Retrovirus replication process different than thought

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How a retrovirus, like HIV, reproduces and assembles new viruses is different than previously thought, according to Penn State College of Medicine researchers. Understanding the steps a virus takes for assembly could allow development of a way to prevent the spread of retroviral diseases.

The team studied a chicken virus called Rous sarcoma virus that causes cancer in chickens and is similar to HIV.

"The question is, how do retroviruses build new virus particles?" asked Leslie Parent, M.D., Ph.D., professor of infectious diseases, department of medicine. "There are no inhibitors of HIV assembly in clinical use. If we can determine how retroviruses are built, we can help stop the spread of infection through the creation of new drugs."

The start of the replication process is the production by the retrovirus of a protein called Gag. Prior to this study, it was thought the building process happened outside the nucleus in the cyctoplasm -- the material that fills the cell -- and then Gag protein was sent to the plasma membrane -- the outer boundary of the cell. The researchers discovered, however, that Rous sarcoma virus takes a detour through the cell nucleus before going to the cell membrane.

The Gag protein has a signal, which tells a receptor to take it into the nucleus. Once in the nucleus, Gag binds to the viral RNA. The viral RNA alters the structure of the protein, changing the way it folds. This

new configuration triggers a different signal that allows the Gag to move out of the nucleus.

"There's a sequence of events that has to happen in a very specific order," Parent explained. "The Gag protein has to find its own RNA, build a virus particle around it, and then release it from the cell." Finding the viral RNA is the first committed step in the assembly process. By focusing on regulatory processes in assembly, researchers are looking for key events that, if disrupted, could stop the virus from spreading.

"We want to understand the smallest building blocks of the virus particle," Parent said. "If we interfere with the first step, the virus will never be released from the cell. Cells are complex, so we use the key elements in a test tube to figure out how Gag and the RNA interact."

This study built on a 2002 paper, which proposed a model for the Gag protein's entry into the nucleus. The researchers reported in the *Proceedings of the National Academy of Sciences* that Gag does travel in the nucleus. Further study will examine how the Gag complex travels from the nucleus to the plasma membrane.

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