Sequence constraints and recognition by CTL of an HLA-B27-restricted HIV-1 gag epitope

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Previous studies on the variation of an immunodominant HLA-B27-restricted HIV-1 gag p24 epitope (KRWIIL GLNK, amino acids 263-272) have demonstrated the persistence of variants recognized by CTL. Sequence comparisons of HIV isolates showed that this region is relatively conserved and as a consequence might restrict antigenic variation. To evaluate the possibility of HIV-1 to yield infectious mutants of this epitope that lack the ability to bind to HLA-B27 or escape HLA-B27-restricted CTL recognition, single-point mutations were constructed in the infectious molecular clone of HIV-1 Lai. Changes of arginine 264, the anchor amino acid for HLA-B27, to lysine or glycine resulted in infectious HIV-1 variants. The respective synthetic peptides showed reduced ability to sensitize target cells for CTL recognition and a corresponding loss of binding affinity to HLA-B27. In contrast, mutation of glycine 269 to lysine or glutamate abrogated HIV-1 infectivity. The corresponding peptides were able to bind to HLA-B27 but were not recognized by CTL. These data show that HIV-1 tolerates some genetic variation of the HLA-B27-restricted CTL epitope in gag p24 and that single-point mutations can alter quantitatively the immunologic properties. Further, it demonstrates that the mere nonrecognition of peptides derived from quasispecies analysis of small regions might simply correspond to nonviable virus variants and cannot be taken as evidence for CTL escape mutants. Together with the previously published data on the persistence of CTL epitopes, these results suggest that CTL do not play a major role in driving HIV-1 evolution in vivo.