CHARACTERISING THE RESPONSES OF 'BONA-FIDE' PLASMACYTOID AND AXL$^+$ SIGLEC6$^+$ DENDRITIC CELLS IN INITIAL HIV INFECTION

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Background:
At mucosal sites of initial HIV infection, type I interferons (IFNs) such as IFN-α/β represent a potent first line of innate immunity, and are produced by a subset of dendritic cell (DC) called plasmacytoid dendritic cells (pDCs). However, previous reports examining pDC responses to HIV have included contaminating Axl$^+$ Siglec6$^+$ (AS)DCs, a recently described myeloid DC that expresses classical pDC markers. As such, the role that pDCs and ASDCs play during initial HIV infection, and how IFNs and other soluble factors produced by these DC subsets mediate these effects remains ambiguous.

Methods:
Sorted 'bona-fide' pDCs and ASDCs were exposed to HIV-1_{BaL} for 18 hours, upon which gene expression was assessed in cell lysates using the nCounter® Human Immunology Codeset on the Nanostring XT Analysis System. The presence of pDCs and ASDCs in human anogenital tissues was also assessed using flow cytometry.

Results:
'Bona-fide' pDCs and ASDCs had distinct gene expression profiles both in mock-infected controls, and following HIV exposure. *IFNA/B* was strongly induced in pDCs alone. The proinflammatory cytokines *IL1B* and *IL15* were expressed in ASDCs only, whilst *TNF* and *IL32* were induced in both pDCs and ASDCs. Chemokines involved in CD4$^+$ T cell recruitment, namely *CCL3-5*, *CXCL10-11* and *CCL22*, were also upregulated in both cell types. In addition, 'bona-fide' pDCs (Axl$^-$ CD123$^+$) and ASDCs (Axl$^+$ Siglec6$^+$) were identified in inflamed rectal samples (n=2) and could be resolved as distinct populations by t-SNE analysis.

Conclusion:
Both 'bona-fide' pDCs and ASDCs have multifaceted responses to HIV – although pDCs remain the predominant IFN-producing cell, both cells produce proinflammatory mediators that may enhance infection in CD4$^+$ T cells. Our data also demonstrates for the first time that both pDCs and ASDCs can be recruited to peripheral tissues, and are therefore likely to influence HIV infection in target cells and ultimately, HIV acquisition.

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