Turning back the clock: Fasting prolongs reproductive life span

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Scientific dogma has long asserted that females are born with their entire lifetime's supply of eggs, and once they're gone, they're gone. New findings by researchers at Fred Hutchinson Cancer Research Center, published online Aug. 27 in *Science,* suggest that in nematode worms, at least, this does not hold true.

Molecular physiologist Marc Van Gilst, Ph.D., and colleagues report that during starvation, sexually mature adult worms stop ovulating and the germline component of their reproductive system - the sex cells, including mature and maturing eggs - dies off and leaves behind nothing but a few stem cells. However, once normal food conditions resume, the conserved stem cells can produce a brand new crop of sex cells, complete with youthful and fertile eggs. This turning back of the reproductive clock all takes place in tiny *C. elegans* soil worms that are up to 15 times older than normally fed worms in their reproductive prime.

"For many, it has been assumed that cells and organs remain relatively stable during periods of starvation or caloric restriction," said Van Gilst, an assistant member of the Hutchinson Center's Basic Sciences Division, who authored the study with postdoctoral research fellow Giana Angelo, Ph.D. "The idea that an entire system would kill itself off during starvation and then regenerate upon food restoration was very surprising. The fact that extremely old worms could generate new eggs and produce healthy offspring long after their normally fed counterparts had reproduced and died was also unexpected," he said.

The mechanism behind the preservation and extension of fertility long past the worms' normal reproductive prime, Van Gilst suspects, is a signaling receptor protein in the cell nucleus called NHR-49, which promotes a major metabolic response to dietary restriction and fasting. While it has been hypothesized that this protein may interface with calorie restriction to extend life span, until now its role in protecting and extending reproductive longevity in the face of starvation had not been known. "In worms that contained an inactive NHR-49 gene, reproductive recovery and fertility after starvation were severely impaired," he said. "We found that reproductive arrest and recovery are highly dependent on a functioning NHR-49 gene."

NHR-49 in worms is analogous to various proteins in humans, all of which belong to a family of proteins called nuclear receptors. Nuclear receptors, such as estrogen receptors and androgen receptors, are particularly good targets for pharmaceutical intervention. "The identification of a nuclear receptor that turns on and off the beneficial response to nutrient deprivation would be of great interest because it would be a candidate for drugs aimed at tricking the body, or specifically the reproductive system, into thinking they are calorically restricted or starved, even when food intake is normal," Van Gilst said.

The biomedical implications of model organisms such as flies and worms cannot be overlooked, he said. "Many paradigm-shifting discoveries in *C. elegans* have since been replicated in humans. Therefore, the idea that our findings will be relevant to human reproduction is a possibility that certainly needs exploration," he said.

However, Van Gilst is quick to point out that even if this mechanism is conserved in humans, it is still unknown what degree of caloric restriction would be required to impact egg production in humans. "If such a process exists in humans, it likely evolved to help our ancestors preserve fertility during periods of famine or food shortage. We certainly don't have a prescription for famine. Consequently, our study should not be used to promote potentially dangerous interventions such as severe caloric restriction and starvation as a means to restore a woman's fertility," he said.

In the meantime, Van Gilst and colleagues will continue to study the tiny worm to better understand the basic mechanisms that control fertility. One question their research may help address is how in some cases women recovering from radiation and bone marrow transplantation - which damages or destroys much of the germline, including mature and immature eggs - can regain their fertility.

"There is controversy over how this occurs," Van Gilst said. "On the one hand, it has been argued that new eggs are generated from the woman's germline stem cells through a process that may mirror the germline regeneration we observed in *C. elegans*. In fact, there is controversy over whether or not germline stem cells exist in adult women. We believe that our work in *C. elegans* throws another hat in the ring, raising the possibility that germline stem cells may indeed be present in women and that their activity may surface under conditions of nutrient deprivation or stress," he said.

This work may also shed new light on cancer. "Cancer cells, when starved, are very susceptible to cell death. However, cancer stem cells, or progenitor cells, often thrive and flourish during starvation in cell-culture experiments. When nutrition is restored, these cells can trigger rapid regrowth. Consequently, understanding how germline stem cells in *C. elegans* survive starvation may help appreciate how cancers survive treatments aimed at starving tumors," he said.

For the study, the researchers withheld food from two types of nematodes: those that were genetically normal and those that lacked a functioning NHR-49 gene. The worms were monitored every few days by microscopy to observe changes in their reproductive system, including ovulation, cell death and germline stem cell survival. After different periods of starvation, food was restored and the worms were again monitored by microscopy to assess the recovery of their reproductive system. Fertility was determined by counting offspring after mating.

Source: Fred Hutchinson Cancer Research Center (news : web)