

# Control of Induced Pluripotent Stem Cell Aging by Modulation of Mitochondrial DNA Deletions

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Induced pluripotent stem cells (iPSCs) could revolutionize patient-specific regenerative medicine, but their premature aging symptoms, currently misunderstood, limit their clinical applicability. In this study, it was hypothesized that the phenomenon is triggered by the age-related mitochondrial DNA (mtDNA) common deletion, and that by modulating mitochondrial genomic damage, rapid aging in iPSCs and other disorders could be controlled. Healthy cells were reprogrammed into iPSCs by three different methods. The common deletion was induced in all cells, suggesting that the mtDNA defect is technique independent. Further disparities were observed in mitochondrial size and morphology between iPSCs and their source cells by transmission electron microscopy and flow cytometry, changes paralleling those seen in cancer cells. Although derived from older patients, the cancer cells tested did not exhibit the age-related deletion, suggesting a unique pathway of mtDNA conservation. Further experiments revealed mediation by Sirtuin 1 (SIRT1), a gene regulating nuclear / mitochondrial cross-talk. Both knockdown and inhibition of SIRT1 induced the common deletion in cancer cells, selectively inducing senescence. Conversely, SIRT1 activation in iPSCs ameliorated aging features, revealing methods to maintain clinically useful iPSCs. Bioinformatic analysis identified 16 genes that could be developed into mitochondrial genome controllers for prevalent age-related diseases including Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, fibromyalgia, and diabetes. The discovery of mitochondrial genome control provides a platform technology with new opportunities in iPSC maintenance and use, cancer treatment, and prevention of multiple age-related disorders.

## Awards Won:

Intel ISEF Best of Category Award of \$5,000

First Award of \$5,000