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Host Cell Proteins Could be HIV's Achilles' Heel

Like all viruses, the human immunodeficiency virus (HIV) depends on its host cell to do much of its molecular dirty work as it promotes infection. Now, in a paper published online January 10, 2008, in *Science Express*, a team of researchers from the Howard Hughes Medical Institute (HHMI) has provided a detailed picture of just how extensively HIV exploits host cells' proteins.

The new study, conducted by a team led by HHMI investigator Stephen J. Elledge of Harvard Medical School, identifies 273 host proteins that serve to keep the AIDS virus healthy and happy as it infects cells. More than 200 of these were not previously known to be needed by the virus during its life cycle. This new catalog of proteins could help researchers devise better treatment strategies to get around HIV's notorious propensity to develop resistance to antiviral drugs.

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Elledge and Abraham Brass, a post-doctoral fellow in his lab, collaborated with Judy Lieberman and other Harvard Medical School scientists on the study. The hope, Elledge said, is that their data will give scientists a more complete picture of just how complicit the host cell is in the viral life cycle. "We wanted to get this information out to the field," Elledge said, noting that pharmaceutical companies are doing similar work privately. "We anticipate it will have a big impact — as what we've really done is provide a hypothesis-generation set. It will allow people to think more deeply about the life cycle of HIV and how to impede it."

What's more, the approach utilized by Elledge's group could be used to expose previously hidden vulnerabilities in other viruses, such as polio or hepatitis, which might even rely on some the same proteins identified in the new screen.

Because the AIDS virus makes only a handful of its own proteins, it must co-opt host cell proteins for successful infection. A key advantage to using these host proteins as therapeutic targets, Elledge emphasized, is that they confer essential abilities that the AIDS virus has not managed to accomplish on its own. If we could make drugs to host cell proteins, they are unlikely to be overcome by HIV. The virus would have to evolve a new ability, and that's not very likely.

To identify the essential proteins, Elledge's group used a technique known as RNA interference to turn off genes in human cells. They began their experiments by shutting off genes four at a time, then narrowed their focus to individual genes. They then exposed these cells to the AIDS virus to see how HIV fared in the absence of each host cell protein.

"There are a lot of proteins in cells that HIV doesn't care about," Elledge noted. "But it cares about some of them a lot. We knocked out known proteins one at a time to see which were required." What they found was that 273 host proteins aided the virus in its infection process.

According to Elledge, the host cell proteins commandeered by HIV help the virus accomplish an array of critical tasks. Some of the host proteins implicated by the HHMI team abet the virus by helping it gain access to the cell, integrate into the cell's genome, replicate, and exit the cell to renew the viral life cycle by infecting more cells.

These proteins participate in a broad array of cellular functions and implicate new pathways in the viral life cycle, according to Elledge. "Some of the proteins had been previously implicated in HIV biology, but had never been demonstrated to be required (by the virus)." Of the proteins identified by Elledge and his colleagues, 237 had never before been implicated as accomplices of HIV.

Many of the host proteins Elledge and his colleagues zeroed in on are more abundant in immune cells than other types of human cells. The data help explain why HIV is so insidious, taking over the very immune cells the body needs to thwart infection. "It suggests immune cells are good hosts because they have lots of the proteins HIV needs to function."

Further work could offer new avenues to treating viral infections of all kinds, Elledge said. "We expect other people will be able to do similar work with other viruses. A lot of viruses have host factors that they need."