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BRWD1 shows its gender bias

Protein necessary for fertility has distinct roles in sperm and eggs.

Pattabiraman et al. add a subtle and unexpected entry to the long list of differences between the sexes. The researchers discovered that a protein that controls gene expression in maturing sperm performs a different function in maturing oocytes, where it promotes chromosome condensation and stability (1).

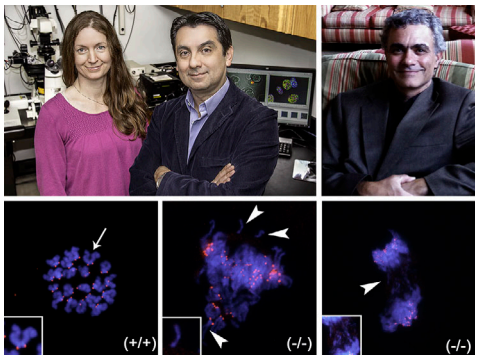
Once meiosis is complete in male mammals, the resulting cells, known as spermatids, undergo a series of changes that shape them into functional sperm. The cells jettison most of their cytoplasm, sprout tails, and replace their histones with proteins called protamines, which scrunch their DNA even tighter. Their chromatin also acquires epigenetic modifications. In the chromosome region that contains two protamine genes, for instance, H3 and H4 histones are acetylated (2). Oocytes also display changes in chromatin structure as they mature. At the same time that their genes shut down, their heterochromatin gathers along the edge of the nucleolus (3).

Pattabiraman et al. suspected that these alterations had a common cause—the protein BRWD1. It binds to histones decorated with acetyl groups, and its loss causes infertility in males and females (4). The researchers hypothesized that this protein orchestrates chromatin changes in the gametes of both sexes.

> "This protein… seems to be doing opposite things in the sperm and egg."

To their surprise, the scientists detected no chromatin abnormalities or epigenetic alterations in spermatids from male mice lacking BRWD1. Just like in normal spermatids, heterochromatin from the rim of the nucleus clustered into a structure called the chromocenter. To determine whether the absence of BRWD1 triggered epigenetic changes, the researchers measured the distribution of four acetylation marks that tag active genes and two methylation marks that indicate shuttered genes. The pattern of these modifications was the same in control mice and in animals lacking BRWD1.

Focal Point



(Top row, left to right) Claudia Baumann, Rabindranath De La Fuente, John Schimenti, and colleagues (not pictured) pin down the different functions of the histone-binding protein BRWD1 in sperm and eggs. (Bottom row) In eggs from control mice, chromosomes display a tidy formation (left). But chromosomes in eggs lacking BRWD1 are often long or broken (center) and don't separate properly (right). In contrast, BRWD1's main function in sperm is to regulate gene expression.

PHOTOS: COURTESY OF CHRISTOPHER B. HERRON [BAUMANN/DE LA FUENTE] AND KERRY SCHIMENTI

The team's results pointed to a different role for BRWD1 in males: regulating gene activity. A burst of gene expression generates the proteins that guide spermatid development. Pattabiraman et al. determined that transcripts from hundreds of genes that are specific to spermatid development were markedly reduced in the absence of BRWD1.

However, managing gene expression isn't BRWD1's main role in female mice, the researchers discovered. In oocytes that were missing BRWD1, only three genes showed a dramatic increase in expression, including the gene encoding the histone-methylating protein MLL5. Instead, Pattabiraman et al. found, loss of BRWD1 unleashed a surge in transcription of noncoding RNAs, such as the transposon LINE-1. The oocytes' chromatin reflected this abnormality. Several sections of heterochromatin didn't cozy up to the nucleolus as they usually would, indicating they were still transcriptionally active.

When the researchers examined chromosomes from BRWD1-lacking oocytes, they saw numerous defects during meiosis. The chromosomes were often abnormally long and frequently fractured. The chromatids often did not condense properly, and sister chromatids tended to stick to one another, stretching and breaking when they tried to separate.

"What makes this protein exciting is that it seems to be doing opposite things in the sperm and egg," says co-author John Schimenti. In spermatids, BRWD1's job appears to be adjusting gene expression, although it doesn't work alone. The protein CREM-τ helps to regulate expression of up to 5,000 genes in the cells. But CREM-τ has no effect on about half of the genes under BRWD1's control, suggesting that BRWD1 is important as well. How BRWD1 switches its target genes on and off remains unclear.

In oocytes, BRWD1 prevents chromosome instability during meiosis. Pattabiraman et al. ruled out one potential explanation for how BRWD1 performs this function. Oocytes normally strip acetyl groups from their histones early in meiosis, and failure to make this change inhibits chromatin condensation and spurs chromosome elongation. When the researchers checked oocytes lacking BRWD1, they found that the cells had pruned the acetyl groups. Hence, "the study suggests a previously unrecognized mechanism that is essential for chromosome condensation and chromosome maintenance," says co-author Rabindranath De La Fuente. This mechanism could work by reducing expression of *LINE-1* and *MLL5*, the researchers speculate.

1. Pattabiraman, S., et al. 2015. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201404109.
2. Martins, R.P., and S.A. Krawetz. 2007. *Proc. Natl. Acad. Sci. USA*. 104:8340–8345.
3. De La Fuente, R., et al. 2004. *Dev. Biol.* 275:447–458.
4. Philipps, D.L., et al. 2008. *Dev. Biol.* 317:72–82.