Lab-grown stem cells initiate key steps of human egg and sperm formation

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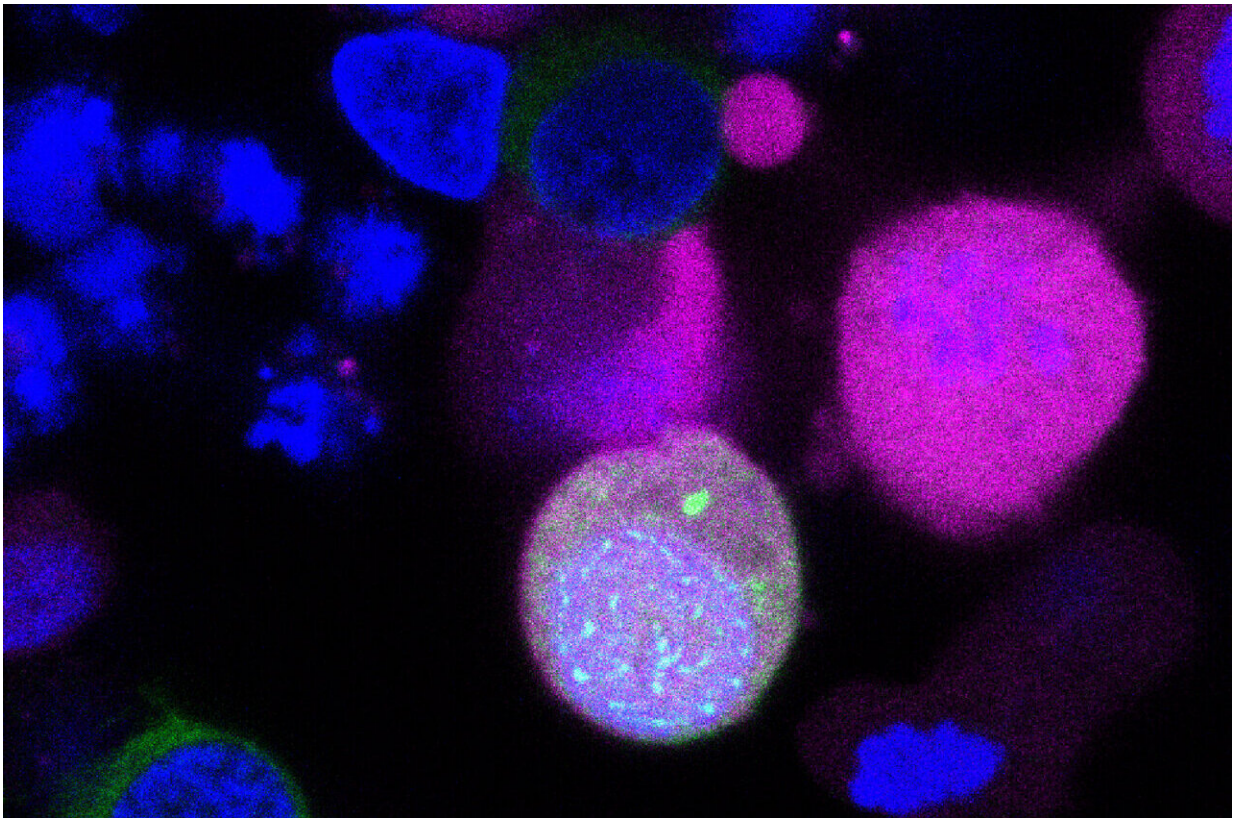

This fluorescence microscopy image shows induced pluripotent stem cells (iPSCs) that, for the first time, have been induced to enter and partially proceed through meiosis, a key process during the development of eggs and sperm, in a culture dish. The punctate marker shown in green indicates that the meiotic cells' chromosomes started to pair and exchange genetic information. Credit: Wyss Institute at Harvard University

More than one-sixth of adults around the world experience infertility in their lifetime. There is a high unmet need not only for increased access to affordable, high-quality fertility care for those in need but, importantly, also for new biomedical solutions that can address the root causes of infertility.

Some of the earliest causes of infertility go back to problems in a biological phenomenon known as "meiosis," a special kind of cell division that cells undergo to form eggs and sperm (gametes). Meiosis starts from a precursor cell with two sets of chromosomes, one inherited from the mother and one from the father, and ends by producing mature gametes.

Along the way, the maternal and paternal copies of each chromosome exchange information, generating a new combination of genetic code, and, ultimately, one and only one copy of each chromosome needs to be distributed into the resulting gametes. Errors in these processes can result in abnormal numbers of chromosomes (aneuploidies), miscarriage, and developmental disorders. However, replicating meiosis outside the human body, which could eventually allow fertility specialists to create healthy gametes for disadvantaged parents, has been extremely challenging.

Now, researchers at the Wyss Institute at Harvard University and Harvard Medical School (HMS) have developed an in vitro method that enables the differentiation of induced pluripotent stem cells (iPSCs) along the path of meiosis. By introducing a cocktail of genes into iPSCs that turn on meiosis-specific gene expression programs, as well as drugs that alter the processing of signals in cells, the team is the first to observe live human cells initiating meiosis outside of the body. Their findings are published in *Science Advances*.

"Healthy eggs and sperm are the product of an extremely complex and

error-prone process. Our study pushes the envelope in replicating one of its quintessential features in the culture dish," said senior author and Wyss Core Faculty member George Church, Ph.D. "We are in an excellent position now to also find the means to steer cells all the way through the remaining steps of meiosis, which would provide a basis for modeling a number of defects, and creating healthy gametes for individuals who can't efficiently get there by themselves." Church is also Professor of Genetics at HMS and Professor of Health Sciences and Technology at Harvard and MIT. He also leads the Wyss Institute's Synthetic Biology Platform.

Shortcut to meiosis

"To create egg and sperm cells themselves, we need to be able to drive cells all the way through the meiotic cell divisions," said Merrick Pierson Smela, Ph.D., the study's first author. In the body, egg and sperm precursor cells transition through what's known as the "primordial germ cell" (PGC) state before entering meiosis. Previous cell culture methods were able to reach the PGC state, but the resulting PGC-like cells could not successfully perform meiosis. "Our protocol entirely bypasses the PGC state to greatly simplify the process of initiating meiosis," explained Smela, who performed his work at the Wyss as a graduate student in Church's group.

To enable this shortcut and reach meiosis, Smela and his colleagues found combinations of genes that, when activated in cells, cause the cells to initiate meiosis. First, the researchers engineered stem cells to become fluorescent if they started to perform meiosis. They then activated combinations of genes predicted to play a role in meiosis. In some of these combinations, the cells became fluorescent, indicating that they were performing meiosis.

The researchers also found that adding two different chemicals to the

culture media—a synthetic mimic of vitamin A, and an inhibitor of DNA methylation—further boosted the efficiency of entry into meiosis. So-called methyl groups suppress the expression of nearby genes and are also eliminated during the normal development of gametes to create a "clean slate" for their differentiation.

By testing combinations of factors in 646,493 individual cells, Smela and colleagues found three regulatory genes, BOLL, MEIOC, and HOXB5, each of which can activate meiosis in their system. The first two of these were previously known to regulate meiosis, but the role of HOXB5 was unexpected. Additionally, BCL2, which stabilizes mitochondria, was required to prevent programmed cell death during meiosis induction.

Taking the temperature of meiosis

Through careful analysis of protein and RNA expression during meiosis induction, as well as varying their culture conditions, the team made additional interesting observations. The cells efficiently progressed through the first two stages of meiosis (leptonema and zygonema) over approximately 12 days, which, respectively, is when they dramatically condense and when corresponding chromosomes from the mother and father pair up. By day 15, a few cells reached the third stage (pachynema), when paired chromosomes exchange information, but did not progress further. The researchers are currently optimizing their system to allow the cells to proceed all the way through meiosis.

Both male and female cells derived from male and female iPSCs entered meiosis more efficiently when cultured at 34°C, the temperature of the testis, instead of 37°C, or body temperature. Sperm development was previously known to require lower temperatures, but the fact that lower temperatures also helped female cells was surprising. In addition, besides the differentiating cells not passing through a PGC-like state, most had signatures of ovarian cells and fewer of testicular cells, which suggested

to the team that their conditions preferentially switched on an egg cell differentiation program, even when starting from male iPSCs.

According to Smela, near-term applications for the new protocol include the development of male contraceptives and testing new drug candidates for potential reproductive toxicities. Over the longer term, he said, "I am excited about the potential of this technology to solve infertility by growing healthy eggs and sperm for people who need them." He is now advancing the technology as the Chief Scientific Officer of Ovelle Bio, a reproductive medicine startup which Church supports as a Scientific Advisor.

In 2023, Smela and other members of Church's team published a method that allows the generation of so-called ovarian granulosa-like cells from iPSCs, but using different stimuli. Organized as ovarian organoids(ovaroids), these cells are able to assist with the maturation of egg cells obtained from mothers who require significantly lower hormone exposure in a facilitated in vitro fertilization procedure. The technology led to the success of Gameto and the birth of the first baby using this novel egg maturation procedure. Ovaroids or similar engineered tissue environments could eventually help mature gametes that have fully completed meiosis to be matured further.

"With the fertility rate in the US being at a historic low and a growing number of couples struggling with fertility problems in their lives, this advance by George Church's group offers researchers a new platform for working towards a solution for many of the underlying causes," said Wyss Founding Director Donald Ingber, M.D., Ph.D., who is also the Judah Folkman Professor of Vascular Biology at Harvard Medical School and Boston Children's Hospital, and the Hansjörg Wyss Professor of Biologically Inspired Engineering at Harvard John A. Paulson School of Engineering and Applied Sciences.

Other authors on the publication are Jessica Adams, Carl Ma, Laura Breimann, Ursula Widocki, Bogdan Dobre, and Toshi Shioda.

More information: Merrick Pierson Smela et al, Initiation of meiosis from human iPSCs under defined conditions through identification of regulatory factors, *Science Advances* (2025). DOI: 10.1126/sciadv.adu0384