Deadly virus's pathway to infect cells identified

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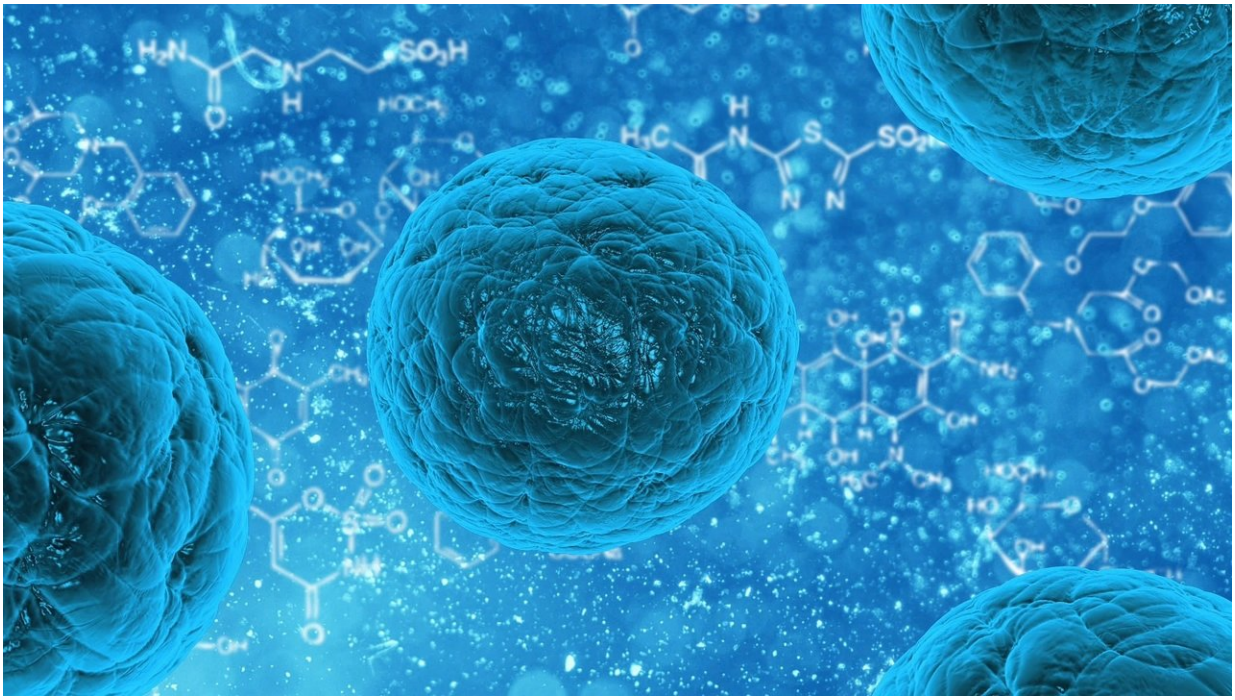

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Rift Valley fever virus causes economically devastating outbreaks of hemorrhagic fever in livestock such as sheep, goats and cattle. These mosquito-borne outbreaks lead to infection in people working with dead or dying animals, sometimes causing hundreds of human cases and dozens of deaths.

Rift Valley fever, for which there is no specific treatment, has been limited to Africa and the Arabian Peninsula. But mosquitoes capable of transmitting the virus can be found all over the world, necessitating a need to understand and control the virus.

Researchers at Washington University School of Medicine in St. Louis and the University of Pittsburgh Center for Vaccine Research and School of Public Health have discovered that the virus gets inside cells by taking advantage of a protein normally involved in taking up low-density lipoproteins (LDL, the carriers of so-called bad cholesterol) from the blood. The discovery, published Sept. 23 in the journal *Cell*, could lead to therapies that prevent Rift Valley fever or reduce its impact by interfering with the ability of the virus to get into cells.

"For people in areas where Rift Valley fever is endemic, an outbreak threatens not only their livelihood but their health," said co-senior author Gaya K. Amarasinghe, Ph.D., a professor of pathology & immunology and of biochemistry & molecular biophysics at Washington University. "People have a 1% to 2% chance of death if they get infected with this virus, which doesn't sound like much, but it's about the same as COVID-19. The disease is much more severe in domesticated animals, especially young animals, which get very ill and die in large numbers. This virus has been flying under the radar, but given that it's transmitted by mosquitoes that are found everywhere, it could spread into other parts of the world and become a serious issue."

The World Health Organization has listed Rift Valley fever as a prioritized disease likely to cause epidemics in the near future. The virus spreads easily among domesticated animals via mosquito bite. People also can be infected by mosquito bite, but most people who become infected are workers exposed to infected animal body fluids as they care for sick animals or dispose of their remains.

To find out how the virus invades cells, first author Safder Ganaie, Ph.D., a postdoctoral researcher who works with Amarasinghe, grew the virus on mouse cells in a dish. By systematically disrupting normal mouse genes, Ganaie and colleagues found that the virus failed to infect mouse cells that lacked certain genes, notably the gene for LDL receptor-related protein 1 (*Lrp1*). Further experiments showed that the virus needs LRP1 to infect mouse, hamster, cow, monkey and human cells, indicating that the virus uses the same protein across distantly related species.

The finding constitutes an opportunity. If the virus needs LRP1 to infect cells, then temporarily taking LRP1 out of commission may limit its ability to spread in the body, thereby reducing disease. The researchers used a protein that effectively does this. Called RAP, the protein attaches to LRP1 and fends off anything else that tries to attach.

The researchers infected a group of mice with the virus and simultaneously treated them with RAP. A second group of mice also was infected but was left untreated for comparison. Most of the treated mice survived, while all of the untreated mice died. Further, the treated mice had lower levels of virus throughout their bodies on the third day after infection compared with the untreated mice.

RAP itself is not a good prospect for drug development, since it's a normal mammalian protein that plays a role in many important biological processes. But the results suggest that targeting LRP1 may lead to therapeutics for Rift Valley fever.

"This finding is the key to understanding how Rift Valley fever virus spreads not only throughout the human body but also how it is able to infect mosquitoes and different species of mammals. Knowing how the virus spreads will help us develop targeted therapies, which currently do not exist for Rift Valley fever," said co-senior author Amy Hartman,

Ph.D., an associate professor of infectious diseases & microbiology at the University of Pittsburgh. "This discovery opens up new opportunities to study virus-host interactions at the cellular and organismal level and enriches our understanding of the basic biology of mosquito-transmitted emerging viruses."

The discovery that Rift Valley fever virus uses LRP1 to get inside cells is interesting because the protein is better known for its role in cholesterol metabolism. It also is thought to play a role in Alzheimer's disease and possibly in infections by the intestinal bacterium *C. difficile*. It's not clear why these disparate biological processes are linked, but Amarasinghe, Hartman and their collaborators already have several projects underway to explore these connections.

More information: Lrp1 is a host entry factor for Rift Valley Fever Virus, *Cell* (2021). DOI: 10.1016/j.cell.2021.09.001

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