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In the Spotlight

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Oogonial Stem Cells Identified in Humans

For decades, it has been generally accepted that female mammals are born with a pool of oocyte-containing follicles that account for all the germ cells they will ever have in their lives. Eight years ago, studies with mice challenged this notion of a fixed ovarian reserve at birth that is depleted throughout life until menopause. The studies were, however, considered controversial and faced criticism by many in the field. Years later, further studies in mice by independent groups supported the idea that oocyte-producing stem cells exist in ovaries of adult female mammals. Despite technical limitations and failure to answer the question of whether the adult oocyte pool could be renewed left the scientific community still skeptical.

The controversy has now been re-challenged by an article by White et al reporting the isolation of oocyte-producing stem cells from the ovaries of reproductive age women, which has recently been published in the journal *Nature Medicine* (*Nat Med*. 2012;18(3):413-422).

Aiming to prove that oocyte-producing stem cells do in fact exist in the ovaries of women during reproductive life, Jonathan Tilly's group and collaborators from Japan started out by developing a fluorescent-activated cell sorting-based protocol to purify rare ovarian mouse and human mitotically active cells that have a gene expression profile that is consistent with primitive germ cells. Once successfully isolated, these cells were established in vitro and expanded for months. The authors observed that these cells could then spontaneously generate oocytes, as determined by morphology, gene expression, and haploid chromosomal content.

In addition, White and colleagues injected these human putative germ line cells, which had been engineered to express GFP, into human ovarian cortical biopsies and observed the formation of follicles containing GFP-positive oocytes 1 to 2 weeks after xenotransplantation into immunodeficient female mice.

These findings led the authors to conclude that oogonial stem cells can be found in the ovaries of reproductive age women. Whether these cells lead to the formation of fertilization-competent oocytes remain to be shown. The observations reported by White and colleagues undoubtedly open a new research field in human reproductive biology, providing a good model system to study human female germ cell development and raising new possibilities for the development of alternative fertility preservation strategies.

A Genetic Marker for Endometriosis

Endometriosis is an invasive and benign disorder resulting from the implant and estrogen-dependent growth of endometrial cells outside the uterus. It affects 5% to 15% of women of childbearing age, it is mostly characterized by chronic pelvic pain and infertility and it has been associated with a higher predisposition to ovarian cancer.

Although intense research in the field has been undertaken and a hereditary component is known to play a role in the disease, the etiology of endometriosis remains unknown and, therefore, there is no established cure for it either.

A recent study by Grechurina et al, published in the journal *EMBO Molecular Medicine* (*EMBO Mol Med*. 2012;4:206-217), may well revolutionize the approach to diagnose and treat endometriosis. The authors of the study report the identification of a polymorphism in a let-7-micro-RNA (miRNA)-binding site in the 3′-UTR of the gene KRAS that is associated with endometriosis. Activation of KRAS has been known to cause endometriosis in mice, however, KRAS activating mutations have never been reported in women. When screening 150 women with endometriosis for the let-7-miRNA-binding site of KRAS polymorphism, Grechurina et al detected a KRAS-variant allele in 31% of the participants with the disease as opposed to 5% of a large diverse control population. In addition, the authors observed that the cultured endometrial stromal cells of women presenting with the KRAS variant showed an increase in KRAS mRNA and protein expression and determined that the later was due to an altered miRNA binding.

Of note, endometrial stromal cells from women with the KRAS variant demonstrated an increased proliferation and invasion in vitro, which was also confirmed when these cells were xenografted into immune-deficient mice.

Altogether the findings presented by Grechurina et al suggest that an inheritable polymorphism in KRAS leads to abnormal endometrial growth and endometriosis, providing a previously unrecognized etiology for the disease that may account for a significant percentage of the cases. This LCS6 polymorphism, which constitutes the first described genetic marker for endometriosis, may have an important role as a diagnostic tool for the disease. Finally, a better understanding of the etiology of endometriosis may lead to the development of new therapeutic strategies to manage and treat the disease.