First atomic-scale view of interaction between HIV capsid and host protein cyclophilin A

A new study offers the first atomic-scale view of an interaction between the protein coat that shepherds HIV into the nucleus of human cells - a protein known as cyclophilin A. This interaction is key to HIV infection, research shows.

A paper describing the research appears in the journal *Nature*.

Cyclophilin A is found in most tissues of the human body, where it plays a role in inflammatory response, immunity and the folding and trafficking of other proteins. When it fails to work properly or is overproduced in cells, cyclophilin A causes diseases such as rheumatoid arthritis, asthma, cancer and cardiovascular disease, and facilitates some viral infections, including HIV.

"We have known for some time that cyclophilin A plays a role in HIV infection," University of Illinois physics professor Klaus Schulten, who led the new study, said. "But we didn't know how the virus hijacked this cellular protein to its advantage."

Schulten, who is also a respondent, said there are several implications for the study. One is that cyclophilin A could be a therapeutic target for HIV. Another is that cyclophilin A can serve as a general model for understanding how viruses hijack other cellular proteins and might serve as a general model for understanding how viruses hijack other cellular proteins.

The HIV capsid somehow tricks this cellular protein into providing cover for the virus as the capsid transits through the cell and makes its way to the nucleus, Schulten said. The capsid interacts with a nuclear pore that offers an entrance to the cell's interior, and the virus uses the pore as a channel to inject its genetic material into the cell.
Studies in cell culture have found that the virus ran cyclophilin disguise. Drugs that interfere with cyclophilin are known to reduce HIV replication in culture. Such drugs cannot be used in human HIV patients because they interfere with the immune response.

In the new study, the researchers used a massive computer model of the interaction of cyclophilin and the HIV capsid, which they developed in a 2013 study. Building this model required simulating the interactions of 64 million atoms, a feat that required the use of a supercomputer at the National Center for Supercomputing Applications.

For the new study, the team used Blue Waters as well as the Titan supercomputer at the Oak Ridge National Laboratory to simulate the interactions between cyclophilin and the HIV capsid. The 3-D structure of cyclophilin A was known from previous investigations.

"We knew every atom of the underlying capsid, and then we put the cyclophilin on top of that, of which we also knew every atom," Schulten said.

The simulations revealed that cyclophilin A binds to the capsid in two ways. First, there is the "classic" binding site, one revealed decades earlier in crystallography studies. But in some places, a single cyclophilin A protein also bound the capsid at a second site, forming a bridge between two hexamers. (The HIV capsid is made up of a lattice of protein hexamers and pentamers.) Cyclophilin's bridging behavior occurred only in highly curved capsids, the researchers found.

Further research with NMR spectroscopy, which can detect unique chemical fingerprints, corroborated the existence of a second binding site.

By varying the amount of cyclophilin A added to the virus, the researchers also saw that cyclophilin did not completely coat the HIV capsid. At low concentrations, individual cyclophilin molecules attached to the capsid in some places, disrupting their ability to bind. At high concentrations, the virus could not infect cells.

"What we think is happening is, where there is no cyclophilin the capsid can be recognized and trigger a process that destroys the virus," Perkins said. "But if the capsid is fully occupied by cyclophilin A, it prevents this complex. So there is an optimal amount of cyclophilin..."
allows the HIV infection to go forward."

"The HIV capsid has to show some of its surface to docks there properly and can inject its genetic mat: "Now, we understand a little bit better the HIV viru: defenses. That gives insight into battling the syster

**Source:**
University of Illinois at Urbana-Champaign

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