NATURE | NEWS

Cell-suicide blocker holds promise as HIV therapy

Approach could complement current treatments.

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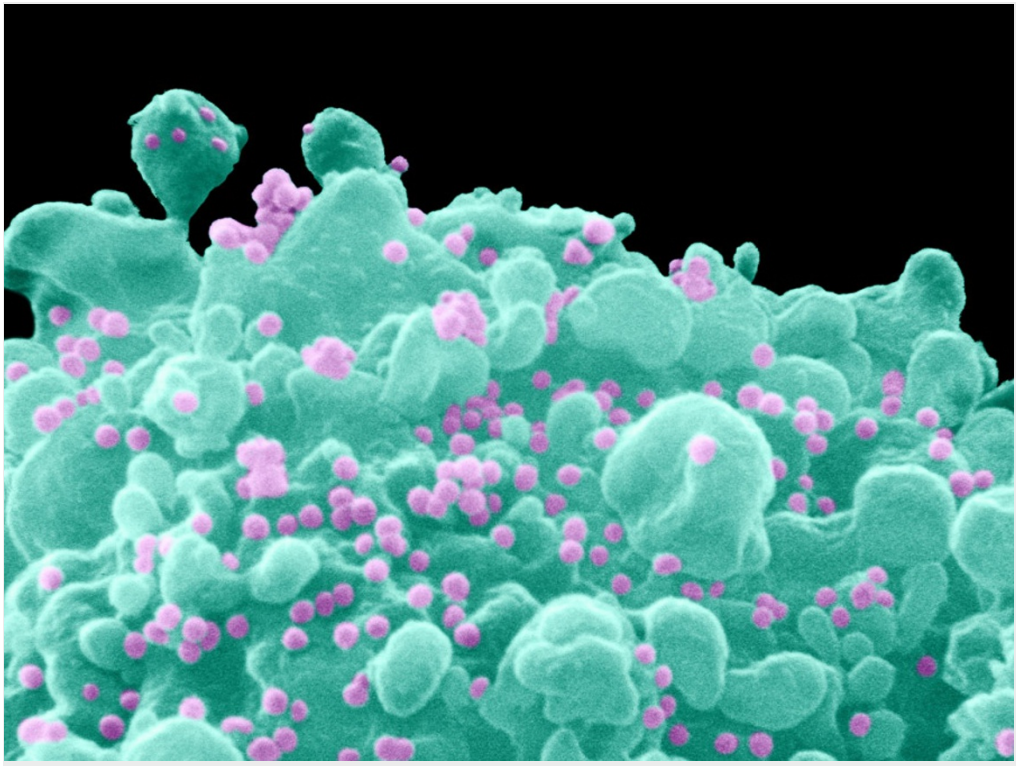

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Immune cells (green) infected with HIV (pink) undergo a cell-suicide process known as pyroptosis.

HIV infection causes a mass suicide of immune cells — a process that can be halted by an experimental drug that blocks cellular self-destruction, studies in cell cultures suggest. Researchers are now proposing a clinical trial of the drug in people with HIV.

Current HIV therapies act by targeting key proteins made by the virus. But findings from cell cultures, published today in *Science*[1] and *Nature*[2], suggest that targeting proteins in host cells might be an alternative approach to preserving the immune system in the face of an HIV infection.

The papers also address a decades-old mystery: why infection-fighting immune cells die off in people with HIV. A 2010 study[3] showed that HIV does not directly kill most of these cells, called CD4 cells. Instead, the cells often self-destruct. “It’s much more a suicide than it is a murder,” says Warner Greene, a molecular virologist at the Gladstone Institute of Virology and Immunology in San Francisco, California, and a co-author of both the latest works.

Ring of fire

In the latest studies, Greene’s team investigated these ‘abortive’ infections. They identified a sensor that detects viral DNA in the cell and activates the suicide response[1]. And they found that most of the cellular suicide occurs via a process called pyroptosis, in which the dying cells unleash a ferocious inflammatory response[2]. A key protein involved in pyroptosis is caspase 1, and an experimental caspase-1 inhibitor made by Vertex Pharmaceuticals in Cambridge, Massachusetts, had already been tested in humans as a potential treatment for epilepsy. The drug, VX-765, failed to help epileptics, but six-week-long studies suggested that it was safe.

Greene and his colleagues tested VX-765 in HIV-infected cells cultured from human tonsils and spleens, and found that it blocked pyroptosis, prevented CD4 cell death, and suppressed inflammation. Greene hopes that the approach could one day provide an alternative or embellishment to the antiretroviral drugs currently used by 9.7 million people worldwide to manage HIV infection.

Because a caspase-1 inhibitor would target a host protein rather than the virus, HIV is less likely to become resistant to the therapy, says Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases in Bethesda, Maryland. But any new HIV therapy will face steep competition from the more than 30 antiretroviral drugs currently available. “You’ve got to be pretty good to replace the antiretrovirals,” says Fauci.

Self-sacrifice

Understanding why HIV infection kills CD4 cells is an important step for researchers, says Gary Nabel, chief scientific officer at Sanofi, a pharmaceutical company headquartered in Paris. “We need to understand when a cell would rather die than let a virus infect it, and how the virus can evade that cellular suicide response to infection,” he says.

But Nabel also urges caution. He worries that some of the infections that Greene and his team consider abortive may progress if the immune cells survive. “Preventing cell death is a double-edged sword in the context of HIV,” he says. “Death can be protective if a T cell says ‘I’m going to die before I let this virus replicate and spread to other cells.’”

Greene counters that his team looked for evidence of progression to active infection, and found none. “Pyroptosis is not a strategy to protect the host from productive infection,” says Greene. “Instead, this is a pathway that actually promotes clinical progression to AIDS.”

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References

1. Monroe, K. M. et al. *Science* http://dx.doi.org/10.1126/science.1243640 (2013).
2. Doitsh, G. et al. *Nature* http://dx.doi.org/10.1038/nature12940 (2013).
3. Doitsh, G. *et al. Cell* **143**, 789–801 (2010).