Discovery of protein that reactivates herpes simplex virus helps solve medical mystery

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Research in *PLoS Pathogens* appears to solve a long standing medical mystery by identifying a viral protein, VP16, as the molecular key that prompts herpes simplex virus (HSV) to exit latency and cause recurrent disease.

Led by researchers at Cincinnati Children's Hospital Medical Center and the University of Cincinnati College of Medicine, the landmark study points to a molecular target for designing improved HSV vaccines and treatments. It also could direct refined engineering of HSV viruses used in cancer therapy, the investigators said.

The study was conducted in collaboration with the Medical Research Council Virology Unit of Glasgow, Scotland.

The two distinct lifestyles of HSV - active and latent - were first proposed 80 years ago. The virus replicates itself at the body surface, producing thousands of copies that can be transmitted to other people. In neurons, however, the virus can enter a silent state, where the viral genetic code can be maintained for the lifetime of the infected person.

"Our current findings show that, in elegant simplicity, the herpes simplex virus regulates this complex lifecycle through the expression of VP16," said Nancy Sawtell, Ph.D., author and researcher in the Division of Infectious Diseases at Cincinnati Children's Hospital Medical Center.

The study points to what causes the virus to periodically reactivate in

latently infected neurons, prompting new rounds of virus replication at the body surface. By understanding how HSV achieves this complex interaction inside the human nervous system, researchers can gain crucial insight into how to control the spread of the virus. At present, there is no way to eliminate latent virus or prevent the virus from exiting latency. There also are no effective vaccines to protect people who are uninfected and transmission rates remain high, the researchers said.

In the study, the research team simulated high fever in a mouse model of HSV infection, demonstrating that VP16 must be produced before the virus can exit the latent state in neurons. Fever has long been known to induce HSV reactivation, and recurrent lesions are often called cold sores or fever blisters because of this association. In the vast majority of neurons, the virus remains latent. In a few neurons, however, the scientists observed that fever in the mice led to a stochastic, or random de-repression of VP16, causing the virus to exit latency and reactivate.

"This completely changes our thinking about how this virus reactivates from latency," said Richard Thompson, Ph.D., co-author and researcher in the Department of Molecular Genetics, Biochemistry and Microbiology at UC. "Instead of a simple positive switch that turns the virus on following stress, it appears instead to be a random de-repression of the VP16 gene that results in reactivation."

The leading infectious cause of blindness and acute sporadic encephalitis in the United States, HSV-1 is usually acquired during childhood. Both HSV-1 and HSV-2 can be sexually transmitted diseases that when passed to newborns during birth causes a severe and often fatal infection. As many as 80 percent or more of people are infected with HSV. Most of the time, people carrying the virus do not have symptoms, although they can still transmit the virus.

The researchers hypothesize that HSV usually remains latent because

VP16, which normally enters the cell with the virus particle, does not make the long trip the virus takes through the nervous system and isn't transported efficiently to the nerve cell nucleus.

Future studies will use this new information to develop strategies to prevent or control herpetic disease, said Dr. Sawtell, who also is an associate professor of Pediatrics at UC.

Source: Cincinnati Children's Hospital Medical Center