How sperm and eggs develop precisely 23 chromosomes each

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There are many "tools" that cells could use to separate DNA strands that cross over during meiosis. UC Davis researchers have identified the right tools for the job. Credit: Neil Hunter, UC Davis

Researchers at the University of California, Davis have discovered a key tool that helps sperm and eggs develop exactly 23 chromosomes each. The work, which could lead to insights into fertility, spontaneous miscarriages, cancer and developmental disorders, is published April 13 in the journal *Cell*.

Healthy humans have 46 chromosomes, 23 from the sperm and 23 from the egg. An embryo with the wrong number of chromosomes is usually miscarried, or develops disorders such as Down's syndrome, which is caused by an extra copy of chromosome 21.

During meiosis, the cell division process that creates sperm and eggs, matching chromosomes pair up and become connected by "crossing over" with each other, said Neil Hunter, a professor of microbiology at UC Davis and senior author of the new study.

These connections are essential for precise chromosome sorting and the formation of sperm and eggs with exactly the right numbers of chromosomes. Crossovers also play a fundamental role in evolution by allowing the chromosomes to swap chunks of DNA, introducing some variety into the next generation.

Each pair of chromosomes must contain at least one crossover. But there shouldn't be more than about two crossovers per pair, or the genome could be destabilized.

In their paper, Hunter and his colleagues describe a "missing tool" that explains how crossovers are regulated.

"There must be enzymes that ensure at least one crossover, but not too many," said Hunter, who is also a member of the UC Davis Comprehensive Cancer Center research program.

Hunter, graduate students Kseniya Zakharyevich and Shangming Tang and research associate Yunmei Ma, looked for enzymes that could cut DNA to form crossovers in yeast, which form sexual gametes, or spores, in much the same way that humans and other mammals form sperm and eggs.

"There were several good candidates, but none turned out to play a major role," Hunter said.

Then they discovered the missing tool for crossing-over: three yeast enzymes, Mlh1, Mlh3 and Sgs1, which work together to cut DNA and

make crossovers.

It turns out that the human equivalents of these enzymes are well known for their role in suppressing tumors. Human MLH1 and MLH3 are mutated in an inherited form of colon cancer. BLM, the human equivalent of Sgs1, is mutated in a cancer-prone disease called Bloom's Syndrome.

"Sgs1 was the biggest surprise," Hunter said. "We previously knew it as an enzyme that unwinds DNA to prevent crossovers. Its role in making crossovers had been hidden by other enzymes that can step in when it is absent."

"While other enzymes cut DNA randomly, Mlh1-Mlh3-Sgs1 only makes crossovers. This unique activity is essential for meiosis and its discovery is a huge step forward," he said.

Provided by University of California - Davis