UC San Diego Health

Protein Could Provide Insight into Unexplained Infertility

By Michelle Brubaker | December 12, 2018

For couples struggling with infertility, one of the most difficult things to hear is that the cause of their infertility is unknown. This is the case for more than 15 percent of couples seeking reproductive assistance. Researchers at University of California San Diego School of Medicine have identified a protein in mice that must be present in eggs for them to complete normal development.

Without the protein, called ZFP36L2, or L2 for short, the eggs appear ordinary, but they cannot be fertilized by sperm. Female mice lacking L2 in their eggs mature and ovulate, but they produce no offspring.

"We never guessed this Zinc Finger Protein (ZFP) in the oocyte may be playing such a key role in fertility – particularly at such an early step in the game," said Heidi Cook-Andersen, MD, PhD, assistant professor of reproductive medicine and biological sciences at UC San Diego School of Medicine and a physician at the UC San Diego-affiliated Reproductive Partners Fertility Center-San Diego.

Cook-Andersen and her research team discovered that L2 is necessary for a process called "oocyte global transcriptional silencing," which creates a critical pause in the message-making, or transcription, that comes from the oocyte DNA. "As it turns out, this brief holiday for the DNA is not only critical for fertility, it is a highly conserved developmental event across species, and we know that this happens in people as well," said Cook-Andersen.

The finding ¬yields interesting insight into the process of early development. It means that as each oocyte matures and is subsequently fertilized by sperm, it begins to develop as an embryo in the absence of new mRNA production. In other words, the early embryo has no new instructions from the nucleus.

Global transcriptional silencing itself is not new. It is a documented key for the transition from oocyte to embryo, and essential for a successful pregnancy. Yet the mechanisms controlling global transcriptional silencing have been poorly understood. L2 activates a process called mRNA decay — a powerful mechanism that quickly degrades targeted RNA in the cell, turning off the expression of affected genes. "This is like stopping the hard-drive in a computer. Programs just can't find files," said Cook-Andersen.

In biological terms, the ¬researchers found that L2 binds and degrades a large group of oocyte mRNAs that encode a class of proteins called histone demethylases. These enzymes remove epigenetic 'methyl marks' from histones, which are the proteins that bind to DNA and provide structure to chromosomes. They also serve as the directions or bookmarks for transcriptional activity.

By turning off this group of histone demethylases, L2 enables the widespread accumulation of histone methylation marks known to occur at the time of global transcriptional silencing.

If researchers can confirm that the same mechanism is conserved in human oocytes, it is possible that abnormal expression of L2 or other factors regulating histone methylation in the oocyte might explain a subset of the currently unexplained cases of female infertility.

"For some patients, all their tests come back normal and we have no idea why it's difficult for them to conceive," said Cook-Andersen. "There are many aspects of fertility that we still haven't discovered. With this pathway now identified, we have a new direction to explore moving forward."

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