An atomic-level look at an HIV accomplice

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(PhysOrg.com) -- Since the discovery in 2007 that a component of human semen called SEVI boosts infectivity of the virus that causes AIDS, researchers have been trying to learn more about SEVI and how it works, in hopes of thwarting its infection-promoting activity.

Now, scientists at the University of Michigan have determined the atomic-level, three-dimensional structure of a SEVI precursor known as PAP248-286 and discovered how it damages cell membranes to make them more vulnerable to infection with HIV. The work is described in two new papers. The most recent, describing the structure, was published online Nov. 17 in the Journal of the American Chemical Society. The paper describing how PAP248-286 interacts with cell membranes appeared in the Nov. 4 issue of *Biophysical Journal*.

PAP248-286 is a peptide---a chain of amino acids not long enough to be considered a protein. Individual PAP248-286 peptides have a tendency to clump together to form amyloid fibers called SEVI (semen enhancer of viral infection). Amyloid fibers are of great interest because they are the calling cards of many neurodegenerative diseases, such as Alzheimer's and Parkinson's, and aging-related diseases like type-2 diabetes. Using NMR (nuclear magnetic resonance) spectroscopy, a technique that not only yields atomic-level details of a molecule's structure, but also shows how the molecule nestles into the membrane with which it interacts, researcher Ayyalusamy Ramamoorthy and coworkers found that the structure of PAP248-286 is unlike that of most other amyloid-forming peptides and proteins.

In solution, SEVI is completely unstructured or has no definite shape and is therefore ineffective. On the other hand, "when bound to the membrane, it's in a spaghetti-like arrangement---a disorganized, loose coil," said Ramamoorthy, a professor of chemistry and of biophysics. In contrast, most other amyloid proteins assume a more ordered, helical configuration. Also unlike other amyloid peptides, SEVI does not penetrate deep into the greasy region of the cell membrane, but is located near the surface. Ramamoorthy and coauthors believe the spread-out, disordered configuration and its location in the cell membrane may explain the ability of SEVI fibers to enhance HIV infection, as the arrangement provides more surface area with which the virus can interact.

A key finding of the second study is that PAP248-286 "shocks" the membrane, inducing a structural change---a kind of dimple that allows HIV to attach to and enter the cell.

Next, Ramamoorthy and colleagues hope to discern more structural details of PAP248-286 and SEVI. They also plan to screen antioxidant compounds such as green tea extract, curcumin and resveratrol (found in red wine) to see if such compounds are capable of blocking SEVI's HIV-enhancing activity.

More information:

• *Journal of the American Chemical Society* paper, "NMR Structure in a Membrane Environment Reveals Putative Amyloidogenic Regions of the SEVI Precursor Peptide PAP248-286 ": pubs.acs.org/doi/abs/10.1021/ja908170s?prevSearch=%255Btitle%253A%2BNMR%2BStructure%2Bin%2Ba%2BMembrane%2BEnvironment%2BReveals%2BPutative%255D

• Biophysical Journal paper, "Helical Conformation of the SEVI

Precursor Peptide PAP248-286, a Dramatic Enhancer of HIV Infectivity, Promotes Lipid Aggregation and Fusion": www.cell.com/biophysj/abstract/S0006-3495%2809%2901394-0

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