Achilles heel discovered in Ebola virus may lead to future treatment

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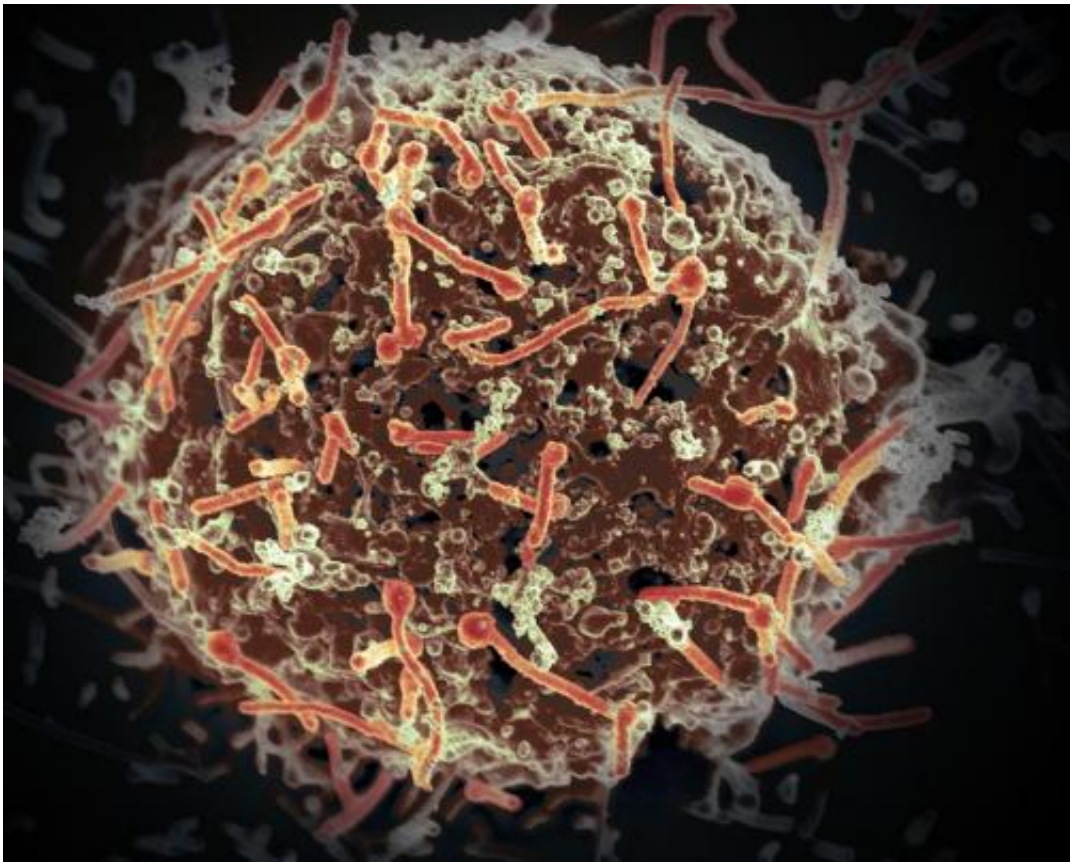

The Ebola virus, isolated in November 2014 from patient blood samples obtained in Mali. The virus was isolated on Vero cells in a BSL-4 suite at Rocky Mountain Laboratories. Credit: NIAID

(Medical Xpress)—A team of researchers working at Oxford University in the U.K. has found what appears to be an Achilles heel in the Ebola

virus—a pocket able to hold destabilizing compounds. In their paper published in the journal *Nature*, the team describes the pocket they discovered and two drugs that when used to occupy the pocket, caused the virus to become unstable and thus unable to reproduce.

The Ebola virus, as the researchers note, has caused massive suffering and the deaths of hundreds of thousands of people during 30 recorded outbreaks over just the past 40 years, including one just last year—the worse yet. Scientists are still struggling in their search for both an inoculation against the disease and a viable treatment for those infected. In this new effort, the researchers report a possible breakthrough in the latter.

Careful study of the mechanism involved when the virus infects a cell revealed that one of the critical factors for the virus in reproduction, is an ability to firmly attach itself to a cell—it does so through the use of a glycoprotein. It was this glycoprotein that the researchers examined at a much higher resolution than ever before. In so doing, they found what they describe as a pocket—a part of the protein that is empty. That suggested to the researchers a vulnerability—if they could find a compound that would fit in that pocket that would cause problems for the virus in attaching itself to a cell, that would prevent the virus from reproducing.

Studies with mice showed that two drugs already on the market fit the bill. One, Toremifene, is currently used as part of chemotherapy to treat cancer; the other Ibuprofen is currently used to treat pain and inflammation. Both fit in the pocket and both destabilized the virus. The fact that both are already in use is exciting because it means they will not have to go through clinical trials. But, there are also reasons to be cautious, neither drug has been tested in any other animal, much less humans, as a treatment for Ebola. The next step will be to test them in macaques, which are of course, a much better match. But, the

researchers note, even if neither drug turns out to be appropriate for treating Ebola, they have demonstrated that it is likely that one can be found.

More information: Yuguang Zhao et al. Toremifene interacts with and destabilizes the Ebola virus glycoprotein, *Nature* (2016). DOI: 10.1038/nature18615

Abstract

Ebola viruses (EBOVs) are responsible for repeated outbreaks of fatal infections, including the recent deadly epidemic in West Africa. There are currently no approved therapeutic drugs or vaccines for the disease. EBOV has a membrane envelope decorated by trimers of a glycoprotein (GP, cleaved by furin to form GP1 and GP2 subunits), which is solely responsible for host cell attachment, endosomal entry and membrane fusion. GP is thus a primary target for the development of antiviral drugs. Here we report the first, to our knowledge, unliganded structure of EBOV GP, and high-resolution complexes of GP with the anticancer drug toremifene and the painkiller ibuprofen. The high-resolution apo structure gives a more complete and accurate picture of the molecule, and allows conformational changes introduced by antibody and receptor binding to be deciphered. Unexpectedly, both toremifene and ibuprofen bind in a cavity between the attachment (GP1) and fusion (GP2) subunits at the entrance to a large tunnel that links with equivalent tunnels from the other monomers of the trimer at the three-fold axis. Protein–drug interactions with both GP1 and GP2 are predominately hydrophobic. Residues lining the binding site are highly conserved among filoviruses except Marburg virus (MARV), suggesting that MARV may not bind these drugs. Thermal shift assays show up to a 14 °C decrease in the protein melting temperature after toremifene binding, while ibuprofen has only a marginal effect and is a less potent inhibitor. These results suggest that inhibitor binding destabilizes GP and triggers premature release of GP2, thereby preventing fusion between the viral

and endosome membranes. Thus, these complex structures reveal the mechanism of inhibition and may guide the development of more powerful anti-EBOV drugs.

Press release