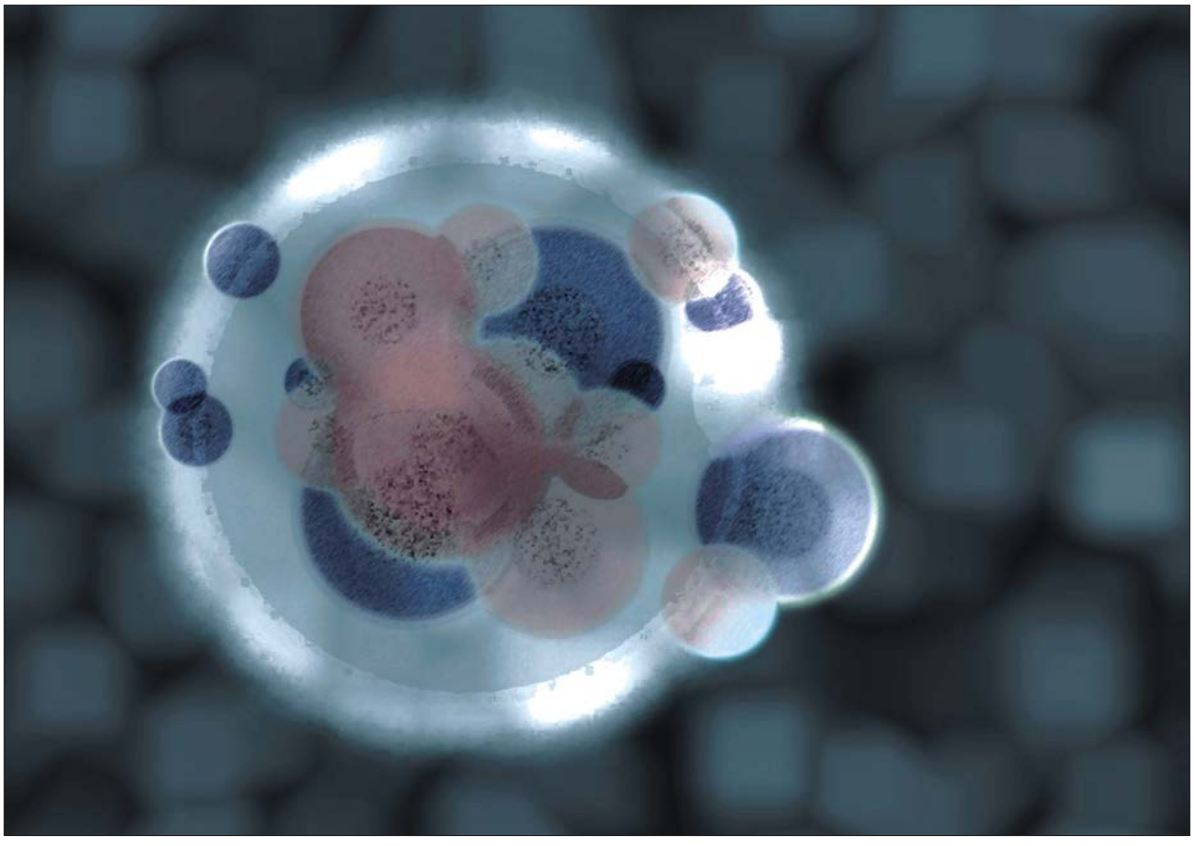

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An Answer to a Longstanding Question: How HIV Infection Kills T Cells ... ?

Researchers appear to have an explanation for a longstanding question in HIV biology: how it is that the virus kills so many CD4 T cells, despite the fact that most of them appear to be "bystander" cells that are themselves not productively infected? That loss of CD4 T cells marks the progression from HIV infection to full-blown AIDS, explain the researchers who report their findings in studies of human tonsils and spleens in the Nov. 24 issue of Cell, a Cell Press publication.

"In [infected] primary human tonsils and spleens, there is a profound depletion of CD4 T cells," said Warner Greene of the Gladstone institute for Virology and Immunology in San Francisco. "In tonsils, only one to five percent of those cells are directly infected, yet 99 percent of them die."

Lymphoid tissues, including tonsils and spleen, contain the vast majority of the body's CD4 T cells and represent the major site where HIV reproduces itself. And it now, appears that those dying T cells aren't bystanders exactly.

The HIV virus apparently does invade those T cells, but the cells somehow block virus replication. It is the byproducts of that aborted infection that trigger an immune response that is ultimately responsible for killing those cells.

More specifically, when the virus enters the CD4 T cells that will later die, it begins to copy its RNA into DNA, Greene and his colleague Gilad Doitsh explain. That process, called reverse transcription, is what normally allows a virus to hijack the machinery of its host cell and begin replicating itself. But in the majority of those cells, the new findings show that the process doesn't come to completion.

The cells sense partial DNA transcripts as they accumulate and, in a misguided attempt to protect the body, commit a form of suicide. Greene says that completed viral transcripts in cells that are productively infected probably don't provoke the same reaction because they are so rapidly shuttled into the nucleus and integrated into the host's own DNA.

The researchers narrowed down the precise "death window" of those so-called bystander cells by taking advantage of an array of HIV drugs that act at different points in the viral life cycle. Drugs that blocked viral entry or that prevented reverse transcription altogether stopped the CD4 T cell killing, they report. Those drugs that act later in the life cycle to prevent reverse transcription only after, it has already begun did not save the cells from their death.

Those cells don't die quietly either, Greene says. The cells produce ingredients that are the hallmarks of inflammation and break open, spilling all of their contents. That may provide a missing link between HIV and the inflammation that tends to go with it.

"That inflammation will attract more cells leading to more infection," Greene said. "It's a vicious cycle."

The findings also show that the CD4 T cells' demise is a response designed to be protective of the host. All that goes awry in the case of HIV and "the CD4 T cells just get blown away," compromising the immune system.

Greene said that all the available varieties of anti-HIV drugs will still work to fight the infection by preventing the virus from spreading and reducing the viral load.

The findings may lead to some new treatment strategies, however. For instance, it may be possible to develop drugs that would act on the cell sensor that triggers the immune response, helping to prevent the loss of CD 4 T cells. His team plans to explore the identity of that sensor in further studies. They also are interested to find out if the virus has strategies in place to try and prevent the CD4 T cells' death.

"The cell death pathway is really not in the virus's best interest," Greene says. "It precludes the virus from replicating and the virus may have ways to repel it."