Double-strand RNA exhibits traits different from single-stranded RNA

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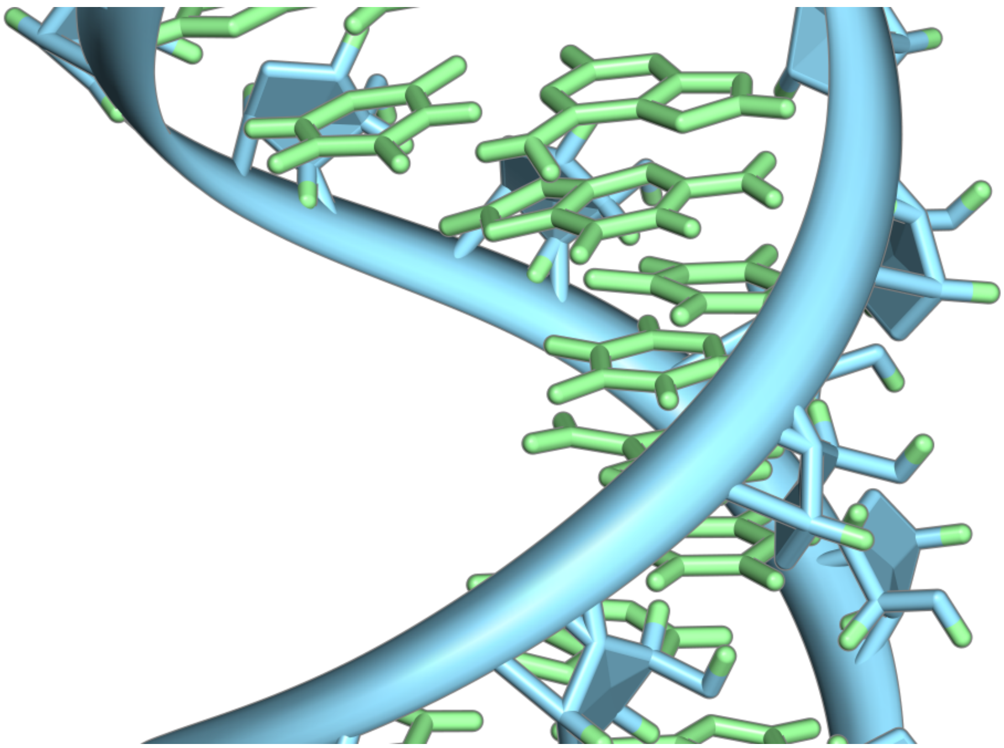

A hairpin loop from a pre-mRNA. Highlighted are the nucleobases (green) and the ribose-phosphate backbone (blue). Note that this is a single strand of RNA that folds back upon itself. Credit: Vossman/ Wikipedia

Messenger RNA, or mRNA, has been in the news recently as a crucial component of the Pfizer-BioNTech and Moderna COVID-19 vaccines. The nucleic acid looks, for all intents and purposes, like a strand of DNA that has been sliced the long way. It's what's known as single-stranded RNA (ssRNA), and it can be found throughout the natural world.

Less common in nature is double-stranded RNA (dsRNA), which has two strands and resembles the well-known DNA double helix. It's found in some viruses, but for the past few decades, people have been developing synthetic dsRNA for a range of purposes.

Despite our growing familiarity with its potential applications, researchers knew little about a key feature of dsRNA, namely how dsRNA degrades—a particularly important question as one of its most promising applications is in agriculture as a type of pesticide.

Research from the lab of Kimberly Parker, assistant professor of energy, environmental and chemical engineering at the McKelvey School of Engineering at Washington University in St. Louis, has upended common assumptions about the chemical stability of dsRNA that may prove useful to fields from agriculture to medicine. The lab's findings even may have implications for our understanding of the origins of life. The results were published this summer in the journal *Environmental Science & Technology*.

"Fundamentally, we are challenging a pervasive assumption that what we know about ssRNA behavior predicts dsRNA behavior," Parker said.

"The general knowledge is that RNA is less stable than DNA," Parker said. That's because the RNA structure has a few extra atoms that causes the nucleic acid to degrade by itself to smaller pieces.

But that's the comparison of ssRNA with DNA. What about the difference between ssRNA and dsRNA?

Parker and first author Ke Zhang, a Ph.D. student in Parker's lab, set out to investigate dsRNA degradation. The team found that, even though dsRNA has the same basic structure as ssRNA, it was substantially more chemically stable than ssRNA. Even at extremely harsh alkaline pH conditions that caused ssRNA to degrade in minutes, dsRNA persisted.

It's fundamental science, but it also has real consequences.

Although little was known about the processes that break down dsRNA, it has been treated as if it behaves the same as ssRNA not only by researchers, but also by institutions such as the Environmental Protection Agency, which regulates pesticide use.

"Fundamentally," says Parker, "we are challenging a pervasive assumption that what we know about ssRNA behavior predicts dsRNA behavior."

Recently, dsRNA has become a hot topic in the world of pesticides. The first crops genetically engineered to contain a dsRNA pesticide might be planted as soon as 2022.

"When we look at the environmental fate of dsRNA pesticides, a key question is, 'Will these things stick around, or are they going to degrade quickly?'" Parker said.

If chemical processes acting on dsRNA cause the structure to break down quickly, "it can be considered potentially safe and you don't have to worry about it as much," Parker said. "But if you need more specific conditions for it to break down, particular enzymes for instance, that changes how you have to think about its safety and potential risk to the environment. You can't rely on chemical instability alone to limit persistence."

The researchers also investigated how the surprising chemical stability of dsRNA might be harnessed for good. Although dsRNA is chemically stable, it still can be degraded by enzymes that occur everywhere in the environment—and even our bodies. This can make it difficult to store dsRNA pesticides and products, as well as challenging to measure levels of dsRNA accurately because the dsRNA can degrade after the sample is collected but before it is analyzed.

To see if the unique chemical stability of dsRNA could be used to stabilize dsRNA in samples, Zhang looked at how ssRNA and dsRNA degraded in human saliva and soils, each of which has enzymes that work to break down both types of RNA.

"In each case, both types of RNA were degraded quickly by the enzymes in human saliva and soils," Zhang said. But when the pH was raised to an alkaline state—which would destroy the enzymes, "things were different; we observed ssRNA was also rapidly degraded by the alkaline conditions. However, dsRNA was actually more stable at the higher pH."

The finding suggests that dsRNA—whether used in pesticides, for medical use or research—should be stored in a high pH environment to confer an extra level of protection.

"Say you work with dsRNA," Parker said. Maybe you sneeze? "You don't want to worry about contaminating your samples with saliva. You can raise the pH of your samples of dsRNA, shut down the enzyme degradation, but also avoid having the chemical degradation process."

The potential to put this knowledge into action goes far beyond pesticides.

There are plenty of viruses that carry their genetic information in RNA instead of DNA; some of them use dsRNA. "I'm interested in how our work lets us know about how viruses might be killed in different conditions," she said. Or if viral dsRNA from wastewater could be preserved better at higher pH to help to follow and predict the spread of disease.

And there's another area, a little different from the rest, in which a better understanding of dsRNA might be useful: unlocking the mysteries of the origin of life on Earth. It's only conjecture, but it's something that captured Zhang's interest.

There is a long-held theory that life on Earth began in hydrothermal vents when smaller molecules came together to form RNA. However, that theory has a fatal flaw: The conditions in these vents would have been alkaline.

"Some scientists think that can't be possible because RNA would degrade in such conditions," Zhang said. "But we have found that it's only true for ssRNA. If we consider dsRNA, at alkaline pH, it can maintain its chemical stability."

More information: Ke Zhang et al, Duplex Structure of Double-Stranded RNA Provides Stability against Hydrolysis Relative to Single-Stranded RNA, *Environmental Science & Technology* (2021). DOI: 10.1021/acs.est.1c01255

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