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HIV control through a single nucleotide on the HLA-I locus

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Background

In correlative studies HLA class I type is consistently found to have the strongest impact on HIV disease progression. However, the exact mechanism involved is complicated by several factors; many alleles are ligands for NK cells as well as CD8 T-cells, and strong linkage disequilibrium between Class I alleles makes it difficult to distinguish the effect of individual alleles from other HLAs or from other important loci found on the HLA haplotype, such as the recently described -35 SNP.

Methods

Here we study two recently diverged HLA alleles, B*4201 and B*4202, which only differ by a single amino acid. Crucially, they occur primarily on identical Class I haplotypes and do not act as NK cell ligands. Therefore, they represent a unique opportunity to study the impact of a single HLA allele on HIV immune control not confounded by other genetic factors in a large outbred cohort (n=2,093) of C-clade infected individuals.

Results

Here we show that the amino acid change in position 9 of the HLA-B molecule, is critical for peptide binding and significantly alters the Gag CTL epitopes targeted ($P=2x10^{-}10$), measured both directly ex-vivo by ELISPOT and indirectly through CTL escape mutation ($P=2x10^{-8}$). Strikingly, HLA-B*4201 is associated with significantly lower viral load setpoint than HLA-B*4202 (P=0.02).

Conclusion

This naturally controlled experiment represents perhaps the clearest demonstration of the direct impact of particular HIV Gag specific CTL on disease control.

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