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Researchers shine the light of venus to learn how the herpes virus invades cells

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University of Pennsylvania researchers have uncovered an important step in how herpes simplex virus, HSV-1, uses cooperating proteins found on its outer coat to gain entry into healthy cells and infect them. Further, the study's authors say, they have demonstrated the effectiveness of monitoring these protein interactions using biomolecular complementation.

The findings, published in the *Proceedings of the National Academy of Sciences*, provide a better understanding of the mechanism that viruses use to conquer healthy cells.

Beginning with the knowledge that HSV-1 glycoprotein gD binds to cell receptors in a healthy cell to begin virus-cell fusion, researchers questioned how other proteins combined or cooperated on the attack. They "tagged" additional HSV-1 proteins with a fluorescent marker to witness the complex battle, thus demonstrating that gD somehow signals to three other herpes proteins -- gB, gH and gL -- to swing into action, continuing fusion and ultimately releasing the viral genome into the cell. Once in the cell, the viral genome takes over and directs the cell to make more virus.

"Watching these proteins interact tells us a lot about HSV and other herpes viruses and how they attack the body," Roselyn Eisenberg, professor of microbiology in Penn's School of Veterinary Medicine, said. "The first thing this virus does when it finds a cell is fool the cell into thinking the virus is a welcome guest when it is actually a dangerous

intruder. But getting in is not easy. It takes four viral proteins to do it, and they must cooperate with each other in ways that we are only beginning to understand."

Monitoring the interactions required a novel technique. Researchers assumed in their hypothesis that these proteins had to physically interact with each other but could not demonstrate the split-second interaction. Penn researchers hypothesized that the encounter might be too brief and decided to look for ways to "freeze" it long enough to take a snapshot.

Knowing that virus-cell fusion starts when gD binds to a cell receptor, these researchers monitored the remaining protein interactions using bimolecular complementation, a newly developed process that employs, in this case, a protein called Venus. Venus, like the planet, shines brightly against a dark background. Researchers split the yellow Venus protein in two, creating tags which were stitched to either gB or gH, the proteins they believed played a role in fusion. When Venus is split in half, it no longer glows yellow. But when half-Venus-gB and half-Venus-gH combine, even very briefly as they do, the two halves of Venus interact and shine again.

The team used microscopy to look for the viral protein-protein interactions during fusion and thus found that fusion requires proteins gB, gH and gL, called the "core fusion machinery" of all herpes viruses.

"This is a complex mechanism we're looking at," Gary Cohen, professor of microbiology in Penn's School of Dental Medicine, said. "We still have a long way to go but this is a major step forward for us and the field, and now we have a new toy to play with to help us with a whole new set of questions. That is the fun of science: there is always another question. "

Source: University of Pennsylvania