Manipulated gatekeeper: How viruses find their way into the cell nucleus

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Adenoviruses cause respiratory diseases and are more dangerous for humans than previously assumed. They manipulate gatekeeper molecules and infiltrate the cell nucleus with the aid of the host cell. A team of researchers headed by cell biologists and virologists from the University of Zurich have succeeded in demonstrating this mechanism in detail for the first time.

They have been around since the dawn of time and are a model of evolutionary success: viruses. Viruses are extremely adaptable but they have a problem: They cannot reproduce, so they smuggle their genes into suitable host cells. In the case of some viruses, the viral DNA has to enter the cell nucleus to reproduce. This has been known for almost 50 years. We know, for instance, that the adenovirus disassembles its protein shell in the first step. Just how the DNA is exposed and infiltrates the host cell, however, remained unclear despite decades of research.

A research group headed by Urs Greber, a cell biologist at the University of Zurich, has now managed to clear up these points. As the scientists recently revealed in the journal *Cell Host & Microbe*, viruses use the cell's own mechanisms. The adenovirus latches onto a gatekeeper molecule, which sits on the nuclear pore complex in the nucleus envelope and controls the passage in and out of the nucleus. Another protein in the nuclear pore complex binds and activates a motor protein from the kinesin family, which regulates the transport of substances near the nucleus.

Virus DNA uncoated with aid of host cell

"The motor protein is in an active condition, can bind to micro-tubules and migrate along them," says Professor Greber, explaining his team's observations. And the docked virus uses precisely this situation for its purposes. The virus binds to the kinesin and uses the energy of the motor to disrupt its own shell, which exposes the virus DNA and prepares it for transport into the nucleus. The action of the activated motor has another effect, too: The nuclear pore ruptures and becomes markedly bigger, which enables the viral DNA to enter the cell nucleus more easily. Surprisingly, the cell repairs the defective nuclear pore so that the virus breach in the nucleus does not leave any visible damage in its wake. The viral DNA is smuggled into the nucleus practically without trace, where it can reproduce easily.

The researchers used adenoviruses for their study. Adenoviruses cause, among other things, respiratory or epidemic ocular disease. Until recently, they were thought to be relatively harmless for healthy humans. However, the results of another research group recently demonstrated that a new kind of adenovirus triggered a dreaded zoonotic disease, meaning it was transmitted from an animal to humans before spreading from one person to another.

More information: Sten Strunze, Martin F. Engelke, I-Hsuan Wang, Daniel Puntener, Karin Boucke, Sibylle Schleich, Michael Way, Philipp Schoenenberger, Christoph J. Burckhardt and Urs F. Greber: Kinesin-1-Mediated Capsid Disassembly and Disruption of the Nuclear Pore Complex Promote Virus Infection, in: *Cell Host & Microbe* 10, 15. September 2011, DOI:10.1016/j.chom.2011.08.010

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