To drive infections, a hijacking virus mimics a cell's signaling system

March 26 2012

New biological research reveals how an invading virus hijacks a cell's workings by imitating a signaling marker to defeat the body's defenses. By manipulating cell signals, the virus destroys a defensive protein designed to inhibit it. This finding, from studies in human cell cultures, may represent a broader targeting strategy used by other viruses, and may lay the scientific groundwork for developing more effective treatments for infectious diseases.

"Learning details of how cells respond to viruses helps us to understand key cellular machinery better," said study leader Matthew D. Weitzman, Ph.D., of the Center for Cellular and Molecular Therapeutics at The Children's Hospital of Philadelphia. "This study tells us how a virus overcomes intrinsic host defenses. In this case the virus mimics signals used during normal DNA repair mechanisms."

The study team, formerly based at the Salk Institute for Biological Studies in La Jolla, Calif., published their current findings online March 8 in *Molecular Cell*.

Biologists have long known that viruses hijack cellular processes to replicate themselves, while host cells have evolved intrinsic defense systems to resist viral invasion. To replicate, viruses must deliver their own DNA into a cell's nucleus, so a viral infection entails a conflict between two genomes—the DNA of the host cell versus the foreign DNA of the virus.

Viruses mount their attack by interacting with specific cell proteins as a way of penetrating the cell's defenses. "In this study, we asked how the herpes simplex virus finds the specific proteins that it interacts with," said Weitzman. "By describing the mechanism of this particular interaction between a virus and a cell protein, we have pinpointed key regulators of a cell's processes, and shed light on how a cell regulates its defenses."

This laboratory study focused on herpes simplex virus type-1 (HSV-1), a common human virus that results in recurrent infections alternating with inactive periods. Like other viruses, HSV-1 is known to manipulate cellular processes in order to infect cells, but the specific mechanisms by which it acts on the DNA repair pathway were previously unknown.

Weitzman's study team was studying a viral protein called ICP0 that overcomes host defenses by targeting cellular proteins for destruction. They found that ICP0 exploits phosphorylation, a chemical mark that is often used in cells to promote interactions between proteins, especially as part of the cellular signaling response to DNA damage. In HSV-1 infection, the phosphorylation signal on ICP0 attracts a cellular DNA damage response protein, RNF8, which binds to the false signaling marker and is then degraded. Because RNF8 normally inhibits viral replication, its destruction leaves the cell vulnerable to HSV-1 infection, as the virus takes over the cell's machinery.

The researchers also found that ICP0 exploits the same phosphorylation signal to bind to other cellular proteins in addition to RNF8, a hint that it may play a broader role in defeating antiviral defenses and manipulating cellular machinery. Weitzman will continue to investigate HSV-1 infection in neurons and in animal models. He also plans to extend his research into other viruses, which may act on different pathways than HSV-1 does. "Ultimately," he added, "better knowledge of molecular mechanisms in infection may suggest strategies to interrupt the viral life

cycle and treat infections."

More information: "Viral E3 Ubiquitin Ligase-Mediated Degradation of a Cellular E3: Viral Mimicry of a Cellular Phosphorylation Mark Targets the RNF8 FHA Domain," *Molecular Cell*, published online March 8, 2012, to appear in print, April 13, 2012. doi: 10.1016/j.molcel.2012.02.004

Provided by Children's Hospital of Philadelphia