# Analysis of entire physiological roles of mammalian mtDNA by generation of mice carrying various pathogenic mutations

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**【Outline of survey】**

Human mtDNAs with pathogenic mutations have been identified to be closely associated with mitochondrial diseases expressing respiratory defects in various tissues. Moreover, thesemtDNA mutations also have been identified in association with human aging and with various age-related disorders including diabetes and neurodegenerative diseases. However, possible involvement of nuclear DNA mutations in expression of respiration defects was not excluded, since respiratory function is controlled by both nuclear DNA and mtDNA. For resolving this issue, we would use XO-type mouse ES cells as recipients, and isolate respiration-deficient ES cells by cytoplasmic transfer of possible pathogenic mtDNAs from respiration-deficient mouse cell lines. Then, we generate trans-mitochondrial mice, mito-mice, sharing the same nuclear-genome background but carrying mtDNAs with various pathogenic mutations.

**【Expected results】**

Generation of mitomice sharing the same nuclear-genome background but carrying mtDNAs with various pathogenic mutations would resolve various controversial issues. For example, why different mtDNA mutations resulted in different clinical phenotypes observed in the patients with mitochondrial diseases, even though all pathogenic mtDNA mutations, irrespective of whether they are created in tRNA genes or structural genes in mtDNA, result in respiration defects. Moreover, these mice also would allow us to resolve the issue of whether mitochondrial theory of aging is correct or not.

**【References by the principal investigator】**

・Akitsugu Sato, Tomohiro Kono, Kazuto Nakada, Kaori Ishikawa, Shin-Ichi Inoue, Hiromichi Yonekawa, and Jun-Ichi Hayashi (2005) Gene therapy for progeny of mito-mice carrying pathogenic mtDNA by nuclear transplantation. Proc. Natl. Acad. Sci. USA 102:16765-16770.

・Kazuto Nakada, Akitsugu Sato, Kayo Yoshida, Takashi Morita, Hiromitsu Tanaka, Shin-Ichi Inoue, Hiromichi Yonekawa, and Jun-Ichi Hayashi (2006) Mitochondria-related male infertility. Proc. Natl. Acad. Sci. USA 103:15148-15153.

**【Term of project】 FY2007−2011**

**【Budget allocation】 35,900,000 yen**
(2007 direct cost)

**【Homepage address】** http://www.geocities.jp/ji_hayashi_lab/index.html