UT SOUTHWESTERN MEDICAL CENTER NEWS

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UT Southwestern researcher maps far-reaching effects of estrogen signaling in breast cancer cells

DALLAS, May 5, 2011 – A UT Southwestern Medical Center researcher has identified the most comprehensive measurement to date of estrogen's effect on breast cancer cells, showing for the first time how immediate and extensive the effect is.

The findings, published online today and in the May 13 print edition of the journal *Cell*, could lead to a new set of therapeutic applications and provide a model for understanding rapid signal-dependent transcription in other biological systems.

"We found that estrogen signaling immediately and directly regulates a strikingly large percentage of all the RNA (ribonucleic acid) molecules in breast cancer cells in a rapid, robust and unexpectedly transient manner," said Dr. W. Lee Kraus, director of the Cecil H. and Ida Green Center for Reproductive Biology Sciences at UT Southwestern and senior author of the study.

It's long been known that estrogen action plays an important role in breast cancer cells. About two-thirds of breast cancers contain estrogen receptors, the proteins that allow the cell to respond to the hormone as a mitogenic signal. Estrogen is an initial driver of the growth of breast cancers, and the estrogen receptor itself has been used as a prognostic indicator as well as a target for anti-hormone therapies such as tamoxifen.

This new study, however, gives researchers a much larger picture of the gene regulation underlying the estrogen-dependent response that causes cells to divide, Dr. Kraus said.

The study showed that estrogen regulates the distribution and activity of all three RNA polymerases and every class of coding and noncoding RNA. Researchers also identified for the first time thousands of previously unannotated or undetected estrogen-regulated intergenic transcripts, which will open up new avenues for future research, he said.

"This is potentially a very rich resource," Dr. Kraus said. "If we can understand what those transcripts are doing, maybe we can modulate them to control cell growth and response to estrogen. This data set has been transformative for my lab. We're now exploring the functions of all of the different classes of previously unannotated transcripts. We think there's great potential there."

(MORE)

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Using a new methodology called Global Run-On Sequencing (GRO-seq), developed by collaborators at Cornell University, the researchers were able to observe in a very short period of time how estrogen regulates the growth of cells on a molecular level. In previous studies, researchers had to make inferences about gene transcription – the process of creating an RNA copy of a DNA sequence – based on steady state gene expression patterns, or static images that are captured over hours and days. Instead, GRO-seq provides a zoomed-in view of genome-wide transcription as it's happening, a virtual "map" of the position and orientation of all engaged RNA polymerases at high resolution.

"We now have a method in which we can look at what estrogen is doing as soon as it enters the cell," said Dr. Kraus, who also serves as vice chairman for basic science for obstetrics and gynecology. "The results were really surprising. The genes get turned on and off in a very short time scale."

In mapping the transcriptome – all the genes that are transcribed in a cell at any one time – Dr. Kraus and his collaborators discovered that short treatments with estrogen regulate one-fourth of all the different types of RNAs produced in the breast cancer cell type.

"This is a profound effect on the genome and something that had never been detected before. It's essentially changing a quarter of the transcripts that are produced in the cell," said Dr. Kraus, who left Cornell last summer to join the UT Southwestern faculty.

"You can really see the logic of this mitogenic response," he said. "It's not just about estrogen stimulating the production of some protein-coding genes. It's about estrogen coordinating transcriptional responses across the genome that allows it to produce this effect."

Lead authors on the study were Drs. Nasun Hah and Charles G. Danko, both members of the former Kraus lab at Cornell. Drs. Leighton Core, Joshua Waterfall, Adam Siepel and John Lis, also from Cornell, participated in the research.

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