MITOCHONDRIA AND LONGEVITY

Revising nuclear-encoded proteins that influence aging through mitochondria

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Introduction and Objectives

The role of mitochondria in aging

Many studies confer mitochondria a key role in aging:

- **MFRTA** (*Mitochondrial Free Radical Theory of Aging*) → Free radicals derived from metabolism are the main driving force of aging process by damaging DNA, lipids and proteins as well as mitochondrial DNA (mtDNA), leading to mitochondrial dysfunction, more free radicals and aging.
- **Polymorphisms on mtDNA** are related to longevity in studies with centenarian populations.
- **Mitochondrion is implicated in many cellular processes** such as apoptosis and cell cycle control and can affect aging through the control of those pathways.

Current Studies

Most studies **only focus on mtDNA-encoded genes** without taking into account nuclear-encoded genes that are involved in mitochondrial processes. The studies of mtDNA polymorphisms **do not explain the functional consequences** of the different variants. Studies focusing on general cell pathways where mitochondria takes place can explain better how aging happens and how mitochondria are involved.

Objectives

To explain how the following nuclear-encoded proteins interact with mitochondria and affect longevity: **Polymerasse Gamma** (PolG), **p53** and **mTOR pathway** (including mTORC1, AMPK, and PGC-1α).

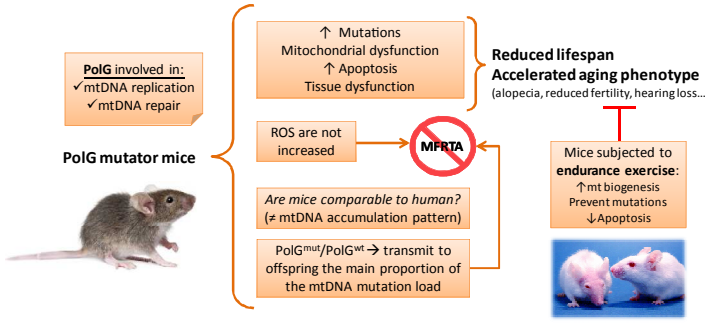
Methodology

This review was done by searching bibliography on **NCBI** and taking the most relevant information, **reviewing current studies and new theories**, specially focusing on recent publications.

State of the art

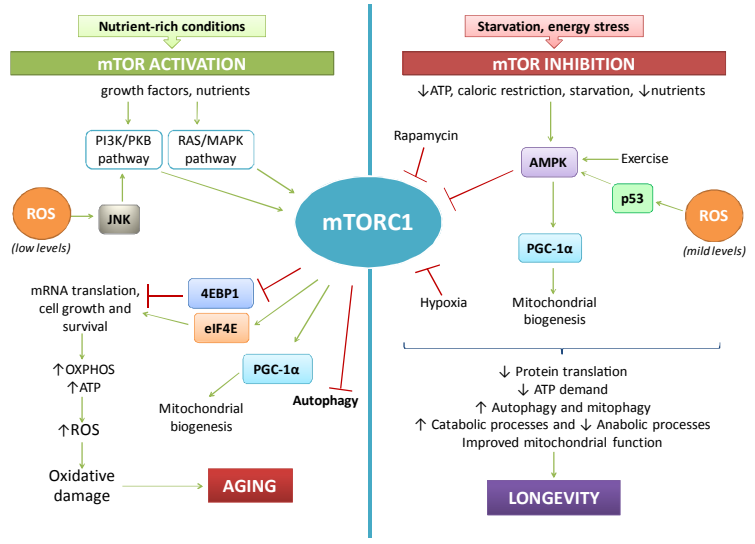
Polymerase Gamma (PolG)

Defects in **PolG** are associated with several mitochondrial diseases. Mutator mice (homozygous for proofreading-deficient polG) display **mitochondrial dysfunction** and an accelerated aging phenotype.



mTOR pathway

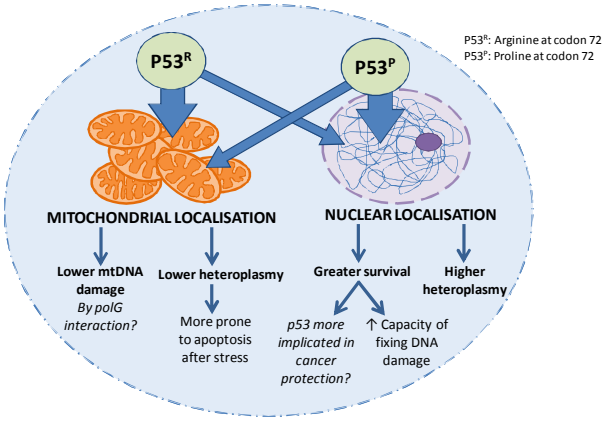
mTOR pathway is related to longevity in front of energy stress. The proteins AMPK and PGC-1α are also considered longevity genes since can inhibit mTORC1 and promote mitochondrial biogenesis.



p53

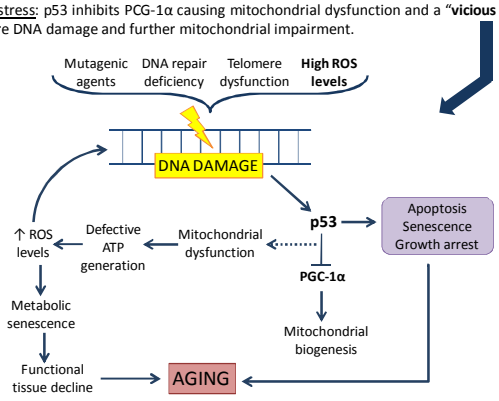
p53 is involved in many cellular processes and plays a role in **maintenance of mtDNA integrity** through its ability to translocate to mitochondria in response to DNA damage.

A polymorphism in codon 72 of p53 leads to different **p53 isoforms** with a different preferential localization, causing different cell effects.



A new **theory of p53 role in aging** has been proposed, where p53 plays a different role depending on the cell stress magnitude:

- Absence/low stress: p53 upregulates antioxidant genes → ROS decrease
- Mild stress: p53 activates AMPK → mTOR inhibition → Longevity
- High stress: p53 inhibits PCG-1α causing mitochondrial dysfunction and a "**vicious cycle**" of more DNA damage and further mitochondrial impairment.



Conclusions

Not only mitochondria participate in aging

- There is **not a single gene or pathway** that carries the whole load of longevity.
- Not only mtDNA-encoded proteins affect longevity. **Nuclear-encoded proteins are very related to aging** process, having repercussions in mitochondrial functionality and affecting longevity.
- Apart of genetic components many **external factors** are closely related to extended lifespan, such as caloric restriction, exercise, and mTOR inhibitors (as rapamycin) .

ROS and aging

- Low **ROS levels** can act as an aging promoter factor while mild levels can repress the aging process.
- **MFRTA looses support** since ROS not always lead to tissue dysfunction, and are not the principal cause of aging as it was thought.

Limitations of current studies

- **Longevity is also not suffering diseases related to aging**, which may be triggered by genetic factors, not taken into account when studying centenarians nor mtDNA variants. Cancer-protecting pathways should also be considered as longevity pathways since cancer is considered an aging-related disease.
- Current studies are done with small **model animals**, such as mice, that are distant to human and can lead to rushed conclusions.
- Future studies should focus on "**healthy aging**".

Bibliography:

- Altilia, S. *et al.* TP53 codon 72 polymorphism affects accumulation of mtDNA damage in human cells. *Aging (Albany. NY).* 4, 28–39 (2012).
- Groenewoud, M. J. & Zwartkruis, F. J. T. Rheb and mammalian target of rapamycin in mitochondrial homoeostasis. *Open Biol.* 3, 130185 (2013).
- Trifunovic, A. et al. Premature ageing in mice expressing defective mitochondrial DNA polymerase. *Nature* 429, 417–423 (2004).
- Sahin, E. & DePinho, R. Axis of ageing: telomeres, p53 and mitochondria. *Nat. Rev. Mol. Cell Biol.* 13, 397–404 (2012).