Colon cancer cells use mysterious RNA strands to avoid cell death

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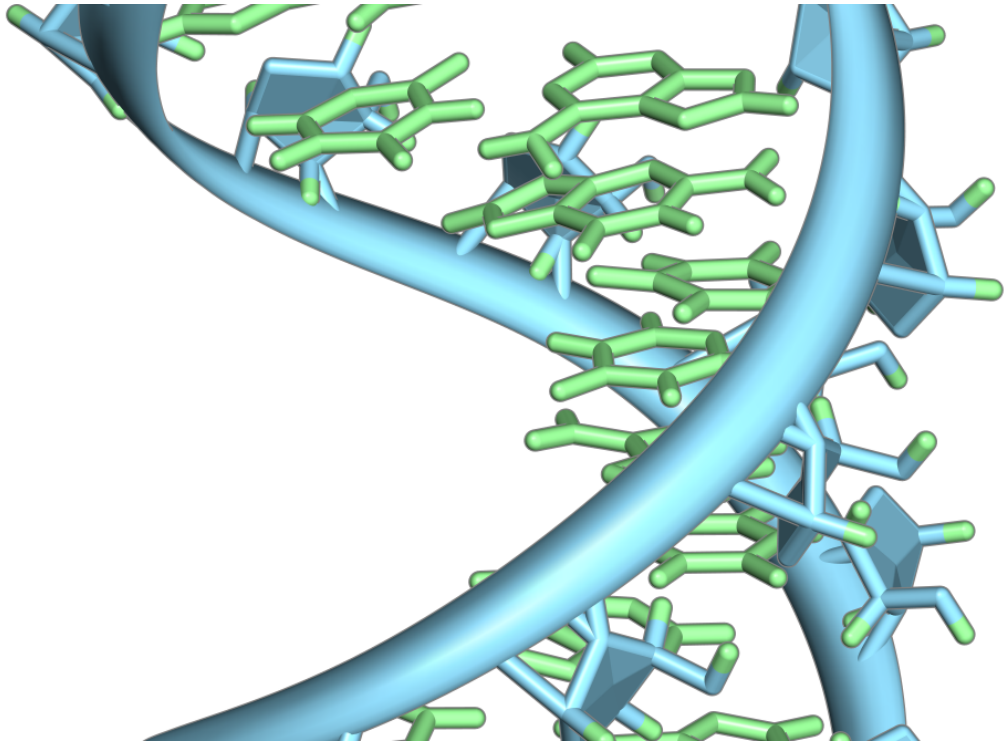

A hairpin loop from a pre-mRNA. Highlighted are the nucleobases (green) and the ribose-phosphate backbone (blue). Note that this is a single strand of RNA that folds back upon itself. Credit: Vossman/ Wikipedia

Researchers from Case Western Reserve University School of Medicine have discovered how unusually long strands of RNA help colon cancer cells avoid death, allowing unregulated growth. Unlike other RNAs, the

intriguing strands do not appear to encode proteins and are termed "long non-coding RNAs" or "lincRNAs."A new study showed some lincRNAs could be targeted by drug developers to halt colon cancer.

In a new study published in *Scientific Reports*, researchers compared lincRNA levels inside tumor cells, to levels inside healthy colon cells. They found over 200 lincRNAs at significantly different levels inside the tumor cells as compared to normal cells. One in particular, called lincDUSP, was overexpressed in 91 percent of the tumor samples. A few tumors had more than fifteen times the normal amount of lincDUSP. The significant increase suggested this mysterious, and previously uncharacterized, RNA could be cancer-causing.

"To determine whether lincDUSP shows oncogenic activity in colon cancer, we decided to test the effects of depleting lincDUSP in patient-derived colon tumor cell lines," wrote the authors. The researchers genetically modified colon cancer cells to deplete lincDUSP, and surprisingly, the cells began replicating at normal rates. They no longer had unrestricted growth associated with colon cancer tumor cells. Small molecules that inhibit lincDUSP, say the researchers, could have similar effects.

"Our work demonstrates that not only protein-coding genes but also non-coding genes contribute to colon cancer progression," says Ahmad Khalil, Ph.D., senior author, assistant professor of genetics and genome sciences at Case Western Reserve University School of Medicine, and member of the Case Comprehensive Cancer Center. "LincRNAs could be exploited as direct drug targets in this and other human diseases."

Khalil's team discovered that depleting lincDUSP restored inherent cell death mechanisms. Colon cancer cells with low levels of lincDUSP became susceptible to cellular checkpoints that keep growth in check. They immediately committed cell suicide—apoptosis—at the first sign

of DNA damage. Depleting the single lincRNA also had widespread genetic effects. Khalil's team discovered that reducing lincDUSP levels affected expression of over 800 other genes. These results, combined with the team's experiments showing lincDUSP interacting with DNA, add to a growing body of evidence that lincRNAs are central to gene regulation. As such, they could represent an intriguing arena for drug developers.

"Not much is known about the role of long non-coding RNAs in colon cancer," says Khalil. "Using new technologies that target RNA molecules, instead of proteins, adds a new dimension to cancer therapies."

More information: Megan E. Forrest et al, Colon Cancer-Upregulated Long Non-Coding RNA lincDUSP Regulates Cell Cycle Genes and Potentiates Resistance to Apoptosis, *Scientific Reports* (2018). DOI: 10.1038/s41598-018-25530-5

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