Researchers explain how viral protein promotes deadly infection by Nipah and Hendra viruses

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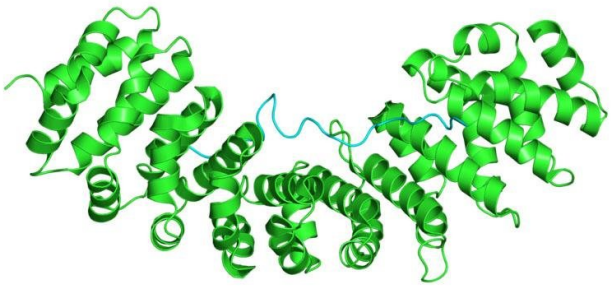

Nipah virus W protein C-terminus in complex with Importin alpha 3. Credit: Australian Nuclear Science and Technology Organisation (ANSTO)

Researchers have identified how a viral protein, which plays a major role in causing deadly Nipah and Hendra virus infections, targets a critical function in human cells to suppress immune responses and promote fatal disease.

The research team found the viral protein, called W protein, binds to two specific proteins in the host cell, importin ?3 and importin ?4, allowing it to move into the nucleus of cells. This allows the protein to disable defenses that protect cells from infection and promote growth of Nipah and Hendra viruses. The findings are published in the journal *Nature Communications*.

Nipah and Hendra viruses, closely related zoonotic pathogens that come from animal sources, are highly lethal in humans. Old World fruit bats are the source of both viruses in nature.

Hendra virus infections have been identified in Australia, mostly in veterinarians who were caring for horses. Scientists believe the virus passed from bats to horses, and then veterinarians came in contact with the sick horses.

Nipah virus was originally discovered in Malaysia in 1998. There was an outbreak of encephalitis, one of the symptoms of Nipah virus, in people working on pig farms. Scientists believe bats transmitted the virus to these pigs, and then people who came in contact with the infected pigs became sick. Forty percent of the people who became ill died. More recently, Nipah virus infections have been recognized in Bangladesh and India, with 70 to 75 percent fatality rates. This time, there seems to be a more direct transmission of the virus from bats to people.

"Right now, for humans, we lack any licensed vaccines or approved drugs to treat the infections," said Dr. Christopher Basler, senior author of the study, professor in the Institute for Biomedical Sciences and director of the Center for Microbial Pathogenesis at Georgia State University and a Georgia Research Alliance Eminent Scholar in Microbial Pathogenesis. "We need vaccines, we need treatments, and we also need to better understand what makes the viruses so deadly.

"The protein we're studying is called the W protein. We've been studying this protein for several years because it suppresses innate immune responses. This means that it blocks the very early defenses that should protect us from virus infection."

In previous work, Basler and his colleagues at the University of Texas Medical Branch at Galveston have studied the behavior of Nipah virus in animals. They wanted to understand how important W protein is for the ability of the virus to cause disease. Using facilities at University of Texas

Medical Branch at Galveston, they engineered a Nipah virus that couldn't produce the W protein and then put this modified virus into animals. This changed the course of disease and demonstrated that the function of the W protein is important for Nipah virus to cause disease.

In this study, a research team led by Dr. Jade K. Forwood of Charles Sturt University in Australia used structural biology approaches to investigate how the W protein travels from the cytoplasm to the nucleus of the cell through the interaction of W protein with importin ? proteins, which allow the W protein to get into the nucleus. The Basler laboratory at Georgia State performed studies in living cells to investigate the W protein interaction with importin ? proteins and define why this interaction is important for W protein function. In prior work, Basler has found the ability of the W protein to enter into the nucleus is important for its ability to block innate immune responses.

"One of the things that's interesting about the W protein being in the nucleus of the cell is that most of the other components of the virus remain in the cytoplasm of the cell throughout the replication cycle," Basler said. "We think that the W protein goes to the nucleus to do something, to somehow specifically target innate immune responses."

Human cells have seven different kinds of importin ? proteins. In this study, the researchers found W protein is using two of them, importin ?3 and importin ?4, to get into the nucleus. They identified specific features on the W protein that allow it to recognize those two members of the importin ? protein family and distinguish them from others.

"We're trying to understand how it selectively uses two of the seven family members for this," Basler said. "There's a broader biological question there. We don't really understand how this selectivity works or even really why it's important. We're trying to better understand the basis of that selectivity.

"I think you can argue that by understanding this, it may suggest strategies by which we can try to block the interaction between the viral protein (W) and the host protein (importin) that might be useful in terms of developing therapies that are designed to block this virus. If you had a drug that somehow prevented that interaction, W would no longer carry on its normal function and that would attenuate the virus and make it less able to cause disease."

More information: Kate M. Smith et al. Structural basis for importin alpha 3 specificity of W proteins in Hendra and Nipah viruses, *Nature Communications* (2018). DOI: 10.1038/s41467-018-05928-5

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