Aging human bodies and aging human oocytes run on different clocks

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Reproductive and somatic aging use different molecular mechanisms that show little overlap between the types of genes required to keep oocytes healthy and the genes that generally extend life span, according to Coleen Murphy, Ph.D., of Princeton University, who described her new findings on oocyte aging at the American Society for Cell Biology Annual Meeting Dec. 6 in Denver.

The different genetic pathways help explain why a woman's fertility begins to decline after she is 35 years old, while her other cells do not show significant signs of aging until decades later, Murphy explained.

To compare the molecular mechanisms that are switched on or off with the aging of oocytes and somatic cells, Murphy's lab turned to the model organism, *Caenorhabditis elegans* (*C. elegans*), the worm-like nematode that set off the whole field of longevity research with the discovery in the 1990s that gene mutations affecting insulin regulation doubled the worm's life span. Insulin/insulin-like growth factor (insulin/IGF) signaling pathways also have been identified in humans. These pathways also seem to regulate longevity in humans.

Using DNA microarrays to measure the expression levels of genes, Dr. Murphy and her colleagues noted a distinctive DNA signature for aging oocytes. They also found that the oocytes of aging insulin and transforming growth factor-beta (TGF-beta) mutant mice had the same DNA profile that characterized young females.

The researchers then compared the oocyte gene expression patterns with microarray transcription data on worms carrying the famous long-life mutations. Murphy and her colleagues found that even though somatic and reproductive aging in *C. elegans* both involve the insulin regulation pathway, the molecular mechanisms to maintain youthful oocyte function and to combat body aging are very different.

"It seems that maintaining protein and cell quality is the most important component of somatic longevity in worms," Dr. Murphy said, "while chromosomal/DNA integrity and cell cycle control are the most critical factors for oocyte health."

In previous studies, the Murphy lab showed that worm oocytes reach the end of their viability about halfway through the *C. elegans* lifespan, a pattern that also characterizes human eggs. Oocyte aging is delayed in mutant worms with decreased signaling activity in both the insulin/IGF and the TGF-beta pathways.

Using microarray technology, Murphy's lab identified the *C. elegans* genes that were being switched on or off as oocytes aged. The researchers revealed a distinctive genetic signature for aging oocytes that is reversed in insulin and TGF-beta mutants.

They then compared the oocyte gene expression patterns with microarray transcription data from whole worms carrying the famous long-life mutations.

Surprisingly, the patterns were different. Even though somatic and reproductive aging in *C. elegans* both involve the insulin regulation pathway, the mechanisms to maintain youthful oocyte function and to combat body aging are very different.

"It seems that maintaining protein and cell quality is the most important

component of somatic longevity in worms," Murphy said, "while chromosomal/DNA integrity and cell cycle control are the most critical factors for oocyte health."

Finding ways to delay oocyte aging would reduce an older woman's risk of giving birth to a child with birth defects, Murphy said.

Provided by American Society for Cell Biology