Study shows that father's age can affect offspring lifespan

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How does the father's age at conception affect his children? Researchers at the German Center for Neurodegenerative Disease (DZNE) and

fellow scientists have studied this question in mice. Their findings, which have been published in the *Proceedings of the National Academy of Sciences (PNAS)*, show that the offspring of elderly mouse-fathers had a shorter lifespan than those of young fathers and featured an exacerbation of a number of histopathological and molecular aging traits. Moreover, sperm of old males as well as the tissue from old father offspring featured shared epigenetic changes and altered activation states of longevity-related signaling pathways. These results are indicative of intergenerational influences on aging processes and they could potentially be of relevance for a human context.

In Western societies, the average age of parenthood has increasingly risen. This is not without complications, as a mother's age, for instance, has long been identified as a risk factor for child health. Moreover, it turns out that an advanced age of the father at the time of conception can also have unfavorable consequences for offspring.

"Statistically, certain diseases occur more often in children of old fathers than in the offspring of young men. This is the case, for example, for psychiatric disorders such as autism or schizophrenia," explains Dr. Dan Ehninger, head of a research group at the DZNE's Bonn site. His team led the current study, which also involved scientists from the German Mouse Clinic in Munich and other institutions. "Associations between paternal age and health outcomes in offspring, described by a number of epidemiological studies, could arise for many reasons. We wanted to address whether age-related biological changes in the male germ line could underlie effects on offspring health. Our study was focused specifically on lifespan and aging-associated pathologies in old father offspring."

Mouse studies

The scientists assessed two groups of mice that included the descendants

of young and old fathers, respectively. Young mouse-fathers were mated at an age of four months—an age at which mice are considered as young adults—while the fathers with an age of at least 21 months were already seniors. The mouse-mothers were all four months old. All fathers belonged to a genetically defined mouse strain. This also applied to the females. All offspring grew up under the same living conditions and never had contact with their fathers. Rodents from both groups were examined at the age of six and 19 months, respectively.

"We looked at 13 biological parameters that had previously been shown to change during natural aging in mice. These included deposits in the kidneys, tissue changes in the lungs, as well as alterations in proteins associated with oxidative stress," says Prof. Martin Hrabe de Angelis, director of the German Mouse Clinic in Munich. Studies with descendants of old mouse-fathers have been performed previously, Hrabe de Angelis points out. "However, data are scarce with regards to paternal age effects on aging-associated changes in progeny."

Shorter lifespan

The studies revealed that age-associated traits were more pronounced in the 19-month-old offspring of elderly mice than in age-matched descendants of young fathers. "If you take our parameters as a reference, then you can certainly say that the descendants of the old mouse-fathers aged faster than the offspring of young fathers," says Dr. Kan Xie, a researcher in Ehninger's team and one of the first authors of the current publication. Paternal age effects were also evident with regards to lifespan: Offspring of young fathers showed a median lifespan about two months longer than that of peers with old fathers.

Control elements of the DNA

The scientists do not assume that the different development was caused by defects in the offspring's genome. "Comparing the two groups of mice, we found no significant differences in mutation rates, at least not with the methodology employed in the present study," says Ehninger. However, the researchers discovered alterations in the sperm of the fathers with regards to epigenetic marks of the genome carried by sperm. This concerned methyl groups attached to the DNA. These chemical modifications help to switch regions of the genome on and off, thus regulating gene activity.

"With regards to the methylation patterns of sperm, we observed notable differences between young and old mouse fathers. In fact, this may not be surprising, given that it has been known for some time that methylation can change with age and living conditions," explains Ehninger. Interestingly, the scientists discovered similar DNA methylation differences in offspring. "We noted an overlap between fathers and offspring, suggesting that these marks may have been passed on to the next generation." Ehninger explains that formerly it was assumed that paternal epigenetic marks are erased completely upon fusion of sperm and egg cell. "However, it is known nowadays that the process of clearing methylation marks from the paternal genome is incomplete."

In the current study, this affected genes with a role in the regulation of lifespan and aging-associated pathologies. "We could show that the offspring of old fathers showed an increased activation state of the mTORC1 signaling pathway. This pathway is known to be an important regulator of growth and many metabolic processes," says Ehninger.

What about humans?

What are the implications of these results for a human context? "What we have described here are fundamental mechanisms in a mammalian

model organism. These could also be relevant for humans. However, whether this is the case and, if so, to what extent has not been tested by our study and remains unknown. In this respect, our results cannot be directly applied to humans," says Ehninger. As he points out, data on the extent to which epigenetic marks of human sperm change with age are limited so far. "However, our results provide a good reason to take a closer look at this."

More information: Kan Xie el al., "Epigenetic alterations in longevity regulators, reduced lifespan and exacerbated aging-related pathology in old father offspring mice," *PNAS* (2018). www.pnas.org/cgi/doi/10.1073/pnas.1707337115

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