Biophysicists target mechanism that makes Zika virus so dangerous

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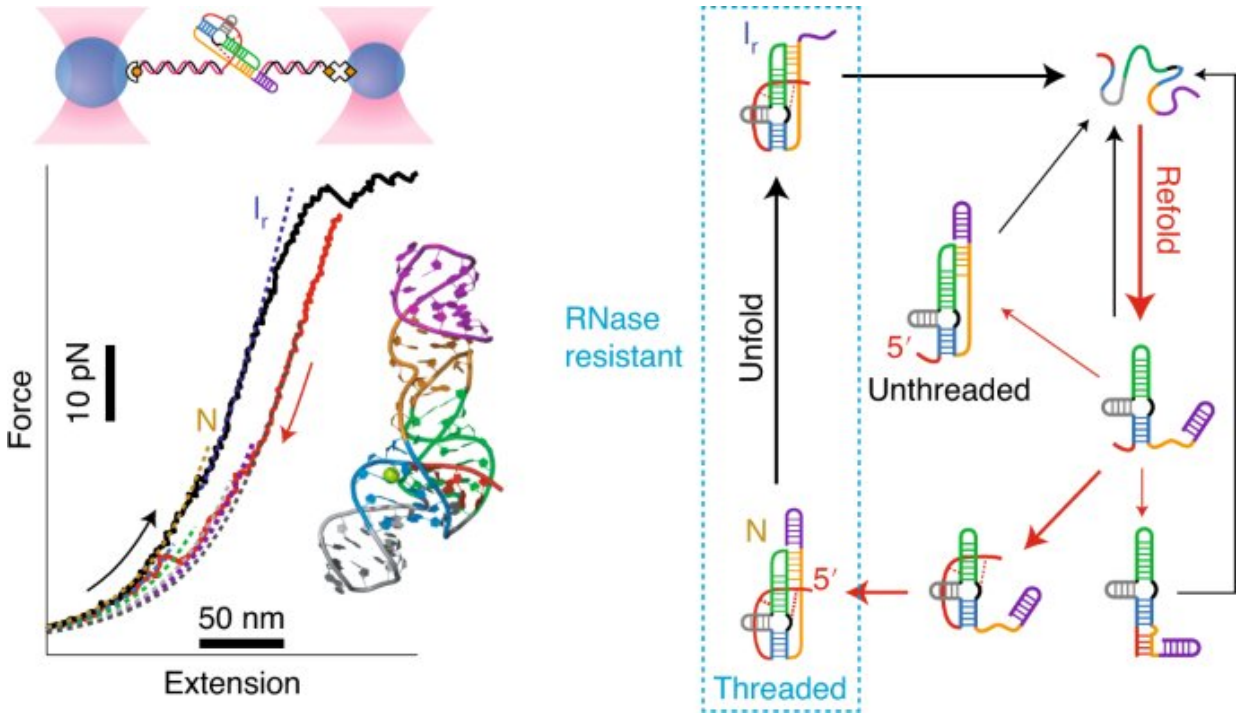

Credit: *Nature Chemical Biology* (2021). DOI: 10.1038/s41589-021-00829-z

A new study by University of Alberta biophysicists has revealed how a rare structure forms within RNA from the Zika virus that makes it resistant to our bodies' immune systems. The results provide a potential target for new drug therapies to combat the virus and others like it.

"Due to the structure formed within the Zika virus genome, pieces of the viral genome remain in our cells and hijack proteins which are crucial for our cells to function properly," said Meng Zhao, lead author and post-doctoral fellow in the Department of Physics. "Targeting this roadblock could be a path to drug treatments for Zika and other viruses that share similar structures, including dengue, yellow fever, West Nile and chikungunya."

Our cells are full of enzymes called RNases that chew up—or degrade—RNA from invading viruses as part of our cells' defenses against infection. The "roadblock" studied by the team is a piece of the Zika virus genome that gives it the ability to resist being degraded by the RNases in our cells.

As a result of this resistance to degradation, viral RNA pieces remain in our cells—and can even be replicated and transmitted from mother to fetus during pregnancy, leading to severe brain defects in babies, such as microcephaly.

"We found that this resistance is due to what is effectively a mechanical roadblock: the RNA makes a knot-like structure that is mechanically extremely strong, and the RNase just can't physically pull the RNA into the machinery that chews it up," explained physics professor and study co-author Michael Woodside. "But if we weaken the mechanical strength of this knot by disrupting some of the bonds that make it rigid, then the RNase can pull it apart and digest the viral RNA properly again."

The scientists found that the formation of this structure from an RNA strand involves a process of several incomplete structures, termed intermediates, that form before assembling into the final RNase-resistant knot—a critical discovery that could pave the way for new approaches to combat Zika by targeting the intermediates before the knot fully forms.

"Even if preventing the knot-like structure is ineffective, our study suggests an alternative treatment strategy: to weaken the mechanical strength of the RNA knot, so it will lose the ability of resisting the purge by the RNase in our cell," said Zhao. "This strategy can be achieved by developing drugs that interrupt the bonds essential for holding the knot-like structure together."

"One of the features that make RNA viruses difficult to combat is that RNA genomes are easily changed in host cells, leading to variants which can be more contagious and dangerous," said Zhao. "Most current efforts toward antiviral treatment target viral proteins. We hope our alternate approach, by studying viral RNA itself, can widen the means to find promising druggable targets."

The study, "Mechanical strength of RNA knot in Zika virus protects against cellular defenses," was published in *Nature Chemical Biology*.

More information: Meng Zhao et al, Mechanical strength of RNA knot in Zika virus protects against cellular defenses, *Nature Chemical Biology* (2021). DOI: 10.1038/s41589-021-00829-z

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