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PRESS RELEASE (2025/06/20)

Chromosomes and spindles in mature oocytes are stabilized by the histone modification

Researchers zero in on a potential molecular target for infertility treatment and miscarriage prevention

Fukuoka, Japan—The accurate distribution of chromosomes in an oocyte is essential for the correct transmission of genetic information to the next generation. Now, researchers from Kyushu University have demonstrated that the histone modification H3K4me3 in mature mouse oocytes is directly involved in chromosome and spindle stabilization and is crucial for normal oocyte development and subsequent embryonic competence. Their results were published in the *Journal of Biological Chemistry*.

Histones are a series of proteins that help package and condense DNA inside the cell's nucleus. They can also undergo a process called 'histone modification' where parts of the histone protein experience chemical and structural changes through the addition or removal of specific molecules. Histone modification is critical in letting the cell have access or protect specific parts of DNA.

Trimethylation of histone H3 at lysine 4 (H3K4me3), is a type of histone modification that usually occurs during active gene transcription when the cell reads the gene to make a protein. However, it is also present in large amounts in a stage of an oocyte's cell cycle called metaphase II (MII). The MII oocyte is the stage just prior to fertilization, at which point gene transcription stops.

"We were intrigued by the paradox that H3K4me3 is abundant in the transcriptionally inactive MII oocyte," says Professor Kei Miyamoto of Kyushu University's Faculty of Agriculture, who led the project. "We began our research by examining the distribution of H3K4me3 in mouse MII oocytes."

The results showed that H3K4me3 accumulates abundantly on the cell membrane side of chromosomes. This accumulation was found to be specific to certain chromosomes such as the X chromosomes, and the actin cap structure, which determines chromosome position in the oocyte, is a probable culprit in determining the localization of H3K4me3.

The researchers then went on to investigate the function of H3K4me3 in MII oocytes. They artificially removed H3K4me3 and found that the spindle structure, which is important for chromosome alignment and distribution, was destabilized. Microscopic observation confirmed that the spindle was shorter than normal. Furthermore, impaired embryonic development was observed when the H3K4me3-removed oocytes were fertilized in vitro. A decrease in H3K4me3 levels was also observed in aged mouse oocytes, indicating that H3K4me3 may contribute to the age-related decline in oocyte quality.

The results demonstrate that H3K4me3 is involved in stabilizing chromosomes and spindles, and is crucial for normal oocyte development and subsequent embryogenic potential.

"We are very encouraged by our new results. Not only did we reveal a new function of a

widely studied histone modification system, but it opens to door for a potential target for infertility treatments and miscarriage prevention," explains Prof. Miyamoto. "We hope to further elucidate the mechanisms underlying chromosome distribution errors in oocytes, and perhaps work to find new ways of novel fertility treatments targeting histone modifications."

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For more information about this research, see "Characterization of H3K4me3 in mouse oocytes at the metaphase II stage," Atsushi Takasu, Toshiaki Hino, Osamu Takenouchi, Yasuki Miyagawa, Zhihua Liang, Shota Tanaka, Tomoya Mimura, Chisato Ida, Yuki Matsuo, Yuna Lee, Haruka Ikegami, Miho Ohsugi, Shogo Matoba, Atsuo Ogura, Kazuo Yamagata, Kazuya Matsumoto, Tomoya S Kitajima, Kei Miyamoto, *Journal of Biological Chemistry*, https://doi.org/10.1016/j.jbc.2025.110308

About Kyushu University

Founded in 1911, Kyushu University is one of Japan's leading research-oriented institutes of higher education, consistently ranking as one of the top ten Japanese universities in the Times Higher Education World University Rankings and the QS World Rankings. The university is one of the seven national universities in Japan, located in Fukuoka, on the island of Kyushu—the most southwestern of Japan's four main islands with a population and land size slightly larger than Belgium. Kyushu U's multiple campuses—home to around 19,000 students and 8000 faculty and staff—are located around Fukuoka City, a coastal metropolis that is frequently ranked among the world's most livable cities and historically known as Japan's gateway to Asia. Through its VISION 2030, Kyushu U will "drive social change with integrative knowledge." By fusing the spectrum of knowledge, from the humanities and arts to engineering and medical sciences, Kyushu U will strengthen its research in the key areas of decarbonization, medicine and health, and environment and food, to tackle society's most pressing issues.

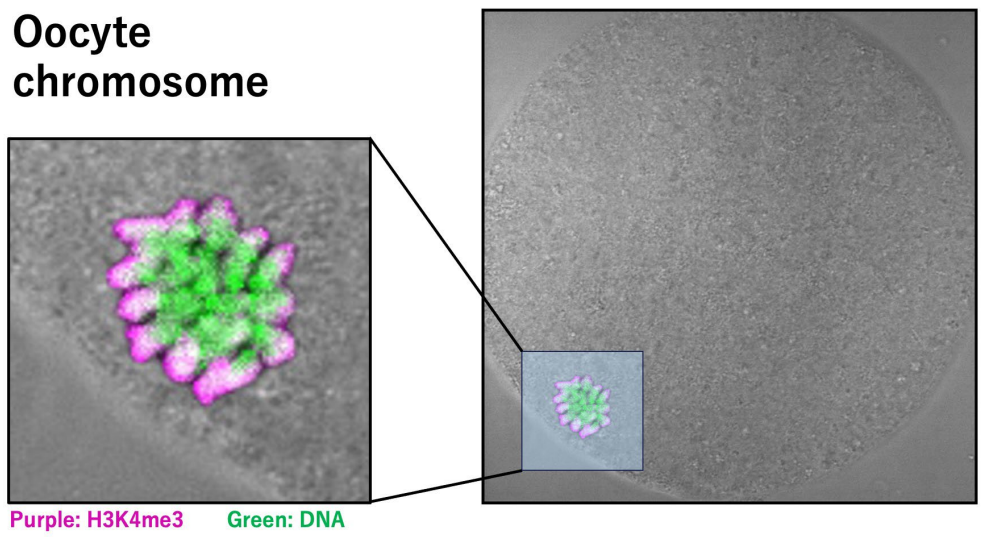

Fig. 1. Localization of chromosomes and the distribution of the histone modification H3K4me3 in mouse oocytes. A picture of a mouse MII stage eggs with the location of chromosomes (green) and the distribution of the histone modification H3K4me3 (purple). The team confirmed that H3K4me3 was significantly accumulated on the cell membrane side of chromosomes. (Kei Miyamoto/Kyushu University)

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