Lymph Node Dendritic cells harbor an altered transcriptomic profile despite years of suppressive ART

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BACKGROUND

Despite significant advances in the efficacy of antiretroviral therapy (ART) and expanded access to people living with HIV, virologic suppression through ART alone is frequently insufficient to fully resolve the immune activation associated with HIV infection.

METHODS

We evaluated the influence of HIV infection on the functional and transcriptomic profile of lymph node (LN) myeloid dendritic cells (DCs) subsets during both chronic infection and after >5 years of suppressive ART by single-cell RNAsequencing (scRNAseq).

RESULTS

The cumulative data indicated that LN DC frequencies correlated with plasma viral load (r=0.875; P<0.05; N=10). LN DCs from viremic individuals harbored an immunostimulatory profile with the ability to secrete pro-inflammatory cytokines (IL-1β, IL-6), higher expression of co-stimulatory molecules (CD40, CD83, CD86) and were more potent stimulators of allogeneic CD4 T cell proliferation ex vivo (N=3; P<0.05) as compared to uninfected individuals. In-depth analyses of LN DC transcriptomic profile by scRNAseq further supported a specific and distinct transcriptomic profile of LN DCs during chronic infection associated with higher DC activation, Type I IFN and Type II IFN production, interferon-stimulated gene (ISG) signature, and activation of key STAT molecules (N=6). Interestingly, 18-26% of LN DCs from viremic individuals harbored detectable HIV transcripts. Notably, the comparison of HIV transcript+ versus HIV transcript- analyses further supported the enhanced expression of pathways involved in immune activation. While HIV transcripts were not detected after suppressive ART, LN DC gene expression profile still harbored markers associated with inflammation and immune activation (IL-1β-signaling, TNFα-signaling, NF-κB activation), while several genes involved in antigen processing and presentation were downregulated. The involvement of epigenetic modifications in this specific profile remains to be determined.

Lymph Node DC Activation: Implications for Inflammation and Low-Level HIV Viral Production during ART

Figure 1:To investigate the influence of HIV infection on the phenotypic heterogeneity of DC subsets across human tissues

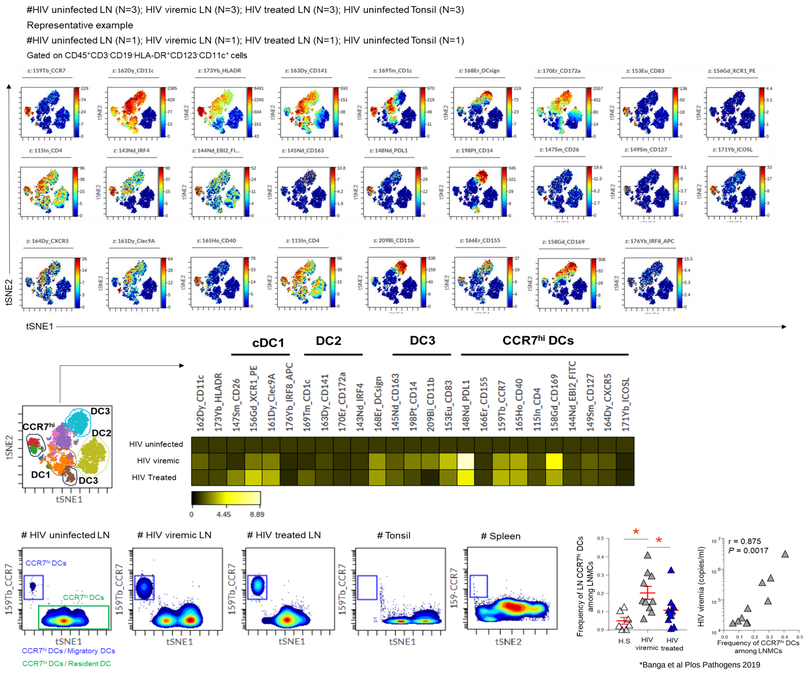


Figure 2: LN DCs from viremic individuals harbor an immunostimulatory profile

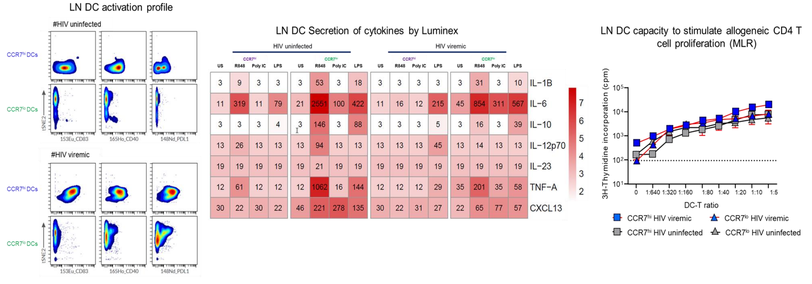
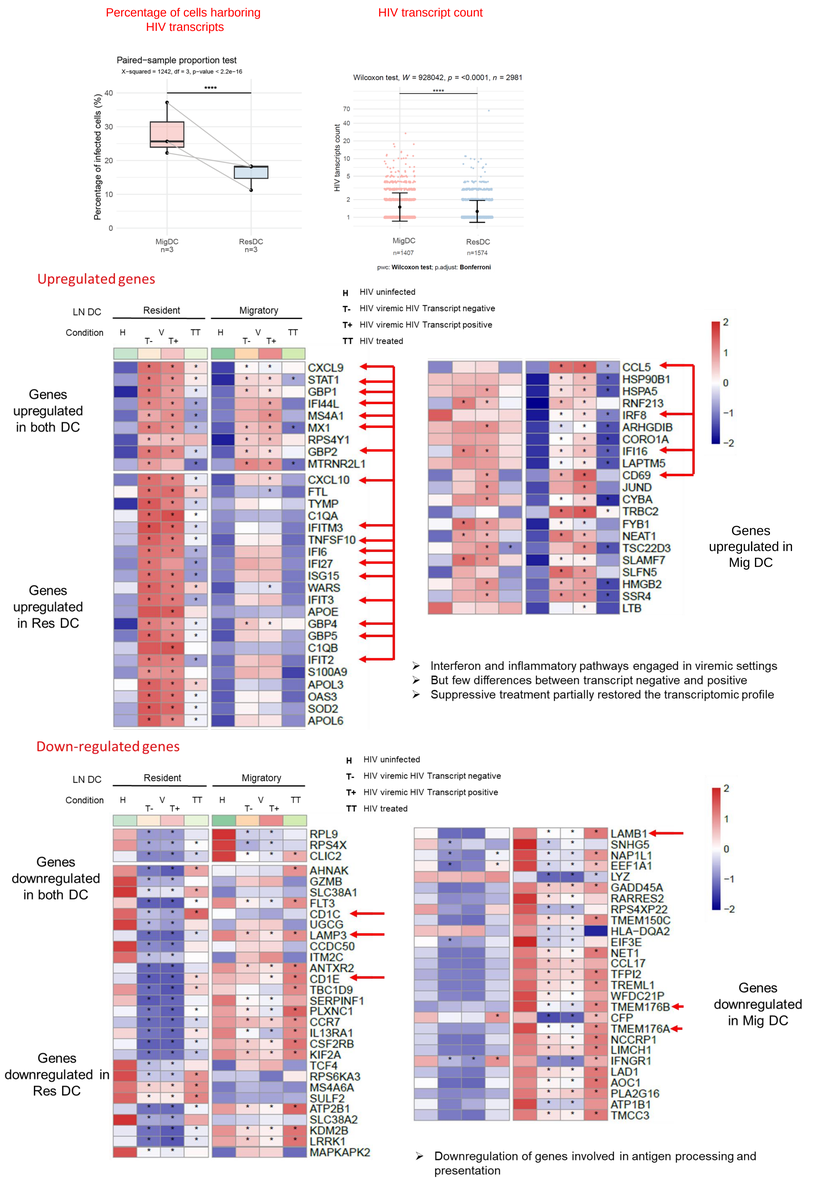


Figure 3: LN DCs harbor a specific and distinct transcriptomic profile during chronic HIV infection



CONCLUSIONS: HIV infection is associated with qualitative and quantitative changes in LN DC transcriptomic, phenotypic, functional profile. HIV-infected LN DCs harbor a specific gene signature associated with inflammation and immune activation, which is only partially restored after suppressive ART.