Scientists prove hypothesis on the mystery of dengue virus infection

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A leading immunology research institute has validated the long-held and controversial hypothesis that antibodies - usually the "good guys" in the body's fight against viruses - instead contribute to severe dengue virus-induced disease, the La Jolla Institute for Allergy & Immunology announced today. The finding has major implications for the development of a first-ever vaccine against dengue virus, a growing public health threat which annually infects 50 to 100 million people worldwide, causing a half million cases of the severest form.

"Our lab has proven the decades old hypothesis that subneutralizing levels of dengue virus antibodies exacerbate the disease," said La Jolla Institute scientist Sujan Shresta, Ph.D, noting this occurs in people with secondary dengue virus infections who have antibodies to the virus due to a previous infection. "This is a situation where antibodies can be bad for you, which is counter to everything we know about the normal function of antibodies. It also presents a special challenge for researchers working to develop a dengue virus vaccine, since most vaccines work by prompting the body to produce antibodies."

Dengue infection is transmitted by mosquitoes and is caused by any of four closely related virus serotypes of the genus Flavivirus. Infection can cause diseases ranging from dengue fever, a flu-like illness, to the severest form -- dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS), which can cause the blood vessels to leak, leading to life-threatening shock. Dengue infection hits hardest in tropical and subtropical areas of Southeast Asia and Latin America.

The dengue virus antibody phenomenon, termed antibody-dependent enhancement of infection (ADE), was first hypothesized in the 1970s by Scott Halstead, M.D., a renowned scientist and one of the world's top experts on dengue virus infection. Dr. Halstead said he got his first inkling of the phenomenon while doing extensive clinical studies of dengue virus patients in Thailand in the 1960s. "We were able to detect that the severe patients all had a secondary antibody response, meaning that they had all been infected before," he said. "That was the first evidence we had that a person had to have a previous dengue infection to get the severe disease." Further epidemiological observations, including cases in which severe dengue virus occurred in infants born to previously infected mothers, along with lab cell studies, prompted Dr. Halstead to put forth the ADE hypothesis. Dr. Shresta's work, conducted in mouse models, provides the first in vivo proof of ADE's occurrence.

Dr. Halstead said he is pleased to see his hypothesis proven in animal studies, but actually finds Dr. Shresta's development of a solid dengue virus mouse model even more exciting. Dr. Shresta is credited with developing the world's first mouse model showing key aspects of human infection.

"A model like this is really a breakthrough in tools," said Dr. Halstead, who is research director for the Pediatric Dengue Vaccine Initiative at the International Vaccine Institute, Seoul, Korea and a consultant to the Rockefeller Foundation in New York. "We've been looking for 40 years for a model to be able to test this (ADE) phenomenon. It will allow us to study the virus and the antibody enhancement in ways never before possible."

Using the mouse model, the Shresta group has already made a key and surprising observation that a type of liver cells, called liver sinusoidal endothelial cells (LSCEs), but not the previously expected cells types (such as macrophages and dendritic cells) support ADE of dengue

infection.

Scientists had long complained that the lack of a good animal model hampered efforts to develop a first-ever dengue vaccine. Dr. Shresta said her group's ADE findings emphasize the importance of special caution in designing a dengue virus vaccine. "Researchers will have to be extremely careful to ensure that, under no conditions, will a dengue vaccine generate these subneutralizing antibody conditions," she said. "Otherwise, it could cause people to develop the severest and potentially lethal form of the disease -- dengue hemorrhagic fever/dengue shock syndrome."

Dr. Halstead agreed and said efforts should focus on a vaccine that protects against all four serotypes to avoid subsequent infections. "The vaccine should cause you to make antibodies to each of the four dengue viruses," he said, noting that he is working with several groups using this approach. "That's what makes it difficult; you have to make four vaccines in one. The kind of model Dr. Shresta has done will be important as researchers work to develop a vaccine."

Dr. Shresta's findings were published online today in *Cell Host & Microbe* in her paper entitled, "Enhanced Infection of Liver Sinusoidal Endothelial Cells in a Mouse Model of Antibody-Induced Severe Dengue Disease."

Dr. Shresta said the fact that dengue viruses exist as four different serotypes that circulate simultaneously underlies the development of the subneutralizing antibodies. Infection with one of these serotypes provides lifelong immunity to the infecting serotype only. In subsequent dengue infections, where a different serotype of the virus is involved, the antibodies do not recognize enough of the virus to neutralize it. "This starts a cascade of unusual molecular events - the ADE process -- which leads to the antibodies contributing to, rather than fighting, the dengue

infection," she said.

The World Health Organization (WHO) estimates that about 2.5 billion people, or 40% of the world's population, live in areas where there is a risk of dengue transmission. About 500,000 cases of dengue's severest form (DHF/DSS) occur annually, resulting in about 24,000 deaths, mostly among children. Tropical and subtropical areas of Southeast Asia and Latin America are hardest hit by dengue infection. Although dengue rarely occurs in the continental United States, it is endemic in Puerto Rico, a U.S. territory. Mosquitoes capable of transmitting the virus have been found in the U.S. over the last 10 years.

Provided by La Jolla Institute for Allergy and Immunology