Mitochondrial mixing mechanism critical for sperm production in mice

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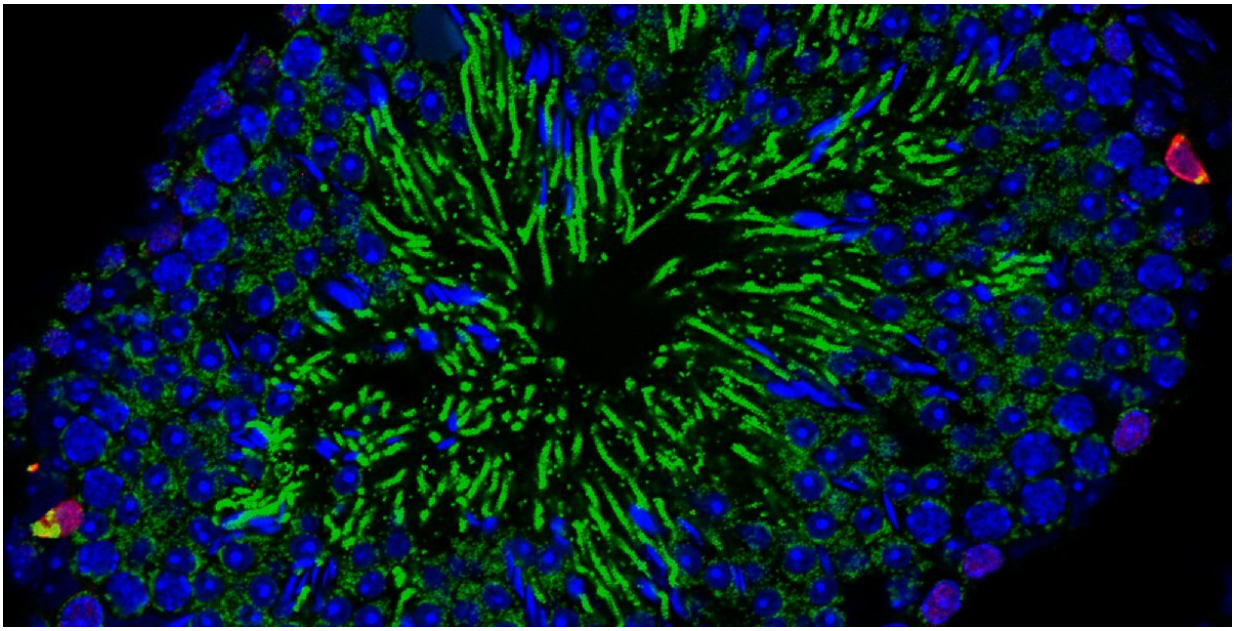

Credit: California Institute of Technology

Mitochondria, often thought of as the powerhouses of cells, are just one part of a larger living thing, but they are unique among cellular structures in that they have their own DNA that is distinct from that of their parent cells. And just like their parent cells, mitochondria need quality-control mechanisms to maintain their DNA and preserve their normal function.

One such mechanism is mitochondrial fusion. Though mitochondria are

often portrayed as static and bean-shaped in textbooks, they are actually much more dynamic. They move throughout the cell, fuse with each other, and divide. In that process, the contents of different mitochondria will mix, including their DNA, a process that is essential for their ability to generate cellular energy.

In 2003, David Chan, Caltech professor of biology, showed that mitochondrial fusion is essential for life. Chan and his colleagues genetically engineered mice to prevent their mitochondria from fusing and found that their embryos died during development. Yet, the exact role that mitochondrial fusion plays during development remained unclear.

In a new study, researchers in the Chan lab investigated the role of mitochondrial fusion during development of male germline cells—the cells that give rise to sperm. They did this by blocking mitochondrial fusion only in male germline stem cells while preserving mitochondrial fusion in all other cell types of the body.

Mutant mice failed to produce sperm and thus were infertile. To understand why, the researchers carefully examined the progression of germline stem cells into sperm cells to see exactly where things went awry. They found the problem occurred during meiosis, a type of cellular division that creates cells that contain half the normal complement of chromosomes (for example, in humans, each of the "daughter" cells produced by meiosis contains 23 chromosomes, instead of the normal 46). These cells then become sperm or eggs, and then, when they fuse with their counterpart during sexual reproduction, gain a full complement of chromosomes.

The germline cells behaved normally right up until meiosis and then got "stuck," unable to proceed further, explains Grigor Varuzhanyan, biology graduate student and lead author of the study. An important

function of meiosis is to swap maternal and paternal DNA to promote genetic diversity in the offspring. "During meiosis, the cell needs a lot of energy to shuffle DNA from mom and dad. Mutant mitochondria, without fusion, were unable to mix their contents and, as a result, their machinery for generating energy was compromised," he says.

When the researchers examined older mice, they found an even more severe depletion of germ cells, but surprisingly the self-renewal activity of germline stem cells actually increased. The researchers therefore concluded that while mitochondrial fusion is required for germ-cell development, it is not needed for maintenance of the germline stem cells. Chan and his colleagues think this is because stem cells rely less on mitochondrial energy than differentiated cells and so are less affected by the loss of mitochondrial fusion.

A number of diseases are caused by abnormalities in mitochondria, affecting tissues such as the heart, muscles, and nerves as well as eyesight and fertility. Studies such as this one, Varuzhanyan says, may help advance the understanding of the mechanisms at work in those diseases.

The paper describing the study, titled, "Mitochondrial fusion is required for spermatogonial differentiation and meiosis," was published in the journal *eLife*.

More information: Grigor Varuzhanyan et al. Mitochondrial fusion is required for spermatogonial differentiation and meiosis, *eLife* (2019). DOI: 10.7554/eLife.51601

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