Gene expression mechanism may have immunity, cancer implications

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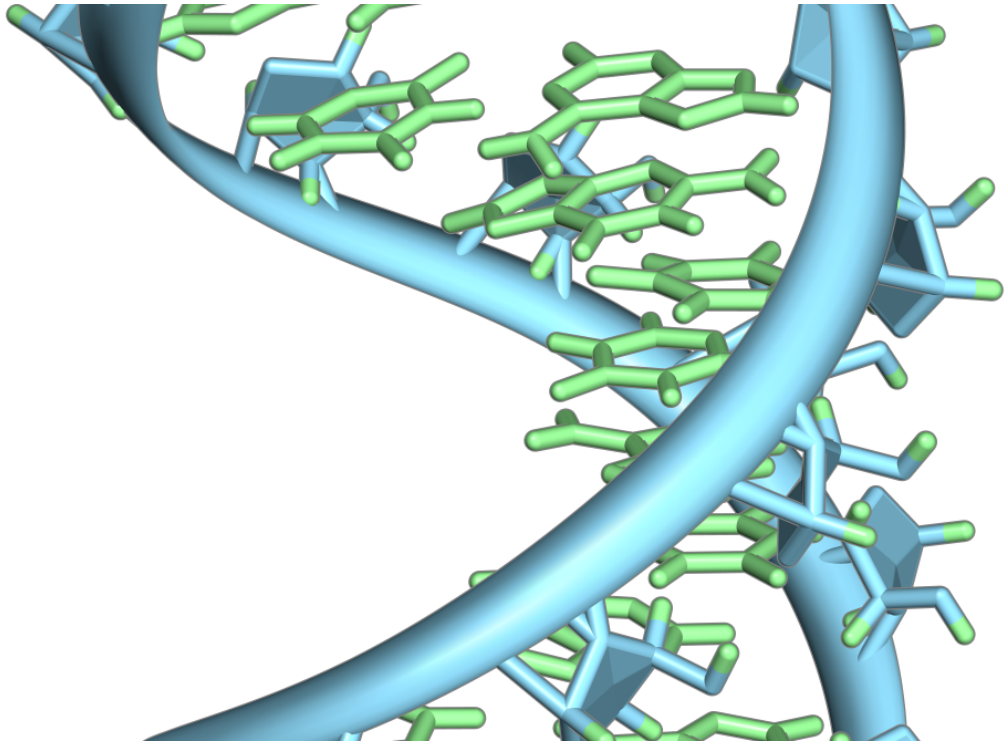

A hairpin loop from a pre-mRNA. Highlighted are the nucleobases (green) and the ribose-phosphate backbone (blue). Note that this is a single strand of RNA that folds back upon itself. Credit: Vossman/ Wikipedia

Alternative polyadenylation (APA) is an RNA processing mechanism that regulates gene expression by generating different ends on RNA transcripts of the same gene. Though it affects more than half of human

genes, the significance of APA was poorly understood. Now a new study by The Wistar Institute describes an important function of APA in allowing certain mRNAs to reach specific sites of protein synthesis and reveals that length, sequence and structural properties can determine the destination (and fate) of mRNAs within the cell. These findings, published online in the journal *Cell Reports*, shed light on the consequences of APA that may represent a paradigm shift in the mRNA metabolism field.

The laboratory of Bin Tian, Ph.D., professor and co-leader of the Gene Expression & Regulation Program at The Wistar Institute Cancer Center and senior author on the study, was among the first to discover the widespread occurence of APA using genomic and bioinformatic approaches.

Following gene transcription, messenger RNAs are chemically modified to become mature RNA molecules that can leave the nucleus and perform their functions. One of these modifications is polyadenylation, which prevents RNA degradation and favors its translation into protein.

Through APA, a gene can be polyadenylated at multiple sites, resulting in mRNAs with different coding sequences and/or regulatory regions (3'untranslated regions or 3'UTRs), called isoforms. Transcripts encoding the same protein can have different fates in the cell because of distinct 3'UTRs, which harbor regulatory elements for mRNA metabolism. This dramatically increases the complexity of our genome, so that fewer genes are needed to encode all the proteins a cell needs.

Tian and colleagues employed functional genomics methods to analyze the distribution of the APA isoforms in mouse cells. Bioinformatic analysis and machine learning approaches revealed that APA, via modulation of mRNA 3'UTRs, impacts the connection between mRNAs and the endoplasmic reticulum (ER), a network of tubes that build,

package and transport proteins.

They named this mechanism translation-independent ER association (TiERA) and found that some mRNAs possess specific sequences and structures that determine their potential to undergo APA and ultimately associate with the ER.

"When mRNAs leave the nucleus and move to the cytoplasm, they need to be properly directed to reach the appropriate site of protein translation," said Tian. "The cytoplasm is a huge space for an RNA molecule: For comparison, imagine entering a baseball stadium and needing directions to reach your seat."

The team found that mRNAs with higher TiERA tend to encode for signaling proteins,which help cells communicate with each other by sending, receiving and processing signals in response to changes in the environment.

They propose that APA renders this process more efficient by anchoring certain mRNA isoforms with the ER in specific cellular locations where important signaling events happen.

"According to our model, the ER would serve as a scaffold to keep proteins 'on hand' where they are most needed," said Tian. "This would provide a platform for signaling events to happen effectively at the right place in the cell."

More information: Alternative 3'UTRs play a widespread role in translation-independent mRNA association with endoplasmic reticulum, *Cell Reports* (2021). DOI: 10.1016/j.celrep.2021.109407

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