Trapping the Ebola virus in transit

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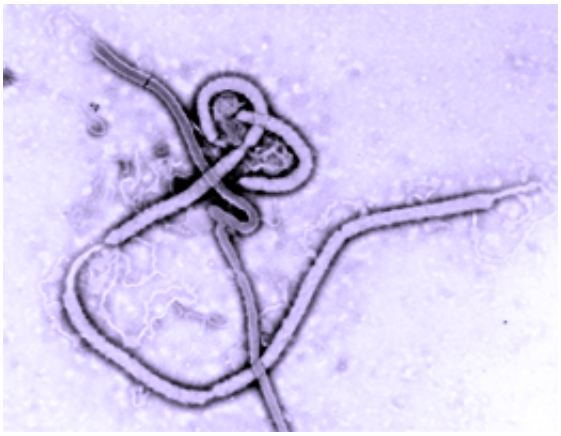

Credit: CDC / wikipedia.org

The deadly Ebola virus makes use of host mechanisms – including a specific type of membrane-bound calcium channel – to gain entry into the cell cytoplasm. LMU researchers now show that blocking this channel markedly inhibits infection.

In recent weeks, reports from West Africa, which has experienced by far the worst Ebola epidemic yet seen, have signaled a turn for the better in the fight against the disease. In the three countries worst affected, the number of new infections has fallen significantly. Indeed, the World Health Organization (WHO) has officially declared that the epidemic in Mali has ended, although that announcement could yet prove premature. After all, no previous outbreak has been so prolonged or so extensive. Furthermore, in areas where the epidemic is still raging, there has been

little change in the incidence of lethality, and the majority of infected patients succumb to the disease. There are still no effective and readily available treatments, although several promising lead candidates are now undergoing early clinical testing. The virus causes a severe hemorrhagic fever, which leads to widespread internal bleeding and ultimately results in death owing to multiple organ failure.

How the virus infects host cells and exploits their metabolism for the production of new virus particles is not fully understood. A collaborative effort involving teams based in Germany and in the US has now supplied one of the missing pieces of the puzzle – and uncovered a new target for therapeutic drugs to combat the infection. The new work, carried out by research groups led by pharmacologists Martin Biel and Christian Wahl at LMU, and virologist Dr. Robert Davey at the Texas Biomedical Research Institute in San Antonio, is reported in the leading American journal "*Science*".

The Ebola virus (EBOV) infects macrophages (whose normal function is to dispose of pathogens that have been marked for destruction by other cells of the immune system) by latching onto specific receptor molecules found on their surfaces. Receptor binding causes the cell membrane to fold inwards like a pouch which is then pinched off, engulfing the receptors and the attached viruses in so-called endocytic vesicles. These "endosomes" then fuse with another type of vesicles called lysosomes. Specific ion-channel proteins in the lysosomal membrane, known as two-pore channels (TPCs), are known to play an important role in the fusion process. Biel and his colleagues have now shown that TPCs are essential for the establishment of an Ebola infection: Upon binding of an endosome, the TPCs release a stream of calcium ions into the cytoplasm that serves as a signal for membrane fusion, which is required to ensure that Ebola infection cycle can proceed. If the TPCs are genetically defective or functionally inhibited, the viruses remain trapped in the endosomes, effectively aborting the infection.

The researchers also found that tetrandrine, an alkaloid derived from plants which has long been used in traditional Chinese medicine, effectively inhibits infection of isolated macrophages by EBOV. Experiments carried out by the American group in their state-of-the art containment facility in San Antonio confirmed that the agent is therapeutically active in mice inoculated with the virus, while displaying relatively low toxicity. Meanwhile, the ion-channel experts in Munich took a closer look at the interaction between tetrandrine and TPCs and analyzed its effect on their function. The fact that the LMU team had previously created mouse strains that lack individual TPCs was the crucial element in this part of the project. Some of this work were carried out under the auspices of the Center for integrated Protein Science Munich (CiPSM) – a Cluster of Excellence – and the Transregio-Collaborative Research Center 152 "TRiPs to Homeostasis: Maintenance of Body Homeostasis by Transient Receptor Potential Channel Modules".

Martin Biel believes that targeting the TPCs represents a promising strategy for fighting the virus. "Instead of trying to kill the virus, we simply ensure that it is no longer infectious," he points out. "We don't attack it directly; we take a roundabout route, interrupting the progress of the infection." This reduces the risk that the virus's propensity to mutate will allow it rapidly to become resistant to this kind of inhibitor. The Munich team now plans to improve the pharmacological and biochemical properties of tetrandrine and enhance its specificity for the ion channel. "I am quite optimistic," says Biel. "I think there's a pretty good chance that a useful drug candidate will emerge from this work."

More information: "Two-pore channels control Ebola virus host cell entry and are drug targets for disease treatment." *Science* 27 February 2015: Vol. 347 no. 6225 pp. 995-998 DOI: 10.1126/science.1258758

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