An RNA key that unlocks innate immunity

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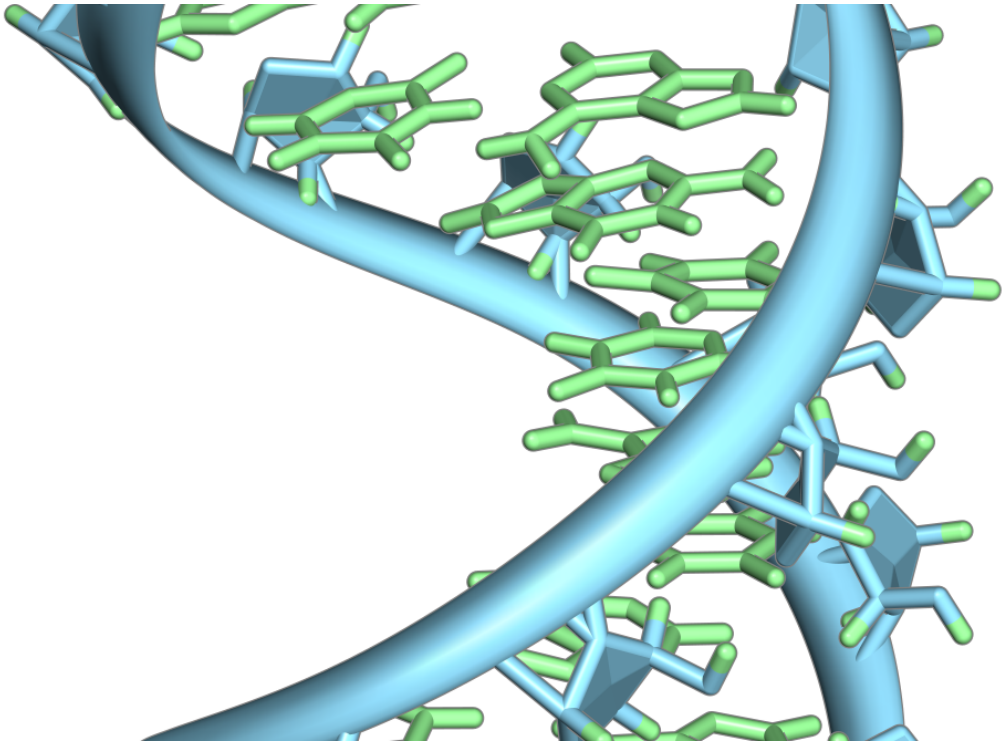

A hairpin loop from a pre-mRNA. Highlighted are the nucleobases (green) and the ribose-phosphate backbone (blue). Note that this is a single strand of RNA that folds back upon itself. Credit: Vossman/ Wikipedia

RNA has long been the neglected middle child of biomolecules, the go-between between DNA, which encodes the cell's instructions, and proteins, which carry them out. Increasingly, though, researchers are recognizing RNA as a versatile molecule with, possibly, as many functions as proteins have. New research from Emory University,

published in the *Journal of Biological Chemistry*, shows that one such versatile RNA molecule may be a key player in human cells' frontline defenses against viruses.

Graeme Conn, the biochemistry professor who oversaw the work, studies how RNA is involved in the body's responses to infections. When a human cell senses a virus, it activates a signaling pathway: a protein called OAS gets turned on and produces a signaling molecule, which in turn activates another protein that both directly defends against the virus as well as activating other parts of the cell's innate immune system.

As it turns out, human RNA might play an important role in this pathway, specifically a human RNA molecule called nc886. The "nc" stands for "noncoding," which means this RNA molecule is not carrying instructions for building a protein. It's doing something all on its own.

What it's doing, the new paper shows, is turning on OAS, thus setting off the chain of events that destroys viruses.

"We saw that (nc886) wasn't just an activator of this pathway, but a very potent activator," said Brenda Calderon, who carried out the research as a graduate student in Conn's lab.

The nc886 molecule can adopt two different shapes, and one of them is much better at activating OAS than the other. This is another way in which this RNA molecule acts like a protein: its function depends strongly on its 3-D shape and structure. Although nc886 is present in all human cells, it's unknown whether the relative abundance of the immune-activating and less-active form might change in response to infection.

"We'll be asking these questions about infected and uninfected cells," Conn said. "How does the level of the RNA change? How do the levels of these two (forms) change?"

Getting deep into the molecular details of cells' first responses to viruses opens the door to new kinds of treatments. Calderon speculates that understanding the factors that activate this pathway may enable researchers to someday manipulate it to strengthen antiviral defenses.

"Such approaches have the potential to underpin novel, broad antiviral therapies (that don't rely) on acquired immunity, and therefore are suitable for infants, elderly, and immunocompromised patients," Calderon said.

More information: Brenda M. Calderon et al, A human cellular noncoding RNA activates the antiviral protein 2′–5′-oligoadenylate synthetase 1, *Journal of Biological Chemistry* (2018). DOI: 10.1074/jbc.RA118.004747

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