Title
Low magnitude and frequency of HSV-2-specific interferon gamma-producing CD4(+) and CD8(+) T cell responses detected in HIV-1 heterosexual discordant couples

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Background: For 26 years a group of HESN women from Nairobi, Kenya who can be epidemiologically described as relatively resistant to HIV infection have provided clues towards the identification of natural correlates of protection against HIV-1 infection. Studies of these HIV-1-resistant women suggest they posses a unique mucosal environment which includes the overexpression of specific antiproteases and a unique proinflamatory cytokine expression patern. Here we describe how these factors contribute to protection against HIV infection during mucosal transmission.
Methods: Cervical lavage fluid (CVL) from 277 women were collected from 76 HIV-1-resistant, 120 HIV-1 uninfected, and 97 HIV-1 infected women. CVL protein was analyzed both independently by SELDI-TOF MS and as pooled groups by 2D-LC-FTICR MS. Of the more than 350 unique proteins identified 29 proteins were differentially expressed ($>$ 2-fold cutoff) between HIV-1-resistant women and controls. These findings were confirmed by traditional ELISA and quantitative Western Blot (WB) analysis.
Results: The majority of overexpressed proteins were serpins, their breakdown products ($p = 2.2 \times 10^{-8}$), and other antiproteases, as well as innate factors with known anti-HIV-1 activity. The overexpression of specific serpins and an epithelial-derived antiproteases was confirmed by ELISA and WB ($p = 0.004$, $p = 0.05$, and $p = 0.02$). Underexpressed proteins in HIV-resistant women included inflammatory proteases and immune response factors. Cytokine/chemokine analysis revealed that antiprotease expression correlated with pro-inflammatory cytokines ($p < 0.0001$). However, this was independent of the elevated antiprotease expression observed in HIV-resistant women who in fact expressed reduced levels of certain inflammatory chemokines ($p = 0.018$).
Conclusion: HIV-1-resistant women have elevated acute phase response antiproteases that may regulate inflammation in the female genital tract. Coupled with elevated expression of anti-viral proteins, this may provide a mucosal environment less susceptible to HIV-1. These antiproteases might contribute to a natural protective environment against HIV-1-infection. Understanding this mechanism could aid in microbicide or therapeutic development.

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Low magnitude and frequency of HSV-2-specific interferon gamma-producing CD4$^+$ and CD8$^+$ T cell responses detected in HIV-1 heterosexual discordant couples

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Background: Herpes simplex virus type 2 (HSV-2), the most frequent cause of genital ulcer disease (GUD), has been shown to play a more important role than any other sexually transmitted infections (STIs) in driving HIV prevalence in Africa. In turn, HIV-1 infection leads to more frequent HSV-2 reactivations and shedding. The exact immune mechanisms involved in this virological negative immuno-synergy are unknown. In the present study we sought to assess whether HIV co-infection would affects HSV-specific T cell immunity.
Methods: Nineteen HSV peptides, derived from HSV-2 glycoproteins gB and gD, were used to analyze the frequency and the magnitude of HSV-2-specific IFN-γ-producing CD4$^+$ and CD8$^+$ T cell responses in 30 HSV-2 seropositive patients and 17 HSV-2 seronegative individuals in a cohort of heterosexual Senegalese HIV-discordant couples, using ELISpot assay. HIV RNA viral load has been run for HIV infected subjects and CD4 count ran for all subjects using a flow cytometry method.
Results: The magnitude and frequency HSV-2-specific T cell responses was compared between 21 HSV-2 co-infected with HIV-1 and 9 HSV-2 mono-infected individuals. A significantly higher magnitude of IFN-γ-producing T cell responses were observed in HSV-2 infected patients compared to seronegative individuals (median, 61 vs. 0 spots/10^6 PBMC, $P = 0.001$). Moreover, twenty-four (80%) out of 30 HSV-2 seropositive patients showed significant HSV-2-specific IFN-γ-producing T cell responses compared with only 6 (35%) out of 17 HSV-2 negative subjects ($P < 0.001$). The HSV-2 mono-infected patients showed significantly higher magnitude of HSV-2-specific T cell responses compared to HSV/HIV co-infected patients (median, 140 vs. 42 spots/10^6 PBMC, $P = 0.024$).
Conclusion: Our finding suggest that co-infection with HIV-1 in HSV-2-infected patients might be associated with reduced HSV-2 cellular immune responses. However, the interaction between HIV and HSV-2 appears complex, and precise longitudinal studies will be required to dissect their exact temporal relationship.

A10 - Mucosal immunity/defenses: responses and dysfunction

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Oral serum-derived bovine immunoglobulin (SBI) administration leads to duodenal gastrointestinal-associated lymphoid tissue (GALT) CD4$^+$ T-lymphocyte increases and improved small intestinal absorption function in an 8-week pilot study in patients with HIV-enteropathy

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Background: HIV-infection leads to GALT CD4$^+$ T-cell depletion that persists despite prolonged antiretroviral therapy (ART). SBI is a medical food that neutralizes bacterial antigens and reduces gut inflammation in animal models.