We now know how RNA molecules are organized in cells

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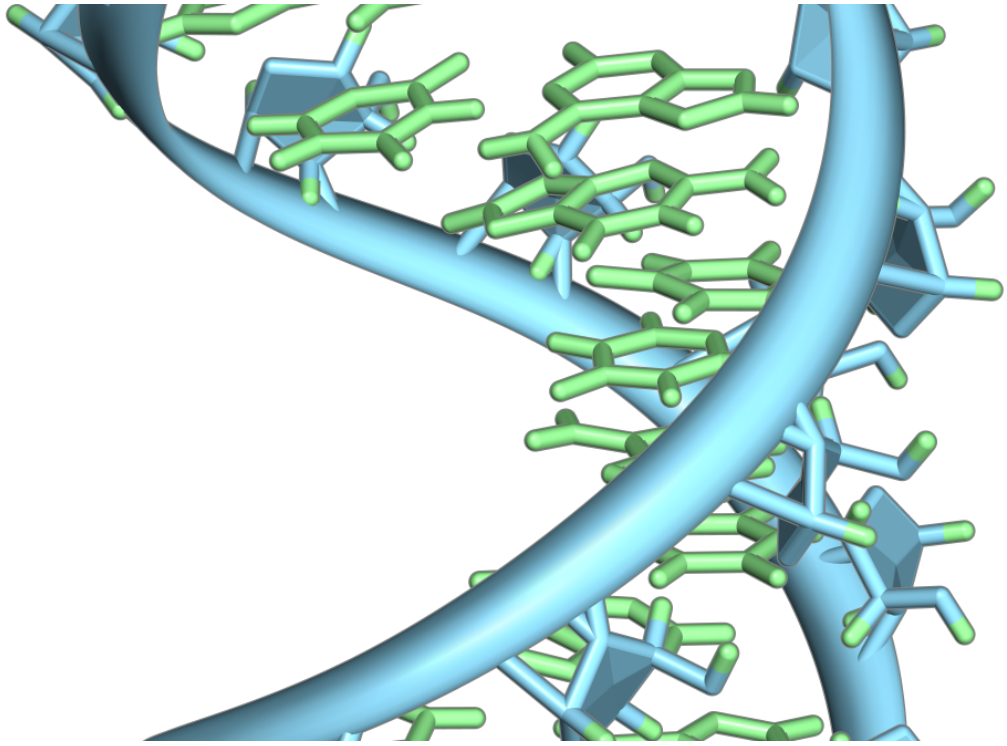

A hairpin loop from a pre-mRNA. Highlighted are the nucleobases (green) and the ribose-phosphate backbone (blue). Note that this is a single strand of RNA that folds back upon itself. Credit: Vossman/ Wikipedia

Working with colleagues in the U.S., a team of Université de Montreal researchers has for the first time visualized how RNA molecules are organized in cells.

In their study published in *Molecular Cell*, scientists at UdeM used super-resolution microscopy to investigate how the 3-D organization of mRNAs changes depending on the location of these molecules in cells and show that a decades-old dogma requires revision.

"The flow of information from DNA to protein implicates a copy of the DNA sequence called messenger RNA that serves as template for protein synthesis," said the study's senior author Daniel Zenklusen, an associate professor at UdeM's department of biochemistry and molecular medicine. "Just like DNA, RNA is a long polymer composed of nucleic acids. How these RNA polymers are compacted and organized in cells to allow protein synthesis was so far unknown, in part because we were lacking technologies to visualize these molecules in high resolution," Zenklusen said.

It has long been thought that all messenger RNA, or mRNA, molecules acquire a specific conformation during protein synthesis: the two ends of the molecule coming together to form a stable so-called closed-loop complex. This new study shows that this long-standing model is oversimplified, according to Zenklusen and his team.

"We observed that messenger RNAs exist in many different configurations in cells, but not in the previously suggested stable closed-loop conformation," said the study's first author Srivathsan Adivarahan, a doctoral student in Zenklusen's lab. "This was very surprising to us since this model is found in every text book describing the essential process of protein synthesis."

In collaboration with the laboratories of Olivia Rissland at the University of Colorado and Bin Wu at Johns Hopkins University in Baltimore, the UdeM scientists found that the messenger RNAs of cells can exist in many conformations but mostly as very compact molecules. This is most pronounced when protein synthesis is suppressed or messenger RNAs

are sequestered to specific subcellular compartments such as stress granules, compartments similar to pathologic aggregates often found in neurodegenerative diseases that form under conditions of environmental pressure on cells.

"Our findings change how we think about many aspects of mRNA metabolism, and in particular on how the mRNA is organized during protein synthesis," said Zenklusen. "Regulating this process is essential for all cells, but it is particularly important for a cancer cell that requires high levels of protein synthesis to allow for unceasing growth. Therefore, different drugs affecting proteins synthesis are currently in development and some of these drugs target proteins previously implicated in the closed-loop model. The models of how these drugs affect protein synthesis will have to be revisited."

The new study also illustrates the importance of basic science and the need to continuously develop new technologies, he added. "Technological advances allow us to revisit questions we long thought to have been solved, just to realize once we look at them with new eyes that we are far from truly understanding them."

One of the next steps in Zenklusen's laboratory is therefore to continue to advance the technological approaches that enabled these new findings—single molecule and super-resolution microscopy—in order to gain an even more detailed insight into the mechanisms of gene regulation and how it's misregulated in various diseases.

More information: "Spatial organization of single mRNPs at different stages of the gene expression pathway," by Daniel Zenklusen et al, was published November 8, 2018, in *Molecular Cell*. The study was financed by the Canadian Institutes of Health Research, Fonds de recherche du Québec - Santé and the Canada Foundation for Innovation. DOI: 10.1016/j.molcel.2018.10.010

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