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Female embryonic sexual development driven by universal factor

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A gene essential to the growth and development of most organ systems in the body also is vital to female – but not male – embryonic sexual development, scientists report this month.

The study, from researchers at the University of Illinois and the University of Texas, appears in *Human Molecular Genetics*. The findings lend support to a controversial hypothesis about mammalian sexual development.

In the beginning – in terms of their sexual organs – all embryos look alike, said Illinois veterinary biosciences professor Humphrey Yao, who led the study.

"They have a common primordium, the foundation for both testis and ovary," he said. "Only at a certain stage of development does this primordium start to follow a different path."

In the early days of research into sexual development, it was thought that all females had two X chromosomes, all males had an X and a Y, and that the Y made all the difference. Unless it had a Y chromosome, an embryo developed ovaries and became female, more or less by default, scientists thought. They even found a specific gene on the Y chromosome, called SRY (for sex-determining region of the Y chromosome) that appeared to be essential for testes formation.

But when researchers discovered some rare cases of individuals who

developed testes even though they had two X chromosomes and no Y chromosome or SRY gene, they realized that the mechanisms of sex determination were more complex than previously thought.

This led to a new theory, called the "Z" hypothesis, which proposed that testes development was actually the default pathway. According to this theory, an unknown gene or process, called "Z," could disrupt this pathway and lead to the development of ovaries.

The "Z" hypothesis explained why SRY appeared essential for testes development. When it is present, SRY suppresses "Z" and allows the default option (development of testes) to occur.

This theory was complex and ambiguous, however, leading some to reject it.

Yao and graduate student Chia-Feng Liu wanted to investigate a particular player in the cast of molecules known to be involved in transforming the primordium into testis or ovary. This molecule, beta-catenin, is an important regulator of cell proliferation and differentiation. When it functions as a transcription factor, it turns other genes on or off. Without beta-catenin, which is expressed in many organs and tissues, an embryo will not survive.

Yao and Liu knew that other proteins also were critical to the development of ovaries in particular. Mice that lacked the genes for a signaling protein, known as Wnt4, or another secreted protein, called R-spondin1, experienced a partial female-to-male sex reversal: They formed ovaries, but with male characteristics, such as blood-vessel structures like those in testes. Humans with mutations in their WNT4 and R-spondin1 genes had similar malformations of the sex organs.

Other studies had indicated that beta-catenin was important to the action

of Wnt4 and R-spondin1 in various tissues. But no studies had found direct genetic proof that beta-catenin was involved in regulating how the ovaries developed.

To determine whether beta-catenin had a role in forming the ovaries, the researchers developed a mouse embryo in which the beta-catenin gene could be shut off at the earliest stage of development of the gonads while remaining functional in other organs.

"To our surprise, the ovaries still formed," Yao said. But male sexual structures also appeared, creating an amalgamation of male and female sexual structures that looked very much like those produced when the Wnt4 or R-spondin1 genes were mutated or missing.

"That tells us very conclusively that beta-catenin is an internal regulator of this pathway," Yao said.

To see how the absence of beta-catenin would affect testes formation, the researchers repeated the experiment in embryos in the early stages of testes development.

"When we looked at the testes without beta-catenin," Yao said, "they developed just fine."

The results were so unexpected that the researchers conducted the experiment again and again to test their findings.

"When I looked at the results in the testes I couldn't believe it. How could such an important gene like beta-catenin function differently in males and females?" Yao said.

When beta-catenin acts as a transcription factor it goes into the nucleus of the cell to interact with the DNA. The proteins, Wnt4 and R-spondin1

(and another one, called follistatin, which is also an important player in this pathway), are all secreted proteins. They are emitted from the cell, Yao said, and yet it appears that their production or secretion relies on an intracellular protein, beta-catenin.

"Wnt4, R-spondin1, follistatin – these genes all code for secreted proteins," Yao said. "How does the cell know to respond to this signal? And how can secreted factors change the fate of an organism?"

Yao said his team's findings provided some support for the "Z" hypothesis, with beta-catenin acting as a vital intermediary in a pathway that includes Wnt4 and R-spondin1 to suppress the development of male sex organs.

Source: University of Illinois at Urbana-Champaign