VIRAL IMMUNITY

Are men and women different?

> “…the percentage of activated CD8$^+$ T cells was significantly higher in women than men…”

It is well documented that there are considerable differences in HIV-1 disease progression between men and women, with women progressing significantly faster to AIDS than men with the same viral load. Meier *et al.* now show that this might be partially due to differential immune responses by plasmacytoid dendritic cells (pDCs) in the two sexes.

pDCs are thought to be key players in immune activation, as they sense viral RNA using pathogen recognition receptors (including Toll-like receptor 7 (TLR7)) and subsequently secrete cytokines, such as interferon-α (IFNα) and tumour necrosis factor. Immune activation is thought to strongly predict HIV-1 disease progression, so the authors investigated cytokine secretion by pDCs following stimulation with different HIV-1-derived ligands *in vitro*. Interestingly, pDCs derived from women produced more IFNα when stimulated with TLR7 ligands than pDCs derived from men, indicating that there are important sex differences in cytokine secretion induced by HIV-1 infection.

IFNα secretion has been shown to upregulate the expression of CD38 by CD8$^+$ T cells, which is an important predictor of disease progression. Consistent with this, the levels of CD38 expression by CD8$^+$ T cells following pDC stimulation by HIV-1-derived TLR7 ligands were significantly higher in women than in men. This was partially mediated by IFNα secretion, as the percentage of CD38$^+$CD8$^+$ T cells was reduced in the presence of a blocking antibody that was specific for the IFNα receptors.

Finally, to investigate whether their observations also applied *ex vivo*, the authors examined the levels of T cell activation (based on CD38 and HLA-DR expression) in chronically infected men and women who had not previously received HIV-1 treatment. Indeed, after adjusting for baseline viral load, the percentage of activated CD8$^+$ T cells was significantly higher in women than in men.

Taken together, these findings show that pDCs produce more IFNα in response to HIV-1 in women than in men, which leads to higher levels of CD8$^+$ T cell activation. The authors propose that this enhanced immune activation might account for the more rapid disease progression with the same level of HIV-1 replication that is observed in women, and suggest that modulation of the TLR7 signalling pathway might be a promising therapeutic avenue.

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ORIGINAL RESEARCH PAPER Meier, A. *et al.* Sex differences in the Toll-like receptor–mediated response of plasmacytoid dendritic cells to HIV-1. *Nature Med.* 13 Jul 2009 (doi:10.1038/nm.2004)