An approach to fighting the Ebola virus

August 21 2014, by David Orenstein

Terrible suffering in Western Africa has refocused the world's attention on Ebola viruses, for which there is no vaccine or cure. The viruses are masters of their attack, but researchers are working hard to fight them, said Dr. Ian Michelow, who has studied an approach.

Infectious disease researcher Dr. Ian Michelow, assistant professor of pediatrics in the Alpert Medical School and at Hasbro Children's Hospital, studied the Ebola virus and a potential therapy earlier in his career. He spoke with David Orenstein about what makes the virus so difficult to treat and about some of the recent research, including his own, that is searching for a way to beat it.

Is there something particular about the basic biology of Ebola that makes it so dangerous?

Like many other pathogens, Ebola viruses have developed and perfected strategies to evade, suppress, or manipulate the host's immune response. To subvert humans' armamentarium, the enveloped Ebola viruses must deposit their genetic material within a cell to survive and propagate without interference. They hijack macrophages and dendritic cells to spread infection to nearly every organ of the body, especially the liver, spleen and lymph nodes.

Ebola viruses strike rapidly to immobilize humans' early innate immune responses. The viruses ensconce themselves in a cloak of glycans in an attempt to shield themselves from neutralizing antibodies and to direct the production of antibodies to highly variable or dispensable regions on

the viral surface. Ebola viruses also produce free glycoproteins that are thought to cause production of non-neutralizing antibodies, thereby preventing effective neutralization of the virus.

In a desperate attempt to counter the viruses, human cells produce large amounts of cytokines and chemokines, but the response is highly dyregulated because the virus disrupts the immune system. The consequent "cytokine storm" leads to systemic inflammatory response syndrome and the death or dysfunction of many immune system cells. As the disease progresses, it leads to problems such as clots and extensive tissue death, hemorrhage in a third of patients, and possible multi-organ failure and death within seven to 10 days in up to 90 percent of cases caused by the most virulent strains.

The overwhelming viral onslaught in conjunction with fragile socio-economic environments and under-resourced healthcare infrastructures in Africa is conspiring to make the latest outbreak in Guinea, Liberia, Sierra Leone, and Nigeria devastating. The implicated virus is related to Zaire ebolavirus, which is the most virulent of the five known Ebola virus species.

Ebola is not necessarily new and is part of a broader family of viruses. Why is the world so challenged by it still?

The first recorded outbreak of Ebola virus disease was in 1976 in what's now the Democratic Republic of the Congo and South Sudan. Since then outbreaks of Ebola virus disease have occurred regularly, but all involved fewer than 500 people.

Research on combating Ebola viruses has not received much attention until the last couple of decades because of their relatively restricted

geographic range, lack of perceived global threat, competing demands such as HIV, absence of reliable small animal models, and lack of political motivation. After the terrorist attacks on the United States in 2001, Ebola viruses were prioritized as CDC Category A biological agents that could be weaponized. For this reason, federal funding agencies have directed considerably more support to researching Ebola viruses more recently, but the fruits have yet to be realized.

Outbreaks in humans are presumed to arise from animal reservoirs. The reservoir is not known but there is evidence to implicate fruit bats. Because humans are immunologically naïve against Ebola viruses, they are highly susceptible to becoming incidental hosts when they come into contact with infected animal products or other infected humans, which explains the intermittent and unpredictable nature of outbreaks.

It is unlikely that Ebola viruses can be eradicated from nature. Therefore, the goal is to develop robust vaccines to prevent and treat disease in humans and effective therapeutics for humans who develop the disease. There are now a number of candidates for these purposes but more time is needed to study their safety and efficacy.

What have you studied about Ebola?

My colleagues at the U.S. Army Medical Research Institute of Infectious Diseases, Massachusetts General Hospital, and I studied new potential treatments for Ebola viruses based on natural human immune proteins called mannose-binding lectin (MBL) and L-ficolin6-8. These defense proteins are synthesized by the liver and secreted into the circulation where they survey the bloodstream for invading organisms. Once they recognize certain patterns of sugars adorning the surface of pathogens, they activate the lectin pathway of complement and mount an immune response to eradicate the microbes. We synthesized MBL and hybrid molecules consisting of MBL and L-ficolin, which we mixed with

authentic and synthetic Ebola viruses and showed that infections of human cells in the laboratory were reduced by more than 90 percent.

We confirmed that human complement was an essential ingredient in the antiviral attack complex. But to our surprise, when we reduced the concentrations of complement in experiments, we noticed that high levels of MBL paradoxically enhanced Ebola virus uptake into human cells. We then determined the mechanism by which that happens.

Our findings reflect the yin-yang nature of MBL. Severe MBL deficiency can predispose infants and immunodeficient humans to infections but MBL levels that are high relative to complement levels may enhance certain infections.

How does MBL appear to work?

We hypothesized that mice infected with massive lethal doses of Ebola virus could be effectively treated with high-dose recombinant human MBL before or 12 hours after the virus's challenge. We demonstrated that almost 50 percent of mice survived regardless of timing of treatment compared with 100 percent mortality among mock-treated animals and complement deficient mice. MBL-treated mice had higher antibody-producing B-lymphocytes and neutrophils, lower proinflammatory cytokines and greater inhibition of viral replication early in the course of infection. Most importantly, surviving MBL-treated mice developed effective adaptive immunity that totally protected them against repeat infection.

Therefore, we concluded that recombinant MBL might bridge the gap between early immune paralysis and recovering adaptive immune responses that enable some mice to survive.

Do you still see this as a pathway to treating Ebola? Do other ideas show promise?

Recombinant human MBL may be useful for treating Ebola virus disease in conjunction with other agents. The World Health Organization recently declared that there is an ethical imperative to offer available experimental interventions that have shown promising results in laboratory and animal experiments to people suffering from disease.

However, there needs to be a cautious approach based on our mice and laboratory experiments. Ebola virus disease often causes a condition in which complement levels are diminished. We demonstrated that high levels of MBL relative to low complement levels could result in enhanced viral uptake in the laboratory and absence of protection in mice. Therefore, it is unknown if MBL therapy will be effective in humans with Ebola virus disease or if it could lead to serious adverse effects.

The most promising therapeutic candidate is ZMapp, a "cocktail" of humanized-mouse antibodies, which has shown promise in nonhuman primates, even when antibodies are administered more than 72 hours after infection. ZMapp was recently administered to two U.S. citizens who were evacuated from Liberia to Atlanta, and both patients improved.

Other therapeutic candidates include RNA-polymerase inhibitors and small interfering RNA nanoparticles that inhibit protein production. BCX4430, a novel synthetic adenosine analogue, inhibits infection of human cells by Ebola viruses as well as several other viruses. It is very encouraging that post-exposure administration of BCX4430 protects mice against Ebola viruses.

The vesicular stomatitis virus-based Ebola vaccines resulted in an unprecedented 50 percent protection against Ebola virus challenge in rhesus macaques when administered ~30 minutes post-infection. This candidate will enter early phase human clinical trials in the next few months.

Provided by Brown University