

HIV is a 'double hit' to the brain

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New evidence reported in the August issue of *Cell Stem Cell*, a publication of Cell Press, offers a novel perspective on how the HIV/AIDS virus leads to learning and memory deficits, a condition known as HIV-associated dementia. A protein found on the surface of the virus not only kills some mature brain cells, as earlier studies had shown, but it also prevents the birth of new brain cells by crippling “adult neural progenitors,” the new study finds. Those progenitor cells are the closest thing to stem cells that have been found in the adult brain.

By elucidating the mechanism responsible for the neurodegeneration and dementia seen in people infected with HIV, the findings made in mice that produce the damaging HIV protein may open the door to new therapies, according to the researchers.

“The breakthrough here is that the AIDS virus prevents stem cells in the brain from dividing; it hangs them up,” said Stuart Lipton of the Burnham Institute for Medical Research and the University of California at San Diego. “It’s the first time that the virus has ever been shown to affect stem cells.”

“It’s a double hit to the brain,” added collaborator Marcus Kaul, who is also of the Burnham Institute and UCSD. “The HIV protein both causes brain injury and prevents its repair.”

Physicians first recognized that HIV infection could lead to a profound form of dementia—most commonly in those with an advanced stage of the disease—early on. The success of antiretroviral therapies in keeping

the “viral load” down has helped to reduce the severity of the dementia in recent years. Nonetheless, the prevalence is rising as HIV-infected people are living longer. The anti-HIV drugs don’t infiltrate the brain well, allowing for a “secret reservoir” of virus, Lipton explained. Such persistent exposure of the central nervous system to HIV is a major risk factor for the development of HIV-associated dementia.

Lipton’s team previously discovered that the brain deficits could be triggered by gp120—the viral coat protein that latches onto human cells—even in the absence of any viral infection. They also showed that the protein disrupts a key cell-cycle pathway (including p38 mitogen-activated protein kinase or MAPK), leading to the death of certain mature neurons.

The researchers now find that gp120 in mice also slows the production of new neurons in the hippocampus, a brain region central to learning and memory. Newborn neurons become integrated into existing brain circuits and are thought to contribute to certain forms of learning and memory, they said.

Moreover, they found that it is the same MAPK pathway earlier linked to the death of mature neurons that lies at the root of the progenitor cells’ dysfunction. That a similar enzyme is involved in both brain-damaging effects is simply “serendipitous,” according to the researchers.

“Knowing the mechanism, we can start to approach this therapeutically,” Lipton said. “This indicates that we might eventually treat this form of dementia by either ramping up brain repair or protecting the repair mechanism,” Kaul added.

Source: Cell Press

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