“Survival of the Shortest” - Evidence for the selection advantage of mtDNA deletion mutations

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1. Introduction

Figure 1 – Electron micrograph of a human mitochondrion

Mitochondria (*left*) are eukaryotic organelles which possess multiple copies of their own genome (mtDNA), and contribute to the ageing process.

Previous studies have demonstrated that aged cells often contain only a single type of clonally expanded mtDNA deletion mutant (Figure 2), which has replaced all other wildtype (WT) molecules; this is known as homoplasmy.

The Free Radical Theory of Ageing is the most widely accepted model of why we age; yet it is unable to explain the clonal expansion of mtDNA deletions.

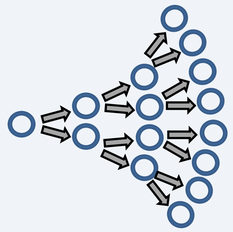

Figure 2 – Clonal expansion of a single mtDNA molecule

Aim: to establish whether the shorter size and faster replication of mtDNA deletion mutations is the underlying mechanism causing clonal expansion.

2. Methods

A computational model was developed to stochastically simulate various aspects of the mitochondrial life cycle (Figure 2).

We investigated whether clonal expansion is affected by the following parameters:

- WT/mutant population size
- Deletion size
- Replication time
- Half life

The probability of the mutant outcompeting the WT (P_{Win}) and the *in silico* time required for homoplasmy to occur (T_{Win}) was measured.

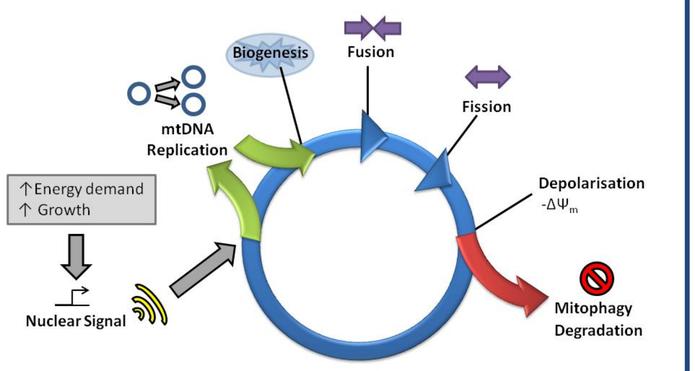

Figure 2 – The mitochondrial life cycle comprises multiple rounds of fusion followed by fission. mtDNAs inside segregated mitochondrial fragments with reduced membrane potential may be degraded by mitophagy. Increases in cellular energy demand activate nuclear genes which trigger mtDNA replication.

3. Results

- Multiple simulations were performed for all parameter combinations, and the relative influence of each system parameter is shown in Figure 3.
- mtDNA replication time and half life have no effect on P_{Win}, however **shorter** mtDNA deletion mutants have a significant advantage over longer WT molecules.

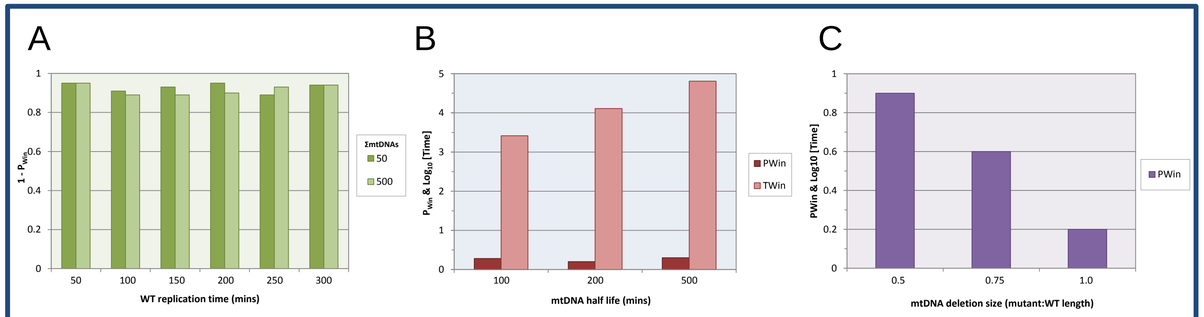

Figure 3 – Only mtDNA deletion size significantly influences the probability of the mutant outcompeting the WT (P_{Win}), however all parameters affect the time taken for homoplasmy to occur (T_{Win}). A) WT mtDNA replication time, mtDNA population size [50 or 500] and B) mtDNA half life have no effect on P_{Win}, whilst C) smaller mtDNA deletion mutants have the greatest probability of outcompeting WT molecules.

4. Conclusions

- It was unclear from previous studies whether shorter length and faster replication are significant for selection as mtDNA replication time (1-2 hours) is so much less than mitochondrial half life (1-4 weeks). Here we show that the smaller size of mtDNA deletions provides the mechanism for clonal expansion to occur.
- This finding speaks in favour of a refinement of the Free Radical Theory of Ageing, and its viability for explaining fundamental contributions to the ageing process.
- mtDNA half life affects only the time taken for homoplasmy to occur, suggesting that differences in control of mtDNA degradation rate may explain variations in interspecies longevity, such as why humans live much longer than mice.