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Starving Dengue Fever Virus of Critical Building Blocks

New research shows that cutting down the amount of fat particles in cells may be an effective way to prevent the dengue fever virus from replicating and spreading.

Howard Hughes Medical Institute international research scholar Andrea V. Gamarnik and her colleagues have shown that the dengue virus hijacks fat droplets inside cells and uses those tiny fat globules to build new infectious virus particles. The scientists have been able to slow down dengue virus assembly in a Petri dish using experimental obesity drugs that deplete cells of fat droplets. The approach prevents the virus from having access to critical building blocks, a strategy that they hope will prove useful in combating the debilitating and sometimes-deadly disease.

No drugs or vaccines exist to treat dengue fever, which is spread through infected mosquitoes and is endemic in many tropical regions. The symptoms include a high fever and headache, joint, muscle, and eye pain, and mild bleeding from the nose and gums. A more severe form of the disease, dengue hemorrhagic fever, includes severe bleeding that can lead to death. According to the World Health Organization, dengue fever infects 50 million people worldwide and kills 25,000 people annually.

“Today, dengue virus is considered the most important viral disease transmitted by mosquitoes, because of the number of cases,” says Gamarnik, a virologist at the Leloir Institute Foundation in Buenos Aires, Argentina. Her work on dengue virus was published October 23, 2009, in the journal *PLoS Pathogens*.

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Two years ago, Gamarnik and her colleagues discovered how the dengue virus replicates its genetic code, which is made of RNA. But to spread beyond the infected cell to the rest of the host, the virus needs to create an outer coating, called a capsid. The capsid is composed of many interlocking pieces called capsid proteins, which enclose and protect the viral RNA.

In the new studies, Gamarnik and her colleagues used fluorescent labels to illuminate the capsid proteins and watched as the virus infected human and mosquito cells. As the virus began to replicate, it produced many copies of the capsid proteins. The researchers saw these proteins accumulating in rings inside the cytoplasm of the cells. Further investigation showed that the capsid proteins were clinging to lipid droplets, fat-filled sacs that play a key role in lipid metabolism. In recent years, other researchers have found that lipid droplets attract hepatitis C virus and other pathogens.

The scientists then set about pinpointing which portion of the dengue virus capsid latched onto the lipid droplets by systematically altering the sequence of amino acids that comprise the capsid protein. That led them to a small section in the middle of the molecule that is vital for latching onto the lipid droplets. When the scientists altered this section of the capsid, the capsid proteins no longer clumped around the lipid droplets. As a result of this alteration, the rate of replication of the dengue virus plummeted.

“When we changed the capsid protein, it did not go to the lipid droplets and the cell produced no viral particles,” Gamarnik says. “So we concluded that the virus needs lipid droplets to replicate and form new particles.”

The experiments suggested that lipid droplets might be essential for viral replication, so Gamarnik reasoned that depleting cells of the tiny fatty orbs would hinder viral activity. And doing so proved easy: existing experimental anti-obesity drugs work by reducing the number of lipid droplets that cells produce. When some of these drugs—called fatty acid synthase inhibitors—were sprinkled on cell cultures, lipid droplets dried up and production of viral particles dropped 100-fold. “This is a new idea, a new strategy,” she says.

Gamarnik hopes this potential treatment strategy proves beneficial in the fight against the dengue virus as well as many of its close cousins in the flavivirus family. Yellow fever virus, West Nile virus, and dozens of related viruses cause millions of cases of human illness each year, but no vaccines or antiviral drugs exist to control most of the infections.

Her team is now trying to dissect the precise relationship between dengue virus capsid protein and the lipid droplets, hoping to find other weak links in the viral life cycle. “We know very little about the biology and the pathogenesis of the virus. So it’s very important to understand how the virus replicates in order to design effective antiviral strategies,” Gamarnik says.