# Would the mice's memory of mitochondrial stress pass on to mice offspring

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**Abstract:**

This study investigates whether the offspring of genetically modified mice with AD-induced UPRmt have genetic memory, which makes the offspring more likely to produce UPRmt or even with a more obvious effect. We first conducted biochemical studies using double transgenic mice of different ages to explore the expression levels of UPRmt-related proteins in hippocampal lysates. The two groups of mice were then mated to produce offspring, then the expression levels of UPRmt-related proteins in the offspring were explored. The offspring were tested for UPRmt characterization and physiological changes. Our analysis shows with inherited mtDNA and the consequent UPRmt, UPRmt can also communicate across tissues via intracellular signals; the cell-autonomous induction of UPRmt enables individuals to engage in global stress responses, whereby individuals exhibit greater resistance to adverse mitochondrial stresses, bacterial infections, and toxins, resulting in longer life. Due to the limitations of experimental materials, we propose more theories without a large amount of experimental data as support. We conclude that stress resistance can also develop in mammalian offspring due to mitochondrial stress-induced mitochondrial nuclear imbalance and the consequent increase in lifespan, thus increasing the survival advantage of the mammalian species.

**Keywords:**mtDNA, The UPRmt system, nDNA, RNA interference (RNAi), Wnt signaling pathways

## 1. INTRODUCTION

Memory is a very important for human beings and plays a vital role in our daily lives. Our brains tend to determine our behavior through memory.

AD is a neurodegenerative disease associated with the degeneration of neurons in the brain that affects memory.

Cross-generational induction of UPRmt is caused by the inheritance of increased mtDNA levels, which lead to a mitotic nuclear imbalance that produces stressed mitochondria in each generation[9].

It has been established in the original literature that AD causes the UPRmt response in the brain of mice[1]. Our experiment aimed to determine whether the offspring of mice genetically modified to produce AD-induced UPRmt have the genetic memory to make the offspring more likely to produce UPRmt or whether the effect is more obvious. Therefore, we repeated the operation in the original paper with the first-generation mice.

## 2. PRINCIPLES

Determine whether the offspring mice have the UPRmt by phenotype.

The mechanism of UPRmt acts as an improving approach to osteoarthritis in mammals, including the APPsw and PS1dE9 double transgenic rats utilized as subjects in the experiment above[2].

Osteoarthritis (OA) is the most common disease in the elderly. However, due to our limited understanding of the mechanism of the disease, there is a lack of effective treatments for OA, which consists of cartilage cells and the surrounding extracellular matrix (ECM). Cartilage is generally considered hypoxic, and the amount of oxygen delivered to cartilage is lower than that delivered to other tissues. Mitochondrial dysfunction is a key feature of chondrocyte homeostasis disorder and leads to increased inflammation, increased cell death, decreased anabolic activity, and increased catabolic activity in OA.

Thus, the UPRmt mechanism is considered to function in the protective process against OA in mice and many other mammals. UPRmt was induced in primary mouse chondrocytes subjected to different stresses and in cartilage from OA mice. Nicotinamide ribose (NR) enhanced UPRmt significantly improved mitochondrial function, reduced chondrocyte death, reduced OA pain, improved OA progression, and significantly reduced protection in chondrocyte-specific Atf5 knockout (ATF5f/fCol2a1-CreERT2) mice. It was the same way in APPsw/PS1dE9 mice. Enhancement of UPRmt improves OA progression, suggesting that UPRmt has a protective effect against OA. [3]

Since the level of perished cartilage cells and inflammation in joint fluid is obliviously decreased in the individuals induced with the UPRmt, we can detect the differences of dead cartilage cells quantity and the pathogen density in joint fluid tissue between resultant

individuals from the reproduction of mice that have been proved to have mtDNA elevated levels in the previous experiment, as phenotype to distinguish offsprings with UPRmt inherited. To generate the conditions of equally spread OA illness among the mice as the background of this phenotype detection, only the mice who tend to be infected with

OA is screened out to engage in the experiment. The mice are trained by apparatus to wear out their leg joints, so they tend to have OA in old age. The frequency of dead cartilage tissues and pathogens in joint fluid tissues is measured as dependent variables.

## 3. METHOD

The APPsw/PS1dE9 double transgenic mice at the age of 5 and 8 months and age-matched C57BL/6 mice were used as a control. Five mice are male; five mice are female (n = 10 per group)

To determine whether the UPRmt occurred in the brain of APPsw/PS1dE9 double transgenic mice[1], we need to conduct biochemical studies to compare expression levels of UPRmt-related proteins in hippocampi of 3- and 9-month old wildtype (WT) and APPsw/PS1dE9 transgenic mice.

Then, part of APPsw/PS1dE9 double transgenic mice of the first generation are subjected to germ cell experiment, and the rest will mate to produce offspring. Conduct biochemical studies to compare expression levels of UPRmt-related proteins in hippocampi to see if the expression levels of Hsp60, CLPP, and HtrA2/Omi in the progenitor would increase. Then, the offspring were tested for UPRmt characterization and physiological changes.[1]

## 4. HYPOTHESIS AND CONCLUSION

The circular DNA (mtDNA) found in mitochondria is known to code for 12 proteins in C.elegans and 13 in mammals. These proteins are involved in ATP synthase production and mitochondrial oxidative phosphorylation (OXPHOS)[4,5]. The mtDNA copy number increase in reproductive glands, which encourages offspring to inherit more mtDNA, is the mechanism of nematode neurons' mitochondrial sensitivity. This imbalance between mtDNA and nuclear DNA in each offspring leads to the activation of the mitochondrial unfolded protein response (UPRmt).[6-7]. Because of the inherited mtDNA and UPRmt, which can also communicate through intracellular signals across tissues, an individual can perform a global stress response through the non-autonomous induction of UPRmt. This increases the individual's resistance to harmful mitochondrial stresses like toxins, high temperatures, and bacterial infections and prolongs their lifespan[8]. This mechanism found in C. elegans has the potential to greatly influence the survival and prosperity of the species. It was a remarkable discovery regarding transgenerational inheritance, which can be passed down through successive generations for over fifty generations. So a hypothesis comes out: what if more complex forms of living organisms such as mammals also have this sort of stress response-inheriting mechanism to help them avoid dangers since mammals also have 13 numbers of mtDNA, even one more than C.elegans? Hypothesize that mammals perform an inheritance that conducts a deeper extent of mtDNA-nDNA imbalance than C.elegans.

In this article, we discuss the possibility of the transgenerational induction of UPRmt from increased mtDNA inheritance, so as the mitonuclear imbalance by stressed mitochondria and the consequent extended lifespan, stress resistivity can also be carried out in mammal offspring, which generates the probability of surviving advantages on mammal species.

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