New clues in mice link cholesterol to fertility

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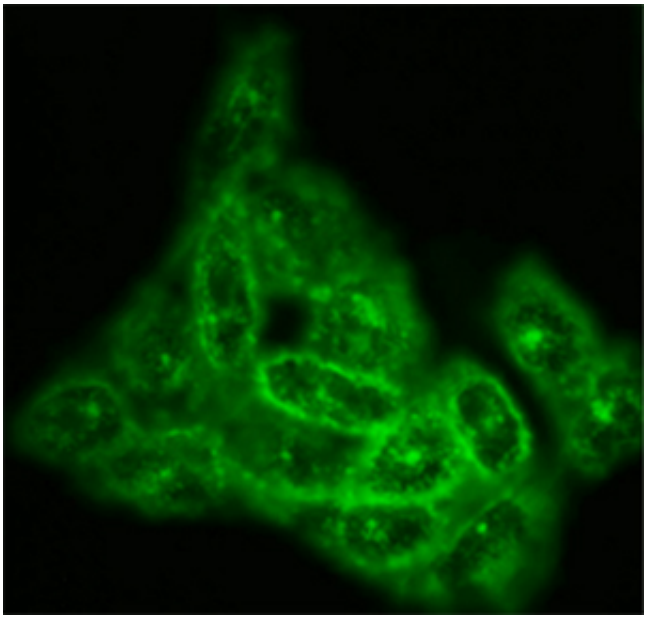

Cholesterol is a building block of steroid hormones, which trigger puberty and support pregnancy. New research implicates a regulator of cholesterol in cells' ability to make these hormones, a finding that may help scientists investigate the causes of infertility and early onset puberty. Above, green staining shows the distribution of cholesterol in normal hamster ovary cells. Credit: D. ORY

Whether made by the body or ingested through diet, cholesterol plays a vital role in cells. Cholesterol also is a building block of steroids and hormones, including those that trigger puberty and support pregnancy. A new study implicates a surprising regulator of cholesterol in cells' ability to make these hormones, especially in tissues associated with fertility, such as the ovaries.

The researchers who conducted the study, at Washington University School of Medicine in St. Louis, said the findings have potential implications for investigating causes of infertility and understanding possible drivers of the trend toward earlier onset puberty, particularly in girls.

The study appears in the June issue of the journal *Cell Metabolism*.

"Disruptions in the pathway we identified may have real implications for fertility," said senior author Daniel S. Ory, MD, the Alan A. and Edith L. Wolff Distinguished Professor of Medicine. "Too much of a key molecule we identified would likely impair proper steroid hormone production and lead to infertility. Conversely, too little of it could lead to premature sexual maturation."

Studying mice, the researchers found that the key molecule—a small strand of RNA—appeared in high levels in the ovaries and testes, parts of the body that manufacture steroid hormones like progesterone and testosterone. RNA is chemically similar to DNA but serves different functions.

In the new study, Ory and his colleagues, including collaborator Jean E. Schaffer, MD, the Virginia Minnich Distinguished Professor of Medicine, showed that levels of this small RNA in healthy mice are high at birth and gradually decrease. At about eight weeks, when the mice reach sexual maturity, levels are very low, which dials up the production of steroid hormones.

"The ovaries need to make steroids to support pregnancy when the mice reach sexual maturation," Ory said. "So we think this small RNA is at least one of the regulators of the processes that govern when a mouse becomes fertile."

In hamster ovary cells deficient in this RNA, the investigators found that cholesterol was directed into the cell's energy factories called mitochondria. Mitochondria are well known for making the fuel required for cellular activities. But mitochondria also are responsible for manufacturing steroids, starting with cholesterol as a raw material.

When cells have less of this RNA, cholesterol is channeled into the mitochondria, where it is used as raw material to build steroids. Conversely, when cells have too much of this RNA, cholesterol doesn't make it to the mitochondria, and without the raw material, mitochondria can't manufacture steroids.

The researchers also showed they could interfere with this RNA in otherwise normal mice that had not yet reached sexual maturity. This allowed cholesterol to be channeled into the mitochondria and triggered steroid production in the mouse ovaries.

"We have not yet investigated whether these mice could breed earlier," Ory said. "But we certainly increased levels of pregnenolone and progesterone, which are steroids necessary to support pregnancy."

Ory said future work will investigate more details of how this RNA interacts with proteins to increase or decrease cholesterol trafficking into mitochondria and subsequent steroid production.

The RNA implicated in the study is surprising, according to Ory, because it is classified as a small nucleolar RNA, or snoRNA, which has important roles in helping cells manufacture proteins. But they are not widely known for having other functions, such as encouraging the production of steroids.

"That this snoRNA has a role in how the body meets the metabolic demands of reproduction at a key time in the organism's life is not

something we would have ever dreamed up," Ory said. "This is one of several hundred snoRNAs. Clearly, some of them have functions beyond the traditional understanding of snoRNAs, and perhaps they should be studied more systematically."

The study also invites new ways to look at influences on fertility and puberty such as chemicals in the environment that mimic hormones.

"There are environmental cues that might be involved," Ory said. "We need to work with our colleagues in fertility research as we think about future directions for this work."

More information: "snoRNA U17 Regulates Cellular Cholesterol Trafficking." *Cell Metab*. 2015 Jun 2;21(6):855-67. DOI: 10.1016/j.cmet.2015.04.010

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