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Single Host Gene May Hold Key to Treating Both Ebola and Anthrax Infections

Research published by Army scientists indicates that a minor reduction in levels of one particular gene, known as CD45, can provide protection against two divergent microbes: the virus that causes Ebola hemorrhagic fever and the bacterium that causes anthrax. Taken together, the results suggest a common host restriction factor and a promising approach to drug development for treating two completely different infections.

Writing in the August 20 online issue of *Cell Host and Microbe*, scientists at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) reported that mice expressing reduced levels of CD45 (between 11 and 77 percent) were protected against Ebola virus. In addition to an overall survival rate of 90 to 100 percent, these mice had reduced levels of virus load in the major organs, and had completely cleared the virus 10 days after challenge.

In contrast, mice that had naturally occurring levels of CD45—or none at all—failed to clear the virus and succumbed to infection within 7 to 8 days following challenge.

The protein encoded by CD45 is a member of the protein tyrosine phosphatase (PTP) family. PTPs are known to be signaling molecules that regulate a variety of cellular processes, including cell growth, cell division, and the development of malignancies that can lead to tumor formation.

Scientists created various "knockdown" mice, which expressed reduced levels of CD45, to determine how those changes may alter the body's immune response to microbial pathogens such as Ebola virus. According to the authors, the "knockdown" mice retained greater control of gene expression and immune cell proliferation following Ebola virus infection. These factors contributed to enhanced viral clearance, increased protection against the virus, and a reduction in cell death.

The team's results suggest that host susceptibility to Ebola virus is dependent on the delicate balance of the body's natural immune system, which can be determined by the levels of a single regulator gene.

Ebola virus, which causes hemorrhagic fever with human case fatality rates up to 80 percent, is a global health concern and a potential biological threat. Currently there are no

available vaccines or therapies. Scientists at USAMRIID study the Ebola virus to support development of medical products to prevent and treat infection.

The recently published work builds upon a related study that appeared in the *Journal of Biological Chemistry* in May of this year. That research showed that CD45 also plays a role in protection from *Bacillus anthracis*, the causative agent of anthrax. Specifically, the USAMRIID team demonstrated that in mice expressing 62 percent of the CD45 gene, about 70 percent were protected following exposure to anthrax.

Bacillus anthracis causes three types of disease—cutaneous, gastrointestinal, and inhalational—depending upon the route of exposure. A licensed vaccine is available, and is protective if administered before exposure. Inhalational anthrax is difficult to diagnose early, and despite antibiotic therapy, has a high fatality rate. In addition, because anthrax spores can remain in the body for extended periods, antibiotic treatment is typically recommended for 60 days or more following exposure.

“This report demonstrates the critical connection between basic research and the potential development of medical products,” said COL John P. Skvorak, commander of USAMRIID. “Understanding pathogenesis of disease and host response is critical to the Department of Defense’s investment in broad spectrum countermeasures.”

The next step for investigators is to look at the mechanism of action to better understand how reduced expression of this gene regulates the pathogenesis of both diseases. That information could one day lead to the identification and discovery of additional promising compounds for treating Ebola and anthrax infections.

Both studies were supported by grants from the Defense Threat Reduction Agency, the National Institutes of Health, the National Cancer Institute, and the National Institute of Allergy and Infectious Diseases.

USAMRIID, located at Fort Detrick, Maryland, is the lead medical research laboratory for the U.S. Biological Defense Research Program, and plays a key role in national defense and in infectious disease research. The Institute conducts basic and applied research on biological threats resulting in medical solutions (such as vaccines, drugs and diagnostics) to protect the warfighter. While USAMRIID’s primary mission is focused on the military, 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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