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Mitochondrial mutations and ageing: Can mitochondrial deletion mutants accumulate via a size based replication advantage?

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HIGHLIGHTS

- We modelled the accumulation of mitochondrial deletion mutants during ageing.
- Can the reduced size provide a selection advantage via a shorter replication time?
- We developed a delay differential equation model and a stochastic simulation.
- The simulations show that the idea only works for very long lived species.

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ABSTRACT

The mitochondrial theory of ageing is one of the main contenders to explain the biochemical basis of the ageing process. An important line of support comes from the observation that mtDNA deletions accumulate over the life course in post-mitotic cells of many species. A single mutant expands clonally and finally replaces the wild-type population of a whole cell. One proposal to explain the driving force behind this accumulation states that the reduced size leads to a shorter replication time, which provides a selection advantage. However, this idea has been questioned on the grounds that the mitochondrial half-life is much longer than the replication time, so that the latter cannot be a rate limiting step. To clarify this question, we modelled this process mathematically and performed extensive deterministic and stochastic computer simulations to study the effects of replication time, mitochondrial half-life and deletion size. Our study shows that the shorter size does in principle provide a selection advantage, which can lead to an accumulation of the deletion mutant. However, this selection advantage diminishes the shorter is the replication time of wt mtDNA in relation to its half-life. Using generally accepted literature values, the resulting time frame for the accumulation of mutant mtDNAs is only compatible with the ageing process in very long lived species like humans, but could not reasonably explain ageing in short lived species like mice and rats.

1. Introduction

Ageing is an intrinsic deterioration of the homoeostatic capabilities of an organism, leading to a constantly increasing risk of death. Although evolutionary considerations suggest that the ageing process is in principle multifactorial (Kirkwood, 1996), a few main mechanisms have been proposed. Among these the mitochondrial theory of ageing is one of the most popular (Harman, 1972, 1983; Miquel et al., 1980; Richter, 1988; Linnane et al., 1989). The theory suggests that the accumulation of defective mitochondria is a major contributor to the ageing process. Reactive oxygen species (ROS) generated during respiration have the potential to damage all kinds of biologically relevant macromolecules such as lipids, proteins and mitochondrial DNA (mtDNA). Damage to mtDNA is quite different from damage to other macromolecules, since mitochondrial DNA represents the ultimate blueprint from which everything else follows. Point mutations and deletions could impair mitochondrial ATP production with negative consequences for all aspects of cellular homoeostasis. And indeed, many studies have shown that mitochondrial deletion mutants accumulate with age in various mammalian species such as rats, monkeys and humans (Brierley et al., 1998; Khrapko et al., 1999; Cao et al., 2001; Gokey et al., 2004; Herbst et al., 2007). These single cell studies have shown that the mitochondrial population of a cell is overtaken by a single deletion mutant type via clonal expansion.

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The mechanism behind the accumulation of defective mitochondria is obviously an important aspect of the theory, but is currently unknown. The "vicious cycle" hypothesis suggests that, because defective mitochondria generate more radicals than intact ones, the cellular radical level progressively rises, leading in turn to an increased production of mitochondrial mutants (Bandy and Davison, 1990; Arnheim and Cortopassi, 1992). In this scenario the individual mutant mitochondria do not need to have a selection advantage; they accumulate because they are constantly generated. However, such a mechanism also implies that one should see a plethora of different mtDNA mutants in a single cell, quite the contrary of what has been observed. It has also been proposed that pure random drift might be sufficient to explain clonal expansion (Chinnery and Samuels, 1999; Elson et al., 2001). Although these authors show that such a process might work for long lived species like humans, we have recently performed computer simulations, which demonstrate that such a process is unsuitable for short lived animals like rodents (Kowald and Kirkwood, 2013), which show a similar pattern of accumulation as in humans but on a twenty times accelerated timescale (Cao et al., 2001). An idea that does identify a selection advantage of deletion mutants is called survival of the slowest (SOS) (Grey, 1997). It notes that the fate of a mitochondrion depends not only on its growth rate, but also on its rate of degradation and proposes that defective mitochondria are degraded less frequently than wild-type organelles. However, this hypothesis has problems with mitochondrial dynamics, since fission and fusion break the required link between genotype and phenotype (Kowald and Kirkwood, 2011). Furthermore, it has been shown that dysfunctional mitochondria are preferentially degraded (Twig et al., 2008; Kim and Lemasters, 2011), instead of being spared.

Finally, it has been proposed that the selection advantage simply stems from the reduced genome size of the deletion mutant (Wallace, 1992; Lee et al., 1998). Deletions encompassing more than half of the mitochondrial genome have been observed (Cao et al., 2001), which could result in a 50% reduced replication time. However, this idea has been criticised because early studies have shown that the time required for the replication of the mtDNA is only 1–2 h (Berk and Clayton, 1974; Clayton, 1982), while the half-life of mtDNA is in the order of 1–3 weeks (Gross et al., 1969; Huemer et al., 1971; Korr et al., 1998). Therefore it has been argued that it is difficult to see how mtDNA replication could be a rate limiting step for mitochondrial growth (Grey, 1999; Elson et al., 2001).

To put these verbal arguments on more solid grounds we developed in this study a detailed mathematical model that describes the fate of a population of wild-type and mutant mtDNA molecules that undergo replication and degradation. Using delay differential equations as well as stochastic simulations we studied the effects of replication time, mitochondrial half-life and deletion size on the outcome of the competition between mutant and wild-type. In recent years it became clear that mitochondria undergo a constant and rapid process of fusion and fission (Duvezin-Caubet et al., 2006; Twig et al., 2008), the evolutionary and functional significance of which we have considered elsewhere (Kowald and Kirkwood, 2011). As a consequence all mtDNAs, wild-type and mutant, effectively exist in a single common mitochondrial compartment. The competing entities are therefore not complete organelles, but individual mtDNA molecules. Our simulations reflect this situation.

2. Model development

Although a reduced size has often been proposed as giving a selection advantage to deleted mtDNAs, the exact molecular mechanism has never been spelled out explicitly. Fig. 1 shows the mechanism that we propose and which we used as the basis to develop the mathematical model. The idea is that mtDNAs can be in a "free", non-replicating, state or in a "busy", replicating, state. We assume that only mtDNAs from the "free" pool can respond to a replication signal, begin replication, and thus enter the "busy" pool. The replicating molecule remains in the busy state for a certain time, Δt, after which replication is finished and two molecules are returned into the free pool. Wild-type and mutant mtDNAs in the free pool have equal probabilities to respond to a replication signal, but deletion mutants will spend a shorter time in the busy pool and return earlier into the free pool than wild-type molecules. This should result in an overall selection advantage, leading to the accumulation of deleted mtDNAs. In our simulation study all types of mtDNAs (wild type, mutant, busy and free) are degraded at the same rate, leading to an identical half-life for wild type and mutant. Replication and degradation together also ensure that the population of mtDNA molecules reaches a stable steady state.

The system contains four variables:

$\mathbf{wt_F}$: number of wild type mtDNAs in the free pool.
$\mathbf{wt_B}$: number of wild type mtDNAs in the busy pool.
$\mathbf{mt_F}$: number of mutant mtDNAs in the free pool.
$\mathbf{mt_B}$: number of mutant mtDNAs in the busy pool.

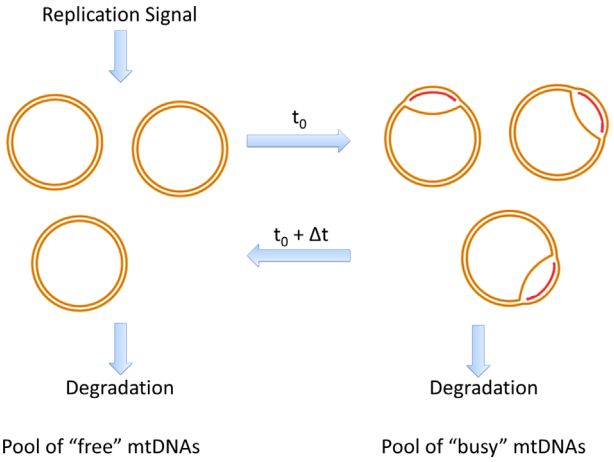

Fig. 1. Model overview. The system consists of a pool of free mtDNAs that can respond to a replication signal and from which a mtDNA molecule can enter the busy state in which replication takes place. After a certain replication time, Δt, two mtDNA molecules return into the free pool. All mtDNAs are degraded at the same rate, resulting in the same half-life for wild type and mutant forms.