No junk: Long RNA mimics DNA, restrains hormone responses

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It arises from what scientists previously described as "junk DNA" or "the dark matter of the genome," but this gene is definitely not junk.

The gene GAS5 acts as a brake on steroid hormone receptors, making it a key player in diseases such as hormone-sensitive prostate and breast cancer.

Unlike many genes scientists are familiar with, GAS5 does not encode a protein. It gets transcribed into RNA, like other genes, but with GAS5 the RNA is what's important, not the protein. The RNA accumulates in cells subjected to stress and soaks up steroid hormone receptors, preventing them from binding DNA and turning genes on and off.

Researchers at Emory University School of Medicine have obtained a detailed picture of how the Gas5 RNA interacts with steroid hormone receptors. Their findings show how the Gas5 RNA takes the place of DNA, and give hints as to how it evolved.

The results are scheduled for publication in *Nature Communications*.

Scientists used to think that much of the genome was "fly-over country": not encoding any protein and not even accessed much by the cell's gene-reading machinery. Recent studies have revealed that a large part of the genome is copied into lincRNAs (long intergenic noncoding RNAs), of which Gas5 is an example.

"There are thousands of long non-coding RNAs that play critical roles in gene regulation, and little data to tell us how they are functioning or where they came from," says lead author graduate student Will Hudson. "We took a deep dive into looking at the interaction of the Gas5 RNA with steroid hormone receptors, and we think this work may serve as a model to understand how lincRNAs interact with other proteins."

Hudson is in the Molecular Systems Pharmacology graduate program at Emory, working with Eric Ortlund, PhD, assistant professor of biochemistry. They and their colleagues probed the interaction of Gas5 RNA with the glucocorticoid receptor, which binds the stress hormone cortisol.

Collaborators at Scripps Research Institute in Florida and Keele University in the UK contributed cellular assays and NMR experiments.

When steroid hormones (examples: cortisol, progesterone, testosterone) are present they bind specific protein receptors and are able to control gene activity by attaching to particular DNA sequences. The Gas5 RNA functions by mimicking those DNA binding sites, competing for steroid receptor proteins within the cell.

"We demonstrated that a slight alteration in Gas5's sequence disrupts its ability to control the growth of prostate cancer cells, for example," Ortlund says. "This is important, because whether the specific sequence of lincRNAs is critical for their function has been an open question."

Their results suggest how genetic variations in Gas5 could account for risk for some forms of cancer. The researchers also examined the Gas5 sequence in various species throughout evolution, and found that the sequence important for regulation of steroid receptors grew out of another genomic sequence important in RNA splicing.

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