UT SOUTHWESTERN MEDICAL CENTER NEWS

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Tiny RNA molecules control labor, may be key to blocking premature birth, UT Southwestern researchers find

DALLAS – Nov. 15, 2010 – Tiny molecules called microRNAs act together with hormones to control the onset of labor, raising the prospect that RNA-based drugs might be able to prevent premature labor, researchers at UT Southwestern Medical Center have discovered in a preclinical study.

"With these findings, we understand better the system that controls labor, so with future research we might have the potential to manipulate it and prevent preterm birth," said Dr. Carole Mendelson, professor of biochemistry and obstetrics and gynecology at UT Southwestern and senior author of the study, which appears in an online issue of the *Proceedings of the National Academy of Sciences.*

Using pregnant mice as well as human uterine tissue, the researchers uncovered a feedback cycle involving microRNAs, proteins called ZEB1 and ZEB2, and the pregnancy-maintaining hormone progesterone, as well as genes and other factors that control contraction of the uterus.

"We've been struggling for a long time to understand how progesterone keeps the uterus from contracting during most of pregnancy," Dr. Mendelson said. "Our findings indicate that progesterone controls a family of microRNAs whose levels dramatically increase right before labor. At the same time, levels of the microRNAs' targets, the ZEB proteins, decrease. This enables uterine contractions."

MicroRNA is one form of RNA, a chemical cousin of DNA. MicroRNAs interact with other protein-making molecules in cells, helping to fine-tune the expression of networks of genes and control cell function, Dr. Mendelson said.

In the new study, the researchers measured microRNA levels in the uteri of mice in mid-pregnancy and near labor. As labor approached, the level of a group of microRNAs called the miR-200 family greatly increased. When the researchers artificially stimulated premature labor, the miR-200 levels also increased.

The miR-200s block the production of two proteins called ZEB1 and ZEB2. In contrast,

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progesterone directly increases ZEB1 levels. The researchers uncovered a feedback cycle involving all these factors that prevents uterine contraction as long as progesterone is present.

"We found that during pregnancy, progesterone acts on the feedback loop to keep the microRNA levels down and the ZEBs up," said Nora Renthal, Medical Scientist Training Program student and lead author of the study. "The ZEBs, in turn, inhibit contraction-associate genes. But then, just prior to labor, there's a switch. Progesterone action decreases; the ZEBs are suppressed; the miR-200s increase; and the contraction-associated genes are turned on."

The researchers directly tested the contractility of cultured human uterine cells containing low or high levels of ZEB1 or ZEB2. In the presence of oxytocin, uterine cells with low levels of ZEBs contracted, while those with high levels did not, mirroring what happened in the pregnant mice.

While the study shows that the miR-200 family might be a likely therapeutic target to fight premature labor, the microRNAs and their interaction with the ZEB proteins also are known to play a role in cancer, so drug development would have to be approached very carefully, Dr. Mendelson said.

Other UT Southwestern researchers involved in the study were Dr. Chien-Cheng Chen, postdoctoral researcher in biochemistry; Koriand'r Williams, MSTP student; Dr. Robert Gerard, associate professor of internal medicine; and Dr. Janine Prange-Kiel, assistant professor of cell biology.

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