Study of Mitochonic Acid 5 to improve neuromuscular dysfunction associated with aging and diseases using C. elegans

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Ph.D. Dissertation

Study of Mitochonic Acid 5 to improve neuromuscular dysfunction associated with aging and diseases using *C.elegans*（線虫を用いた老化や疾患に伴う筋・神経損傷を改善するミトコニックアシッド５の研究）

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呉欣桐

Background:

Aging is a degenerative process caused by atrophy with cell dysfunction, tissue damage, and cell death. For decades, the theory of mitochondrial free radical aging has been the main focus. Also, mitochondria function declines with age. As a result, it has recently been reported that senescent cells accumulate dysfunctional mitochondria and induce senescence-related secretory phenotypes through retrograde signaling from mitochondria to the nucleus. In summary, maintaining normal mitochondrial function is well known to be an essential key to overcoming aging.

Mitochondria-homing drug Mitochonic acid-5 (MA-5), 4-(2,4-difluorophenyl)-2-(1H-indol-3-yl)-4-oxobutanoic acid is a newly developed chemical compound. It's synthesized as a derivative of the plant hormone, indole-3-acetic acid which is also produced in human organs under micromolar concentrations and accumulates in patients with renal failure

MA-5 increases cellular ATP levels, reduces mitochondrial reactive oxygen species (ROS) production, and protects cells with mitochondrial dysfunction from fibroblast death. It can also prolong the survival of a mitochondrial disease model "Mitomouse" with mtDNA deletion mutant.

Purposes:

1) To study the effect of MA-5 on general age-related dysfunction.

2) To study the effect of MA-5 on skeletal muscle dysfunction in Duchenne muscular dystrophy (DMD) and dopaminergic neurodegeneration in Parkinson's disease (PD)

Methods and materials:

The nematode *C. elegans* has an advantage in conducting aging studies due to its relatively short lifespan and body wall muscles that resemble the skeletal muscles of vertebrates, including the sarcomere, the functional unit of a muscle fiber. Age-related changes in *C. elegans* muscle structure and activity have also been studied in the mammalian sarcopenia model, the decline of skeletal muscle mass and strength. In addition, several genes associated with human diseases, such as DMD and PD are highly conserved in nematodes. These disease models have been used to develop new drugs.

Results:

The results clearly show that MA-5 has similar homing activity and penetration into mitochondria. MA-5 suppresses age-related decline in ATP level and motility. In addition, mitochondria fragmentation and volume loss along with age are well known to occur in body wall muscle (BWM) cells. By contrast, MA-5 significantly suppressed mitochondrial volume

reduction and mitochondrial calcium overload in BWM cells with age. In addition to muscle cells, the Administration of MA-5 significantly reduced the age-dependent puncta formation which reflects dopamine neurodegeneration. These results clearly show that MA-5 promotes healthy life expectancy in *C. elegans* through maintaining mitochondria quality and quantity.

Furthermore, MA-5 alleviated the symptoms of the DMD model, such as movement decline, muscle tone, mitochondria fragmentation, and mitochondrial Ca^{2+} over-accumulation in BWM cells. To assess the effect of MA-5 on mitochondria perturbation, worms were employed with chronic exposure to a low concentration of rotenone in the presence or absence of MA-5. MA-5 significantly suppressed the increase in mitochondria ROS in muscle cells. In addition, rotenone-induced fragmentation of mitochondrial networks and nuclear destruction of BWM cells were suppressed. The decline in endogenous ATP levels was also repressed. Besides, rotenone-induced degeneration of dopaminergic cephalic neurons in the PD model was extensively suppressed by MA-5 treatment.

Moreover, the application of MA-5 reduced mitochondrial swelling due to the *immt-1* null mutation, one of the two mitofilin molecules in *C. elegans*. These results indicate that MA-5 has broad mitochondrial homing and MINOS stabilizing activity in metazoans and may be a therapeutic agent for these by ameliorating mitochondrial dysfunction in both aging and genetic diseases on neuromuscular dysfunction.

Conclusion:

Here, I show that MA-5 improves *C. elegans* age-related sarcopenia, neurological dysfunction, and neuromuscular disease model. Furthermore, these results indicate that MA-5 has the effect of extending healthy life expectancy by a mechanism different from Calorie restriction (CR) and Dietary restriction (DR). In particular, the suppression of mitochondrial Ca^{2+} overload while maintaining mitochondrial Ca^{2+} level homeostasis, is considered to be an important role of MA-5 as a mitochondrial homing drug.