Of worms and women: Common causes for reproductive decline with age

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In worms as in women, fertility declines at a rate that far exceeds the onset of other aging signs. And now a new report in the October 15th issue of *Cell,* a Cell Press publication, suggests that worms' and humans' biological clocks may wind down over time for similar underlying reasons.

"For us, what's most important is that there are so many shared genes involved," said Coleen Murphy of Princeton University. "This isn't just about worms and how they reproduce." That such commonalities would exist wasn't obvious, she adds, given that reproduction in the nematode worm Caenorhabditis elegans "goes to pot" in a matter of days compared to three decades or more in humans.

The newfound similarities suggest that studies of worms can provide a window into the ticking of our own biological clocks, and might ultimately point toward ways to preserve fertility in women who plan to delay having children, the researchers say.

The findings come just after the announcement that the pioneer of in vitro fertilization (IVF) – a treatment that has allowed many women to extend their reproductive spans – has won the Nobel Prize for Medicine.

There are important differences in human and worm reproduction. For one, the oocytes that are the immature egg cells are continually produced in worms, whereas humans' total oocyte supply is present at birth. Still, both human and C. elegans females reproduce for about one-third to one-

half of their lives and there are similarities in the process by which our oocytes mature.

In humans, reproductive aging takes place a decade or so before the oocyte supply runs out, suggesting that quality, not quantity, is the limiting factor. The question was whether the same is true in worms, and it appears the answer is yes.

Earlier studies found that some long-lived C. elegans mutants, including those with an aberrant insulin/IGF-1 receptor, also show delayed declines in reproduction. Murphy's team more recently found that mutants of the so-called TGF-?? Sma/Mab pathway also showed extended reproductive spans.

In the new study, the researchers sought to detail exactly what happens in C. elegans as reproductive aging sets in, and what changes in mutants who can reproduce into what is, for worms, a ripe, old age. They show that C. elegans oocytes, like human oocytes, degrade functionally and morphologically with age and that reduction of TGF-? Sma/Mab and insulin/IGF-1 signaling delays reproductive aging by maintaining oocyte and germline quality.

The insulin/IGF-1 and TGF-?? Sma/Mab pathways influence reproductive aging at every step of the way. The signals affect the integrity of embryos, the ability of oocytes to be fertilized, the proper segregation of chromosomes, DNA damage resistance, and the shape of oocytes and of the germline.

Genes involved in chromosome segregation, the cell cycle and DNA damage response are all expressed at higher levels in the oocytes of TGF-?? mutants with a longer reproductive lifespan and are important for maintaining oocyte quality. Those same genes decline in aged mammalian oocytes.

The similarities in reproductive aging in worms and humans "may allow us to use worms as genetic and molecular models to study this important human problem, enabling the development of therapies to address maternal age-related birth defects and reproductive decline," they write.

As an interesting aside, Murphy says there is one complication for the TGF-?? mutant worms: unlike insulin/IGF-1 mutants, their reproductive span increases but their lifespan does not. As a consequence, at 13 days the worms are still reproducing even though their body has decayed to the point that they can't actually lay the fertilized eggs. The mothers are killed as a result.

"It's like an 80-year-old woman trying to have a baby," she said.

Provided by Cell Press