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Anti-parasite drug may provide new way to attack HIV

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A drug already used to treat parasitic infections, and once looked at for cancer, also attacks the human immunodeficiency virus (HIV) in a new and powerful way, according to research published today online in the open access journal *Retrovirology*.

Past research has established that HIV has "learned" to hide out in certain human cells where it is safe from the body's counterattack, cells that come to serve as viral reservoirs. Operating from these havens, the virus slowly builds its numbers over more than a decade until it finally becomes capable of dismantling human immune defenses. In the end stages, this process leaves patients vulnerable to the opportunistic infections of AIDS. The newly published work explains for the first time how the virus makes chemical changes that keep its chosen reservoirs alive long past their normal lifespan. The new study also provides the first evidence that an existing ant-parasite drug can reverse this deadly longevity.

"AIDS continues to take nearly 3 million lives worldwide each year, and novel treatment approaches are urgently needed," said Baek Kim, Ph.D., associate professor in the Department of Microbiology & Immunology at the University of Rochester Medical Center. "We think our results are profound because, in discovering exactly how HIV hides in the body, we think we have learned how to take away its hiding places. Without them, the virus would have a much harder time causing disease," said Kim, lead author of the new study.

Secret to Long Life

Cell division is a process central to life. A parent cell divides into two cells, each containing copies of the same genes. This enables a single-cell human embryo to divide and grow into the vast number of cells that make up the human body. Different cell types divide at various speeds. T cells, for example, sense foreign organisms have invaded the body, and quickly divide and grow into a large, specifically designed army to attack the invader. Macrophages, on the other hand, are designed to roam the body engulfing and digesting dead tissue and bacteria. To assume this special role, they give up the ability to divide.

Unlike most viruses in its family, HIV has the ability to infect both non-dividing macrophages and rapidly dividing T cells, a key to its deadliness. Given its choice, HIV would prefer to infect rapidly dividing T cells, because with each division comes another opportunity for the virus to copy itself using the T cells' genetic machinery. On the other hand, T cells sense they are infected and quickly commit suicide, taking out the virus as well. So quickly do T cells self-destruct that the virus would lose its battle with the human immune system if it did not have long-lived macrophages to hide in during the early years of infection, Kim said.

Many cells can "choose" to die when they sense cancer-causing flaws in their own genes, or when they are being used as a virus factory. Certain biochemical pathways call for cell suicide and others postpone it, with the two forces counterpoised to control lifespan. Cancer and AIDS result in part from problems in these pathways.

Past studies found that HIV-infected macrophages can serve as viral reservoirs because some unknown factor extends their lifespan. In the brain, for example, macrophages secrete toxins produced by the virus they carry, including the transactivator (tat) protein, which causes nearby

nerve cells to commit suicide. When enough nerve cells die, patients gradually lose memory, speaking ability and decision-making skills despite the best available treatment. Presumably, such toxicity should cause brain macrophages to self-destruct as well, but that is not the case. Macrophages live on, and no one had known why until the publication of two papers by Kim's team, one today and the other in January 2007.

The earlier paper reported that macrophages infected with HIV live abnormally long, and that the long life may be related to the presence of the HIV protein tat. In the current study, researchers found the exact mechanism by which HIV turns on a series of cell survival signals in human macrophages: tat-related manipulation of the PI3K/Akt kinase pathway. Phosphatidylinositol 3 kinases (PI3K) are enzymes that turn on another enzyme, Akt, to prevent cell suicide and extend cell lifespan. Akt has been implicated in cancer, where cells live too long.

Kim's team discovered that a molecule called PTEN (phosphatase and tensin homologue deleted on chromosome 10) normally interferes with Akt signaling, and thus, limits cell lifespan. That is unless something interferes with PTEN. In a series of experiments, Kim's team observed that the presence of HIV tat in infected macrophages lowers PTEN levels by 40 percent, enabling the PI3K/Akt pathway to kick back on and keep macrophages alive. The study also found that an existing drug, miltefosine (Impavido®), inhibits PI3K/Akt pathway, and thus, promises to counter the effect of HIV tat on PTEN, Kim said. The treatment was first identified in Germany in the early 1980s as a potential treatment for breast cancer, but is used today to treat a common, parasitic infection called leishmaniasis.

Furthermore, researchers found that HIV-infected macrophages survive longer only when exposed to stress (e.g. toxins secreted by the virus infecting them). Most cells are expendable, and are ordered to self-destruct if exposed to enough stress. The PI3K/Akt pathway, however,

kicks on when cells are designed to survive despite surrounding toxicity (e.g. immune cells). Thus, the toxic environment created by HIV ensures the long-term production of HIV within long-lived macrophage reservoirs.

The current study was conducted jointly by the Medical Center and the University of Utah School of Medicine. Along with Kim, joining the effort in Rochester were Pauline Chugh, Birgit Bradel-Tretheway, Sanjay B. Maggirwar and Stephen Dewhurst. Carlos Maximiliano and Vicente Planelles led the effort in Utah. Retrovirology publishes peer-reviewed, high-impact articles on basic retrovirus research. The journal is edited by Kuan-Teh Jeang, M.D., Ph.D., head of the Molecular Virology Section at the National Institute of Allergy and Infectious Diseases, with the help of a respected editorial board, and has an impact factor of 4.32.

“Miltefosine puts an end to the long lives of HIV-infected macrophages,” Kim said. “The fact that it is already used in humans could accelerate the process of seeking government approval for a new, anti-HIV use for miltefosine, or something like it. In the next phase, we will conduct studies seeking to show that Akt inhibition ends the survival of HIV-infected macrophage reservoirs under real-life conditions.”

Source: University of Rochester

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