Cellular and molecular events that restrict HIV transmission identified

July 1 2010

Researchers from Boston University School of Medicine (BUSM) have identified two molecules that when activated by drugs, can inhibit a number of specific aspects of HIV transmission. These findings, published July 1 in the open-access journal *PLoS Pathogens*, may lead to therapies that target mucosal HIV transmission.

Worldwide, heterosexual transmission accounts for most new HIV infections, with a majority of these occurring in developing countries. Immune cells within the vaginal, cervical, or rectal mucosa are thought to be the primary targets of infection in the sexual transmission of HIV.

According to the authors, dendritic cells (DCs) that reside in mucosal tissues play a critical role in HIV transmission. They can efficiently capture viruses, migrate to lymph nodes, and there, in a process called trans-infection, transmit virus to T cells, the main cell supporting virus replication. In addition, DCs can promote mucosal inflammation that helps to create a favorable environment for virus replication.

Certain members of the nuclear receptor family of gene regulators, including PPARγ and LXR, have been shown to be potent inhibitors of inflammation. The BUSM researchers therefore sought to determine whether drugs that activate PPARγ and LXR could inhibit steps in HIV transmission. To do so, they isolated DCs and T cells from blood and examined the effects of PPARγ and LXR activation on HIV transmission.

The researchers report that drugs that activate PPARγ and LXR inhibit the ability of DCs to capture HIV and transfer it to T cells. In addition, these same drugs were shown to inhibit inflammation that can be induced in response to bacterial infections such as Neisseria gonorrhoeae, which is known to increase the incidence of sexual transmission of HIV.

"Most importantly, we found that these drugs inhibited DC-mediated trans-infection up to 5-fold, underscoring their potential to limit HIV transmission," said senior author Gregory Viglianti, PhD, an associate professor of microbiology at BUSM.

"In the absence of an effective vaccine, there is an increasing demand for the development of effective microbicides that block HIV sexual transmission. Our studies suggest that PPARγ and LXR may be targets for drugs that can simultaneously inhibit a number of aspects of HIV mucosal transmission, including inflammation, DC migration and DC-mediated HIV dissemination. Our findings therefore, provide a rationale for combining drugs that target PPARγ and LXR with conventional anti-viral microbicides that target other aspects of mucosal HIV transmission," he added.

More information: Hanley TM, Blay Puryear W, Gummuluru S, Viglianti GA (2010) PPARc and LXR Signaling Inhibit Dendritic Cell-Mediated HIV-1 Capture and trans-Infection. PLoS Pathog 6(7): e1000981. doi:10.1371/journal.ppat.1000981