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A class of RNA molecules protects germ cells from damage, researchers show

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Passing one's genes on to the next generation is a mark of evolutionary success. So it makes sense that the body would work to ensure that the genes the next generation inherits are exact replicas of the originals.

New research by biologists at the University of Pennsylvania School of Veterinary Medicine has now identified one way the body does exactly that. This protective role is fulfilled in part by a class of small RNA molecules called pachytene piwi-interacting RNAs, or piRNAs. Without them, germ-cell development in males comes to a halt. Because these play such an important role in allowing sperm to develop normally, the research indicates that defects in these molecules or the molecules with which they interact may be responsible for some cases of male infertility .

Jeremy Wang, an associate professor of developmental biology and director of the Center for Animal Transgenesis and Germ Cell Research at Penn Vet, and Ke Zheng, a postdoctoral researcher in Wang's lab, authored the study, which appears in PLOS Genetics.

Scientists know of 8 million different piRNAs in existence; they are the most abundant type of small non-coding RNA. The molecule piRNA gets its name because it forms complexes with piwi proteins. Earlier work had indicated that these piwi-piRNA complexes suppress the activity of transposable elements or "jumping genes," which are stretches of DNA that can change position and cause potentially damaging genetic mutations. These sequences are also known as transposons.

"There are about 50 human diseases caused by transposable elements, so it's important for the body to have a way to try to repress them," Wang said.

This transposon-suppressing activity had been confirmed in a group of piRNAs called pre-pachytene piRNAs, which are expressed before meiosis, the unique process by which germ cells divide. But Zheng and Wang wanted to investigate if a separate group of piRNAs that emerge during meiosis, called pachytene piRNAs, were also required for "silencing" transposons.

Working in male mice, the researchers manipulated an enzyme called MOV10L1, which is known to interact with piwi proteins and is believed to help produce piRNA molecules. They created a mutant mouse in which they could selectively inactivate MOV10L1 at specific stages before, during and after meiosis. The mice that lost the function of MOV10L1 before or at the pachytene stage of meiosis were sterile. When Zheng and Wang examined their germ cells more closely, they found that spermatogenesis had apparently come to a halt at the post-meiotic stage: Early stages of the germ cells were present, but the mice completely lacked mature sperm.

Further experiments allowed Zheng and Wang to pinpoint that MOV10L1 was playing a critical role at the pachytene stage. MOV10L1 mutants lacked pachytene piRNAs, but their levels of pre-pachytene piRNAs were unaffected, as the mutation was "turned on" after they had already been produced.

The researchers also found that, in the MOV10L1 mutants, piwi proteins congregated together along with mitochondria, suggesting that mitochondria may be involved in the generation or organization of pachytene piRNAs. Furthermore, the spermatids, or early-stage sperm, of the mutants had severe DNA damage. While the researchers

suspected that the damage may have been caused because of transposons that had been freed from repression in the absence of piRNAs, they actually found that two common transposable elements were not de-repressed in the mutants. They also found a build-up of pachytene piRNA precursors in the testes of the mutants. Their findings raise the possibility that there is another mechanism by which damage occurs.

"It could be the accumulation of precursor molecules is causing some of the damage," Wang said.

This new function for MOV10L1, in playing an essential role in producing pachytene piRNAs, gives researchers a greater understanding of germ-cell development.

"This is the first time we've shown that pachtyene piRNA is required for maintaining genome integrity in the post-meiotic germ cells," Wang said. "It turns out that MOV10L1 is a master regulator of the piRNA pathway and is required for the production of all piRNAs, both pre-pachytene and pachytene."

Any disruptions to this "master regulator" role, therefore, could lead to problems.

"I think we're just beginning to appreciate the significance of this pathway," Wang said. "Mutations at various points in the pathway could lead to infertility."

Provided by University of Pennsylvania