and -B*3503 (Px) tetramers refolded with two dominant B*35-restricted epitopes to stain mDC from HIV-1 infected individuals. Functional consequences of the altered recognition of these tetramers by ILT4 were performed using mix lymphocyte reaction.

Results

HLA-B*3503 complexes had significantly higher ($p = 0.01$) ILT4-mediated binding intensities to mDC, compared to the respective p/B*3501 complexes refolded with identical epitopes. Biacore experiments confirmed a significantly higher binding affinity between recombinant ILT4 and HLA-B35-Px molecules compared to HLA-B35-PY molecules. Higher recognition of the B*35-Px complexes by ILT4 led to DC dysfunction and significantly impaired the proliferation of allogeneic T cells ($p = 0.0027$) compared to B*35-PY tetramers; this effect could be reversed by si-RNA-mediated ILT4 knockdown. *Ex vivo* MLR assays showed that mDCs isolated from HIV-1 infected carriers of HLA-B*35-Px had a significantly weaker capacity for allogeneic T cell expansion compared to DCs from B*35-PY carriers ($p = 0.002$).

Conclusion

Inhibitory impulses resulting from preferential recognition of B*35-Px subtypes by ILT4 and subsequent DC dysfunction might contribute to the accelerated HIV-1 disease progression associated with HLA-B*35-Px subtypes. Differential interactions between HLA class I alleles and immunoregulatory MHC class I receptors on DCs provide a novel perspective for the understanding of how MHC class I impact HIV-1 disease progression.