Possible Cure in Protein That Starves HIV of Needed Building Blocks

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Focusing on a protein called SAMHD1, a team of researchers believes it has stumbled upon the mechanism in which some immune system cells keep HIV from hijacking their cellular machinery to produce new virus. The findings, published online ahead of print by the journal Nature Immunology, pave the way for novel methods to treat—and potentially cure—HIV infection.

SAMHD1, the international team of scientists explains, is found in white blood cells known as macrophages and related cells known as dendritic cells. Building upon research published last year, demonstrating that SAMHD1 makes it difficult for HIV to infect macrophages, the scientists have helped close the knowledge gap with the discovery that the protein cuts off the supply line of deoxyribonucleotide triphosphate (dNTP)—the building blocks of DNA—which HIV needs to re-create its genetic contents.

When a virus, like HIV, infects a cell, it hijacks the cell's dNTP. Once the virus replicates

, the resulting DNA molecule contains all the genes of the virus and instructs the cell to make more virus.

SAMHD1, the researchers found, protects the cell from viruses by destroying the pool of dNTPs, leaving the virus without any building blocks to make its genetic information, a process known as nucleotide pool depletion.

"SAMHD1 essentially starves the virus," explained Nathaniel Landau, PhD, a professor of microbiology at New York University School of Medicine and a lead author of the Nature Immunology paper in an accompanying news announcement. "The virus enters the cell, and then nothing happens. It has nothing to build and replicate with, so no DNA is made."

As a result, the most common form of HIV—HIV-1—does not readily infect these cells. Instead, the virus has evolved to replicate mainly in CD4 cells, which do not contain SAMHD1 and therefore have a healthy pool of dNTPs.

The virus, the researchers suggest, may have evolved in such a way that it deliberately avoids trying to infect immune cells that have SAMHD1, in order to avoid alerting the greater immune system to activate a variety of antiviral mechanisms to attack the virus.

The team also discovered how a protein in the other form of HIV—HIV-2, which is found mainly in Africa—knocks out SAMHD1. They found that the protein Vpx destroys SAMHD1, clearing the way for HIV-2 to infect macrophages. While scientists have known that HIV-2 needs Vpx to infect macrophages, they hadn't known precisely why.

Interestingly, while one might think that a virus that is able to replicate itself in crucial cells like macrophages might be more dangerous than one that cannot, that's not the case with HIV. The researchers note that HIV-2 is generally actually less virulent than HIV-1.

One possible explanation for this is that, like a starving man who becomes increasingly desperate for food, HIV-2—when faced with a shortage of raw materials—puts its mutation capabilities into overdrive, creating the Vpx proteins necessary to circumvent the pathway blocked by SAMHD1.

"Viruses are remarkably clever about evading our immune defenses," Landau said. "They can evolve quickly and have developed ways to get around the systems we naturally have in place to protect us. It's a bit of evolutionary warfare, and the viruses, unfortunately, usually win. We want to understand how the enemy fights so that we can outsmart it in the end."

Understanding the mechanism by which SAMHD1 protects cells may provide a new idea about how to stop or slow the virus's ability to spread, the researchers explained. Potential future research efforts, for example, might focus on finding a way to increase the amount of SAMHD1 in cells where it does not exist, such as CD4 cells, or to reduce the amount of dNTPs in cells vulnerable to infection.

This could potentially force HIV to remain dormant in all immune system cell lines, unable to replicate—another functional cure strategy.

"Over the past few years, a number of these natural resistance mechanisms have been identified, specifically in HIV," Landau sad. "This is a very exciting time in HIV research. Many of the virus's secrets are being revealed through molecular biology, and we're learning a tremendous amount about how our immune system works through the study of HIV."

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