Assessing the Role of Antigen-Specific CD8+ T cells in Delayed Progression to AIDS

M.M. Herman[1], L.R. McKinnon[2], S. Kiazyk[3], F.A. Plummer[1,3,4], T.B. Ball[1,3,4]
[1]University of Manitoba, Medical Microbiology, Winnipeg, Canada, [2]University of Toronto, Toronto, Canada, [3]Public Health Agency of Canada, Winnipeg, Canada, [4]University of Nairobi, Institute for Tropical and Infectious Diseases, Nairobi, Kenya

Background: One major challenge in the creation of an HIV-1 vaccine is the extreme genetic diversity of the virus. It is thought that a more cross-reactive T-cell response would be beneficial in circumventing this issue. Despite this, little is known about the characteristics of these responses in nature, and many aspects of the variant-epitope CD8+ T-cell response remain poorly defined. Here, we characterize CD8+ T-cells specific to 4 immunodominant HIV-1 epitopes, and their common variants, to better understand the level of cross-reactivity between them, and how this changes over time with progression to AIDS.

Methods: PBMC samples were collected from HIV+ female commercial sex workers from Nairobi, Kenya. Samples were stimulated for 6 hours with HIV-1 Gag and Envelope peptides, and IL2, IFNy, TNF, and MIP1B were assessed via intracellular flow cytometry. Each sample was also stained with tetramers specific to each stimulating peptide to assess which cells were actively secreting the cytokines. Samples were collected from multiple time points in the same patients over 1-6 years when available.

Results: Intracellular cytokine and tetramer staining revealed that the vast majority of cytokine production was by CD8+ T cells specific to the stimulating peptide. In some cases, cross-reactivity existed between epitopes and their variants, indicating that those regions may be better targets for future therapeutic agents. IL2 production was found to be absent or very low in nearly all patients; however, it was found that IL2 production in response to PMA was primarily in a subset of $CD8^{lo}$ cells, unlike the other cytokines, which were more likely produced by the $CD8^{hi}$ population. Cytokine production varied greatly in individual patients over time during progression to AIDS.

Conclusion: Considering the ease with which HIV-1 mutates, it is important to consider how effective CD8+ T cell responses are to these common HIV variants, and how they may change as disease progresses. This study provides unique insight into not only how responses to these variants differ, but how they change throughout long-term HIV infection. A better understanding of the dynamics of these important responses will be essential in guiding future vaccine or therapeutic candidates.