Mummified HIV: It's Still Dangerous

In a perverse twist of nature, the body's mechanism for conferring long-term immunity against mumps or measles may also keep HIV infections going, report researchers at Virginia Commonwealth University in Richmond.

Specialized cells in the lymph nodes called follicular dendritic cells (FDCs) constitute a reference library for immune memory. But the new work indicates that FDCs somehow prompt the AIDS-causing virus to become highly infective, even when it's surrounded by antibodies that would normally neutralize it.

The lymph tissues thus become the major site of activity for HIV, especially during the "latent" period of the disease.

Earlier studies had hinted that lymph tissues harbor infection, but this work gives the first clear sign of how HIV infects immune cells in these sequestered sites, the group reports in the Oct. 26 NATURE.

With their "octopuslike extensions," explains coauthor Gregory F. Burton, FDCs form a web within the spongy tissues of the lymph nodes, tonsils, and spleen. There, they catch and hold antigens—foreign molecules from bacteria, viruses, and the like—as a mesh screen catches lint. For months or even years, the immune system's memory cells refer back to the antigens for information on how to combat these bacteria or viruses.

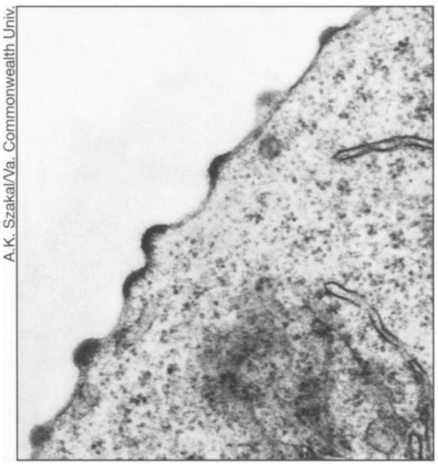
FDC surfaces can also trap whole viruses. In the case of HIV, the surfaces bind not to the virus directly but to antibodies coating it. These antibodies remain from earlier attempts by the body to neutralize the virus.

Immunologists have known for years that lymph tissues trap HIV. Researchers at the National Institutes of Health in Bethesda, Md., for example, showed that HIV congregates on FDC "fingers" as the infection grows. Since 1993, they've also known that HIV infects cells there.

No one knew, however, whether the molecularly mummified HIV, filtered from the blood and held in lymph tissues, could still infect. "One wouldn't expect HIV to be infectious here," says Burton, "because it's covered with antibody."

The new work clearly shows that HIV in lymph tissues remains active. In a test-tube experiment, researchers combined antibody-coated HIV with FDCs from the tonsils of uninfected people. They then added CD4+ T cells, the white blood cells that the virus typically attacks. Within a short time, the virus had infected the T cells.

Researchers also injected HIV into mice and then collected FDC cells from the animals' lymph nodes. The cells were dotted with antibody-coated HIV.



A.K. Szakal/Va. Commonwealth Univ.

In this electron micrograph, new AIDS viruses bud from the surface of infected cells in cultures of human lymph tissue and CD4+ T cells.

The group later added human T cells to the mouse lymph cells and found that HIV readily infected the T cells.

In a final test, the researchers added antibody-coated HIV to laboratory-grown T cells either with or without FDCs. In the absence of FDCs, the coated HIV did not infect the T cells, Burton says, "but if we put [FDCs] into the culture, all of a sudden there was tremendous infection." The researchers conclude that, once in the lymph tissue and linked with FDCs, the antibody-coated virus becomes infective.

"We don't know exactly what's happening," he adds. But the researchers suspect that the FDCs somehow push the virus' antibody coat aside, revealing areas that react with T cells.

What does this mean for experimental vaccines that aim to quell HIV by stimulating antibody production? Thailand, for example, is conducting tests of HIV vaccines on people. "The antibody vaccines may have some usefulness," Burton says, "but I don't think they will ever block infection completely because of what goes on at the FDCs." NIH's Anthony S. Fauci adds: "To say from this that the vaccines are no good is too major a leap."

— M. Centofanti

Viruses reveal the brain's fright circuits

If a mischievous child wearing a ghostly sheet or a witch's hat jumps out from behind a bush this Halloween, the surprise may start your heart pounding. Don't be embarrassed. That reaction is natural, part of the fight-or-flight response programmed into many animals.

When startled, an animal may quickly signal its adrenal gland to start pumping out hormones and its cardiovascular system to go into overdrive. For decades, investigators have known that the sympathetic nervous system, a series of neural connections that includes links from the brain to the heart and the adrenal gland, controls this involuntary response.

Yet brain imaging devices have indicated only roughly the brain regions driving the fight-or-flight reaction. Now, using genetically engineered viruses, researchers from Germany and the United States have tracked down specific brain cells that appear to direct both the adrenal and cardiovascular responses.

Using weakened versions of a herpesvirus that kills pigs, researchers tracked back from the organs to the brain cells controlling them. The viruses "infect sequential chains of neurons. . . . It's an extremely high-resolution way of analyzing brain circuits," explains Arthur D. Loewy of Washington University School of Medicine in St. Louis.

Loewy and his colleagues injected one form of the herpesvirus into the adrenal glands of rats and another into the animals' stellate ganglia, the main nerve bundles connecting heart and brain. After 4 days, investigators examined the rats' brains with antibodies that bind to a distinct protein made by each virus. Brain cells in the medulla and hypothalamus showed evidence of infection by both viruses, they report in the Oct. 27 SCIENCE.

"It's real solid work and quite innovative," says J. Patrick Card of the University of Pittsburgh, who also uses viruses to unravel brain circuits.

The viral tracking technique has enabled Loewy to examine what kinds of brain cells command the fight-or-flight response. "These viruses are so weak that they don't destroy the chemicals in neurons," he says.

Loewy and his colleagues hope to identify what other parts of the brain connect to the identified command neurons.

— J. Travis