Scientists block Ebola infection in cell-culture experiments

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Researchers at the University of Texas Medical Branch at Galveston have discovered two biochemical pathways that the Ebola virus relies on to infect cells. Using substances that block the activation of those pathways, they've prevented Ebola infection in cell culture experiments — potentially providing a critical early step in developing the first successful therapy for the deadly virus.

Ebola inflicts severe and often fatal hemorrhagic fever on its victims, producing 90 percent mortality rates in some outbreaks. No vaccine exists for the virus, and it is considered a high-risk agent for bioterrorism. Natural Ebola outbreaks strike periodically, often with devastating effect; recent examples include outbreaks in Uganda in 2008 and the Democratic Republic of the Congo in 2007.

The UTMB team took a new approach to stopping viral infection, using powerful new computational and analytical techniques to focus more on the host cell than the virus, according to microbiology and immunology associate professor Robert Davey.

"The premise for this work is that the virus is essentially nothing without a cell," said Davey, lead author of a paper on the research appearing this month in the journal *Drug Discovery Research*. "It needs to rely on many cell proteins and factors for it to replicate. The idea is that if we can suppress the expression of those cell proteins for just a short time, we can then stop the disease in its tracks."

To identify the critical proteins, the UTMB researchers — including research scientist Andrey A. Kolokoltsov, assistant professor Mohammad F. Saeed, postdoctoral fellow Alexander N. Freiberg and assistant professor Michael R. Holbrook — first conducted large-scale screening experiments using sets of cells treated with small interfering RNA (siRNA) to block 735 different genes that might produce proteins important to Ebola infection. They then added Ebola "pseudotype" viruses, artificially created virus particles made by wrapping Ebola envelope proteins around a core of genetic material from another virus. (The resulting viruses behave just like Ebola when infecting a cell, but are safe enough to work with in an ordinary lab.)

"We got a number of hits, quite a lot of places where the virus wasn't infecting the cells," Davey said. "The problem was then to understand what those hits meant."

To make sense of the data, the researchers turned to a newly developed statistical algorithm designed especially to prioritize the results of siRNA screens. After subjecting that output to further computational analysis, they found that two networks of biochemical reactions seemed particularly important to Ebola's entry into cells: The PI3 kinase pathway and the CAMK2 pathway. Since drugs to block both pathways are available, the UTMB group decided to investigate whether they would interfere with Ebola infection of cells — first using virus pseudotypes, and then, in UTMB's maximum containment BSL4 "spacesuit" lab, with Ebola Zaire itself, the variety of the virus most associated with high mortality rates.

"With the real virus in the BSL4, we found that the PI3 kinase inhibitor dropped virus titers by 65 percent, and if we used drugs which block CAMK2 function, it was just killed — stopped dead," Davey said. "This is really, very, very interesting because this pathway has a lot of potential for future pharmaceutical exploitation."

Source: University of Texas Medical Branch at Galveston (news : web)