MedicalXpress

Real-time Ebola fusion system yields clues to stopping infection

February 10 2016

Researchers have developed the first real-time system to watch directly through the microscope as Ebola-like virus particles fuse with human cells to infect them. Their findings, published this week in mBio, an online open-access journal of the American Society for Microbiology, reveal key host cell and viral proteins that direct fusion and Ebola infection. Such knowledge is crucial for designing future drugs or vaccines to prevent this deadly disease.

"The 2014-2015 Ebola epidemic caused a regional health emergency in West Africa, shattering the healthcare infrastructure there and causing more than 11,000 deaths," says Kartik Chandran, associate professor of microbiology and immunology at Albert Einstein College of Medicine in Bronx, New York. "But we don't know when and where the next outbreak will occur. There is a serious need for treatments that protect against Ebola and related viruses."

Chandran's laboratory studies the first stages of Ebola infection—how the virus first enters cells, required to make more copies of itself. Like other viruses, Ebola has evolved to convince cells to engulf it and deliver it to the 'recycling yard' of the cell, the endosome. This endosomal pathway normally breaks things down to absorb and recycle their components, but Ebola virus hijacks the pathway's functions to infiltrate cells.

Led by postdoctoral researcher Jennifer Spence, Chandran's team designed a system to watch in real time and track the initial step of

infection. At this stage, Ebola virus, enveloped in its own membrane, fuses with the cell's endosomal compartment membrane to release the virus' genes into the cell's inner workings. "This entire entry step is rich in targets for developing antiviral treatments," explains Chandran.

The researchers engineered an Ebola-like virus that contained a special, self-quenching fluorescent dye in its membrane. When the viral membranes mixed with the unlabeled cellular membrane during fusion, the dye lit up, allowing the researchers to monitor fusion events directly.

Using this system, Spence and Chandran showed that a specific cellular protein, called NPC1, must interact directly with the Ebola glycoprotein for fusion to occur. They also found that the ZMappTM antibody cocktail—used to fight Ebola infections in the latest epidemic—works by blocking the first stages of fusion. Finally, they identified the specific cellular compartment where fusion begins, and showed that full fusion also requires other cellular proteins, called cathepsin proteases, at a later stage.

"This is the first time we are able to robustly follow the Ebola fusion initiation in real time, and it will allow us to look at even more aspects of the process and cellular factors involved in the future," says Spence. The researchers also learned that a very low percentage, just 10%, of viral particles initiate fusion.

Ultimately, Chandran's team would like to rebuild the entire Ebola infection process in the lab, including the final fusion event that releases the viral RNA genome into the cell. Identifying the most vulnerable links in that process would give drug developers the best molecules to target with drugs or vaccines. "Our work shows that preventing the virus from binding NPC1 would be a great way to block Ebola infection," he says.

More information: Jennifer S. Spence et al. Direct Visualization of

Ebola Virus Fusion Triggering in the Endocytic Pathway, *mBio* (2016). DOI: 10.1128/mBio.01857-15