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Semen ingredient 'drastically' enhances HIV infection

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A plentiful ingredient found in human semen drastically enhances the ability of the human immunodeficiency virus (HIV) to cause infection, according to a report in the December 14, 2007, issue of the journal *Cell*, a publication of Cell Press. The findings help to understand the sexual transmission of HIV and suggest a potential new target for preventing the spread of AIDS, the researchers said.

Collaborating research groups in Hannover and Ulm, Germany, show that naturally occurring fragments of so-called prostatic acidic phosphatase (PAP) isolated from human semen form tiny fibers known as amyloid fibrils. Those fibrils capture HIV particles and help them to penetrate target cells, thereby enhancing the infection rate by up to several orders of magnitude.

"We were not expecting to find an enhancer, and were even more surprised about the strength," said Frank Kirchhoff of the University Clinic of Ulm, noting that they were initially looking for factors in semen that might help to block HIV infection. "Most enhancers have maybe a two- or three-fold effect, but here the effect was amazing—more than 50-fold and, under certain conditions, more than 100,000-fold. At first, I didn't believe it, but we ran the experiment over and over, always with the same result."

"The fibrils act like a ferry," said Wolf-Georg Forssmann of VIRO PharmaCeuticals GmbH & Co. KG and Hannover Medical School. "They pick the viruses up and then bring them to the cell."

HIV-1, the causative agent of AIDS, has infected about 60 million people and caused over 20 million deaths, the researchers said. More than 90 percent of those HIV-1 infections are acquired through sexual intercourse. Globally, most infections result from genital exposure to the semen of HIV-positive men, earlier studies showed. Women who acquired HIV-1 through vaginal intercourse constitute almost 60 percent of new infections in Africa. Yet the factors influencing the infectiousness of HIV in semen are poorly understood.

To identify natural agents that might play a role in sexual transmission of HIV/AIDS in the new study, the researchers sifted through a complex peptide/protein library derived from human seminal fluid in search of novel inhibitors and/or enhancers of HIV infection.

That comprehensive search turned up PAP fragments as a potent enhancer of HIV infection. They then verified that synthetic PAP fragments also enhanced HIV, confirming it as the active ingredient. Interestingly, they found that individual PAP fragments are inactive but efficiently form amyloid fibrils, which they call Semen-derived Enhancer of Virus Infection or SEVI, that enhance HIV-1 infection by capturing virions and promoting their physical interaction and fusion with target cells.

The enhancing activity of SEVI is most pronounced when the levels of infectious virus are low, resembling the conditions of sexual HIV-1 transmission, they reported. Physiological concentrations of SEVI amplified HIV infection of immune cells known as T cells and macrophages, most likely the cell types first targeted by HIV-1. SEVI lowered the amount of virus required to infect tissue taken from human tonsils and significantly enhanced the viral infection of transgenic rats with human receptors for HIV-1 infection.

The researchers said they will continue to explore SEVI's role in HIV

transmission. While the peptide that conglomerates into fibrils is always present in large quantities in semen, they don't yet know if the absolute levels vary from man to man. "We also plan to further explore how exactly the fibrils allow the virus to enter cells and to search for compounds, with our technology, that might block the process," Forssmann said.

If such inhibitors can be found, they might be added to microbicide gels now under development for HIV prevention, added Kirchhoff. There could also be other ways to take advantage of the fibrils. "The high potency of SEVI in promoting viral infection together with its relatively low cytotoxicity suggests that it may not only play a relevant role in sexual HIV transmission, but could also help to improve vaccine approaches and gene delivery by lentiviral vectors," the researchers said.

Source: Cell Press