# Possible new route to fight dengue virus pointed

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This graphic depicts structures in the dengue virus that are critical for the infection process. Researchers have learned details about how the virus alters lipids in membranes surrounding structures called organelles, suggesting a potential new approach to control the aggressive mosquito-borne pathogen. Credit: Purdue Department of Biological Sciences/Rushika Perera

Researchers have identified enzymes and biochemical compounds called lipids that are targeted and modified by the dengue virus during infection, suggesting a potential new approach to control the aggressive mosquito-borne pathogen.

Findings also suggest that medications used to treat high cholesterol and other lipid-related conditions might also inhibit dengue's replication and could represent a potential new therapy. The researchers have identified how infected mosquito cells undergo changes to certain lipids in membranes and in biochemical sensors that alert cells of invading viruses.

"The virus reorganizes the internal architecture of the cell to support its own needs," said Purdue University research scientist Rushika Perera. "Many details are unknown. This is our first attempt to understand how the virus alters lipids as part of the infection process. Part of what we looked at in this work was how the virus changes the cell, and the next step will be to figure out why."

The researchers uncovered new details of how the virus alters lipids in membranes surrounding structures inside cells called organelles, including the mitochondria, which provide energy critical for a cell to function, and the endoplasmic reticulum, where proteins and lipids are synthesized.

"Findings also show that important host enzymes are used by the virus and may be targets for future antiviral drugs," said Richard J. Kuhn, a professor and head of Purdue's Department of Biological Sciences and director of the Bindley Bioscience Center. "It turns out, the pills you take to control your cholesterol might have some capability to control dengue."

The work was led by Perera in collaboration with researchers at Purdue's Bindley Bioscience Center and the Pacific Northwest National Laboratory. Findings are detailed in a research paper to appear Thursday (March 22) in the journal PLoS Pathogens.

The findings could apply to viruses similar to dengue, including the West

Nile virus, yellow fever and hepatitis C.

Dengue causes 50 million to 100 million infections per year and is considered one of the most aggressive mosquito-borne human pathogens worldwide. It is a leading cause of serious illness and death among children in some Asian and Latin American countries.

"Identifying pathways of infection will help us understand how these viruses work," Kuhn said. "Many viruses, including dengue, dramatically alter a host cell upon infection, and in this paper we begin to dissect the precise changes that occur. Ultimately, we are trying to understand how the virus subverts and exploits the host and uses it for its own purpose, which is to replicate."

The team learned specifically that an enzyme called fatty acid synthase, which cells use to synthesize lipids, is affected by the virus. Researchers showed that compounds inhibiting production of the enzyme also inhibit virus replication, suggesting drugs already on the market to treat diseases related to lipid synthesis and storage, including diabetes and cancer, also might be used to treat dengue, Kuhn said.

The research paper was written by Perera; Kuhn; Bindley researchers Catherine Riley, Amber S. Hopf-Jannasch and Jiri Adamec; and PNNL researchers Giorgis Isaac, Ronald J. Moore, Karl W. Weitz, Ljiljana Pasa-Tolic and Thomas O. Metz.

The researchers had previously studied a compound that inhibits the production of fatty acid synthase in human cells. In the new findings, the researchers showed that the virus commandeers some of the same enzymes in both mosquito and human cells, meaning the same compound could work to attack the virus in mosquito cells.

"This is important because it may be easier to control the virus in

mosquitoes than in humans," Kuhn said.

Globally, dengue has grown dramatically in recent decades, placing about half the world's population at risk of infection. The infection causes flulike illness and occasionally develops into a potentially lethal complication called dengue hemorrhagic fever. Prompt medical care for this severe form of dengue virus infection has been shown to decrease mortality rates from more than 20 percent to less than 1 percent, according to the World Health Organization.

The research hinges on recent advances in two areas: high-resolution mass spectrometry and "informatics," or using computers to process volumes of information.

"You generate a large quantity of data that has to be interpreted in terms of what molecules you are looking at," Perera said. "The mass spectrometer takes hundreds of lipids and breaks them apart, and then a computer is needed to put it all back together and identify them. It's only in the past five years or so that we've had the capability to do this with the required accuracy."

The researchers also detail changes in the curvature of membranes, using another technique called cryoelectron microscopy, and pinpointed an isolated part of the cell where most of the virus replication takes place, a complex of membranes modified by the infection. The virus is thought to commandeer enzymes, relocating them to this region where virus replication factories are situated.

Because the research tools enable scientists to see how changes in membranes and signaling lipids alter how a cell functions, a long-term benefit of the research is learning how to use a virus as a tool to better understand cellular processes, Perera said.

**More information:** Dengue Virus Infection Perturbs Lipid H 1 homeostasis in Infected Mosquito Cells, *PLoS Pathogens.*

**ABSTRACT**
Dengue virus causes ~50-100 million infections per year and thus is considered one of the most aggressive arthropod-borne human pathogen worldwide. During its replication, dengue virus induces dramatic alterations in the intracellular membranes of infected cells. This phenomenon is observed both in human and vector-derived cells. Using high-resolution mass spectrometry of mosquito cells, we show that this membrane remodeling is directly linked to a unique lipid repertoire induced by dengue virus infection. Specifically, 15% of the metabolites detected were significantly different between DENV infected and uninfected cells while 85% of the metabolites detected were significantly different in isolated replication complex membranes. Furthermore, we demonstrate that intracellular lipid redistribution induced by the inhibition of fatty acid synthase, the rate-limiting enzyme in lipid biosynthesis, is sufficient for cell survival but is inhibitory to dengue virus replication. Lipids that have the capacity to destabilize and change the curvature of membranes as well as lipids that change the permeability of membranes are enriched in dengue virus infected cells. Several sphingolipids and other bioactive signaling molecules that are involved in controlling membrane fusion, fission, and trafficking as well as molecules that influence cytoskeletal reorganization are also up regulated during dengue infection. These observations shed light on the emerging role of lipids in shaping the membrane and protein environments during viral infections and suggest membrane-organizing principles that may influence virus-induced intracellular membrane architecture.

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