MITOCHONDRIAL DYSFUNCTION AND LONGEVITY

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Introduction

Mitochondria are double membrane organelles found in nearly all eukaryotic cells with their own DNA (mtDNA). Their most important function is to generate ATP via aerobic respiration, but they are also essential in many other signalling pathways.

In 1995, a *Caenorhabditis elegans* mutant with dysfunctional mitochondria displayed longer lifespan than wild-type worms. Long-lived *C. elegans* where later called "Mit mutants" and have been the focus of recent research.

Many different groups have since then reported that mild mitochondrial distress relates to salutary effects and extended lifespan, from yeasts to mammals.

Materials and methods

Search on most common scientific data bases: consulted ISI WOK, Scope and Pubmed data bases. Key words: (("Mitochondria"[Mesh]) AND "Aging"[Mesh]) AND "Longevity"[Mesh]

The mit mutant phenotype in *C. elegans*

- **Longer** livespan and increased longevity
- **Delayed** embryonic and larval development
- **Small** adult size
- **Slow** muscle function
- **Reduced** fertility and fecundity

Mechanisms involved in Mit mutant phenotype

Mitochondrial Unfolded Protein Response (UPR^{mt})

The UPR^{mt} is a mechanism by which the cell reacts to the accumulation of unfolded or misfolded proteins within the mitochondrial matrix through the expression of mitochondrial chaperone genes. It is activated in most Mit mutants but excessive protein import deficiency generates Reactive Oxygen Species (ROS) and triggers autophagy or even apoptosis.

Cell monitors mitochondrial protein import efficiency thought the import a key protein, Activating Transcription Factor associated with Stress-1 (ATFS-1).

- **Normal protein import:** ATFS-1 is imported to mitochondria and degraded by Lon protease
- **Compromised protein import:** ATFS-1 accumulates on cytosol, enters the nucleus and triggers the UPR^{mt}

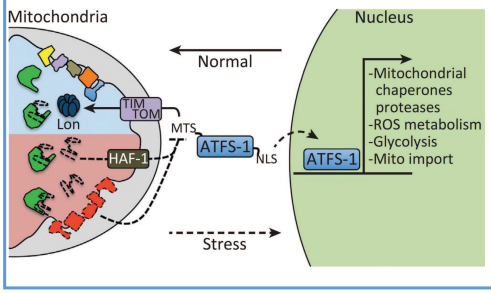


Figure 1. **UPR^{mt} response.** Abreviations: TIM, Translocase of the Inner Membrane; TOM, Translocase of the Outer Membrane; MTS, Mitochondrial Targeting Sequence; NLS, Nuclear Localization Sequence; ATFS-1, Activating Transcription Factor associated with Stress-1. Adapted from Haynes *et al. 2013*

Reactive Oxygen Species (ROS) signalling

ROS signalling defines the mechanism by which the cell reacts to free radicals caused mostly by aerobic respiration.

The **mitohormesis hypothesis** claims that low levels of ROS in fact play an active role in longevity by triggering signalling cascades that are protective to the cell. Possible mechanisms:

- **General Control Non-depressible 2 (GCN2).** Inhibits protein translation. Reported as activated on Mit Mutants.
- **Hypoxia Inducing Factor-1 (HIF-1).** Protects cell agains hypoxic conditions. Its absence abrogates life extension in several Mit Mutants

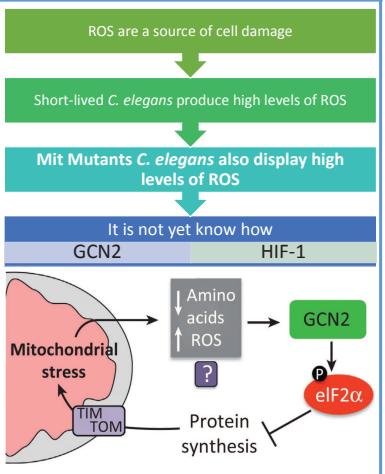
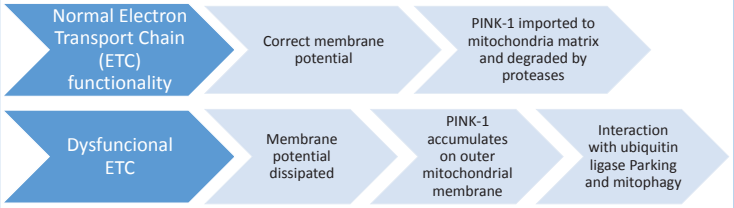


Figure 2. **GCN2 response.** Abreviations: TIM, Translocase of the Inner Membrane; TOM, Translocase of the Outer Membrane; ROS, Reactive Oxygen Species; GCN2, General Control Non-depressible 2. Adapted from Haynes *et al. 2013*

Mitochondrial autophagy (Mitophagy)

Autophagy is a conserved degradation process by which intracellular components, from soluble macromolecules to dysfunctional organelles, are degraded by the lysosome. Mitophagy, selectively targets crippled mitochondria for its degradation. Overexpression of its main regulator, Transcription Factor HLH-30, increases lifespan of wild-type worms.

Cell monitors Mitochondrial membrane potential by PINK-1, a protein similar in functionality to ATFS-1.



Conclusions

Many isolated mechanism explain part of the Mit mutant phenotype. All of them have unanswered questions, and none of them explain all Mit mutant traits. However, It seems to be clear that a narrow equilibrium between the benefits of every mechanism and the potential damage they can do exists.

There is a need for a unified system and hypothesis that tries to converge all these mechanisms, but until all questions and mechanisms are correctly described and answered, it is an incredibly difficult task to perform. Still, although we are still at the beginning of the research, the potential to explain many human mitochondrial related diseases and how aging works in organisms lies here.

Bibliography

Only relevant references are cited below. A detailed references list is available upon request for the committee:

1. Haynes, C. M., Fiorese, C. J. & Lin, Y.-F. Evaluating and responding to mitochondrial dysfunction: the mitochondrial unfolded-protein response and beyond. *Trends Cell Biol.* **23,** 311–8 (2013).
2. Munkácsy, E. & Rea, S. L. The paradox of mitochondrial dysfunction and extended longevity. *Exp. Gerontol.* (2014). doi:10.1016/j.exger.2014.03.016
3. Lionaki, E., Markaki, M. & Tavernarakis, N. Autophagy and ageing: insights from invertebrate model organisms. *Ageing Res. Rev.* **12,** 413–28 (2013).