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Scientists find a protein that inhibits Ebola from reaching out to infect neighboring cells

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Scientists at the University of Pennsylvania School of Veterinary Medicine have identified a protein, ISG15, that inhibits the Ebola virus from budding, the process by which viruses escape from cells and spread to infect neighboring cells.

This study shows for the first time how ISG15 slows the spread of Ebola virus budding, an observation that could help explain how ISG15 successfully inhibits other viruses, including HIV-1 and herpes simplex virus type I. The findings, reported in the current issue of the *Proceedings of the National Academy of Sciences*, offer the promise of future treatments for Ebola outbreaks that now prove fatal for as many as 90 percent of victims.

According to the Penn Vet research team, ISG15 inhibits budding in an indirect way, by blocking the behavior of a particular host cell protein which is used by Ebola and other viruses to efficiently escape from cells. ISG15 specifically inhibits the host protein, Nedd4, used by the viral protein VP40 to escape from cells and allow for virus spread.

“Inhibit the proteins used by a virus to reproduce and you are inhibiting the virus itself,” Ronald Harty, lead author of the study and associate professor in the Department of Pathobiology at Penn Vet, said. “Without host Nedd4, the Ebola virus still buds and attacks, but it doesn’t bud as well. The long-term goal of our research is to understand the interplay between host and virus, with the hope of creating an anti-viral drug or inhibitor, much like how Tamiflu doesn’t cure the flu but slows down the

viral process," Harty said. "The drug would be designed to dampen or slow down viral budding to allow an infected person's immune system to fight back."

The Ebola virus VP40 protein is the key player in the process of virus assembly and release from infected cells. VP40 buds from mammalian cells independent of other viral proteins, and efficient release of VP40 virus-like particles, VLPs, requires interactions with host proteins such as tsg101 and Nedd4, an E3 ubiquitin ligase. Ubiquitin itself is thought to be exploited by Ebola virus to facilitate efficient virus egress.

The study showed that expression of free ISG15, or the ISGylation System, UbE1L and UbcH8, inhibits budding of Ebola virus VP40 VLPs. Addressing the molecular mechanism of this inhibition, the researchers demonstrated that ISG15 interacts with Nedd4 ubiquitin ligase and inhibits ubiquitination of VP40, thus blocking budding of VP40 VLPs. These data provide evidence of antiviral activity of ISG15 against Ebola virus and suggest a mechanism of action involving disruption of Nedd4 function and subsequent ubiquitination of VP40.

This newest study has extended the team's knowledge of the reproductive process of Ebola and other viruses with similar reproductive mechanisms. Prior research by Harty and his team had shown that a sequence of four amino acids in VP40 was critical to the spread of the Ebola virus. VP40 appeared to be the necessary protein component to begin the viral budding process. The findings allowed researchers to target VP40 as a key to viral reproduction.

Penn researchers performed this research using only the VP40 protein found in the Ebola and other viruses. VP40 is not harmful in vitro, yet forms a virus-like particle, a unique phenomenon that allows for study of viral behavior without the danger associated with the virus.

Source: University of Pennsylvania