

Researchers identify RNA molecules that regulate action of male hormone in prostate cancer

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Study performed in Brazil identified hundreds of RNAs that do not encode proteins but appear to regulate effects of androgens and androgen receptors on gene expression in tumors. Credit: David Bushnell, Ken Westover & Roger Kornberg, Stanford University / NIH

In most cases of prostate cancer, tumor cell growth is stimulated by the action of male hormones, or androgens, such as testosterone and dihydrotestosterone (DHT). For this to happen, these hormones have to

bind to androgen receptors, proteins located mostly in the cytoplasm of prostate cells. When hormone and receptor bind, they migrate to the cell nucleus, where they either activate or inhibit a number of genes to create a gene expression pattern that favors tumor proliferation.

A study published in the journal *Frontiers in Genetics* has identified 600 novel long noncoding RNA molecules (lncRNAs) that appear to be responsible for the fine regulation of this process. LncRNAs are a large class of RNA molecules that have a length of more than 200 nucleotides and do not encode proteins.

"The study raises the hypothesis that some of these lncRNAs make a prostate tumor more aggressive. If confirmed by future research, the discovery opens up a world of new possibilities," said Sergio Verjovski-Almeida, a researcher at Butantan Institute in São Paulo State, Brazil, and principal investigator for the project supported by São Paulo Research Foundation—FAPESP.

As Verjovski-Almeida explained, only 2 percent of the human genome produces messenger RNA molecules, which carry the genetic information needed for protein synthesis. The other 98 percent, formerly dismissed as "junk DNA," produces different types of noncoding RNA that are generally not translated into proteins but modulate the expression of neighboring genes or the action of proteins produced by those genes. In other words, they govern the functioning of the genome by means of epigenetic regulation—not altering DNA itself but influencing gene expression.

"These lncRNAs are powerful regulators of gene expression. They interact with and magnify the effect of regulatory proteins. This is what we believe the molecules we identified are doing to androgen receptors in a [prostate tumor](#)," said Verjovski-Almeida, who is also a professor in the University of São Paulo's Chemistry Institute (IQ-USP).

The FAPESP-supported investigation began with deep sequencing of molecules expressed in a prostate cancer cell line. The deep-sequencing technique enables billions of nucleotides to be sequenced at the same time, increasing the likelihood of detecting molecules that are expressed in small amounts and that would go unnoticed in more superficial studies.

"The more deeply we sequence a tissue, the more we discover RNA molecules expressed specifically at the site in question, as is typically the case for lncRNAs," Verjovski-Almeida said. Some 3,000 different lncRNAs expressed in prostate tumors had already been described in the scientific literature. The study performed by the group at Butantan Institute revealed another 4,000 novel molecules of the same kind. In light of these new findings, the researchers then decided to reanalyze raw data from studies published by other groups in which molecules expressed in tumors from patients with prostate cancer were compared with those expressed in healthy prostate tissue.

"Most of these previous studies used the microarray method, which sequences tissue using a panel of known target genes. So unknown genes or genes not included in the panel simply don't show up in the results of the analysis, even if they're expressed in the tissue," Verjovski-Almeida said.

When they reanalyzed the raw data from previously published research, the Butantan Institute group found that 65 lncRNAs were more highly expressed in prostate tumors than in healthy tissue. "The original studies had identified increased expression of only 40 of these molecules. The rest were passed over for lack of a complete benchmark on prostate lncRNAs. These are genes that could be involved in the development of prostate cancer and need to be better explored," Verjovski-Almeida said.

Regulation of hormone action

The next step was to find out whether these lncRNAs interacted with androgen receptors. To do so, the researchers used a technique known as RNA immunoprecipitation (RIP).

"We detected more than 600 lncRNAs bound to androgen receptors in [prostate](#) tumors. These are [molecules](#) that bind to the complex formed by androgen and its receptor in the cell nucleus, possibly for the purpose of fine regulation of the gene activation and inhibition process," Verjovski-Almeida said.

Androgen receptors are known to be capable of binding to more than 10,000 different genome sites upon migrating to cell nuclei. However, they do not alter the expression of 10,000 genes when this occurs.

"In order to find out what will be activated and inhibited, we need an additional program, and we believe some of the lncRNAs identified do indeed play this role," said the FAPESP-funded researcher.

The next technique used by the group was a machine learning algorithm, a type of artificial intelligence tool that analyzes a large amount of data by statistical methods in search of repeating patterns that can be used as a basis for prediction or decision making. In this manner, they found that lncRNAs were present at the genome sites where gene expression was altered (activated or inhibited) by androgen receptors.

The same sites were also found to contain concentrations of certain histones, a family of basic proteins that modulate the spatial organization of DNA in the nucleus and activate or inhibit gene expression. Generally speaking, genes were more active in the presence of these regulatory proteins.

"We can't yet say whether the presence of these lncRNAs is a cause or effect of the abundance of certain activating histones and of the

alterations to [gene expression](#), but the fact is that they mark specific regions of genes that are activated or inhibited in the presence of androgen. With these findings, we built a panel of possible regulators of the receptor's action in [prostate cancer](#)," Verjovski-Almeida said.

Only one of these lncRNAs had been shown to bind to [androgen receptors](#) and associated with increased tumor aggressiveness in previous research, he added.

"It may be that more of these 600 lncRNAs we found to bind to the receptor also act through a similar mechanism," he said. "If you identify lncRNAs that regulate important [genes](#), you can try to intervene in their transcription or in the regulation process. It opens up a world of possibilities."

More information: Lucas F. daSilva et al, Chromatin Landscape Distinguishes the Genomic Loci of Hundreds of Androgen-Receptor-Associated LincRNAs From the Loci of Non-associated LincRNAs, *Frontiers in Genetics* (2018). [DOI: 10.3389/fgene.2018.00132](https://doi.org/10.3389/fgene.2018.00132)

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