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A new strategy to beat Ebola virus at its own game

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ABSTRACT

We investigated how Ebola virus interacts with proteins in human cells. Doing this, we identified candidate drug targets including a human protein called RBBP6 that reduces the virus' growth. Using a small part of RBBP6 we could slow down the infection in the lab – a promising finding for future treatments.

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Ebola virus causes a deadly and highly contagious infection, known as Ebola hemorrhagic fever. Repeated outbreaks of severe, often deadly epidemics since Ebola was first identified in the 1970s have killed thousands of people and scared the world. The West African Ebola epidemic in 2014 was the most severe of all, where around 28,000 people got infected, resulting in 11,000 deaths. Giving the world no break, a new outbreak is currently raging in the Democratic Republic of the Congo. Ebola can easily spread from person to person and has a death rate of 50%, which makes it a ticking time bomb until outbreaks also outside of Africa will happen. Although there have been some promising experimental vaccines and drugs for use on an emergency basis, none of these are yet officially approved for use in patients. The lack of treatment options is a reflection of how little is known about this invasive disease that's inflicting serious harm globally.

Viruses are so small that they rely on the help of the cells they infect to replicate and spread. To enter our body and successfully grow, they mimic parts of the human cells. Understanding how viruses hide within plain sight by these tactics of mimicry, as well as how

they manage to hijack the unwitting patient's resources will help us find much-needed treatments, and thus save many lives. In a recently published report, we did just this: we set out to find out how Ebola virus interacts with human components and found the first hint for a potential new way to fight off Ebola infection.

To hunt for and catalogue the interactions that Ebola virus makes with the human body, we used Mass Spectrometry, a technique that can be used to identify the composition of a given sample based on the different weights of the components in the mixture. In our study, we used all the individual proteins Ebola virus contains (6 in total) to 'fish' for the human proteins that bind to them. Then, we used Mass Spectrometry to identify what we 'caught', and learn about which parts of the cell Ebola relies on most. This allowed us to pick out the most interesting results, and study them in detail.

Our Ebola 'fishing' method helped us find 194 human proteins the virus uses while growing. Going further, a strong interaction between one Ebola virus protein (called VP30) and a human protein (called RBBP6) stood out. We found that when we engineered human cells to have no RBBP6, Ebola could grow much faster than in normal cells. Further, we employed a technique called X-ray Crystallography that allows us to visualize the (very!) small structures of these proteins, and learn important things. In this case, the structure indicated that the human protein RBBP6 mimics another Ebola virus protein (called NP) in binding to VP30, and therefore prevents a critical interaction (NP with VP30) that is needed for the virus to grow. Moreover, it seems that VP30 cannot distinguish between human protein (RBBP6) and viral protein (NP), because they look so similar. This knowledge allowed us to use a small piece of RBBP6 to reduce Ebola virus replication – at least in the lab. This is an exciting first step towards a new drug against Ebola virus infection!

Unable to reproduce on their own, viruses have evolved to use parts of the infected human cell to grow and spread. In our studies, we have identified a human protein called RBBP6, which mimics an Ebola virus protein, and can help fend off a viral attack. Thus, it appears that the human body has a natural way to combat Ebola virus infection, and without this protection, the deadly virus would be even more fatal. This defense mechanism has therapeutic potential, too: we were able to show that by using a small part of RBBP6, we could slow down Ebola growth in the lab. We foresee that a small molecule drug mimicking the human protein RBBP6 could lead to a therapeutic against the deadly disease. This wasn't the only point of attack we identified: the remaining 193 human proteins we found to bind to Ebola could also be leveraged for suppressing Ebola virus growth, and to find new ways of treatment. With each discovery in our ongoing research, we come one step closer to new methods to intervene in the Ebola virus disease, and thus finding the cure for the virus.