Bleeding symptom leads scientists to intracellular trafficker's role in virus propagation

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Rodent-borne pathogens like hantaviruses and arenaviruses are simple, but resourceful, and very successful at propagating. Due to a tiny genome generating a mere four proteins compared to humans' thousands, they rely on human biological machinery to do their replication dirty work, facilitating infection, plus a high mortality rate. Vermont researchers have discovered a mechanism that when targeted, may stop these deadly viruses in their tracks.

A new study published in *Cell Host & Microbe* by the University of Vermont's Jason Botten, Ph.D., assistant professor of medicine and microbiology and molecular genetics, and graduate student Joseph Klaus and colleagues offers a paradigm shift for scientists' understanding of the functionality of a protein that resides in the cell's secretory pathway and gets "shuttled" from one end of the cell to the other.

Antivirals or vaccines do not exist for these pathogens, so gaining a better understanding of how they replicate was at the heart of Botten and colleagues' investigation.

"The 'catch' with these viruses is that each different species has a tailor-made mouse host, like a deer mouse, white-footed mouse, etc.," explains Botten. In addition, he says, because these viruses and their rodent hosts have co-evolved for millions of years, they do not cause any apparent disease in the mice. "It's a beautiful relationship," he remarks, noting

that because these viruses are not dependent on humans for their maintenance in nature, when humans do get infected, they get very sick.

The team closely examined the interaction between the virus proteins and the host proteins, a process that yielded the creation of a map – the first ever – of human protein partners of arenavirus and hantavirus glycoproteins (GPs). "The mapping allowed all kinds of analysis regarding which pathways of human cells the virus is tapping into," says Botten.

GPs reside on the surface of the virus and allow it to bind and enter host cells. After defining the human proteins that interact with each viral GP, the researchers examined which host proteins were common to both viruses, selecting one for further investigation – ERGIC-53, one of only three known intracellular cargo receptors.

"People who don't make ERGIC-53 have combined Factor V and Factor VIII deficiency, a mild form of hemophilia," Botten says. "Despite having this condition, these individuals are in good health, provided they get synthetic clotting factors or fresh frozen plasma following a major trauma or surgery. So in essence, people don't need ERGIC-53 to survive, which makes this an attractive antiviral target."

That initial connection – the fact that people with this deficiency bleed and people who get these types of hemmorhagic fever viruses bleed – was what got the researchers interested in ERGIC-53; they believed this protein could be important for both the propagation of these viruses as well as their ability to make people bleed.

The team got to work, seeking to determine just how ERGIC-53 might impact virus propagation. They quickly discovered that ERGIC-53 is absolutely essential for the propagation of arenaviruses. Additionally, "we found a new means for ERGIC-53 to associate with its viral partners

– binding to arenavirus GPs via a previously unknown, lectin-independent mechanism," Botten says. In fact, the team discovered that ERGIC-53 also interacts with the GPs of additional pathogenic RNA viruses such as orthomyxoviruses (e.g., influenza), coronaviruses (e.g., SARS), and filoviruses (e.g., Ebola and Marburg). Importantly, they discovered that virus particles decorated with Ebola or SARS virus GPs also critically depend on ERGIC-53 to be infectious.

New information centering on viral particles, which are produced when a person gets infected, were another important finding of the study. The group determined that ERGIC-53 is a "virion component" – it gets into the viral particle – and while virions still form without it, they are noninfectious. According to Botten, even in cases where ERGIC-53 is absent, a person could still make virus particles in his/her blood, but these particles would essentially be duds that cannot harm the infected person. However, these same particles will presumably be seen by the immune system, allowing the person to mount an effective immune response. Therefore targeting ERGIC-53 with an antiviral could result in an immunizing form of antiviral therapy.

"Overall, our findings show that ERGIC-53, which was already an interesting and important host protein due to its normal cargo receptor functions, has a new class of pathogen-derived ligands, namely the GPs encoded by a broad range of highly pathogenic viruses," says Botten, adding that "while ERGIC-53 represents a potential broad-spectrum antiviral target for arenaviruses, coronaviruses, and filoviruses, it may also be required for additional human pathogens, such as the New World hantaviruses, orthomyxoviruses, or retroviruses (e.g., HIV), based upon its conserved interaction with their GPs."

In the future, Botten and his colleagues hope to determine exactly how these viruses harness ERGIC-53 to ensure their reproductive success.

"If we can uncover this common mechanism, it might be possible to engineer a single therapeutic treatment that could be used to treat each of these devastating pathogens," he concludes.

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