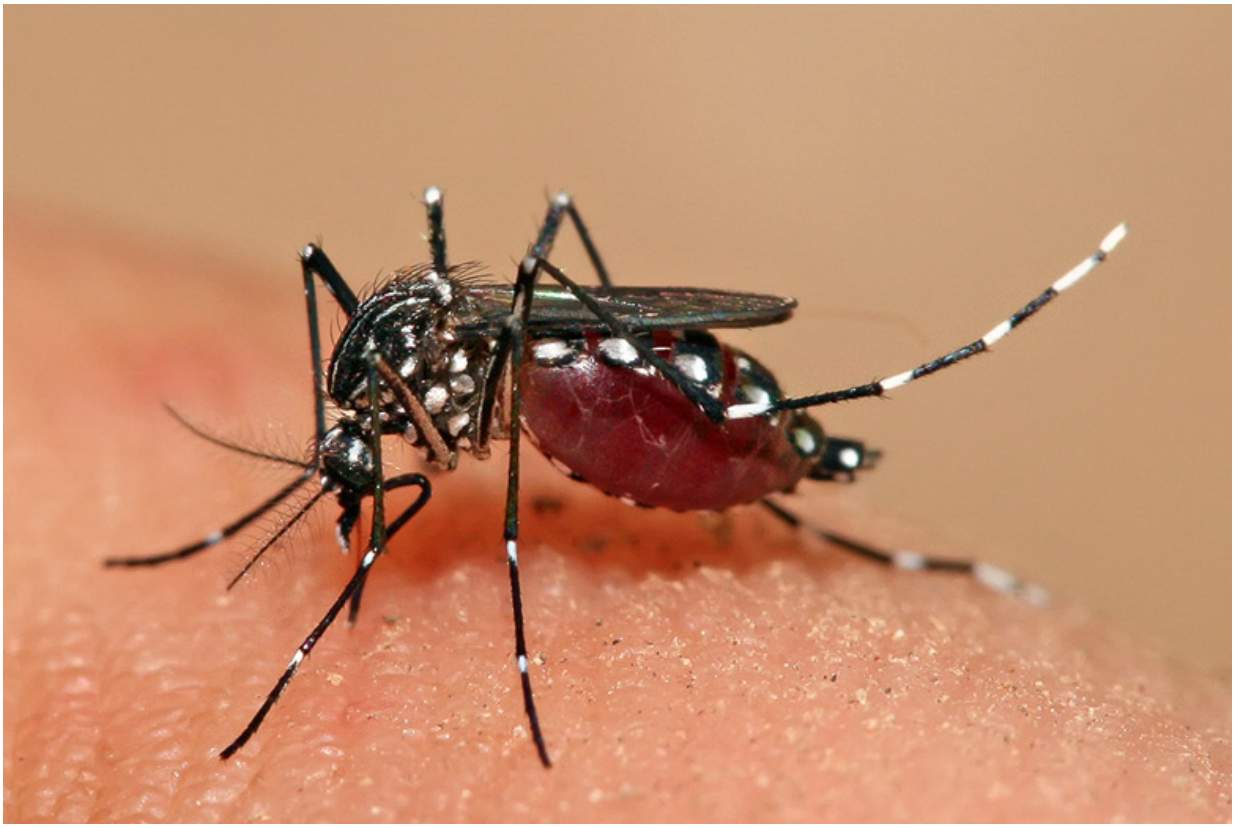
Biologists develop novel antiviral approach to dengue fever

December 2 2015, by Bjorn Carey



The mosquito Aedes aegypti feeding on a human host. Biologists at Stanford have developed an approach to preventing infections that cause dengue fever, the most prevalent mosquito-borne virus in the world. Credit: Muhammad Mahdi Karim/Wikimedia Commons

The virus that causes dengue fever infects an estimated 390 million

people per year. Infection often leads to symptoms so severe that it was once called "breakbone fever" for the pain it causes, or even death. It's the fastest-growing and most prevalent mosquito-borne virus in the world, and although a third of the world's population is at risk of infection, there currently aren't any effective antiviral treatments or vaccines.

A new study of the virus, led by Judith Frydman, a professor of biology and of genetics at Stanford, shows how disrupting a critical cellular pathway in the host can block the virus's life cycle at multiple steps. Drugs targeting this pathway could prevent virus infection in human and mosquito cells without eliciting drug resistance, the main problem in most antiviral therapies.

This strategy, detailed in the journal *Cell*, could offer novel therapies against the dengue fever virus, also known as DENV, as well as other related human pathogens, such as West Nile virus, yellow fever and tick-borne encephalitis.

Shutting down the chaperone

Like all viruses, DENV relies heavily on the host to replicate. In particular, the infected host's cellular machinery is essential to produce and manage the viral proteome – the proteins that the virus expresses in order to survive and thrive in an infected host. By studying how the virus manipulates this machinery, the Frydman lab obtained insights into a new strategy to fight viral infection.

Frydman's group focused on Hsp70, a type of protein found in most organisms and known as a "chaperone." Hsp70's main job is to help other proteins fold into their functional shape, and to then protect them from damage by environmental stresses. DENV, like many other viruses, also relies on Hsp70, to help replicate the viral genome, and ultimately

produce the viral proteins it needs to take control of the host cells and spread infection.

By defining how Hsp70 helps the virus replicate, the Frydman lab identified a strategy to block viral replication with very little toxicity to the host cell. In collaboration with labs at the University of California, San Francisco, and the Icahn School of Medicine at Mount Sinai, they tested a series of drugs that target the host activities required by the virus, and showed that the virus is much more dependent on this chaperone than the host. This produces a very good therapeutic window against the virus with little toxicity.

In the lab, Frydman's team found that inhibiting Hsp70 in human blood cells could block several strains of dengue, without harming the host cells. The result, Frydman said, provides a promising roadmap for addressing a virus for which there is currently no preventative treatment.

Outmaneuvering the virus

A constant challenge with developing preventive therapies for DENV and other viruses, however, is that they can rapidly produce a mutant strain that becomes resistant to the drug. Restricting Hsp70 proves to be an attractive antiviral approach for a number of reasons. First, because Hsp70 is involved in so many steps of the viral cycle, the virus could not produce mutant strains resistant to the drug, even after multiple attempts.

"This unusual lack of DENV drug-resistance to Hsp70-targeting compounds opens the way to both therapeutic and prophylactic use for short courses of treatment without losing effectiveness due to resistance, the major concern of most existing antivirals," Frydman said. "We feel this important study targets a field of biology that is very poorly explored and will provide a new paradigm for a new way of thinking about antiviral drugs."

Second, because these compounds modulate Hsp70 rather than fully block its activity, they exhibit negligible toxicity to the relevant human target cells at concentrations that completely block virus production. Third, in the case of DENV, the antiviral dampened the release of small virally-induced proteins called cytokines, which can contribute to severe disease and create the "cytokine storm" associated with hemorrhagic fever forms of dengue.

Perhaps most excitingly, Frydman said, the compounds are effective against different types of DENV and even different insect-borne flaviviruses, including West Nile virus, yellow fever and tick-borne encephalitis. The broad-spectrum action of this class of inhibitors suggests a strategy for pan-flavivirus antivirals with low potential for resistance.

"Our findings have major implications for our understanding of the interface between viral and chaperone biology, and provide a new way of thinking about strategies to develop a novel class of antivirals that will not be rendered ineffective by the emergence of drug-resistance," Frydman said. "This unique property of targeting viral proteostasis therapeutically may close a fundamental gap in antiviral drug development."

More information: Shuhei Taguwa et al. Defining Hsp70 Subnetworks in Dengue Virus Replication Reveals Key Vulnerability in Flavivirus Infection, *Cell* (2015). DOI: 10.1016/j.cell.2015.10.046

Provided by Stanford University