Map of herpes virus protein suggests a new drug therapy

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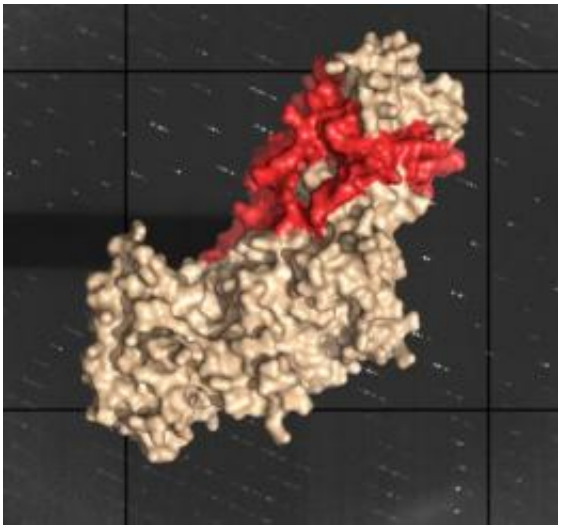

An image shows the structure of the cell-entry protein complex from herpes simplex virus type 2. One protein is represented in red, the other in beige. The background shows the x-ray diffraction pattern used to determine the structure of the protein complex. Credit: Image courtesy of Tirumala K. Chowdary, Tufts University School of Medicine

The mechanism by which a herpes virus invades cells has remained a mystery to scientists seeking to thwart this family of viruses. New research funded by the National Institutes of Health and published online in advance of print in *Nature Structural & Molecular Biology* reveals the unusual structure of the protein complex that allows a herpes virus to invade cells. This detailed map of a key piece of the herpes virus "cell-

entry machinery" gives scientists a new target for antiviral drugs.

"Most viruses need cell-entry proteins called fusogens in order to invade cells. We have known that the herpes virus fusogen does not act alone and that a complex of two other viral cell-entry proteins is always required. We expected that this complex was also a fusogen, but after determining the structure of this key protein complex, we found that it does not resemble other known fusogens," said senior author Ekaterina Heldwein, PhD, assistant professor in the molecular biology and microbiology department at Tufts University School of Medicine.

"This unexpected result leads us to believe that this protein complex is not a fusogen itself but that it regulates the fusogen. We also found that certain antibodies interfere with the ability of this protein complex to bind to the fusogen, evidence that antiviral drugs that target this interaction could prevent viral infection," Heldwein continued. Heldwein is also a member of the biochemistry and molecular microbiology program faculties at the Sackler School of Graduate Biomedical Sciences at Tufts.

"Katya Heldwein's work has resulted in a map of the protein complex needed to trigger herpes virus infection. The NIH Director's New Innovator Awards are designed to support such breakthroughs. This research not only adds to what we know about how herpes viruses infect mammalian cells, but also sets the stage for new therapeutics that restrict herpes virus's access to the cell," said Jeremy M. Berg, PhD, director of the National Institute of General Medical Sciences (NIGMS) at the National Institutes of Health.

"We hope that determining the structure of this essential piece of the herpes virus cell-entry machinery will help us answer some of the many questions about how herpes virus initiates infection. Knowing the structures of cell-entry proteins will help us find the best strategy for

interfering with this pervasive family of viruses," said first author Tirumala K. Chowdary, PhD, a postdoctoral associate in the department of molecular biology and microbiology at TUSM and member of Heldwein's lab.

Currently, there is no cure for herpes viruses. Upon infection, the viruses remain in the body for life and can stay inactive for long periods of time. When active, however, different herpes viruses can cause cold sores, blindness, encephalitis, or cancers. More than half of Americans are infected with herpes simplex virus type 1 (HSV-1), which causes cold sores, by the time they reach their 20s. Currently, about one in six Americans is infected with herpes simplex virus type 2 (HSV-2), the virus responsible for genital herpes. Complications of HSV-2, a sexually-transmitted disease, include recurrent painful genital sores, psychological distress, and, if transmitted from mother to child, potentially fatal infections in newborn infants.

Heldwein teamed up with colleagues at University of Pennsylvania and used x-ray crystallography along with cell microscopy techniques to study the structure and function of this cell-entry protein complex in HSV-2. Heldwein is currently developing a molecular movie that illustrates how herpes virus enters the cell.

More information: Chowdary TK, Cairns TM, Atanasiu D, Cohen GH, Eisenberg RJ, Heldwein EE. Nature Structural & Molecular Biology. 2010. "Crystal structure of the conserved herpesvirus fusion regulator complex gH-gL." Published online July 4, 2010, doi: 10.1038/nsmb.1837

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