

Study Identifies How Hantaviruses Infect Lung Cells

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11/26/2018

Blocking a Cell Receptor Could Protect Against Deadly Disease.



Hantaviruses cause severe and sometimes fatal respiratory infections, but how they infect lung cells has been a mystery. In today's issue of *Nature*, an international team reports that hantaviruses gain entry to lung cells by "unlocking" a cell-surface receptor called protocadherin-1 (PCDH1). Deleting this receptor made lab animals highly resistant to infection. The findings show that targeting PCDH1 could be a useful strategy for developing drugs to treat deadly hantavirus pulmonary syndrome (HPS).

The study was co-led by Kartik Chandran, at the Albert Einstein College of Medicine; Thijn R. Brummelkamp, at the Netherlands Cancer Institute; John M. Dye, at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID); and Zhongde Wang, at Utah State University.

An Emerging Threat

HPS was first identified in 1993. A total of 728 cases have so far been reported in the United States, mainly in rural areas of western states. "While hantavirus infections are rare, they're expected to increase in the coming decades as temperatures across the globe rise due to climate

change. And we're totally unprepared for this possibility," said Chandran, professor of microbiology & immunology and Harold and Muriel Block Faculty Scholar in Virology at Einstein.

Hantavirus is transmitted to humans who inhale the virus from the urine, feces or saliva of infected rodents. Early HPS symptoms include fatigue, fever and muscle aches, followed after a week or so by coughing and shortness of breath. HPS has a mortality rate of around 40 percent, according to the Centers for Disease Control and Prevention. No treatments or vaccines are available. "Our findings provide new insights into how these infections develop and how they might be prevented or treated," added Chandran.

Detecting a Viral Entry Point

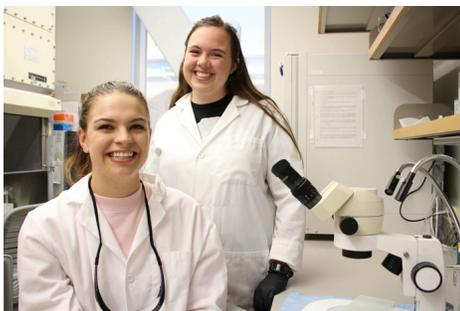
In seeking host factors that enable hantavirus infection, the researchers performed a "loss-of-function" genetic screen to see whether knocking out particular cellular genes could block hantavirus entry. The screen spotlighted the gene PCDH1, which codes for the protein receptor PCDH1 that is found on cell membranes. Strikingly, PCDH1 had previously been implicated in human respiratory function and lung disease but was not known to play a role in infection by hantaviruses or any other viruses.

To confirm that PCDH1 plays a role in hantavirus infection, the researchers deleted the gene from human pulmonary endothelial cells (i.e., cells that line the lung). These cells became highly resistant to infection by the two major HPS-causing hantaviruses found in North and South America: Sin Nombre virus and Andes virus.

Providing final proof that PCDH1 is a receptor required for hantavirus to enter cells required an animal model. Utah State University researchers contributed to this work by successfully employing the CRISPR/Cas9 system to develop the first PCDH1 knockout hamster model for the test.

Syrian golden hamsters (the primary rodent model for hantavirus studies) that were genetically engineered to lack the PCDH1 receptor were largely resistant to infection and lung injury caused by Andes virus. In contrast, most of the control animals, which possessed the receptor, succumbed to the virus. The work at USU is led by postdoctoral researcher Rong Li in the Wang lab. Also involved were USU undergraduate student researchers Riley Hunter and Kyra Bramwell, both working toward bachelor's degrees in the Department of Animal, Dairy and Veterinary Sciences.

The researchers also pinpointed a specific part of the PCDH1 protein that is directly recognized by hantaviruses, making this protein region a promising target for drug development.



“Our work not only provides the final proof that PCDH1 is a cellular receptor for hantavirus to establish infection and cause diseases but also establishes a much-needed animal model for developing anti-hantavirus therapeutics by using PCDH1 as the drug target,” said Wang, professor in USU’s Department of Animal, Dairy and Veterinary Sciences.

A major focus of the ongoing studies will be to reveal how PCDH1 mediates hantavirus infection. To accomplish this, USU researchers are employing gene-editing techniques to pinpoint the domains and amino acids required for hantavirus to bind and enter cells. These studies will provide the groundwork for developing highly specific inhibitor drugs, such as monoclonal antibodies, that interrupt hantavirus binding to PCDH1, thus preventing viral infection. Indeed, the team has generated monoclonal antibodies with a high affinity for this region of PCDH1 that could bind to lung endothelial cells and protect them from infection by Andes and Sin Nombre viruses.

Interestingly, a different group of hantaviruses that cause severe kidney disease in Europe and Asia and occasionally in the U.S. did not require the PCDH1 receptor for infection. “These viruses have other ways of invading cells that remain to be discovered,” said Rohit Jangra, research assistant professor at Einstein.

The article, *Protocadherin-1 is essential for cell entry by New World hantaviruses*, maybe read on [Nature’s website](#).

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The study is titled, “Protocadherin-1 is Critical for Cell Entry by New-world Hantaviruses.”

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This work is supported by funds from the National Institutes of Health (AI101436, AI132633 and AI125462), U.S. Joint Science and Technology Office/Defense Threat Reduction Agency,

Netherlands Organisation for Scientific Research, Cancer Genomics Center (Netherlands), Ammodo KNAW Award for Biomedical Sciences (Netherlands), Integrative Biology of Emerging Infectious Diseases Labex project (France), Investissements d’Avenir program (France), Canadian Institutes of Health Research, Comisión Nacional de Investigación Científica y Tecnológica (Chile), and the Irma T. Hirsch/Monique Weill-Caulier Trust.