HIV-1 Vif- and Nef-responses in controllers present higher magnitude and target more conserved, less promiscuous epitopes than responses seen in typical progressors

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Background: Understanding on the protective cellular immune responses seen in HIV-1-infected controller individuals has been believed to be important in order to delineate successful vaccination strategies for HIV-1 control. Here, we explore cellular immune responses against Vif and Nef in 29 HIV-1-infected subjects presenting durable control of viremia and compared them to responses seen in eight typical progressors.

Methods: ELISPOT-IFN-γ assays were carried out using 15-mer peptides, overlapping by 11 amino acid, encompassing the whole sequences of HIV-1 consensus B Vif and Nef proteins. On the 15 amino acid sequences targeted by controllers or by progressors, we characterized *i*) the intra-subtype B genetic variation, *ii*) the number of potential HLA-I *loci* A and B-restricted epitopes, and *iii*) the number HLA-I *loci* A and B molecules that potentially bind to each epitope in the 15-mer sequences by assessing *in silico* data from the Los Alamos HIV database.

Results: Collectively, our data indicate that responses mounted by controllers have same breadth of targets, but are of higher magnitude than responses presented by progressor individuals. Furthermore, after investigating more specifically the responses showed exclusively by controllers or by progressors, we observed that controllers target viral sequences more conserved and less promiscuous to HLA-I binding. Vif- and Nef-sequences targeted by controllers seem to be less exposed to cellular immunity-mediated selective pressure, as the number of HLA-I molecules that could recognize an epitope on them is lower. This is reflected by correspondent lower genetic variation we observed in these sequences.

Conclusion: These findings suggest that different amino acid sequences, in the viral proteome, are able to elicit host cellular responses with differential impact on viral control. We believe that the identification of such phenomenon provides clarification about the nature of the successful cellular responses against HIV-1, seen in controller individuals.