Researchers identify key proteins needed for ovulation

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Researchers from the National Institutes of Health and other institutions have identified in mice two proteins essential for ovulation to take place.

The finding has implications for treating infertility resulting from a failure of ovulation to occur as well as for developing new means to prevent pregnancy by preventing the release of the egg.

The proteins, called ERK1 and ERK2, appear to bring about the maturation and release of the egg.

The study, appearing in the May 15 issue of *Science*, was funded in part by two NIH institutes, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Cancer Institute (NCI).

"Ovulation results from a complex interplay of chemical sequences," said Duane Alexander, M.D., director of the NICHD. "The researchers have identified a crucial biochemical intermediary controlling the release of the egg. The finding advances our understanding and may one day contribute to new treatments for infertility as well as new ways to prevent pregnancy from occurring."

The study's senior author, JoAnne Richards, Ph.D., of Baylor College of Medicine, worked with Esta Sterneck and Peter Johnson, of the NCI's Center for Cancer Research; with Heng-Yu Fan and Zhilin Liu of Baylor; Masayuki Shimada, of Hiroshima University, in Japan; and

Stephen Hedrick, of the University of California, San Diego.

The immature egg is contained inside a covering of cells, known as the ovarian follicle. The follicle is made largely of cells known as granulosa cells. Each month, the pituitary gland releases follicle-stimulating hormone and luteinizing hormone which cause the egg and the ovarian granulosa cells surrounding it to grow and develop into a mature follicle. Midway through the woman's monthly cycle, the pituitary releases a large surge of luteinizing hormone, which causes the follicle to rupture, releasing the egg cell. The granulosa cells in the ruptured follicle transform into luteal cells.

Previously, researchers did not know how luteinizing hormone triggered the ovary's release of the egg and the production of progesterone by the granulosa cells. In the current study, the researchers discerned that luteinizing hormone appears to signal the release of molecules known as extracellular-regulated protein kinases 1 and 2 (ERK 1 and ERK 2). In turn, these molecules trigger a chain of chemical sequences that bring about the release of the egg, the transformation of granulosa cells into luteal cells, and the production of progesterone.

ERK1 and ERK2 are a critical nexus between the surge in luteinizing hormone and ovulation, explained the NICHD project officer for the study, Louis V. De Paolo, Ph.D., chief of the NICHD Reproductive Sciences Branch.

"This a key chemical pathway that affects not only ovulation, but egg cell maturation and granulosa cell differentiation into luteal cells," Dr. De Paolo said.

Although ERK1 and ERK2 are essential intermediaries to ovulation, there are other molecules, yet to be discovered, which presumably also play important roles in the process. The Reproductive Sciences Branch is

supporting studies to decipher these other intricate chemical sequences.

"We're still at the tip of the iceberg," Dr. De Paolo said. "We need to understand it all."

While understanding the function of ERK1 and ERK 2 may yield important information for treating infertility in women, this understanding might also lead to ways to prevent ovulation from occurring, for the development of new means of contraception Dr. De Paolo said.

To conduct the study, Dr. Richards and her colleagues used mice that lacked the genes needed to produce ERK1 and ERK2. The ovaries of these mice still produced eggs, but did not release them after exposure to luteinizing hormone. Moreover, the granulosa cells did not transform into luteal cells and begin producing progesterone, the normal course of events when the two genes are present.

In contrast, mice with working versions of the genes for ERK1 and ERK 2 were fertile.

To date, no other genes have been discovered that are essential to both ovulation and the conversion of the other cells to progesterone producers, according to Dr. Richards. An important role of the ERK1 and ERK2, she said, appears to be to stop the granulosa cells from growing, so that they take on their final role of producing progesterone.

More information: www.sciencemag.org

Source: NIH/National Institute of Child Health and Human Development