

Pushing HIV out the door: How host factors aid in the release of HIV particles

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Human Immunodeficiency Virus (HIV) – which causes AIDS – invades human immune cells and causes them to produce new copies of the virus, which can then infect new cells. A research team led by Professor Don C. Lamb (Ludwig-Maximilians-Universität in Munich) and Priv.-Doz. Dr. Barbara Müller of Heidelberg University Hospital have now analyzed the involvement of particular components of the infected cell in virion release, and discovered that the enzyme VPS4A plays a more active role in the process than was previously thought. VPS4A was already known to act after virus budding was complete. Using an advanced microscopy technique, the group was able to show that complexes containing about a dozen VPS4A molecules form at points in the membrane at which newly assembled virions later emerge.

According to Lamb, "We can now demonstrate in detail, for the first time, how host proteins interact with components of HIV, to enable them to bud from [infected cells](#). Our ultimate goal is to elucidate the entire life cycle of the virus." "With the methods we have at our disposal, we can also study the effects of drugs on infected cells, which may allow us to improve their efficacy or even lead to the development of new classes of active compounds." (*Nature Cell Biology* online, 10 March 2011)

Viruses are like pirates: they board a suitable cell and alter its course to suit their own purpose. More specifically, they smuggle their own genetic material into a host cell and reprogram the cell to produce new virus particles. For release of the newly synthesized viruses, HIV exploits cellular proteins involved in the loading, sorting and budding of cellular

vesicles known as ESCRT proteins. During budding, HIV makes use of ESCRT to cut the last connection between the virion coat and the cell surface, allowing it to exit the cell. The enzyme VPS4A forms part of the ESCRT machinery and is known to be necessary for the disassembly of the complex after use, allowing its components to be recycled.

The results from ultrasensitive live-cell imaging experiments showed that VPS4A also acts at an earlier stage in the budding process. In the new work, the researchers labeled the enzyme by fusing it with the Green Fluorescent Protein (GFP). This allowed them to track the protein in living cells. By recording the fluorescent signals, they observed how several VPS4A molecules came together to form larger complexes. "In this case, we were able to count how many enzyme molecules assembled at the HIV budding site during its interaction with the nascent virion" says Müller.

Complexes made up of about three dodecamers of VPS4A were observed to undergo transient activation (for about a minute) at a budding site. Shortly thereafter, the virions were observed to emerge from the cell at these locations. Because virion release does not follow immediately upon activation of the enzyme, the investigators believe that at least one further intermediate step is required for budding.

Perhaps this postulated step can be pinned down in a later project. "Our current methodology allows us to monitor the assembly of individual virions, and we are working on further refinements that will allow us to follow the complete life cycle of [HIV](#)," says Lamb. "We can already visualize some steps of the life cycle at the level of a single virus, observe interactions and determine the kinetics of different processes. Of course, this means that we can also label therapeutic agents and observe what effects they have in infected cells. This can help us to optimize the currently available drugs and even allow us to develop new ones."

Provided by Ludwig-Maximilians-Universität München

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