THE ROLE OF MITOCHONDRIAL DNA IN HUMAN AGING

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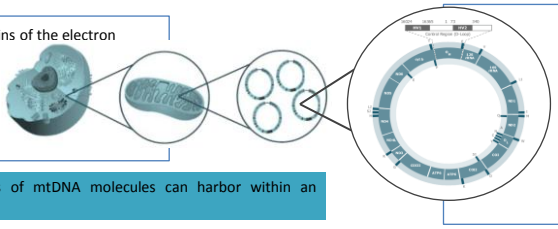
INTRODUCTION

Human mitochondrial DNA (mtDNA) is a small, circular and double-stranded molecule present in several copies in our mitochondria. Mitochondrial genome damages are involved in several mitochondrial pathologies and diseases. Deleterious mtDNA somatic mutations accumulate throughout our life in our post-mitotic tissues. Point mutations and deletions generally strike only a fraction of the mitochondrial genomes of an individual, leading to the coexistence in cells and tissues of two mtDNA populations, wild-type and mutant. This condition is called heteroplasmy and can be both inherited from our mothers or somatic. Only when the mutated genomes reach a critical threshold over the normal genomes then physiological effects arise. Although the relation between mtDNA mutations and aging is well-know, there is still a lack of knowledge about the effects of mutations at a molecular level.

HUMAN MITOCHONDRIAL GENOME

- 16569 bp, encodes for 13 proteins of the electron transport chain
- Maternal inheritance
- Lack of recombination
- High number of copies per cell
- High mutation rate



- **Heteroplasmy:** Different types of mtDNA molecules can harbor within an individual, among tissues and cells

AGING

- Accumulation of impairment of tissue function over time, leading to growing risk of disease and death.
- Age-associated diseases (type II diabetes, cardiovascular diseases, hypertension) and neurodegenerative diseases (Alzheimer's Disease; Parkinson's Disease) tend to increase significantly in elderly.
- Theories of aging

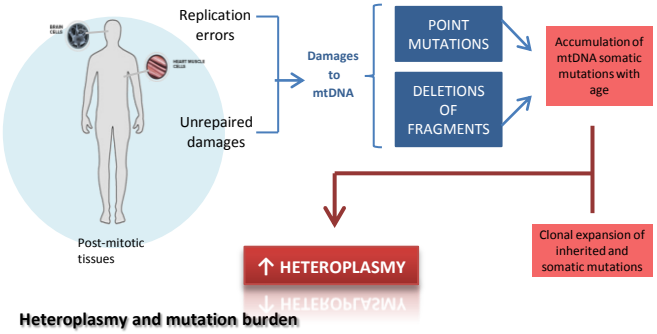
FREE RADICAL THEORY → MITOCHONDRIAL THEORY → DISPONSABLE SOMA THEORY

Stochastic | Evolutionary

AGING and mtDNA

Somatic mutations

During a person's life the mitochondrial polymerase (mtDNA Pol γ) generate errors that lead to point mutations (changes in one NT) and deletions of large fragments of mtDNA. These mutations occurs more frequently in the control region (D-loop) where the hyper variable regions are located. Point mutations and deletions are tissue specific; the mutation rate is higher in post-mitotic tissues than in proliferative tissues.



Heteroplasmy and mutation burden

The heteroplasmy is the coexistence of mutated and wild-type copies within cells and tissues. This condition is universally spread and, usually, in low levels which don't lead to any physiological effect. With the pass of the years heteroplasmy frequency of mutated copies become higher in our cells.

SOMATIC HETEROPLASMY ⟷ INHERITED HETEROPLASMY

Mitochondrial heteroplasmy across the genome increase significantly with advanced age in 75 % of 138 SNPs analyzed in the mitochondrial genome of human tissues.

Maternally transmitted mtDNA mutations lead to premature aging phenotypes in mtDNA mutator mouse PolgA $^{mut/mut}$.

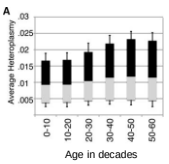


Figure 1. Increase in heteroplasmy across the mitochondrial genome with age. Sondeherimer et al., 2011.

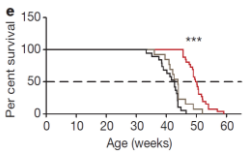


Figure 2. Lifespan of PolgA mut/mut mice (black line) is shorter that mice after re-introduction of wild-type mtDNA into females (red line). Ross et al., 2013.

Effects of mtDNA mutations in aging

Over a threshold level of heteroplasmy (60 % for deletions and 80-90 % for point mutations) these damages can lead to impairment of the respiratory chain function and, subsequently, to physiological effects related to aging.

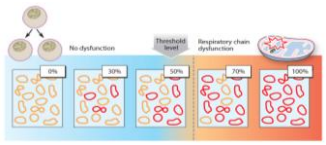


Figure 3. The segregation by clonal expansion of the mutations in mtDNA of post-mitotic cells. After the threshold level of the mutated copies (red circles) it will cause respiratory chain dysfunction. Larsson, 2010.

RESPIRATORY CHAIN DYSFUNCTION → Mosaic organism

Only few cell within a tissue will arise the threshold level, leading to mosaic tissues that harbor `wild-type´ and `respiratory chain deficient´ cells. This condition has been reported for heart, skeletal muscle, hippocampal neurons, dopaminergic neurons and colon, among others.

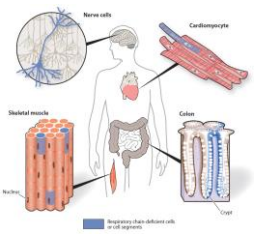


Figure 4. Mosaic respiratory deficiency in human aging. Larsson, 2010.

Physiological consequences

- ↓ Mitochondrial energy production (ATP generation, NAD/NADH balance,...)
- ↑ Apoptosis; Histocompatibility antigens

→ AGING AND AGE-RELATED DISEASES
→ NEURODEGENERATIVE DISEASES

LONGEVITY VARIANTS

- Beneficial D-loop mutations
- Inherited and somatically acquired
- Transition C150T
  - Changes replication origin from 149 to 151
  - Population specific: North Italian and Finnish populations
  - Increase heteroplasmy frequency in very elder people

CONCLUSIONS

✓ Inherited and somatic mtDNA mutations in heteroplasmy are related to aging in human. Errors are mediated by Pol γ, and accumulate with years in the mtDNA leading to point mutations and deletions.

✓ Heteroplasmy frequency can increase with aging by mechanism of clonal expansion. The heteroplasmy pattern observed is a combination of both inherited and somatic mutations.

✓Over a certain threshold of heteroplasmy, mtDNA mutations lead to impairment of the respiratory chain function and have consequences in the aging process.

✓ Longevity variants (C150T transition) have been reported for Italian and Finnish long-living populations. These studies show the involvement of inherited and somatic mutations play a role in longevity.

✓Further studies are necessary for a clear comprehension of the molecular and cellular processes of aging involving mtDNA mutations.

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