A key process in asymmetric cell division preserves the immortality of the germline

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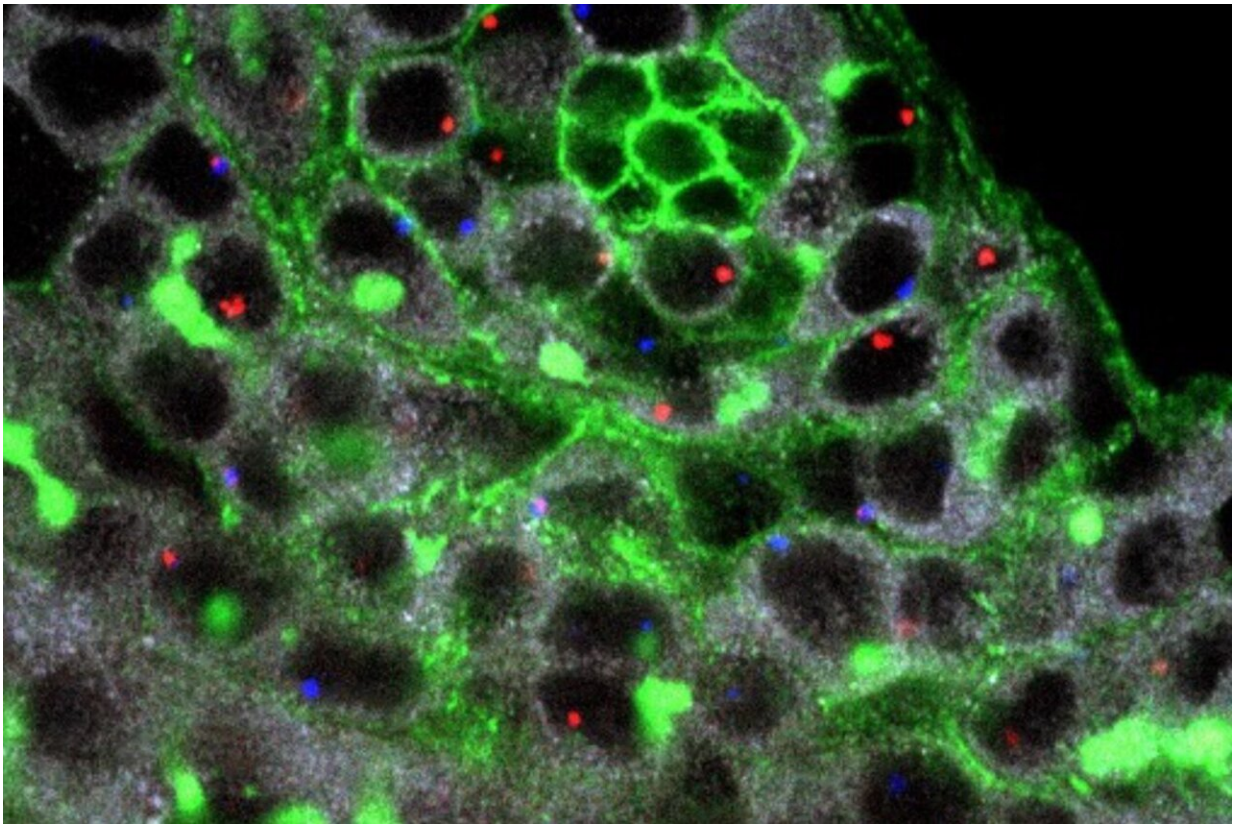

Chromosome orientation fluorescence in situ hybridization (CO-FISH) is performed on Drosophila testis to experimentally distinguish sister chromatids (red vs. blue). Credit: George Watase/Whitehead Institute

During cell division, chromosomes are replicated into two copies—one

for each daughter cell. These copies, called sister chromatids, are usually considered identical. In fact, it's the two pairs of sister chromatids that make up the symmetrical X shape usually shown when visualizing chromosomes.

A 2013 paper from the lab of Whitehead Institute Member Yukiko Yamashita showed that in the case of asymmetric cell division—such as when a stem cell is dividing into two different kinds of daughter cells (i.e. a stem cell and a differentiating daughter)—sister chromatids of sex chromosomes actually may carry distinct information, and the dividing cell "chooses" which of the daughters receive a specific copy.

What that "choice" means, and how it's executed, has been a mystery—until now. A new paper from Yamashita, who is also a professor of biology at the Massachusetts Institute of Technology and an investigator with the Howard Hughes Medical Institute, published in *Science Advances* on July 27, illuminates the mechanisms that underlie nonrandom sister chromatid segregation, and suggests that the whole process may serve as a way to maintain the amount of ribosomal DNA (or rDNA) that is passed on to subsequent generations. "Tying together these two processes—rDNA copy number maintenance and nonrandom chromatid segregation—is an unexpected and exciting advance in our understanding of how germ cells are able to maintain their immortality," said Yamashita.

George Watase, a postdoctoral scholar in the Yamashita Lab, led the study. Watase began his research intent on discovering the genetic underpinnings of nonrandom segregation of X and Y chromosomes in the fruit fly Drosophila melanogaster. As he surveyed the genome for genes that were essential to nonrandom segregation, it became apparent that ribosomal DNA was key for the process.

When rDNA was left intact, the sister chromatid with more rDNA was

preferentially chosen by the daughter stem cell instead of the differentiating daughter cell. When rDNA was removed from X and Y chromosomes, however, Watase found that the sister chromatids segregated randomly to the daughter cells.

Ribosomal DNA, or rDNA, is composed of a long stretch of repeats of certain base pairs. The rDNA provides the instructions and material to make ribosomes, which are essential for cells to create proteins. "Most genes exist only as a single copy, but in the case of rDNA we have hundreds of copies in our genome," Watase said. "The reason for this is that we need a massive amount of ribosomes to synthesize proteins to maintain our cells' viability."

As organisms age, most of their cells naturally lose some of those rDNA repeats, including germline stem cells. However, germline cells are sometimes called "immortal"—while all other cells in the body are made anew with each generation and die when an organism dies, germline cells such as sperm and eggs must carry DNA between generations. Therefore, the stem cells that produce sperm and eggs thus cannot keep losing rDNA repeats, and must bypass the mortality of other cells, by maintaining a high number of rDNA repeats over time.

By isolating proteins that bind to rDNA, Watase discovered one specific gene, the protein product of which bound to rDNA and somehow assigned the sister chromatid with more rDNA repeats to the daughter cell that was destined to remain a germline stem cell.

This particular gene had not been described before, and Watase and Yamashita were now tasked with naming it. Fruit fly genes are named after what happens to the animal when the gene is removed. When this new gene was knocked down, the germ cells of subsequent generations gradually lost the immortality that separates germline stem cells from their differentiated counterparts.

Watase wasn't sure how to convey the intricacies of this outcome. In the end, it was Watase's wife who came up with the perfect name: Indra. In Hindu scriptures, Indra, the lord of all deities, was given a garland of fragrant flowers by a sage called Durvasa. Indra placed the garland on the trunk of his elephant, but the animal was irritated by the smell of the flowers and threw the garland down, trampling it underfoot. When Durvasa saw this, he became enraged and cursed Indra, taking away his immortality.

The name also opened up a world of possibilities for naming future genes that are important in nonrandom sister chromatid segregation. "People sometimes pull from Roman or Greek myths when naming genes, but not as many people use names from Hindu myths," he said. "And since this is new biology, if we identify additional related genes in the future, we can use names from Hindu myths again."

Watase and Yamashita's study opens new avenues for future research. For example, the paper focused primarily on male fruit flies and the production of sperm via asymmetric division. Indra is expressed in the female germline as well, and when the gene is knocked down in females, the resulting phenotype is much more severe. "There must be some mechanism in female germ cells to avoid rDNA copy number reduction," said Watase. "We just don't know what that mechanism is."

In the future, Watase and Yamashita also hope to elucidate how exactly Indra is interacting with cell division machinery to influence which chromatid ends up in the stem cell and which in the differentiating cell, and beyond this mechanism, how the stem cell "selects" the longer chromatid.

"Many biologists study germ cells, but few specifically study how they maintain their immortality," said Yamashita. "This study is a step towards understanding this fascinating property of germ cells. It's a

really fascinating area and we really have to keep digging deeper into this phenomenon."

More information: George J. Watase et al, Nonrandom sister chromatid segregation mediates rDNA copy number maintenance in Drosophila, *Science Advances* (2022). DOI: 10.1126/sciadv.abo4443

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