Eliminating Bad Mitochondria with Polar Bodies

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Researchers have prevented transmission of mutant mitochondria between generations by transferring the genetic information of a polar body from an affected oocyte into a recipient oocyte with normal mitochondria [1]. The method, tested in mice, may offer advantages over current experimental techniques, which involve transfer of either the pronucleus or the spindle-chromosome complex.

In individuals with mitochondrial disorders, mutant and non-affected mitochondria are often mixed together in a cell. When a certain threshold is reached, generally about 60 percent mutant mitochondria in humans, severe disease, including myopathies and neuropathies, can result. Mitochondrial diseases affect about 1 in 10,000 individuals.

Since mitochondria are transmitted in the oocyte cytoplasm, previous efforts to prevent transmission have involved transfer of the pronucleus or spindle-chromosome complex of an affected oocyte to the enucleated oocyte of an unaffected donor [2, 3]. Results in primates and human zygotes have been promising enough that human trials are now being considered by the US Food and Drug Administration.

Despite such success, Tian Wang, Hongying Sha, and colleagues reasoned that polar body nuclear transfer might offer some advantages. Polar bodies are relatively easy to manipulate—in contrast to the spindle-oocyte complex, which demands a high level of technical skill. And since it has very little cytoplasm, the polar body genome may bring fewer mitochondria along with it during transfer.

The researchers tested the polar body procedure in mice, comparing them with pronuclear and spindle-oocyte transfer. Transfer of the first polar body into an enucleated donor oocyte resulted in undetectable levels of mitochondria in the offspring and subsequent generations. A procedure involving transfer of the second polar body resulted in offspring with under 4 percent mutant mitochondria. In contrast, pronuclear transfer resulted in 6 to 40 percent mutant mitochondria in offspring, while spindle-oocyte complex transfer yielded 0 to 7 percent.

All of the procedures produced apparently healthy embryos and offspring in mice. Moreover, when the researchers tested the polar body procedure in human zygotes, they saw no aberrations in chromosome number or other gross DNA abnormalities.

The researchers point out an additional advantage to the polar body method—it offers a way to conserve precious eggs. For instance, a single egg from an affected woman can be used as a source for both a pronuclear and spindle-oocyte complex transfer in human oocytes.

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A new study by Birgit Samans, Yang Yang, and colleagues [1] examines genome-wide nucleosome retention in humans and cattle, deploying a technique that deep sequences nucleosome-containing DNA. By comparing the patterns of retention between the two species, the researchers emerged with conserved patterns that may have regulatory significance.

One major finding of the new study is that nucleosome retention tended to occur preferentially in distal intergenic regions in certain repetitive DNA elements. These include centromeric repeat elements, and LINE1 and SINE1 retrotransposons, which are scattered throughout the genome. As a result, the sperm genome is littered throughout with nucleosomes. The researchers speculate that this condition might be relevant for rapid and comprehensive decondensation and activation of paternal chromatin after fertilization.

Nucleosome retention also occurred in a subset of genes within their gene bodies, preferentially introns and promoters. These genes were enriched for factors relevant for RNA- and protein-processing, signal transduction, and mitochondrial function. These genes were also found to have low levels of methylation at their transcription start sites, and many of them have previously shown to be active during the very early cleavage stages of embryogenesis. The researchers suggest that such nucleosome-preserving genes in sperm may have a role in an embryogenesis initializing program during pre-implantation development.

The researchers also examined nucleosome-free genomic regions in sperm and found enrichment for genes involved in cell fate commitment, system and organ development, and morphogenesis. This finding contrasts with previous research that found that such “developmental” genes retained post-translationally modified histones. That research had relied on results generated with ChIP (chromatin immunoprecipitation), whereas the new study did not rely on this chromatin-enrichment step. The researchers suggest that genes lacking nucleosomes, and instead packaged solely into protamines, have a role in post-implantation development.

Many mysteries remain about the complex ways that sperm transmit genetic and epigenetic information. For instance, previous research has hinted that histone retention in sperm DNA may be involved in conveying epigenetic information between generations [2, 3]. Research into such questions should be bolstered by this new study, which delivers a genome-wide overview of the nucleosome-preservation pattern in two mammalian species.

References


The Nucleosomes that Stick Around

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