Cancer-associated long non-coding RNA regulates pre-mRNA splicing

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Researchers report this month that MALAT1, a long non-coding RNA that is implicated in certain cancers, regulates pre-mRNA splicing - a critical step in the earliest stage of protein production. Their study appears in the journal *Molecular Cell*.

Nearly 5 percent of the human genome codes for proteins, and scientists are only beginning to understand the role of the rest of the "non-coding" genome. Among the least studied non-coding genes - which are transcribed from DNA to RNA but generally are not translated into proteins - are the long non-coding RNAs (lncRNAs).

Before the human genome was fully sequenced, it was a "protein-centric world," said University of Illinois cell and developmental biology professor Kannanganattu Prasanth, who led the study. With the sequencing of the genome it became clear, however, that a majority of genes code for RNAs that are not translated into proteins.

In recent years, research on non-coding RNAs has blossomed, but most studies have focused only on small non-coding RNAs, which play critical roles in several aspects of cellular function. There have been comparatively fewer studies on lncRNAs, Prasanth said. As a result, researchers are only beginning to understand the functions of a few lncRNAs.

Prasanth's laboratory focuses on understanding the role of lncRNAs, such as MALAT1, which normally are distributed in the nucleus of

mammalian cells.

Preliminary studies suggest that lncRNAs carry out vital regulatory functions in cells. When those functions go awry, Prasanth said, serious consequences can result. Abnormal expression of the MALAT1 gene, for example, is implicated in many cancers, including breast, lung and liver cancers, "so the scientific world was interested in what this RNA could be doing in normal cells, and how changes in its expression correlate with cancer," he said.

Prasanth was also the co-first-author of another study, recently published in The EMBO Journal, that found that MALAT1 plays a role in recruiting important proteins, called pre-mRNA splicing factors, to the site of gene transcription in the nucleus.

Pre-mRNA splicing involves cutting out unneeded sequences and piecing the mRNAs together before they are exported from the nucleus and translated into proteins.

"That study gave us the clue that MALAT1 is an important gene that might be involved in pre-mRNA metabolism," Prasanth said.

In the new study, Prasanth and his colleagues tested the hypothesis that MALAT1 interacts with and modulates the behavior of a group of pre-mRNA splicing factors known as the SR-family splicing factors.

The researchers found that the MALAT1 sequence contains multiple regions that can bind SR-splicing proteins. Further experiments showed that MALAT1 does indeed bind to several members of the SR-proteins the team analyzed.

Furthermore, depleting cells of MALAT1 or over-expressing the splicing factors to which it can bind led to the same alteration in the splicing of a

large number of pre-mRNAs in the cells, suggesting that MALAT1 latches onto the splicing factors and regulates their access to new transcripts.

"All of the data strongly suggest that MALAT1 is acting as a regulator of splicing by modulating the levels of the splicing factors in the cell," Prasanth said.

This study verifies that MALAT1 plays a key role in pre-mRNA processing, with broad implications for human health, Prasanth said.

"Numerous studies have shown that aberrant splicing of pre-mRNA is a major issue associated with several diseases, including cancer," he said. "Some of the factors we know interact with MALAT1 have been shown to be oncogenes. If you over-express these genes you can make a cell cancerous."

"Similarly, some of the genes whose pre-mRNA splicing is controlled by MALAT1 are members of the cancer 'signature genes,' " Prasanth said. "This means that their abnormal expression is directly correlated with several cancers."

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