Researchers identify protein essential for embryo implantation

February 21 2011

Researchers funded by the National Institutes of Health have identified a key step in the establishment of a pregnancy. Their discovery shows how the hormone progesterone suppresses the growth of the uterus's lining so that a fertilized egg can implant in the uterus.

This key step, the researchers discovered, occurs when a protein called Hand2 suppresses the chemical activity that stimulates growth of the uterine lining, also known as the uterine epithelium.

At the start of each menstrual cycle, levels of the hormone estrogen begin to rise. Estrogen stimulates the cells in the uterine lining to increase in number, causing the epithelium to thicken. However, as the ovary releases an egg, levels of the hormone progesterone begin to rise. The elevated progesterone levels put the brakes on the estrogen-driven growth of the uterine epithelium. In this study, the researchers discovered that Hand2, previously found to increase in uterine cells as progesterone levels rise, is the switch that turns off estrogen's stimulating effect on the epithelium.

The finding may contribute to understanding some forms of unexplained female infertility. The finding also has implications for understanding disorders in which growth of the uterine epithelium surges out of control, such as endometrial cancer or endometriosis, a disease in which endometrial tissue appears on the ovaries, bowel, or other tissues outside the uterus.

"Progesterone-like medications are used to treat a wide variety of conditions, such as relieving the symptoms of menopause, as part of infertility treatments, and for preventing preterm birth," said Louis DePaolo, Ph.D., head of the Reproductive Sciences Branch at the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), the NIH institute that funded the study. "Understanding how Hand2 exerts its effect on the growth of the uterine lining may lead to the development of new medications and therapeutics that make progesterone treatment more effective but which have fewer side effects. Also, understanding how Hand2 functions might provide insights into disorders like endometriosis, which resist progesterone treatment."

First author Quanxi Li, of the University of Illinois at Urbana-Champaign, was joined on the research team by University of Illinois colleagues Athilakshmi Kannan, Paul S. Cooke, Milan K. Bagchi and Indrani C. Bagchi; Francesco J. DeMayo and John P. Lydon of Baylor College of Medicine, Houston; Hiroyuki Yamagishi of Keio University School of Medicine, Japan; and Deepak Srivastava of the University of California, San Francisco. Their findings appear in the Feb. 18 issue of *Science*.

The research was supported by the NICHD Specialized Cooperative Centers Program in Reproduction and Infertility Research, a collaborative network of basic and clinical scientists who study ways of improving reproductive health.

For the current study, the researchers developed a laboratory strain of mice in which the uterus fails to make Hand2.

The researchers found that, after exposure to progesterone halted growth of the uterine epithelium in mice with functioning genes for Hand2. However, despite exposure to progesterone, epithelial growth

continued unchecked in the mice without Hand2 genes.

The researchers also discovered that, at the time of implantation, Hand2 was expressed in uterine cells that lie beneath the surface layer of epithelial cells. Through a series of experiments, the researchers determined that estrogen stimulates the production of growth factors, which cause cells in the epithelial layer to multiply and grow. When progesterone is produced, it spurs the release of Hand2, which stops the production of growth factors. The uterine epithelial cells then stop multiplying, mature, and become receptive to the embryo.

"This information helps us understand how the interplay of hormones prepares the uterus to host and support the embryo as it grows," said Dr. Milan Bagchi. "Our next priority will be to examine whether Hand2 plays a critical role in the human uterus as well."

Provided by National Institutes of Health