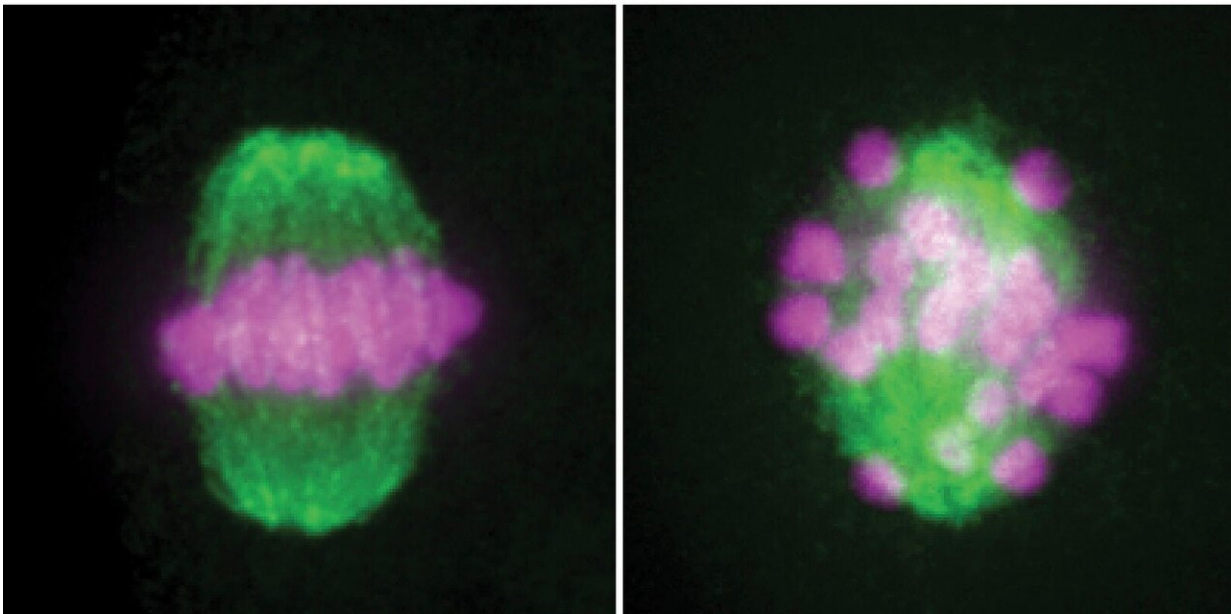


A critical enzyme for sperm formation could be a target for treating male infertility

March 25 2020, by Katherine Unger Baillie



The activity of the Skp1 protein is crucial for sperm formation, Penn Vet scientists found. In a dividing sperm precursor cell, chromosomes (in purple) normally align in the middle, as shown on the left. But in cells lacking Skp1, as shown on the right, chromosomes fail to align and are instead distributed chaotically around the cell. Credit: Wang laboratory

While some of our body's cells divide in a matter of hours, the process of making sperm, meiosis, alone takes about 14 days from start to finish. And fully six of those days are spent in the stage known as the pachytene, when pairs of chromosomes from an individual's mother and

father align and connect.

"This stage is really important, because the pair needs to be aligned for the exchange of genetic material between those two chromosomes," says P. Jeremy Wang, a biologist in Penn's School of Veterinary Medicine.

"If anything goes wrong at this stage, it can cause a defect in meiosis and problems in the resulting [sperm](#), leading to infertility, pregnancy loss, or birth defects."

In a new paper in *Science Advances*, Wang and colleagues have identified an enzyme that plays a crucial role in maintaining this chromosomal pairing during the pachytene stage of meiosis. Without this protein, named SKP1, meiosis cannot proceed to metaphase, the next major developmental stage involved in generating [sperm cells](#).

The finding may help overcome hurdles that have stood in the way of treating certain forms of male infertility, in which a man makes no sperm but in whom sperm's precursor cells, spermatogonia, can be found.

"Reproductive technologies like in vitro fertilization have made a huge difference for infertile patients, but the male needs to have at least some sperm," says Wang. "If the male has no sperm, then the only option is to use donor sperm. But if you can find these spermatogonia, the pre-meiotic germ cells, they could be induced to go through meiosis and make sperm. So SKP1 could be part of the solution to ensuring meiosis continues."

Wang is also hopeful that his finding could aid in basic research on sperm development that his and many other labs pursue.

"Right now we use animals to do our research; we don't have a [cell culture system](#) to produce sperm," he says. "Manipulating SKP1 and the

pathway in which it acts could allow us to set up an in vitro system to produce sperm artificially, which would be a boon for our studies."

The publication represents nearly a decade of work, led by Wang's postdoctoral researcher Yongjuan Guan, with major contributions from former postdoc Mengcheng Luo.

The team began focusing on SKP1 after conducting a screening test to look for proteins found in the area where the paired chromosomes come together during the pachytene stage of meiosis. From earlier studies, the researchers knew that SKP1 also plays a role in [cell division](#) in cells throughout the body, not just sperm and eggs. Without it, cells die.

That fact forced the Penn Vet team to get creative to understand the protein's function. Unable to simply eliminate it, they created a model system in mice in which they could turn off the protein only in the germ cells and only in adulthood.

"Taking this inducible, germ-cell-specific model, we found that taking away SKP1 caused the chromosomes to prematurely separate," says Wang.

While the normal alignment process in the pachytene stage takes six days in mice, in the cells that lost SKP1 the paired chromosomes separated far earlier.

Scientists had hypothesized the existence of a metaphase competence factor, or some protein required for a cell to enter metaphase. Wang believes that SKP1 is it.

While introducing a compound known as okadaic acid to sperm [precursor cells](#) can coax them into an early entrance to metaphase, cells lacking SKP1 did not progress to metaphase.

Experiments in developing eggs showed the researchers that SKP1 is also required for females to maintain viable eggs. Oocytes, the cells that develop through meiosis to form mature eggs, that lacked SKP1 developed misaligned chromosomes and many eventually were lost.

In future work, Wang and his colleagues want to dig deeper into the mechanism of action by which SKP1 works to ensure [cells](#) can progress to metaphase, with the idea of eventually manipulating it to find strategies for addressing infertility and innovative laboratory techniques.

"Now that we know SKP1 is required, we're looking for the proteins it interacts with upstream and downstream so we can study this pathway," says Wang.

More information: "SKP1 drives the prophase I to metaphase I transition during male meiosis" *Science Advances*, [DOI: 10.1126/sciadv.aaz2129](https://doi.org/10.1126/sciadv.aaz2129) , advances.sciencemag.org/content/6/13/eaaz2129

Provided by University of Pennsylvania

Citation: A critical enzyme for sperm formation could be a target for treating male infertility (2020, March 25) retrieved 25 April 2024 from <https://phys.org/news/2020-03-critical-enzyme-sperm-formation-male.html>

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