Research reveals details of how HIV becomes infectious

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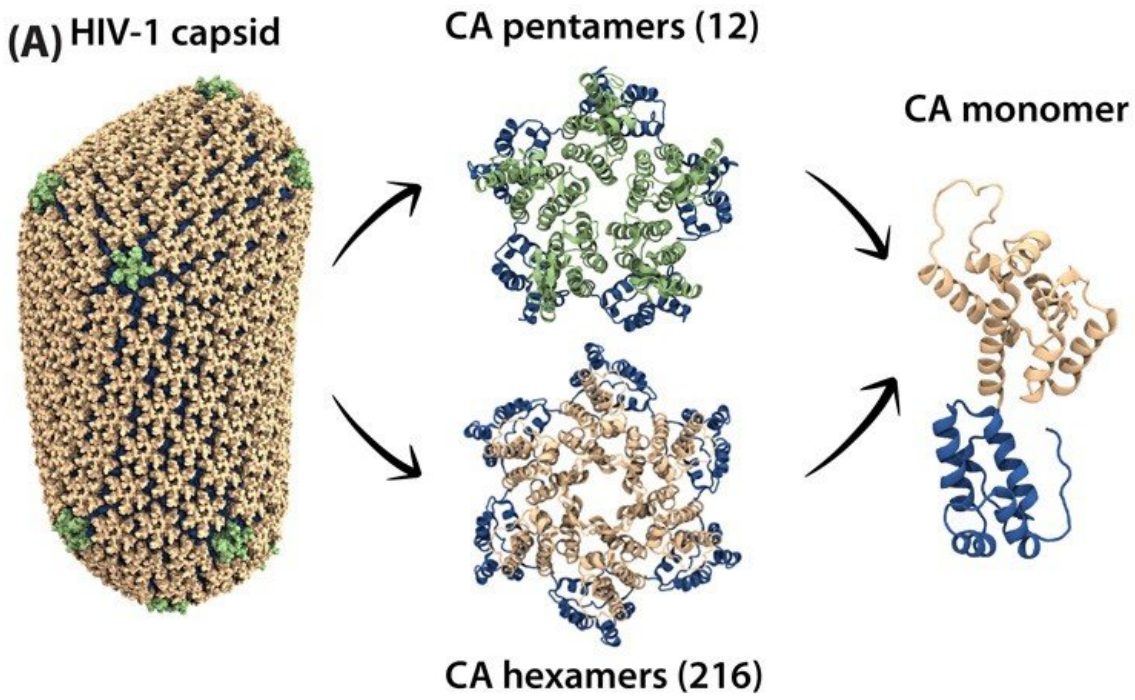

The cone-shaped HIV capsid (left) is made up of capsid, or CA, proteins (right). Those proteins assemble into five-sided pentamers and six-sided hexamers to form the lattice-like structure of the protective capsid. Credit: University of Delaware

HIV, the virus that causes AIDS, has been studied extensively ever since the AIDS epidemic was officially recognized by health professionals in the early 1980s.

During that time, research has led to the development of effective antiretroviral drugs that in many cases prevent an HIV-infected person from developing AIDS.

Despite that medical success, about 37 million people worldwide—including an estimated 2 million children younger than 15—are living with HIV infection, and about a million AIDS-related deaths occur each year.

And many aspects of the process in which the HIV virus matures and becomes infectious continue to baffle scientists.

With a great deal of recent research focusing on the capsid, a protein shell that encloses the virus itself, researchers at the University of Delaware have collaborated with University of Pittsburgh scientists to gain new insights into this structure.

Their latest findings, published in October in the journal *Proceedings of the National Academy of Sciences* (*PNAS*), identify some specific interactions that occur between the capsid and a key protein that interferes with the protective shell's integrity.

The findings are just one step in better understanding the mechanism of HIV infection, but the researchers believe it's an important advance.

"This is basic science, fundamental research, and you never know which direction it will lead us," said Tatyana Polenova, professor of chemistry and biochemistry at UD, who helped lead the study. "But understanding the structural biology of HIV gives us clues to a better understanding, and we hope that this might be a possible step toward treatment."

The research team used a combination of high-tech methods to study the capsid and its interactions with a protein called TRIM5-alpha, which is

known to disrupt the capsid structure and therefore restrict the virus's ability to become infectious.

The HIV capsid is a cone-shaped shell made up of different-shaped proteins. In each capsid, about 12 of these protein building blocks are pentamers, with five sides, and a much larger, variable number are hexamers, with six sides.

The building blocks fit together to form a shell that encloses and protects the virus until it is able to infect healthy cells. If the structure of the capsid breaks apart prematurely, infection won't occur.

"Despite extensive studies, the mechanistic details of capsid assembly and disassembly are not well understood," the researchers write in *PNAS*.

The team focused on the restriction factor TRIM5-alpha protein and its interactions with the capsid assembly for various reasons. Among them is a puzzling fact about that protein:

"Old World monkeys [such as rhesus monkeys] have TRIM5-alpha, and in those primates, it stops the HIV infection," Polenova said. "Humans have the same protein, with some primary amino acid sequence differences, but in humans, it doesn't disrupt the capsid and it doesn't stop the infection."

At UD, capsid interactions with the TRIM5-alpha protein were observed with a nuclear magnetic resonance (NMR) spectrometer, an instrument that reveals details about the structure and movement of molecules, with atomic level detail.

Caitlin M. Quinn, NMR spectroscopist in the Department of Chemistry and Biochemistry and the first author of the *PNAS* paper, began working on these observations in 2014.

At the same time she was using NMR to observe the capsid at the atomic level, Juan Perilla, an assistant professor of chemistry and biochemistry at UD (at the time, a postdoctoral scientist at the University of Illinois), was investigating the same subject. Perilla and his team used the Bridges supercomputer at the Pittsburgh Supercomputing Center to perform what are known as all-atom molecular dynamics (MD) simulations.

MD simulations allow researchers to study the way molecules move in order to learn how they carry out their functions in nature. Computer simulations are the only method that can reveal the motion of molecular systems down to the atomic level and are sometimes referred to as the "computational microscope."

"We wanted to understand how the HIV capsid interacts with the TRIM5-alpha protein," Quinn said. "That was the most difficult question to answer."

For years, researchers had been unable to observe capsid interactions with TRIM5-alpha experimentally, but the team "gave it a shot" with NMR spectroscopy, Polenova said.

"The TRIM5-alpha protein binds to the outside of the capsid" and affects its rigidity, Quinn said. "We were really surprised to find that even in areas of the capsid where it didn't directly interact, there were still effects on the structure."

The researchers believe that the protein uses several mechanisms to destabilize the lattice-like structure of the capsid and cause it to disassemble prematurely, while the capsid in the absence of TRIM5-alpha does not break apart as easily.

The capsid itself is a dynamic entity, and the motions occurring in the constituent molecules span many motional timescales, from picoseconds

to seconds and slower. These motions are critical in the capsid function and have been observed independently in MD simulations and NMR experiments.

The most surprising recent discovery is that pentameric and hexameric units in the capsid appear to have different motional behavior, which may be critical in the mechanism of the capsid's disassembly.

"Nobody before us was able to see these effects experimentally, and it's exactly as predicted by the molecular dynamic simulations," said Perilla, who is continuing to analyze some three years' worth of data from the project.

The findings are further proof of how complex and dynamic the HIV development and infection process is, Polenova said.

"People used to think that viruses have static structures, that the [building blocks] came together and closed the capsid, and that was that," she said. "But it's not rock-solid. The capsid is a highly dynamic entity. The TRIM5-alpha protein breaks it apart, and it does it through a very complicated mechanism, which involves interference with the intrinsic motional properties of the capsid."

The article "Dynamic Regulation of HIV-1 Capsid Interaction with the Restriction Factor TRIM5α" was published Oct. 17 in the *Proceedings of the National Academy of Sciences*.

In addition to Quinn, Polenova and Perilla, the authors are Mingzhang Wang, Matthew P. Fritz, Brent Runge and Chaoyi Xu, all doctoral students at UD, and Jinwoo Ahn and Angela M. Gronenborn of the Pittsburgh Center for HIV Protein Interactions and the Department of Structural Biology at the University of Pittsburgh School of Medicine.

Gronenborn is a University of Pittsburgh School of Medicine Rosalind Franklin Professor and chair of the Department of Structural Biology. She is the director of the National Institutes of Health-funded Pittsburgh Center for HIV Protein Interactions, which brings together high-caliber scientists and facilities to study the HIV virus and its interactions with host cell proteins.

More information: Caitlin M. Quinn et al. Dynamic regulation of HIV-1 capsid interaction with the restriction factor TRIM5α identified by magic-angle spinning NMR and molecular dynamics simulations, *Proceedings of the National Academy of Sciences* (2018). DOI: 10.1073/pnas.1800796115