Researchers Identify Key Mechanisms Underlying HIV-Associated Cognitive Disorders

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While antiretroviral therapies have significantly improved and extended the lives of many HIV patients, another insidious and little discussed threat looms for aging sufferers – HIV-associated neurocognitive disorders (HAND). The disorders, which strike more often in HIV patients over age 50, can result in cognitive impairment, mild to severe, making everyday tasks a challenge.

But new findings, published today by researchers at the University of California, San Diego School of Medicine, open the door to the development of new therapies to block or decrease cognitive decline due to HAND, estimated to affect 10 to 50 percent of aging HIV sufferers to some degree.

The study is published in the Feb. 4 issue of the *Journal of Neuroscience*. Eliezer Masliah, MD, a professor of neurosciences and pathology, is senior author; Jerel Adam Fields, PhD, a postdoctoral researcher in Masliah's lab, is first author.

"Most people know HIV affects the immune system's ability to fight disease, but they may not be aware that HIV gets into the brain and can damage brain cells," said Masliah, an investigator with the HIV Neurobehaviorial Research Center at UC San Diego.

There are several types of HAND, the most common being Mild Neurocognitive Disorder (MND). "Most of the cases we see are mild to moderate," said Masliah. But even mild cognitive problems can interfere with everyday functioning and reduce quality of life, he added, noting that sufferers may have difficulty with daily activities like balancing a checkbook or driving directions.

In their study, the researchers sought to understand the mechanisms by which HIV damages brain cells. They focused on the HIV tat protein's role in a critical disposal process, known as autophagy, in neurons. "Neurons produce a lot of proteins as part of their normal functions, some of which are damaged and need to be cleared away," said Masliah. "Autophagy acts like a garbage disposal and removes and destroys the damaged proteins."

Masliah and colleagues found that HIV tat "hijacks" the disposal process by interfering with key pathways. "HIV tat is secreted from infected cells in the brain, and subsequently enters neurons

where it binds to a protein that is important for multiple autophagy pathways," explained Fields. "This binding disrupts the neuronal autophagy process, resulting in the accumulation of damaged proteins and death of the neuron. Overtime, this may lead to impaired cognitive abilities."

To counteract this disruption, Fields said the team conducted mouse studies using the cancer drug rapamycin, which has been reported to promote autophagy in other cell types. "By speeding up neuronal autophagy, we hoped to override the disruptive effects of HIV tat on the process," he said.

The experiments produced positive results. "We found that rapamycin reduced the incidence of neurodegeneration in the mice and in cell models," said Fields. While the feasibility of rapamycin as a neurological treatment in humans is currently inconclusive, Fields said the study's results are exciting because they prove, in principle, that enhancing autophagy reduces tat-induced neurodegeneration.

"By understanding the molecular underpinnings of how HIV proteins kill nerve cells, we can design drugs that will block this process," said Masliah.

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