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P18-01. Exquisite specificity of CTL response to the M184V mutation

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Background

The M184V mutation confers resistance to lamivudine and emtricitabine and falls within a HLA-A2 restricted CTL epitope, RT181-189, suggesting that it could be possible to vaccinate against drug resistance. In ART naïve patients, CTL directed against this epitope recognize both the wild-type 184M peptide, and the 3TC-resistant 184V peptide, while in patients with 3TC-resistant virus it is possible to detect CTL against the 184V peptide that do not cross-react with the 184M peptide. To determine whether the 184V or the 184M peptide would be the best candidate for therapeutic vaccination, we studied the specificity and functional avidity of clones and cell lines specific for the RT181-189 epitope.

Methods

CTL lines and clones were obtained from PBMC of one ART naïve HLA-A2+ patient and two HLA-A2+ patients with lamivudine-resistant virus. Functional responses to a panel of variant peptides were studied using IFN-gamma ELISPOT.

Results

One 184M/184V cross-reactive clone and two CTL lines specific for 184V were obtained. The cross-reactive clone showed high functional avidity (EC50 100 pM) for both 184M and 184V peptides, and also recognized 184I, 184A, 184G, 184F and 184D mutant peptides. Both cell lines from patients with 3TC-resistant virus showed selectivity for 184V. Although the functional avidities of the two cell lines were lower (EC50 1 nM and 1 μM) than that found in the cross-reactive clone, they fell within the range of values observed in PBMC from HLA-A2+ ART-naïve patients showing a cross-reactive ELISPOT response to the 184M and 184V peptides.

Conclusion

The CTL response directed specifically against the 184V peptide is characterized by high selectivity, and its functional avidity is similar to that of the cross-reactive response generated against the 184M peptide.