

Study reveals Zika's shape-shifting machinery—and a possible vulnerability

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Transmission electron micrograph (TEM) of Zika virus. Credit: Cynthia Goldsmith/Centers for Disease Control and Prevention

Viruses have limited genetic material—and few proteins—so all the pieces must work extra hard. Zika is a great example; the virus only produces 10 proteins. Now, in a study published in the journal [PLOS](#)

[Pathogens](#), researchers at Sanford Burnham Prebys have shown how the virus does so much with so little and may have identified a therapeutic vulnerability.

In the study, the research team showed that Zika's enzyme—NS2B-NS3—is a multipurpose tool with two essential functions: breaking up proteins (a protease) and dividing its own double-stranded RNA into single strands (a helicase).

"We found that Zika's enzyme complex changes function based on how it's shaped," says Alexey Terskikh, Ph.D., associate professor at Sanford Burnham Prebys and senior author of the paper. "When in the closed conformation, it acts as a classic protease. But then it cycles between open and super-open conformations, which allows it to grab and then release a single strand of RNA—and these functions are essential for viral replication."

Zika is an RNA virus that's part of a family of deadly pathogens called flaviviruses, which include West Nile, [dengue fever](#), yellow fever, Japanese encephalitis and others. The virus is transmitted by mosquitoes and infects uterine and placental cells (among other [cell types](#)), making it particularly dangerous for pregnant women. Once inside host cells, the virus re-engineers them to produce more Zika.

Understanding Zika on the molecular level could have an enormous payoff: a therapeutic target. It would be difficult to create safe drugs that target the domains of the enzyme needed for protease or helicase functions, as human cells have many similar molecules. However, a drug that blocks Zika's conformational changes could be effective. If the complex can't shape-shift, it can't perform its critical functions, and no new Zika particles would be produced.

An efficient machine

Researchers have long known that Zika's essential enzyme was composed of two units: NS2B-NS3pro and NS3hel. [NS2B-NS3pro carries out](#) protease functions, cutting long polypeptides into Zika proteins. However, NS2B-NS3pro's abilities to bind single-stranded RNA and help separate the double-stranded RNA during viral replication were only recently discovered.

In this study, the researchers leaned on recent crystal structures and used protein biochemistry, fluorescence polarization and computer modeling to dissect NS2B-NS3pro's life cycle. NS3pro is connected to NS3hel (the helicase) by a short amino acid linker and becomes active when the complex is in its closed conformation, like a closed accordion. The RNA binding happens when the complex is open, whereas the complex must transition through the super-open conformation to release RNA.

These conformational changes are driven by the dynamics of NS3hel activity, which extends the linker and eventually "yanks" the NS3pro to release RNA. NS3pro is anchored to the inside of the host cell's [endoplasmic reticulum](#) (ER)—a key organelle that helps shepherd cellular proteins to their appropriate destinations—via NS2B and, while in the closed conformation, cuts up the Zika polypeptide, helping generate all viral proteins.

On the other side of the linker, NS3hel separates Zika's double-stranded RNA and conveniently hands a strand over to [NS3pro](#), which has positively charged "forks" to grab on to the negatively charged RNA.

"There's a very nice groove of positive charges," says Terskikh. "So, RNA just naturally follows that groove. Then the complex shifts to the closed conformation and releases the RNA."

As NS3hel reaches forward to grab the double-stranded RNA, it pulls the complex with it; however, since the NS3pro is anchored in the ER

membrane, and the linker can only extend so far, the complex snaps into the super-open conformation and releases RNA. The complex then relaxes back to the open conformation, ready for a new cycle.

Meanwhile, when NS3pro detects a viral polypeptide to cut, it forces the complex into the closed conformation, becoming a protease. The authors call this process "reverse inchworm," because grabbing and releasing the single-stranded RNA resembles inchworm movements, but backward, with the jaws (the protease) trailing behind.

In addition to providing a possible therapeutic target for Zika, this detailed understanding could be applied to other flaviviruses, which share similar molecular machinery.

"Versions of the NS2B-NS3pro complex are found throughout the flaviviruses," says Terskikh. "It could potentially constitute a whole new class of drug targets for multiple viruses."

More information: Sergey A. Shiryayev et al, Dual function of Zika virus NS2B-NS3 protease, *PLOS Pathogens* (2023). [DOI: 10.1371/journal.ppat.1011795](https://doi.org/10.1371/journal.ppat.1011795)

Provided by Sanford-Burnham Prebys

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