Abstract

Background: The primary receptive portals of entry for HIV are through mucosal surfaces. Our previous studies show that HIVexposed uninfected individuals (HESN) have unique innate responses associated with resistance to HIV infection, including increased anti-viral antiprotease expression coupled with a reduced immune activation phenotype. However, we do not know whether this immune state is static or induced upon viral exposure. To answer this question we challenged HESN women with a live attenuated Flumist vaccine and analyzed their mucosal and systemic immune responses using a systems biology approach.
Methods: HESN women (n = 10) and HIV-susceptible controls (n = 10) were challenged with an intranasal Flumist vaccine, and clinical samples (cervicovaginal lavage (CVL), plasma) were collected at Day 0, 1, 7 post-challenge. Mucosal/plasma were analyzed by a combination of label-free tandem mass spectrometry, hierarchical clustering, and pathway analysis.
Results: HESN women exhibited significant changes both mucosally and systemically upon vaccine challenge 1 and 7 days post-exposure. Of the > 450 proteins identified in CVL, 62 were overexpressed ($p < 0.05$), and 48 overexpressed in plasma (of 220 proteins) ($p < 0.05$), over that of controls. Expression profiles showed significant correlations between compartments. Hierarchical clustering identified two major functional pathways distinguishing HESN individuals, including the acute phase and LXR-RXR response pathways ($p < 1 \cdot 10–17$). Many of these factors include antiproteases (serpins), apolipoproteins, complement components, and SAA proteins which have known inhibitory properties against HIV.
Conclusion: As the acute phase response pathway has been implicated as important for controlling inflammation and early stage viremia in HIV-infected individuals, overexpression of this pathway supports the hypothesis that these factors are contributing to reduced susceptibility to infection. Understanding the role of these pathways in mucosal susceptibility to HIV may help guide existing microbicide/vaccine strategies against HIV.