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Single Protein, Key to Ebola Virus Infection, Could Aid in Drug Design

Research published by two teams of Army scientists and collaborators has identified a cellular protein that plays a critical role in Ebola virus infection. The findings, published online today in separate studies in the journal *Nature*, suggest a possible strategy for combating one of the world's most deadly viruses.

Ebola causes hemorrhagic fever with case fatality rates as high as 90 percent in humans. The virus is of concern both as a global public health threat and as a potential agent of biological terrorism. Currently there are no available vaccines or therapies to combat the disease. In addition, much is still unknown about the exact mechanism by which Ebola virus invades cells and causes infection.

In one *Nature* study, scientists from USAMRIID, Albert Einstein College of Medicine, the Whitehead Institute for Biomedical Research, and Harvard Medical School searched for proteins that Ebola virus might use to enter cells. One such cellular protein, known as Niemann-Pick C1 (NPC1), stood out: The team found that if cells don't make NPC1, they cannot be infected by Ebola virus.

According to the authors, the NPC1 protein is embedded within cell membranes, where it helps transport cholesterol within the cell. However, the absence of NPC1 due to gene mutations causes a rare degenerative disorder called Niemann-Pick disease, in which cells become clogged with cholesterol and eventually die.

To confirm the group's finding that NPC1 is crucial for Ebola virus infection, John M. Dye, Ph.D. and colleagues at USAMRIID used mice that were partially deficient in NPC1 expression, challenging the animals with lethal doses of Ebola virus. Remarkably, most of the mice survived the challenge. Other studies using cells from people with Niemann-Pick disease found that those cells also were resistant to Ebola virus infection. In addition, the researchers showed that treating cells with a compound that blocks NPC1 function inhibited infection.

In the second *Nature* article on this topic, another team of USAMRIID scientists, working with investigators from Brigham and Women's Hospital and Harvard Medical School, independently arrived at the same conclusion—that Ebola virus needs NPC1 to enter the cell and cause infection.

The BWH group used a robotic method developed by Harvard's National Small Molecule Screening Laboratory to screen tens of thousands of compounds for activity against Ebola virus. They identified a novel small molecule that inhibits Ebola virus entry into cells by more than 99 percent.

Next, USAMRIID investigators Lisa Hensley, Ph.D. and Claire Marie Filone, Ph.D. verified that the newly identified inhibitor, or compound, blocked cell-to-cell transmission of Ebola virus. Using the inhibitor as a probe to investigate the pathway of infection, they found that the target of the inhibitor is NPC1—the same cell protein described by the other research team. The findings suggest that small molecules that target NPC1 and inhibit Ebola virus infection have the potential to be developed into antiviral drugs.

"The fact that two groups identified the same protein, using two different experimental approaches, is significant," Dr. Dye commented. "This independent corroboration greatly increases our confidence in the findings."

Dr. Hensley said both studies represent the first step in a promising line of research that could make it possible for scientists to design therapeutics that impede the ability of the Ebola virus to infect and spread.

Both projects received funding support from the Defense Threat Reduction Agency (DTRA).

The work completed at USAMRIID using authentic Ebola virus was critical for validating the role of NPC1 in Ebola virus infection. This research can only be conducted in maximum containment Biosafety Level 4, or BSL-4, laboratories, where investigators wear positive-pressure suits and breathe filtered air as they work.

USAMRIID, located at Fort Detrick, Maryland, is the only Department of Defense laboratory with BSL-4 capability. The Institute is the lead military medical research laboratory for DTRA's Joint Science and Technology Office for Chemical and Biological Defense, and plays a key role in national defense and in infectious disease research.

USAMRIID's mission is to conduct basic and applied research on biological threats resulting in medical solutions (vaccines, drugs and diagnostics) to protect the warfighter, but its research often has applications that benefit society as a whole. USAMRIID is a subordinate laboratory of the U.S. Army Medical Research and Materiel Command.

For more information, visit www.usamriid.army.mil

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