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P09-15. Selection of higher avidity HLA-restricted T cell responses as a viral adaptation strategy

N Keane*, S Roberts, R Laird, A Chopra, T Krishnan, C Almeida, C Bronke, S Mallal, I James and M John

Address: Centre for Clinical Immunology and Biomedical Statistics, Royal Perth Hospital, Perth, Australia

* Corresponding author

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Background

Loss of immune reactivity due to HIV mutational escape is well described. Data generated from a large population-based study (n>800) suggested that certain CD8 T cell epitopes are created as a result of HIV adaptation and are associated with enhanced viral replication. Here we sought to investigate the HLA-restricted T-cell responses associated with seven such adaptations.

Methods

180 cryopreserved PBMC samples from 112 patients were assayed for IFN-γ production and functional avidity to HIV peptides in ELISpot assays. CTL lines generated from short term PBMC cultures were confirmed and phenotyped by flow cytometry and cytotoxicity was assessed by chromium release.

Results

Responses were detected to non-adapted peptides in 48 samples (327 median [68–3067] range spot forming units (SFU)/10^6 cells) and adapted peptides in 54 samples (317 [63–2332] SFU/10^6). Responses to both non- and adapted peptides were detected in 19% (35/180) of samples (480[68–2225], 638[74–2332] SFU/10^6 respectively). Overall, responses to adapted epitopes were significantly greater than responses to non-adapted epitopes in patients with detectable viral load in screening assays (n = 14, p = 0.0413, Wilcoxon Rank Sum Test) and when half maximal peptide concentration data was analysed ($p < 0.05$ paired t-test). The frequency of IFN-γ producing cells from cultured CTL restricted by HLA-C*0702-KY11 (n = 7) was higher in central memory (p = 0.03) and effector memory CD8 T cell (p = 0.02) populations from adapted epitope (KRQEILDLWVY) stimulated cultures compared with non-adapted epitope (KRQDILDLWVY) stimulated T cells. No difference in central or effector memory population size or IL-2 production was detected and preliminary data from chromium release assays suggests that CTL cultured with adapted peptides have differential killing against adapted versus non-adapted epitopes.

Conclusion

These data suggest that some high avidity and high IFN-γ-producing CD8 T cell responses are the result, rather than the cause, of viral adaptation. These data have implications for vaccine development.