Human antibodies that block human and animal SARS viruses identified

July 3 2007

An international team of investigators has identified the first human antibodies that can neutralize different strains of the virus responsible for outbreaks of severe acute respiratory syndrome (SARS).

The researchers used a mouse model and in vitro assays (lab tests) to test the neutralizing activity of the antibodies. The research team was led by scientists from the National Cancer Institute (NCI) and the National Institute of Allergy and Infectious Diseases (NIAID), both parts of the National Institutes of Health, and included collaborators from the U.S. Army (USAMRIID), academic institutions in the United States, Switzerland, and Australia. The research findings appear after the July 2, 2007, early online edition of the *Proceedings of the National Academy of Sciences*.

SARS outbreaks occurred in humans in 2002-2003 and again in 2003-2004, and each outbreak was thought to have occurred when the virus jumped from an animal host to humans. Therefore, it appears that animal strains of the virus may be capable of triggering a future human outbreak.

“This study is important because the viral strain that caused the outbreak in people in 2002 probably no longer exists in nature,” explains Kanta Subbarao, M.D., NIAID, whose laboratory verified the efficacy of the anti-SARS antibodies in animal models. “What we need to prove for any vaccine, therapeutic, antibody, or drug is that it is effective not only against the strain of SARS virus isolated from people, but also against a

variety of animal strains, because animals will be a likely source for re-emergence of the SARS virus."

The research team was led by Dimiter S. Dimitrov, Ph.D., head of the Protein Interaction Group at NCI's Frederick, Md., campus. When the first SARS outbreak occurred in 2002, Dimitrov responded to the public health crisis by applying his laboratory's expertise in how viruses enter cells, which was gained in the study of HIV, to understand how this new virus enters and exploits human cells. Their research into the spike glycoprotein, the part of the virus that binds and allows entry into human cells, provided the knowledge needed to identify several human antibodies against the SARS virus.

"Our researchers at NCI Frederick have an extraordinary breadth of expertise, ranging far beyond cancer to areas such as AIDS research, advanced biotechnology, and vaccine manufacturing," said NCI Director John E. Niederhuber, M.D. "We are realizing, as never before, that cancer is a model for many diseases, and NCI's research is a rich resource to our NIH colleagues and the biomedical research community at large."

Dimitrov and his colleagues identified two human antibodies that bind to a region on the SARS virus' spike glycoprotein that is called the receptor binding domain (RBD). One of the antibodies, called S230.15, was found in the blood of a patient who had been infected with SARS and later recovered. The second antibody, m396, was taken from a library of human antibodies the researchers developed from the blood of 10 healthy volunteers. Because humans already have immune cells that express antibodies that are very close to those that can effectively neutralize the SARS virus, m396 could be fished out from healthy volunteers. Dimitrov's team next determined the structure of m396 and its complex with the SARS RBD and showed that the antibody binds to the region on the RBD that allows the virus to attach to host cells.

If the antibodies were successful in binding to the SARS RBD, they would prevent the virus from attaching to the SARS coronavirus receptor, ACE2, on the outside of human cells, effectively neutralizing it. When tested in cells in the laboratory, both antibodies potently neutralized samples of the virus from both outbreaks. The antibodies also neutralized samples of the virus taken from wild civets (a cat-like mammal in which strains of the virus were found during the outbreaks), though with somewhat lower potency.

The investigators next tested the antibodies in a mouse model of SARS virus infection. Mice were given an injection of one of the two antibodies, and then were exposed 24 hours later either to samples of the SARS virus from one of the two outbreaks or to virus isolated from civets. Mice that received m396 or S230.15 were fully protected from infection by SARS from humans, the researchers found. Similar to the experiments in cells in the laboratory, mice that received either antibody were also protected against infection by SARS from civets, though not completely.

Further analysis of the structure of m396 and its interactions with experimental mutations in the SARS virus receptor binding area suggested that the antibody can successfully neutralize all known forms of the virus. “This antibody neutralizes all strains of SARS we tested and is likely to neutralize all strains of the virus with known sequences,” said Dimitrov. “There are no other reports for such antibodies available.”

“This elegant research leaves us better prepared for the possible re-emergence in people of viruses similar to those that caused more than 8,000 documented SARS cases and nearly 800 deaths in 2002-2003,” noted NIAID Director Anthony S. Fauci, M.D. “This work, which could help inform the development of therapeutics, vaccines, and diagnostics, is a pre-emptive strike against a pathogen with the potential to re-emerge.”

The discovery of two effective antibodies has the advantage that a newly emergent variation of the SARS coronavirus might be insensitive to neutralization with one, but still susceptible to the other. “Our results demonstrate novel potential antibody-based therapeutics against SARS that could be used alone or in combination...these human antibodies could be also used for diagnosis and as research reagents in the development of vaccines and inhibitors,” summarized the authors.

Source: National Cancer Institute