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Study may explain why HIV progresses faster in women than in men with same viral load

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One of the continuing mysteries of the HIV/AIDS epidemic is why women usually develop lower viral levels than men following acute HIV-1 infection but progress faster to AIDS than men with similar viral loads. Now a research team based at the Ragon Institute of Massachusetts General Hospital (MGH), MIT and Harvard has found that a receptor molecule involved in the first-line recognition of HIV-1 responds to the virus differently in women, leading to subsequent differences in chronic T cell activation, a known predictor of disease progression. Their paper, which will be published in an upcoming issue of *Nature Medicine*, is receiving early online release.

"This study may help to account for reported gender differences in HIV-1 disease progression by demonstrating that women and men differ in the way their immune systems respond to the virus," says Marcus Altfeld, MD, PhD, of the Ragon Institute and the MGH Division of Infectious Disease, the study's senior author. "Focusing on immune activation separately from viral replication might give us new therapeutic approaches to limiting HIV-1-induced pathology."

It has become apparent in recent years that HIV-1-infected patients with a high level of immune activation progress to AIDS more rapidly. Why this happens is an area of intense investigation. To explore whether gender-based differences in immune activation were responsible for faster disease progression in women, the Ragon Institute team and their collaborators focused on plasmacytoid dendritic cells (pDCs), among the first cells of the immune system to respond to HIV-1 and other viral

pathogens. Earlier studies indicated that pDCs recognize HIV-1 using a receptor called Toll-like receptor 7 (TLR7), leading to production of interferon-alpha and other important immune system molecules.

After initial in vitro experiments showed that a higher percentage of pDCs from uninfected women produced interferon-alpha in response to TLR7 stimulation by HIV-1 than did cells from uninfected men, the researchers examined whether women's hormone levels had any effect on pDC activation. Supporting previous evidence that progesterone may modulate pDC activity, the researchers found that pDCs from postmenopausal women produced levels of interferon-alpha in response to HIV-1 that were closer to levels observed in men. They also found that, in premenopausal women, higher progesterone levels correlated with increased activation of pDCs in response to HIV-1.

Since it is known that the activation of T cells predicts the progression of HIV-1 infection to AIDS, the research team conducted a series of in vitro experiments showing that the stimulation of pDCs in response to HIV-1 led to the subsequent activation of CD8+ T cells by means of interferon-alpha secretion. They then tested blood samples taken from a group of chronically HIV-1-infected women and men prior to treatment initiation and confirmed that women had higher levels of CD8+ T cell activation than did men with the same blood levels of HIV-1.

"Taken together, these results support a model in which the same amount of virus induces stronger pDC activation in women than in men. While stronger activation of the immune system might be beneficial in the early stages of infection, resulting in lower levels of HIV-1 replication, persistent viral replication and stronger chronic immune activation can lead to the faster progression to AIDS that has been seen in women," Altfeld explains.

He adds that the study's results raise a number of important new

questions, including exactly how sex hormones modulate the TLR7-mediated response of pDCs to HIV-1 and whether anti-TLR agents may help reduce immune activation in chronic HIV-1 infection. His team is beginning preliminary laboratory studies of the ability of TLR antagonists to reduce HIV-1-induced activation of pDCs.

Source: Massachusetts General Hospital (news : web)