Medical Xpress

Researchers identify Achilles heel of dengue virus, target for future vaccines

April 11 2012

A team of scientists from the University of North Carolina at Chapel Hill and Vanderbilt University have pinpointed the region on dengue virus that is neutralized in people who overcome infection with the deadly pathogen. The results challenge the current state of dengue vaccine research, which is based on studies in mice and targets a different region of the virus.

"In the past researchers have relied on mouse studies to understand how the immune system kills dengue virus and assumed that the mouse studies would apply to people as well," said senior study author Aravinda M. de Silva, PhD, associate professor of microbiology and immunology at the UNC School of Medicine.

"Our study for the first time shows what region the immune system of humans target when they are fighting off the virus. The region on the virus targeted by the human immune system is quite different from the region targeted by mice."

The new research, which will appear online during the week of April 11-14, 2012 in the Proceedings of the National Academy of Sciences, was performed using blood cells from local travelers infected with dengue virus.

The global incidence of dengue has grown dramatically in recent decades, putting about half of the world's population at risk. Creation of a vaccine is complicated by the fact that there are four distinct, but

closely related forms of the virus that cause dengue. Once people have recovered from infection with one form of the virus, they have lifelong immunity against that form.

But if they become infected with one of the other three forms of the virus, they increase their chances of developing the severe bleeding and sometimes fatal dengue hemorrhagic fever and dengue shock syndrome. The leading theory to explain why some people develop dengue hemorrhagic fever is that under some conditions the human immune response can actually enhance the virus and disease during a second infection.

"This is a huge issue for vaccine development," said lead study author Ruklanthi de Alwis, a graduate student in de Silva's lab. "We have to figure out a way to develop dengue vaccines that induce the good response that protects against infection, at the same time avoiding the bad response that enhances disease."

de Alwis looked at a particular subset of the immune response – specialized molecules called antibodies. UNC investigators identified 7 local individuals who had contracted dengue during travel to an endemic region and sent blood cells from these individuals to Vanderbilt School of Medicine. Drs. Scott Smith and James Crowe at Vanderbilt were able to isolate dengue antibodies from these cells for further study at UNC. The team found that instead of binding to small fragments of the virus -- like mouse antibodies do -- human antibodies that neutralized the virus bound to a complex structure that was only present on a completely assembled dengue virus.

"Though this is the first time this phenomenon has been shown with dengue, just last year there were a number of studies showing that antibodies recognize similar complex epitopes in both HIV and West Nile Virus," said de Alwis. "New vaccines as well as those already in the

pipeline will need to be assessed to see if they bind just a small fragment or the whole virus, which may determine whether or not they work in humans."

Provided by University of North Carolina School of Medicine

Citation: Researchers identify Achilles heel of dengue virus, target for future vaccines (2012, April 11) retrieved 23 April 2024 from https://medicalxpress.com/news/2012-04-achilles-heel-dengue-virus-future.html

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