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OA011-05. TLR-mediated pDC responses to HIV-1 ligands

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Background

Comparisons of HIV-1 disease between women and men have demonstrated that given the same viral load, measured early in HIV-1 infection, the time to AIDS progression is faster in women than in men. There is increasing consensus that faster disease progression is associated with elevated immune activation and this is consistent with our recent findings that women have higher immune activation than men given the same HIV-1 viral load. Plasmacytoid dendritic cells (pDCs) appear to play a central role in this HIV-1-induced activation of the immune system, as they can sense HIV-1 ssRNA via Toll-like receptor (TLR) 7 and produce proinflammatory cytokines.

Methods

PBMC from HIV-1-negative subjects enrolled at Massachusetts General Hospital were stimulated with HIV-1 derived TLR7/8 ligands and cytokine secretion by pDCs, mDCs and monocytes as well as T-cell activation were measured by flow cytometry. Polymorphisms of genes encoding for TLR7 and its downstream molecules were also examined to determine how these affect the resulting immune response.

Results

pDCs derived from women produce significantly more IFN- α in response to HIV-1 derived TLR7/8 ligand stimulation than pDCs derived from men ($p < 0.05$). Furthermore, HIV-1 derived TLR7/8 ligands resulted in a significant up-regulation of CD38⁺ CD8⁺ T-cells *in vitro* and this TLR7/8-induced T-cell activation was also higher in

women compared to men ($p < 0.05$). Polymorphisms in genes encoding for TLR7 and its downstream signaling molecules modulated the IFN- α production by pDCs following stimulation with HIV-1 derived TLR7/8 ligands.

Conclusion

These data show that sex differences in TLR-mediated activation of pDCs might account for the described higher immune activation in HIV-1-infected women compared to men at a given viral load and subsequently faster HIV-1 disease progression in women. The data further suggest that polymorphisms within TLR genes can modulate TLR-induced cytokine production which may have implications for adjuvant use in HIV-1 vaccine design.