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Why females live longer than males: is it due to the father's sperm?

Researchers in Japan have found that female mice produced by using genetic material from two mothers but no father live significantly longer than mice with the normal mix of maternal and paternal genes. Their findings provide the first evidence that sperm genes may have a detrimental effect on lifespan in mammals.

The research, which is published online on Wednesday 2 December in Europe's leading reproductive medicine journal *Human Reproduction* [1], found that mice created from two female genomes (bi-maternal (BM) mice) lived an average of 186 days longer than control mice created from the normal combination of a male and female genome. The average lifespan for the type of mice used in the study is between about 600-700 days, meaning that the BM mice lived approximately a third longer than normal.

Professor Tomohiro Kono (PhD), from the Department of Bioscience, Tokyo University of Agriculture, and Director of the Nodai Research Institute (Tokyo, Japan), and Dr Manabu Kawahara (PhD), associate professor at the Laboratory of Animal Resource Development, Faculty of Agriculture, Saga University (Japan), carried out the research. They believe the reason for the difference in longevity could relate to a gene on chromosome 9 associated with post-natal growth.

Prof Kono said: "We have known for some time that women tend to live longer than men in almost all countries worldwide, and that these sex-related differences in longevity also occur in many other mammalian species. However, the reason for this difference was unclear and, in particular, it was not known whether longevity in mammals was controlled by the genome composition of only one or both parents."

To answer this question, Prof Kono and Dr Kawahara set out to study the life span of mice produced without sperm. To do this, they collected non-growing oocytes (eggs) from day-old mice, manipulated the genetic material in these eggs so that the genes behaved like sperm genes, and then transplanted this manipulated genetic material into the fully grown, unfertilised oocytes of adult mice that had their nuclei removed (enucleated oocytes). These reconstructed oocytes developed into embryos, which were transferred into surrogate mother mice. The mice that were born as a result were bi-maternal, having genetic material from two mothers, but no father.

The researchers created control mice through natural mating that were genetically identical to the BM mice, apart from the fact that they were created in the normal way with genes from male and female mice.

There were 13 BM mice and 13 control mice born between October 2005 and March 2006, and Prof Kono found that the average lifespan was 186 days longer in the BM mice than in the controls (841.5 days versus 655.5 days). The longest time that any of the control mice lived was 996 days, with all but one of them dying by 800 days, while the longest time alive for the BM mice was 1045 days, with all but three of them living for more than 800 days. The researchers checked the weight of the mice at 49 days and 600 days (around 20 months after birth) and found that the BM mice were significantly lighter and smaller than the control mice. The BM mice also seemed to have better immune systems, with a significant increase in one type of white blood cell, eosinophil.

Both sets of mice were kept in the same, infection-free environments, with free access to food, making it unlikely that some external environmental factor was the cause of the difference in life spans.

Prof Kono said: “We believe that the most likely reason for the differences in longevity relates to the repression of a gene called *Rasgrf1* in the BM mice. This gene normally expresses from the paternally inherited chromosome and is an imprinted gene on chromosome 9 associated with post-natal growth. Thus far, it's not clear whether *Rasgrf1* is definitively associated with mouse longevity, but it is one of the strong candidates for a responsible gene. Furthermore, we cannot eliminate the possibility that other, unknown genes that rely on their paternal inheritance to function normally may be responsible for the extended longevity of the BM mice.”

Imprinted genes are genes that are turned on, or “expressed”, according to whether they are inherited from the mother or the father.

The researchers write: “Our results are consistent with models based on sex-specific selection of reproductive strategies, e.g. male individuals maximizing fitness by an intense investment in reproduction by way of a larger body size in order to achieve more breeding opportunities, resulting in shorter longevity.... In contrast, female individuals usually do not engage in such costly male behaviours and instead tend to optimize their reproductive output by conserving energy for delivery, providing for offspring, foraging and predator avoidance. Our results further suggested sex differences in longevity originating at the genome level, implying that the sperm genome has a detrimental effect on longevity in mammals.”

Prof Kono concluded: “The study may give an answer to the fundamental questions: that is, whether longevity in mammals is controlled by the genome composition of only one or both parents, and just maybe, why women are at an advantage over men with regard to the lifespan.”

(ends)

[1] Longevity in mice without a father. *Human Reproduction* journal. doi:10/1093/humrep/dep400

Notes:

A pdf of the full research paper is available at:

<http://humrep.oxfordjournals.org/cgi/content/full/dep400v1>

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