MedicalXpress

Research suggests new cellular targets for HIV drug development

May 27 2009

Focusing HIV drug development on immune cells called macrophages instead of traditionally targeted T cells could bring us closer to eradicating the disease, according to new research from University of Florida and five other institutions.

In the largest study of its kind, researchers found that in diseased cells — such as cancer cells — that are also infected with HIV, almost all the virus was packed into macrophages, whose job is to "eat" invading disease agents.

What's more, up to half of those macrophages were hybrids, formed when pieces of genetic material from several parent HIV viruses combined to form new strains.

Such "recombination" is responsible for formation of mutants that easily elude immune system surveillance and escape from anti-HIV drugs.

"Macrophages are these little factories producing new hybrid particles of the virus, making the virus probably even more aggressive over time," said study co-author Marco Salemi, Ph.D., an assistant professor in the department of pathology, immunology and laboratory medicine at the UF College of Medicine. "If we want to eradicate HIV we need to find a way to actually target the virus specifically infecting the macrophages."

The work was published recently in the journal PLoS ONE.

At least 1.1 million people in the United States and 33 million in the world are living with HIV/AIDS, according to the Kaiser Family Foundation.

The researchers set out to see if HIV populations that infect abnormal tissues are different from those that infect normal ones, and whether particular strains are associated with certain types of illness.

They tackled the question using frozen post-autopsy tissue samples, pathology results and advanced computational techniques. They analyzed 780 HIV sequences from 53 normal and abnormal tissues from seven patients who had died between 1995 and 2003 from various AIDS-related conditions, including HIV-associated dementia, non-Hodgkin's lymphoma and generalized infections throughout the body. Four patients had been treated with highly active antiretroviral therapy, called HAART, at or near the time of death.

The researchers compared brain and lymphoma tissues, which had heavy concentrations of macrophages, with lymphoid tissues — such as from the spleen and lymph nodes— that had a mix of HIV-infected macrophages and T cells.

The analyses revealed great diversity in the HIV strains present, with different tissues having hybrid viruses made up of slightly different sets of genes. A high frequency of such recombinant viruses was also found in tissues generally associated with disease processes, such as the meninges, spleen and lymph nodes.

The researchers concluded that HIV-infected macrophages might be implicated in tumor-producing mechanisms.

The higher frequency of recombinant virus in diseased tissues likely is because macrophages multiply as a result of an inflammatory response,

the researchers said.

"The study points to macrophages as a site of recombination in active disease," said neurobiologist Kenneth C. Williams, Ph.D., a Boston College associate professor and AIDS expert who was not involved in the study. "So people can say this is one spot where these viruses come from."

T cells — the so-called conductors of the immune system orchestra, whose decline is the hallmark of HIV disease — are an obvious target for HIV drug development because they die soon after infection, and are readily sampled from the blood and cultured. But although current drugs are effective at blocking infection of new cells and lowering viral loads to barely detectable levels, they never reduce the viral level in an infected person to zero.

"Where is it coming from?" said Michael S. McGrath, the University of California, San Francisco, professor who led the research team. "We believe it's coming from these macrophages."

Macrophages, like T cells, can be infected multiple times by HIV. But unlike T cells, when they get infected, they don't die within days, but live for several months, all the while being re-infected with multiple viruses of different genetic makeup. That situation is ripe for the emergence of hybrids.

"Most people who look at viral sequences assume that evolution of the virus is linear. In the real world that doesn't happen — large parts of the virus are swapped in and out. This group has shown that in this model," Williams said. "It sort of overturns the old way of trying to match virus sequence with pathology."

McGrath's group is now developing macrophage-targeting drugs that,

through a grant from the National Institute of Mental Health, should be in human clinical trials in a few years.

"This is one of the last frontiers — killing off what we believe is a so far untouched reservoir," he said.

Source: University of Florida (news : web)