Sponge-like action of circular RNA aids heart attack recovery

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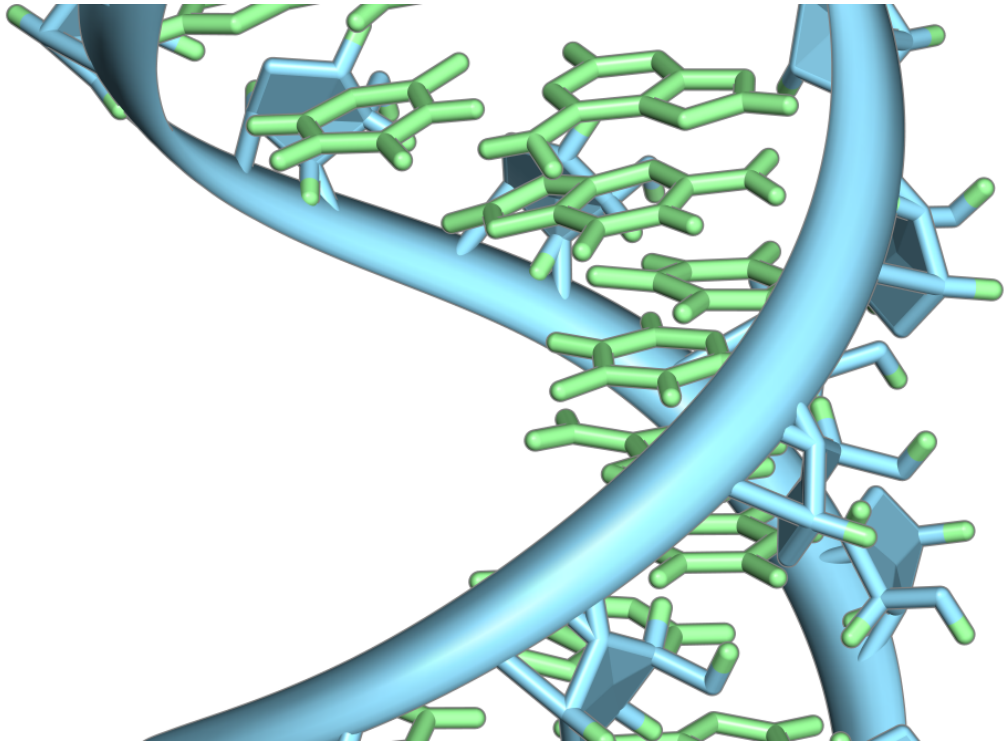

A hairpin loop from a pre-mRNA. Highlighted are the nucleobases (green) and the ribose-phosphate backbone (blue). Note that this is a single strand of RNA that folds back upon itself. Credit: Vossman/ Wikipedia

The human genetic blueprint is like a string of code. To follow it, the code, or DNA, is transcribed into shorter strings of RNA. While some of these shorter strings carry instructions for making proteins—the

functional units of cells—most RNA is not involved in protein production. Among these noncoding RNAs are the recently discovered circular RNAs, so-named because of their unusual ring shape (most other RNAs are linear).

Circular RNAs, like other noncoding RNAs, were thought to be nonfunctional, but recent evidence suggests otherwise. Circular RNAs may in fact act like sponges to "soak up," or bind, other molecules, including microRNAs and proteins, and now, new work by researchers at the Lewis Katz School of Medicine at Temple University (LKSOM) and colleagues supports this idea. They describe, for the first time, a circular RNA that fills a critical role in tissue repair after heart attack, thanks to its ability to soak up harmful molecules.

The study was published online September 20 in the journal *Nature Communications*.

"We discovered that a circular RNA known as circFndc3b, when added therapeutically to the injured heart after surgically induced heart attack in mice, enhances cardiac repair and helps restore heart function," explained Raj Kishore, Ph.D., Professor of Pharmacology and Medicine and Director of the Stem Cell Therapy Program in the Center for Translational Medicine at LKSOM and senior investigator on the new report. "We attributed these effects of circFndc3b to its ability to function like a 'sponge,' binding a protein called FUS that mediates cell death and reduces vascular growth, which hinders heart tissue repair."

Dr. Kishore and colleagues focused their investigation on circFndc3b after finding that this particular circular RNA was significantly decreased in the heart in mice that had experienced a heart attack. "This observation led us to wonder whether the change in circFndc3b expression meant that it was important functionally in the heart," Dr. Kishore said.

To investigate this possibility, a gene product to induce circFndc3b overexpression was injected into the heart in mice after heart attack. Subsequent examination showed that within eight weeks of injection, treated mice experienced gains in heart function and in survival compared to their untreated counterparts. There was also evidence within heart tissue that new blood vessels had started to form, greatly aiding the tissue repair process.

The findings offer exciting insight into circular RNAs and the significance of their potential role as molecular sponges that limit the activity of damaging molecules. "CircFndc3b specifically soaked up an RNA binding protein that suppresses blood vessel formation," Dr. Kishore explained. "In doing so, it made way for new vessels to grow."

Dr. Kishore and colleagues are now in the process of developing a large animal model to further investigate the therapeutic potential of circFndc3b. The team also wants to begin analyzing plasma samples from patients just after heart attack to investigate whether specific circulating RNAs could serve as biomarkers for heart disease or injury and to get a better sense of their clinical significance.

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