Ebola is a master of disguise

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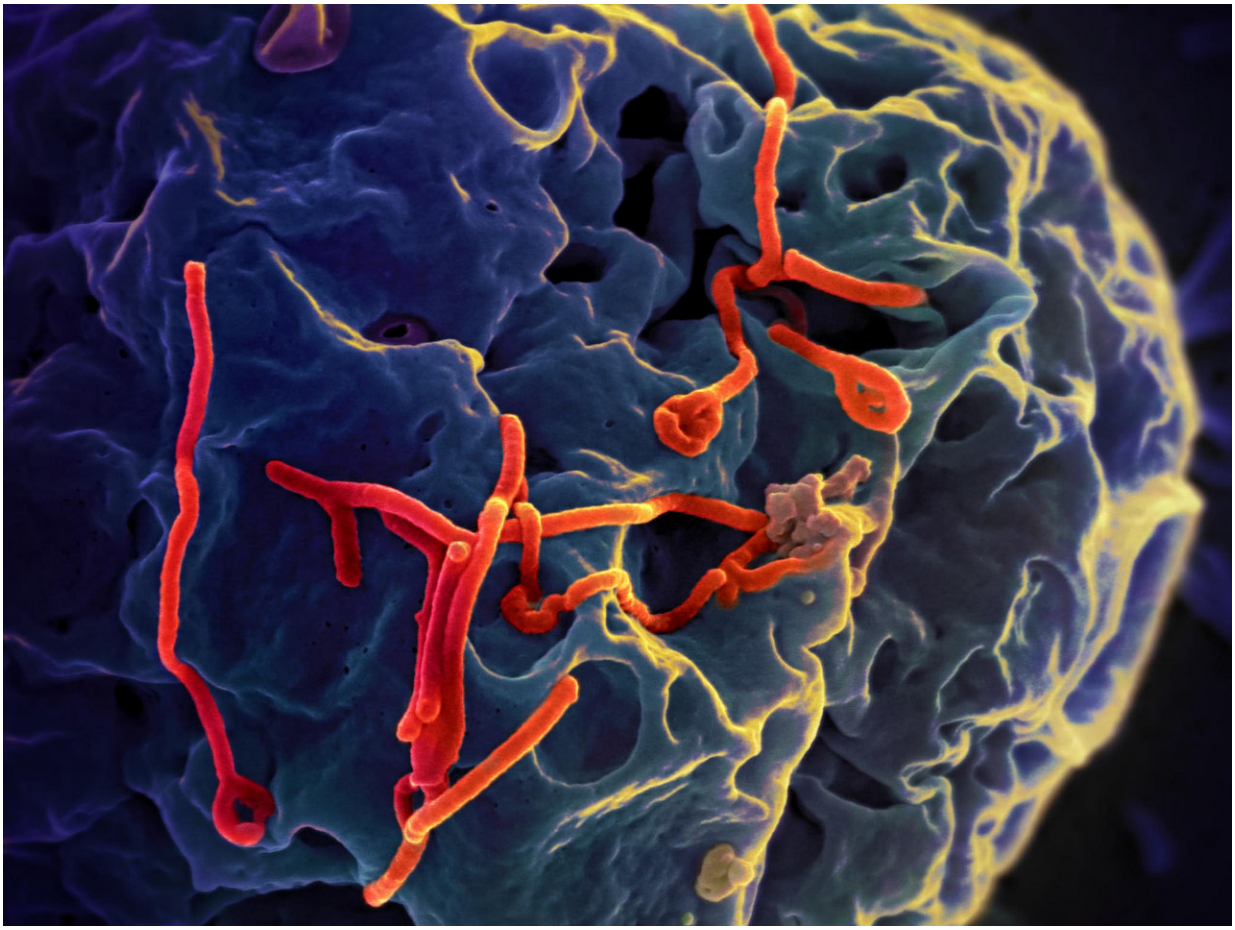

Ebola virus particles (red) on a larger cell. Credit: NIAID

It was once thought that Ebola and related filoviruses were more or less contained to Central Africa. After a West African outbreak and the discovery of Reston ebolavirus in the Philippines, cuevavirus in Spain

and various bat filoviruses in China, researchers now understand that this viral family—causing hemorrhagic fevers with up to 90% case fatality rates—has been widespread around the world for millions of years.

Our defenses against it are more embryonic, and though we have a vaccine against one species of Ebola and some therapeutic antibodies on the horizon, both have production or distribution issues. What doctors have been hoping for is a regular drug that can treat Ebola as soon as it rears its terrifying head. A study published today in the journal *PLOS Pathogens*, identifies a pathway that all filoviruses use to gain entry into our cells—and shows how they can be stopped in their tracks by at least one FDA-approved drug.

Ebola is so pernicious because it pulls a fast one on the body, disguising itself as a dying cell.

"It's cloaking itself in a lipid that is normally not exposed at the surface of a cell. It's only exposed when the cell is undergoing apoptosis," says Dr. Marceline Côté, an associate professor in the department of Biochemistry, Microbiology and Immunology, Canada Research Chair in Molecular Virology and Antiviral Therapeutics and the primary investigator on this study. Dr. Côté is a leading global expert on how viruses get into us, an understanding that is key to any effort to keep them out.

The malingering virus is then taken up by immune system cells that unwittingly carry the virus to other parts of the body, disseminating the infection. Virtually all organs become active sites of replication, and the result is a vicious, multi-system disease. Once it tricks its way into the cell, the virus needs to find a specific receptor that serves as the lock for its glycoprotein key, kicking off the process that will allow it to multiply. A drug that prevents it from any one step in turning that key could defeat the disease.

Dr. Côté's team, in particular Ph.D. student Corina Stewart, tested a library of drugs against a virus in cell cultures. It's not safe to work with a replicating Ebola virus in a regular lab, so the uOttawa team used a surrogate system.

"We use a safe virus disguised as an Ebola virus. They will enter just the same way as an Ebola virus, but actually the inside core when they uncoat is all safe stuff," says Dr. Coté. "It's murine leukemia virus or engineered retroviruses, so nothing to worry about."

Once they found a collection of drugs that seemed to work, they passed the data to collaborator Dr. Darwyn Kobasa at the National Microbiology Laboratory in Winnipeg, where a biosafety level 4 rating allows researchers to handle the bona fide virus. Dr. Kobasa confirmed that a small number of cancer chemotherapy drugs were effective in preventing Ebola from gaining a foothold in the cells.

Though these types of drugs can be tough on the body, an Ebola infection carries a high risk of death. What's more, the infection doesn't last long, so any unpleasant treatment can be similarly brief.

Knowing which drugs worked against Ebola also tells the team more about how the virus gets in. In particular, this study shows that Ebola virus has evolved ways to be active in its invasion of a cell. Previously, it was thought that viral entry was left mostly up to chance, with many particles being left behind while a random few were taken up into the cell. Dr. Côté's study shows the virus has evolved to get in very efficiently, rather than just going along for the ride.

"They are not passive passengers," says Dr. Côté. "They have their hands on the steering wheel."

More information: Corina M. Stewart et al, Ebola virus triggers

receptor tyrosine kinase-dependent signaling to promote the delivery of viral particles to entry-conducive intracellular compartments, *PLOS Pathogens* (2021). DOI: 10.1371/journal.ppat.1009275