Targeting amyloid to stop HIV

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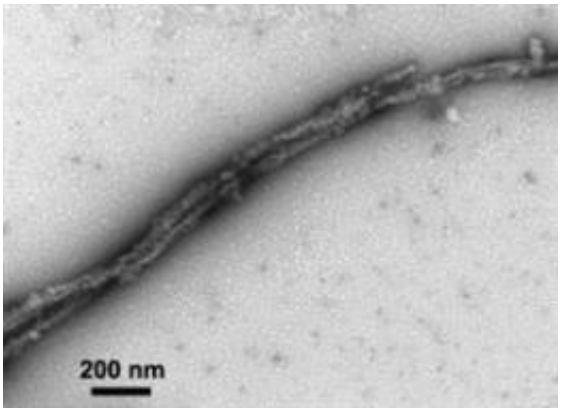

Electron micrograph of a SEVI amyloid structure

(PhysOrg.com) -- Amyloid protein structures are best known for the troubles they pose in the brains of Alzheimer's patients. Now researchers are trying to exploit their presence in a very different place - in semen - to find a new way to stop HIV.

Scientists have created a substance that targets amyloid structures in semen and have used it to weaken the ability of HIV to infect the body's immune cells in the laboratory. The experimental compound, originally designed to help Alzheimer's patients by disrupting the actions of amyloid in the brain, make it much more likely that HIV particles will simply slide past human immune cells instead of gaining a foothold for infection during sexual intercourse

The work by scientists at the University of Rochester Medical Center, in

collaboration with chemists at the University of California at San Diego, offers a new lead in the effort to develop a microbicide to prevent HIV transmission from one person to another. The findings were published online recently in the Journal of Biological Chemistry.

The focus of the work is an amyloid structure that was discovered in semen three years ago by German researchers. The structure, known as SEVI for Semen-derived Enhancer of Viral Infection, enhances infection by sticking both to HIV particles and to the immune cells that HIV infects. It's a middle man in the infection process - one that researchers believe is a powerful driver of HIV's ability to infect a person during heterosexual intercourse. SEVI has offered a new target to researchers trying to stop the virus.

"HIV viral particles are tiny and adrift amid a sea of semen and cervical mucus during sexual intercourse," said Stephen Dewhurst, Ph.D., the microbiologist who heads the team. "The virus must sink quickly in this fluid to have the opportunity to contact the cells that it infects.That's what SEVI allows it to do - to literally stick around."

So Dewhurst teamed with Jerry Yang, Ph.D., a chemist at UCSD who previously created a compound designed to minimize the harmful interactions of amyloid with other proteins and lipids in the brain. Yang created a molecule called BTA-EG6 which fits in between the individual small proteins that cluster to form SEVI and blocks SEVI's interactions with both the virus and the target immune cells. One key to the chemistry is the compound ethylene glycol - the central component of anti-freeze - which makes it particularly difficult for SEVI to stick to the virus or to cells.

"The compound drives a wedge between SEVI and both HIV particles and human cells, making it difficult for SEVI to interact with either. It's like surrounding SEVI with air bags so it can't bring HIV and the body's

cells together," said Dewhurst. "Jerry Yang is the one who came up with this, and it's ingenious."

In experiments led by first author Joanna Touger Olsen, an M.D./Ph.D. student in the Dewhurst laboratory, the presence of SEVI boosted the ability of HIV to infect cells dramatically, roughly three to six times what it was without SEVI. When the non-stick compound was added, that advantage was muted, and rates of infection dropped nearly to levels when SEVI was absent. The investigators say the results must be interpreted cautiously, though, as the influence of factors such as the strain of HIV and the human cell line used in the study need to be looked at further.

"Other scientists have tried to lower the rate of HIV infection by targeting the virus or the cells it infects," said Yang. "What we do is target the mediator between the virus and the cells. By neutralizing SEVI, we prevent at least one way for HIV to attach to the cells."

The findings come on the heels of work announced by other researchers this summer about a microbicide based on the anti-retroviral agent tenofovir. That compound, when applied by women before and after sex, reduced their risk of contracting HIV by 39 percent.

"Recent studies have shown for the first time that a topical microbicide gel can protect women from HIV-1 infection," said Dewhurst. "This is a huge step forward but not a perfect solution. We need to figure out ways to further improve protection - and our studies suggest one way of doing so. It may be possible to produce a next-generation microbicide that includes both an antiviral agent, as has been used in the past, and an agent that targets SEVI. We're very excited about exploring this idea."

Yang's molecule offers an advantage over most microbicides under study: It doesn't cause inflammation in cervical cells. That's a particular

advantage because the cells that drive such inflammation are among precisely the cells that HIV infects.

Provided by University of Rochester Medical Center