Innate Immune Reconstitution With Viral Suppression in HIV-1 Infection

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Background: HIV-1 infection leads to both marked immunodeficiency and to dysregulated immune activation and inflammation. Given the broad nature of immune dysfunction and pathogen susceptibility, we hypothesized that HIV-1 viremia would alter innate immune responses, the fundamental mediators of pathogen recognition. Using longitudinal samples collected before and after initiation of antiretroviral therapy (ART), we tested the capacity of myeloid dendritic cells (mDCs) and monocytes to respond to a panel of innate stimuli. We combined these direct measures of ex vivo cellular responses with measures of T cell activation and plasma inflammatory markers to elucidate the inflammatory environment and viral parameters associated with impaired innate immune function.

Methodology: Pre and multiple post-ART peripheral blood mononuclear cell (PBMC) samples were selected for 8 subjects identified in early HIV-1 infection. Cells were stimulated with heat killed Listeria monocytogenes (HKLM, TLR2 agonist), lipopolysaccharide (LPS, TLR4 agonist), or N-muramyl glycopeptide (NOD agonist), and stained for intracellular cytokine production (TNF-alpha, IL-1beta, IL-23) after 20 hours of culture. Matched plasma samples were tested for levels of LPS, soluble CD163 and CD14, and a panel of inflammatory cytokines.

Results: Declining viral load was correlated with increasing magnitude of monocyte and mDC response to LPS stimulation (% TNF alpha+; repeated measures analysis: p<0.01 for both cell types, rank correlations = -0.57 and -0.54). Responses also negatively correlated with CD8 T cell activation level (p<0.01) but were not related to CD4 count. Exploratory analyses indicate similar associations of declining viral load with increasing TNF alpha and IL-1beta responses to TLR2 agonists, and IL-1beta responses to NOD stimulation. Suppression of HIV-1 was associated with an increase in polyfunctional responses by monocytes and mDCs to LPS, NOD, and HKLM. Plasma viral load had the strongest association to innate cell function, although paired analysis of plasma samples revealed trends towards association between increasing magnitude of innate response and declining sCD163, sCD14 and LPS.

Conclusions: Suppression of HIV-1 viral load with ART was associated with increased innate immune cell responsiveness in longitudinal samples. Depressed innate immune function was most strongly tied to high viral load and T cell activation, possibly suggesting an innate exhaustion in HIV-1 viremia parallel to that seen in adaptive immunity. Identifying the drivers of innate immune dysfunction offers important insights into the determinants of HIV-1-associated immune deficiency and may help to identify patients at risk for immune reconstitution inflammatory syndrome following ART.