Eliminating mitochondrial diseases in embryos

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Mitochondrial diseases are characterized by the degeneration of tissues and organs with high energetic demands. Currently there is no cure for mitochondrial diseases. For mitochondrial-disease patients, genetic counseling and pre-implantation genetic diagnosis (PGD) represent the best therapeutic options to prevent the transmission of mitochondrial diseases. However, due to the non-Mendelian inheritance of mitochondrial DNA (mtDNA) and potentially different levels of mutated mtDNA among different blastomeres, PGD only allows a small but not complete reduction in the risk of transmitting the disease. Recently, two novel mitochondrial replacement techniques known as “Spindle Transfer” and “Pronuclear Transfer” have been reported. These techniques are based on the transfer of spindle or pronucleus from a patient’s oocyte/zygote to an enucleated donor oocyte/zygote. The use of donor oocytes results in the generation of embryos carrying DNA from three different origins. We recently developed genome-editing approach to prevent the transmission of mitochondrial diseases by selective elimination of mutated mtDNA present in the oocytes. The technique is based on the introduction of nucleases (molecular scissors) into oocytes that enter mitochondria and specifically identify and eliminate the mutated mtDNA. The feasibility of this approach was recently demonstrated by using nucleases in the mouse embryos where the transmission of targeted mtDNA to next generation was successfully prevented. In collaboration with Dr. Norbert Gleicher’s IVF clinic, we are currently testing similar strategy in human oocytes from mitochondrial disease patients to selectively target and eliminate the mutated mtDNA. The assessment of safety and efficacy of this approach will benefit in moving this technology to the clinics in the near future.

Translational relevance:
Currently, preventing the transmission of mitochondrial diseases by the selective elimination of mutated mtDNA in the oocytes is the best alternative approach. Evaluating the efficacy and safety of mitochondrial genome-editing technology in human oocytes will help in moving this technology into next stages of clinical testing. The targeted elimination of mutated mtDNA in the germline could help in eradicating the mitochondrial disorders that affect thousands of families.