Germ stem cells produce oocytes in adult female mice

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The foundations underpinning the field of mammalian reproductive biology are looking shaky with the report that adult female mice can produce eggs from germ stem cells. The findings have important clinical implications for the treatment of infertility, say US researchers.

Central dogma

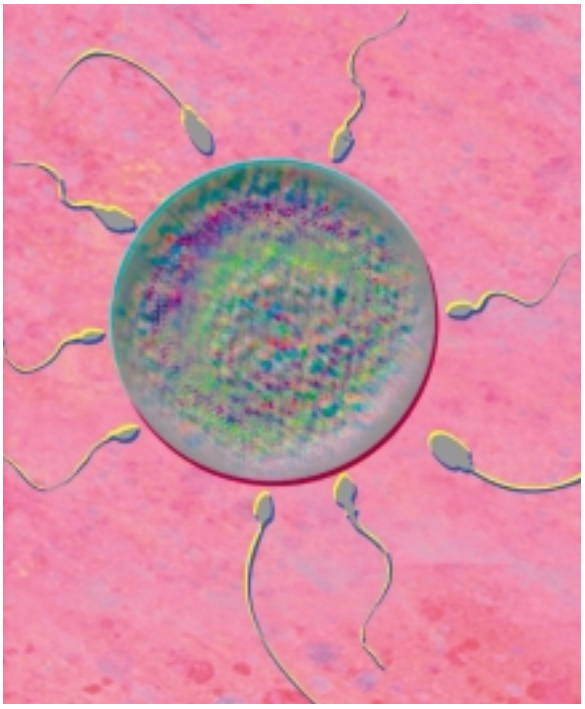
This is contrary to the central dogma of mammalian reproductive biology that females are born with a finite non-renewing pool of germ cells, says Jonathan Tilly of the Vincent Center for Reproductive Biology at Massachusetts General Hospital in Boston (http://www.mgh.harvard.edu/depts/vcrb/). The dogma has been used for more than 50 years to explain the reproductive decline females experience as they age, and it 'represents one of the most basic underpinnings of reproductive biology.'

'If these findings hold up in humans, all theories about the aging of the female reproductive system will have to be revisited,' said Tilly. The mechanisms that underlie how environmental factors such as smoking and chemotherapy affect fertility will also need to be reconsidered, he says. 'Eventually, this could lead to totally new approaches to combating infertility in cancer patients and others.'

Oocyte numbers gradually decrease throughout life, eventually leaving the ovaries barren, and driving menopause. To look at this process, Tilly and his colleagues examined the follicles in ovaries in mice, to see how many were in the process of degenerating.

Follicle loss

Like previous studies, they found that about a third of the peak endowment of follicles were lost during development to young adulthood. But, unexpectedly, after 20 days of age, the process of degeneration speeded up, eventually peaking at more than



1200 dying follicles per day per ovary. However, the total number of follicles only gradually declined over time.

Examining the ovaries more closely, the team found cells that expressed a conserved germ-cell protein called Vasa. What's more, the cells were dividing and importantly, the dividing cells expressed the meiotic entry protein synaptonemal complex protein 3.

The researchers confirmed that the progeny of the germ stem cells did indeed develop into mature follicles by grafting parts of wild-type ovaries into a transgenic mouse that expresses green-fluorescent protein in all its cells. The wild-type ovary was infiltrated with fluorescent germ cells that went on to form follicles.

'Collectively these data establish the existence of proliferative germ cells that sustain oocytes and follicle production in the postnatal mammalian ovary,' conclude Tilly and colleagues [1].

Do human ovaries have germ cells?

The next big question is whether human ovaries also have germ cells, according to Allan Spradling of the Howard Hughes Medical Institute Laboratory at the Carnegie Institute of Washington in Baltimore, Maryland (http://carnegieinstitution.org/). 'Germline stem cells in humans might easily have been missed for the same reason that they escaped detection in mice for so long,' he said – they cannot be recognized definitively by their morphology, and they are expected to be rare.

'This important finding seems destined to greatly enhance our understanding of mammalian oogenesis and of its precipitous decline during adulthood,' concludes Spradling.

Reference

1 Johnson, J. *et al.* (2004) Germline stem cells and follicular renewal in the postnatal mammalian ovary. *Nature* 428, 145–150

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