Scientists uncover Ebola cell-invasion strategy

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University of Texas Medical Branch at Galveston researchers have discovered a key biochemical link in the process by which the Ebola Zaire virus infects cells — a critical step to finding a way to treat the deadly disease produced by the virus.

Ebola produces severe and often fatal hemorrhagic fever in its victims and inflicts mortality rates close to 90 percent in some outbreaks. No vaccine or antiviral therapy has been developed against the virus, and it is considered a high-risk agent for bioterrorism. In addition, recent devastating outbreaks hit in Uganda in 2008 and the Democratic Republic of the Congo in 2007.

The UTMB group tied Ebola's cellular invasion mechanism to a series of biochemical reactions called the phophoinositide-3 kinase pathway (named for an enzyme found in the cell membrane). By activating the PI3 kinase pathway, they found, an Ebola virus particle tricks the cell into drawing it into a bubble-like compartment known as an endosome, which is pulled, together with the virus, into the cell. Then – at a critical point — the virus bursts free from the endosome and begins to reproduce itself.

However, if the PI3 kinase pathway is shut down — as the UTMB team did with a drug designed for that purpose — Ebola virus particles can't escape from the endosome, and the disease process comes to a halt.

"The nice part about identifying entry mechanisms is you can prevent

the virus from infecting the cell," said UTMB microbiology and immunology associate professor Robert Davey, senior author of a paper on the investigation appearing online in the current issue of the journal *PloS Pathogens*. "You can stop the whole show before it even gets started."

The researchers did some of their work using the Ebola Zaire virus itself, working in UTMB's Robert E. Shope, MD, Biosafety Level 4 laboratory to ensure their safety. They also conducted experiments using harmless, hollow, virus-like particles coated with the critical envelope proteins that activate the PI3 kinase pathway.

Using a unique test created at UTMB that adds a light-emitting molecular beacon, called luciferase, to Ebola viruses and the virus-like particles, the investigators were able to determine exactly when and where each broke out of its bubble, and track its progress.

"Up to that point, it's really a bus ride for these viruses, and PI3 kinase is the bus driver," Davey said. "Whether you're talking about Ebola or Ebola virus-like particles, they've all got the virus envelope proteins that trigger the PI3 kinase pathway, which is the first step of getting the virus onto that bus."

Davey noted that while other viruses had been found that activated the PI3 kinase pathway, Ebola was the first with envelope proteins that had been seen doing so. In addition, he said, it was the first virus to be discovered interacting with the PI3 kinase pathway in order to enter cells, which could have profound implications.

"It's actually triggering the reorganizing of the cell for its own devious outcomes — infecting the cell," Davey said. "But there are other possible outcomes of fiddling around with the PI3 kinase. You can get the cell to move, you can get it to live longer, all advantages for a virus. So I'm sure

that this is going to be important in other viruses."

In addition, a new generation of drugs are being developed that target PI3 kinase, since the enzyme is often activated in cancers. It is possible that these could also be used to defend against Ebola virus.

Source: University of Texas Medical Branch at Galveston