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For Immediate Release

How Zika virus knocks out our immune defenses

LJI and UC San Diego scientists make striking discovery as they work to combat Zika and related viral threats

LA JOLLA, CA—Zika virus and dengue virus are very close relatives. Both are mosquito-borne flaviviruses, and both specialize in infecting a host's dendritic cells.

But a new *Nature Communications* study, led by scientists at La Jolla Institute for Immunology (LJI) and UC San Diego shows that these two viruses have vastly different ways of making us sick.

Zika virus uses stealth. Zika virus slips into dendritic cells and blocks the dendritic cells from alerting nearby T cells to danger. It's the classic horror movie cliche—the creeper is already in the house, and the phone lines have been cut.

Dengue virus prefers shock-and-awe. Dengue virus pushes dendritic cells to churn out molecules called pro-inflammatory cytokines, which send the immune system into overdrive. The virus spreads to new host cells as the body grapples with this overwhelming immune response.

Understanding these different infection strategies is key for developing life-saving vaccines, says LJI Professor Sujan Shresta, Ph.D. Her team is working to develop vaccines that harness virus-fighting T cells to combat Zika virus, dengue virus, and other flaviviruses with pandemic potential.

"Our ultimate goal is to develop vaccines against these very difficult viruses," says Shresta, who co-led the new study with UC San Diego Professor Aaron Carlin, M.D., Ph.D. "Understanding how these viruses manipulate the immune response can help guide the development of the best vaccine approach."

Why Zika-infected dendritic cells can't call for help

This new collaboration is the first to show exactly how Zika virus accomplishes its sneak attack. Using a technique pioneered by Carlin during his postdoctoral work at UC San Diego and LJI, the researchers isolated only Zika- or dengue-infected dendritic cells derived from human blood

samples. Then they examined gene expression in these cells to see how they responded to the infection.

The Zika-infected dendritic cells did very little—and the researchers could finally see why. They found that Zika virus actively suppresses an important molecule in cells, called NF-κB p65. Without NF-κB p65, dendritic cells get stuck in an immature state and cannot promote T cells to fight the infection.

In contrast, dengue virus really stimulates dendritic cells to make lots of pro-inflammatory cytokines and respond aggressively to the presence of the virus.

This discovery helps explain why many people develop a weaker immune response to Zika virus versus dengue virus, says Ying-Ting Wang, Ph.D, former LJI postdoctoral fellow and first author of the current study. The new research also provides a clue to how Zika virus manages to break past immune defenses in the placenta to infect developing fetuses.

"Zika virus inhibits any kind of productive dendritic cell response," says Carlin. "We think that's a key to its pathogenesis, its ability to spread silently and persist within humans that it infects."

Right now, there are no effective vaccines or therapeutics against Zika virus or dengue virus. The new findings may help scientists outsmart these viruses.

"Looking at these human cell cultures helps us understand what's going on in people," says Shresta. " Our findings inform how we might develop vaccines and antivirals that manipulate these cellular pathways."

Why Zika and dengue vaccines are critical

Shresta and Carlin are eager to move forward with flavivirus research. They know there's no time to lose.

Many mosquito-borne viruses are spreading rapidly as disease-carrying *Aedes* mosquitoes expand into new habitats. In fact, last year was the worst on record for reported dengue virus cases. Dengue virus infected between 100 million and 400 million people in 2024, according to the World Health Organization (WHO). These cases included the first-ever cases of locally transmitted dengue virus infection in San Diego County.

Many flaviviruses also have pandemic potential. In a 2024 report, WHO listed Zika virus, dengue virus, West Nile virus, tick-borne encephalitis virus, and yellow fever virus among the top pathogens for research “prioritization” in preparation for the next pandemic.

Shresta has monitored the spread of these viruses in recent years. As she explains, many of these viruses overlap in the same regions. As a result, millions of people are at risk of infection from a variety of flaviviruses that attack dendritic cells from different angles.

Shresta is leading efforts at LJI to develop a "pan-flavivirus" vaccine that might combat many flaviviruses at once. "Our challenge is to develop vaccines that are both safe and effective against not just one virus, but all these closely related flaviviruses," says Shresta.

At the same time, Carlin is looking to develop antivirals that might interfere with Zika's ability to suppress NF-κB p65. He'd also like to investigate exactly how dengue virus over-stimulates the immune system.

"Understanding how dengue virus stimulates that shock-like phenotype in people would allow for precision guided therapies that prevent death and hospitalization without inhibiting our immune system's ability to clear the virus," says Carlin.

Additional authors of the study, "Zika but not Dengue Virus Infection Limits NF-κB Activity in Human Monocyte-Derived Dendritic Cells and Suppresses their Ability to Activate T Cells," included Ying-Ting Wang, Emilie Branche, Jialei Xie, Rachel E. McMillan, Fernanda Ana-Sosa-Batiz, Hsueh-Han Lu, Qin Hui Li, Alex E. Clark, Joan M. Valls Cuevas, Karla M. Viramontes, Aaron F. Garretson, Rubens Prince dos Santos Alves, Sven Heinz, and Christopher Benner.

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