Researchers identify HIV-inhibiting mechanism

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Researchers at Case Western Reserve University School of Medicine have discovered a long-sought cellular factor that works to inhibit HIV infection of myeloid cells, a subset of white blood cells that display antigens and hence are important for the body's immune response against viruses and other pathogens.

The factor, a protein called SAMHD1, is part of the nucleic acid sensing machinery within the body's own immune system. It keeps cells from activating immune responses to the cells own nucleic acids, thus preventing certain forms of autoimmunity from developing.

SAMHD1 factor, researchers have found, can also sense and interfere with infection of myeloid cells, such as macrophages and dendritic cells, with HIV-1 and related immunodeficiency viruses. As such, SAMHD1 prevents the synthesis of virus copies in these cells, according to research led by Jacek Skowronski, PhD, a professor in the Department of Molecular Biology and Microbiology and member of the Center for AIDS Research at the Case Western Reserve University School of Medicine.

The findings appear in a manuscript published in the June 30 issue of *Nature* featuring Dr. Skowronski as the paper's senior author. The research was carried out in his lab at Case Western Reserve in collaboration with a research group led by Michael P. Washburn, PhD, at the Stowers Institute for Medical Research in Kansas City.

This issue of *Nature* also carries an independent report by a team from France headed by Monsef Benkirane, PhD, that identifies SAMHD1 as a factor that limits HIV growth in myeloid cells. The research broadens the understanding of how the immune system of the infected people handles HIV, and how HIV evades the immune system's response.

"The identification of SAMHD1 and its function may help to explain why some infected individuals can control HIV infection better than others," Dr. Skowronski says. "Ultimately, it could also provide a basis for conceiving of new therapies and treatment approaches to block HIV infection and/or its replication in infected individuals, and to stimulate body's own immune response to HIV."

Prior to this research the normal function of SAMHD1 was thought to be the prevention of the inappropriate activation of a class of the anti-viral responses mediated by production of anti-viral factors termed interferons, in the absence of virus infection. Mutations in SAMHD1, as well as two other cellular genes that encode nucleases, TREX1 and RNAse H2, cause a condition called Acairdi-Goutieres syndrome (AGS). The condition mimics congenital viral infection, and is due to unwarranted induction of the immune system's interferons in the absence of the virus. SAMHD1 and other AGS-causing cell proteins work to dispose cellular nucleic acid debris, thereby preventing inappropriate activation of the interferon system.

In the work described in the Nature manuscript, the researchers led by Dr. Skowronski discovered that in addition to preventing inappropriate autoimmune responses such as those seen in AGS, SAMHD1 possesses the ability to inhibit infection of myeloid cells by HIV by effectively interfering with the production of viral nucleic acids. Through this action SAMHD1 may prevent efficient activation of immune responses to HIV-1 virus in infected individuals, Dr. Skowronski explains.

The research also shows HIV-2 and related simian immunodeficiency viruses (SIVsm/mac) are able to overcome the protective mechanism within myeloid cells by using the protein Vpx they encode, to dispose of SAMHD1, thereby allowing infection with these viruses. Interestingly, viruses possessing Vpx, such as HIV-2, are much less pathogenic than HIV-1. This could be because by being able to establish infection in myeloid cells they provoke much more robust immune responses that HIV-1 does, since HIV-1 can not infect these cells efficiently, Dr. Skowronski says.

As a result, "One might expect that manipulation of SAMHD1 function in the context of HIV-1 infection may lead to more robust immune response to this virus" according to Dr. Skowronski.

Moving forward, researchers will focus on better understanding the molecular pathway SAMHD1 uses to inhibit HIV-1 infection. They will likewise strive to learn more about how SAMHD1 shapes the development of AIDS in HIV-infected individuals, Dr. Skowronski says.

Provided by Case Western Reserve University