Scientists unmask key HIV protein, open door for more powerful AIDS drugs

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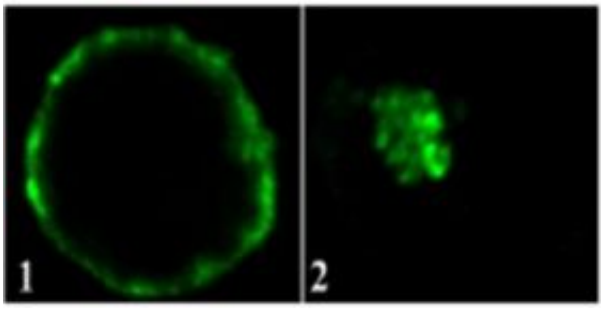

At left, a normal, uninfected cell with green-stained MHC-I protein on the cell surface. At right, an HIV infected cell -- most of the MHC-I builds up inside, keeping the cell from telling the immune system that it harbors a virus. Credit: Kathleen Collins, University of Michigan

University of Michigan scientists have provided the most detailed picture yet of a key HIV accessory protein that foils the body's normal immune response. Based on the findings, which appear online in the journal *PLoS Pathogens*, the team is searching for new drugs that may someday allow infected people to be cured and no longer need today's AIDS drugs for a lifetime.

"There's a big hole in current therapies, in that all of them prevent new infection, but none attack the cells that are already infected and hidden from the immune response," says Kathleen L. Collins, M.D., Ph.D., the study's senior author and a U-M associate professor in both internal

medicine and microbiology and immunology.

In people infected with HIV (human immunodeficiency virus), the virus that causes AIDS, there's an unsolved problem with current anti-viral drugs. Though life-saving, they cannot root the virus out of the body. Infected cells are able to live on, undetected by the immune system, and provide the machinery for the virus to reproduce and spread.

"People have to be on the existing drugs, and when they're not, the virus rebounds. If we can develop drugs that seek out and eradicate the remaining factories for the virus, then maybe we could eradicate the disease in that person," Collins says.

The new research details the complex actions of a protein, HIV-1 Nef, that is known to keep immune system cells from doing their normal jobs of detecting and killing infected cells.

Collins and her team show how Nef disables two key immune system players inside an infected cell. These are molecules called major histocompatability complex 1 proteins (MHC-1) that present HIV antigens to the immune system, and CD4, the cell-surface receptor that normally locks onto a virus and allows it to enter the cell.

Collins likens MHC-1 to motion detectors on a house, which send the first signal to a monitoring station if an invader breaks in.

"The immune system, especially the cytotoxic T lymphocytes, are like the monitors who get the signal that there's a foreign invader inside the cell, and send out police cars," she says. "The 'police' are toxic chemicals produced by T lymphocyte cells, which kill the cell that harbors the invader."

By in effect pushing the MHC-I proteins into an infected cell's "trash

bin" so they fail to alert the T lymphocytes, Nef's actions allow active virus to hide undetected and reproduce. Also, once a cell has been infected, Nef destroys CD4. The result is that this encourages new virus to spread to uninfected cells.

Nef's activities are variable and complex. But the research team's findings suggest that the many pathways involved may end in a final common step. That could make it possible to find a drug that could block several Nef functions.

Collins' lab is now screening drug candidates to find promising Nef inhibitors. Such drugs, which are at least 10 years away from use in people, would supplement, not replace, existing anti-viral drugs given to HIV-infected people. The new drugs would target the reservoirs where the virus hides.

In developing countries, the new drugs could have a huge impact, Collins says. Today, children born with HIV infection start taking the existing anti-HIV drugs at birth. It's very hard to continue costly treatments for a lifetime. But if children could be cured within a few years, global HIV treatment efforts could spread their dollars further and be much more successful, she says.

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