Cells use Velcro-like mechanism to keep viruses from spreading

December 7 2007

Like mobsters, cells keep their friends close and their enemies — at least some of them — closer. According to new results from HIV researchers at Rockefeller University, one way that human cells prevent certain viruses from raging out of control is by blocking new viral particles from ever leaving an infected cell's surface. And, they believe, HIV thrives in part because it has evolved the ability to get around this obstacle.

Viruses can only reproduce using the mechanisms and material of their hosts. Some of them — the so-called "enveloped" viruses, which are encapsulated inside a lipid membrane — assemble at the host cell's outer membrane and then bud off during their release.

Now, a recent study by Associate Professor Paul Bieniasz, head of Rockefeller's Laboratory of Retrovirology and a researcher at the Aaron Diamond AIDS Research Center, has shown that a human protein thwarts the spread of these enveloped viruses by preventing them from departing from the cell's surface. By watching particles of HIV as well as virus-like particles made from Ebola virus structural proteins, Bieniasz and first author Stuart Neil, a postdoc in the lab, found that an immune protein, known as interferon, actually instructs cells to tether enveloped viruses to the cell membrane like Velcro.

Prior research by Neil and Bieniasz has shown that when HIV particles lack a protein called Vpu, they're usually unable to free themselves from the plasma membrane and remain stuck on the cell surface. "If a virus-infected cell behaves altruistically, by keeping virus particles tethered to

its surface, it can prevent its brothers (or sisters) from becoming infected," Bieniasz says. "And so we think HIV has evolved the Vpu protein in order to counteract that behavior."

When they treated HIV-infected cells with interferon, the researchers found that they were able to almost completely eliminate replication of a mutant HIV-1 strain that lacked Vpu. "The virus won't grow in the presence of interferon unless it has the Vpu gene. And in a person, it's very likely to encounter interferon," Neil says. "In fact, we know that people infected with HIV make reasonable amounts of interferon, probably in response to that infection."

To see whether interferon-induced virus retention was specific to HIV or whether it could work against other enveloped virus particles, Neil and Bieniasz used a protein from Ebola to create particles that act like the Ebola virus and tested interferon against them. Despite the fact that Ebola has a totally different genetic makeup, interferon restrained the release of these particles too. But when the researchers then expressed Vpu in cells that were also making Ebola-like particles, the budding particles freed themselves from the membrane with little difficulty.

"We think that the 'stickiness' induced by interferon is completely non-specific, because it works on viruses that are totally different from each other. The only thing they have in common is an outer membrane," Neil says. It's a way for cells to inhibit virus replication broadly without having to launch attacks specific to each invader.

This suggests that HIV evolved Vpu specifically to overcome the human interferon response. "It acquired a whole new gene whose function is to counteract a defense mechanism that the cell has evolved," Neil says. "If one could devise a way to inhibit Vpu activity, that could, in principle, be a reasonable treatment strategy, and perhaps allow an interferon system to work more effectively against HIV."

Citation: Cell Host & Microbe 2(3): 193–203 (September 13, 2007)

Source: Rockefeller University