HIV Causes AIDS by ’Cellular Suicide,’ Not ’Viral Murder’

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Defining for the first time exactly how HIV causes AIDS, scientists have found that, without treatment, the virus successfully spurs the immune system into a suicidal overdrive, MedPage Today reports. While the virus initiates this effective death spiral, the primary driver of the damage to the immune system is actually the immune response itself. Researchers at the Gladstone Institutes, which is affiliated with the University of California, San Francisco, have published two simultaneous papers, in Nature and in Science, on their discoveries.

“Our studies have investigated and identified the root cause of AIDS—how CD4 T cells die,” Gladstone staff research investigator Gilad Doitsh, PhD, who is one of the Nature paper’s lead author, said in a release. “Despite some 30 years of HIV research, this key HIV/AIDS process has remained pretty much a black box.”

The process is "much more of a cellular suicide than a viral murder," according to Warner Greene, MD, PhD, of the Gladstone Institutes and the University of California San Francisco.

The investigators have also found an existing anti-inflammatory drug that blocks the death of immune cells; they’re hoping for a Phase II clinical trial with the drug in the near future.

Ninety-five percent of a person’s CD4 cells are in a resting state at any given time, and therefore HIV cannot infect them. But the virus can still lead to these cells’ death through this immune response, the mechanics of which are now more completely understood. After HIV attempts and fails to infect a resting CD4 cell—this is called an abortive infection—particles of the virus remain in the cell and are detected by a protein called IFI16. This protein then activates the human enzyme caspase-1, leading to a highly inflammatory death known as pyroptosis.

The Nature paper shows that this inflammatory process attracts more CD4 cells to the site, which in these tissue studies led to to the cycle of more abortive infection, cell death, inflammation and the recruitment of further CD4s. Thus, in humans, the immune system would eventually be depleted and the host would be vulnerable to AIDS-defining illnesses. When HIV infects active CD4 cells, this dramatic process does not occur; the cells eventually die in a quieter process called apoptosis, without attracting all the extra immune response.

The researchers found that, in tissue experiments, inhibiting caspase-1 with a drug known as

VX-765, a Vertex-owned compound which Phase IIb clinical trials have found safe and effective for the treatment of epilepsy and psoriasis, both prevents the death of the abortively infected resting CD4s and prevents the resulting inflammatory response.

If the drug proves effective in the hoped-for trials and is one day cheap and widely available, it might serve as a means to slow the progression to AIDS for people with HIV around the world who are waiting for access to antiretroviral (ARV) treatment. The drug might also serve as an adjunct to ARVs.

Also, because inflammation leads the body to generate cytokines that then spur the development of memory T cells, which are a part of the viral reservoir, a caspase-1 inhibitor might become a component of a multi-pronged HIV cure approach that slowly depletes the reservoir.

To read the MedPage Today story, click here.

To read the Gladstone Institutes press release, click here.

To read the Science abstract, click here.

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