Keeping herpes infection in check: researchers describe immune system strategies

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Herpes simplex virus type I can cause bouts of cold sores, blindness and potentially lethal encephalitis when it reawakens from a quiescent state in the nerve cells it infects.

To prevent these consequences, the stealthy virus is kept under constant guard by the immune system, say University of Pittsburgh scientists. Their research challenges the once common notion that latent HSV-1 in sensory neurons is invisible to the immune system.

Actually, immune cells keep the infection under close surveillance, actively holding HSV-1 in check without destroying the neurons harboring it, said Robert L. Hendricks, Ph.D., Joseph F. Novak professor and vice-chair for research in the Department of Ophthalmology and professor in the Departments of Immunology and Microbiology and Molecular Genetics at the University of Pittsburgh School of Medicine. Sensory neurons may not regenerate, so an immune system attack that destroys them could do more harm than good.

In a paper published in the October 10 issue of *Science*, teams led by Dr. Hendricks and Paul R. Kinchington, Ph.D., also a professor in the University of Pittsburgh School of Medicine Department of Ophthalmology, show one way this balancing act is carried out.

Immune cells called CD8 T cells attack virus-infected cells with lytic

granules, which are packets of potentially toxic enzymes. Transport of lytic granule contents into infected cells typically initiates a process that leads to a form of cellular suicide called apoptosis.

However, according to the researchers' experiments, that isn't the case when CD8 T cells target infected sensory neurons.

"Instead, the lytic granules attack the viral infection in neurons without killing them," explained Dr. Hendricks, senior author. "One way is through a lytic granule enzyme called granzyme B, which cleaves an important HSV-1 protein required for viral replication. That means the neuron and the virus survive, but the infection can't spread to other cells."

Recurrences of cold sores, eye disease and other forms of herpetic lesions occur if the balance shifts and the virus can bypass surveillance by the immune system.

Dr. Hendricks noted that up to 90 percent of people eventually become infected with HSV-1, many in childhood. The initial infection typically produces mild symptoms or none at all, but the virus remains in the neurons for a lifetime, occasionally waking up to cause disease. It repeatedly scars the cornea when this occurs in the eye, making HSV-1 a leading infectious cause of blindness.

Previous studies showed CD8 T cells can use interferon-gamma to block reactivation without killing the neuron, but only some sets of neurons are controlled in this manner, Dr. Hendricks said. His team will continue to try to identify how immune cells, HSV-1 and neurons interact, which could have implications for treatment and vaccine development for HSV-1 infections, as well as for gene therapy applications that use harmless versions of the herpes virus as a vector to ferry treatment genes into cells.

Source: University of Pittsburgh Schools of the Health Sciences