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REVIEW

Role of Mitochondrial DNA in Yeast Replicative Aging

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Abstract—Despite the diverse manifestations of aging across different species, some common aging features and underlying mechanisms are shared. In particular, mitochondria appear to be among the most vulnerable systems in both metazoa and fungi. In this review, we discuss how mitochondrial dysfunction is related to replicative aging in the simplest eukaryotic model, the baker's yeast *Saccharomyces cerevisiae*. We discuss a chain of events that starts from asymmetric distribution of mitochondria between mother and daughter cells. With age, yeast mother cells start to experience a decrease in mitochondrial transmembrane potential and, consequently, a decrease in mitochondrial protein import efficiency. This induces mitochondrial protein precursors in the cytoplasm, the loss of mitochondrial DNA (mtDNA), and at the later stages – cell death. Interestingly, yeast strains without mtDNA can have either increased or decreased lifespan compared to the parental strains with mtDNA. The direction of the effect depends on their ability to activate compensatory mechanisms preventing or mitigating negative consequences of mitochondrial dysfunction. The central role of mitochondria in yeast aging and death indicates that it is one of the most complex and, therefore, deregulation-prone systems in eukaryotic cells.

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INTRODUCTION

Aging is the process characterized by a decrease in fertility and an increase in mortality over time [1], a phenomenon that inevitably emerges in the process of living systems evolution. This is attributed to the fact that natural selection diminishes in the post-production period, as it primarily affects genes and traits associated with reproduction. Consequently, as an organism generates more offspring, the impact of natural selection on traits (and the corresponding genes) that emerge after reproduction begins to wane [2, 3]. This is applicable to microorganisms as well, including bacteria and unicellular fungi. Bacterial and yeast species that divide asymmetrically – those that produce a mother cell and a daughter cell of differing sizes – usually exhibit aging [4-7].

The baker's yeast, *Saccharomyces cerevisiae*, is the most extensively studied unicellular organism where aging has been described [8-10]. Investigations into yeast aging mechanisms have expanded our understanding of the fundamental principles of aging. Moreover, yeast aging studies have facilitated the identification of targetable systems that, upon intervention, can lead to lifespan extension. A significant advantage of baker's yeast over other model organisms is the high proliferation rate of yeast cells. Additionally, it is relatively easy to produce genetically stable mutant yeast cell lines, which are instrumental in identifying gene and protein functions [11]. Presently, several collections of yeast mutant strains are available, these collections have been utilized to conduct genetic screenings aimed at discovering longevity genes [12, 13]. For example, caloric restriction dietary mimetics, including resveratrol, were identified using the yeast aging model [14]. The efficacy of these mimetics was later confirmed in animal studies [15]. A screening of mutations altering *S. cerevisiae* lifespan revealed 238 genes whose deletion increases it [16]. These genes comprised orthologs of genes whose mu-

Abbreviations: ERC, extrachromosomal rDNA circle; mtDNA, mitochondrial DNA; OxPhos, oxidative phosphorylation; RLS, replicative lifespan.

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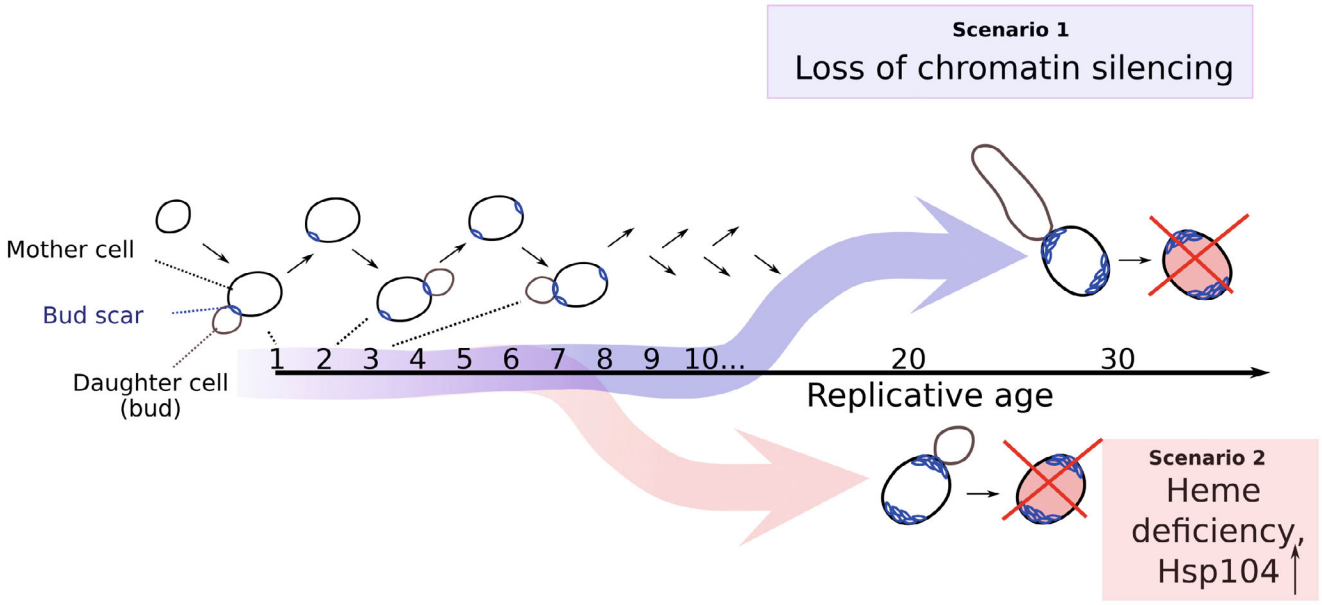

Fig. 1. Two scenarios of replicative aging in yeast. Approximate replicative ages are based on the literature cited in the text.

tations altered the lifespan of the nematodes *Caenorhabditis elegans* [16]. The results of this screening were enriched with genes encoding tricarboxylic acid cycle enzymes and proteins required for mitochondrial protein translation, including mitochondrial ribosome protein components [16]. In a separate study, the authors demonstrated that deleting yeast orthologs of nematode aging genes increased, rather than decreased, the lifespan of yeast [17]. Taken together, these results suggest a conservation of aging mechanisms among eukaryotes.

The aging process of baker's yeast *S. cerevisiae* is typically defined not by chronological time but by the number of daughter cells a mother cell generates. Therefore, it is usually referred to as replicative aging [18] (Fig. 1). Accordingly, the number of daughter cells that a mother cell can produce before its death is termed the "replicative lifespan" (RLS). A single yeast mother cell can only generate a limited number of daughter cells, usually ranging between 15 and 25 [19]. Meanwhile, the first aging manifestation in the yeast mother cell, such as changes in the expression of stress response genes, occurs after the formation of the first few buds [20].

As yeast cells age, they undergo deregulation in gene expression and protein biogenesis. This process results in disproportion of subunits in protein complexes, such as vacuolar ATPase, in replicatively old yeast cells [21]. In recent years, advancements in microfluidics techniques have facilitated the examination of replicative aging at the individual cell level [22, 23]. The aging trajectory of each individual cell is predetermined during the initial cell cycles, leading to one of two scenarios. Though both scenarios inevitably result in cell death, the causes of cell viability loss differ between them [24].

The first scenario is characterized by the loss of chromatin silencing. This is evidenced by the elevated expression of *rDNA-GFP*, a *GFP* gene integrated into the non-transcribed rRNA spacer region. Yeast cells aging through this first scenario maintain a relatively consistent cell cycle duration throughout their lifetime up to their late life. However, during the last few cell cycles, which precedes death, such yeast cells form elongated daughter cells, as depicted in Fig. 1.

The second scenario correlates with an increased cell cycle length during early life stages and the production of rounded daughter cells. Moreover, in yeast cells aged under the second scenario, a deficiency of heme is observed [25]. Given that the final stages of heme synthesis occur within mitochondria, and a lack of heme leads to mitochondrial dysfunction [26], the aging via this scenario is linked to mitochondrial dysfunction. The death of yeast cells is preceded by a decrease in Leu4-GFP levels. Leu4p, or alpha-isopropylmalate synthase, is a crucial part of the leucine biosynthesis pathway; hence, a reduction in Leu4p triggers leucine deficiency in older cells. The second aging scenario is linked to increased expression of *HSP104*, a gene that encodes the cytosolic heat shock protein, Hsp104p [27]. Hsp104p binds and temporarily stores mitochondrial protein precursors in the cytoplasm [28], whereas increased concentration of Hsp104p is a hallmark of the accumulation of unfolded proteins [29]. Recently, the information about the described above scenarios inspired the creation of a genetic oscillator designed to make yeast cells alternate between these two aging trajectories, thereby boosting their lifespan by 82% [30].

Replicative aging in yeast can be considered as a deterministic developmental program that progresses

along one of at least two possible trajectories (Fig. 1). Deregulation of certain cellular systems restrict yeast lifespan while concurrently the same systems contribute to the longevity of multicellular organisms [17]. One of these yeast aging trajectories is likely associated with mitochondrial dysfunction. In this review, we discuss the causal relationship between mitochondrial dysfunction and other replicative aging manifestations in yeast.

MITOCHONDRIAL DYSFUNCTION IN YEAST REPLICATIVE AGING

The division of baker's yeast cells is highly asymmetrical, resulting in mother and daughter cells of differing sizes and varying concentrations of certain proteins [31]. This protein content asymmetry is primarily due to diffusion limitations, which restrict the transport of large cellular structures, such as large protein aggregates and the organelles harboring them, between the cells [32]. Moreover, the protein aggregates and cell organelles are actively transported and can be selectively anchored in either the mother or daughter cell cortex [33, 34]. The transport of mitochondria from mother to daughter cells is facilitated by the actin cytoskeleton and the myosin protein, Myo2p [35]. These cytoskeleton components anchor the mitochondria with the mean of mitochondrial outer membrane protein, Mmr1p [36]. Concurrently, the Num1p and Mfb1p proteins ensure that a portion of the mitochondria remain at the pole of the mother cell [37, 38]. This active transport and selective retention of mitochondria make it possible to distribute them between the mother and daughter cells. This process primarily sends the most functional mitochondria to the daughter cell, while ensuring that the mother cell retains a portion of functional mitochondria, along with the damaged ones [39].

The asymmetric distribution of mitochondria between mother and daughter cells results in accumulation of mitochondria with oxidized matrix molecules in the mother cell compared to the mitochondria passed on to the daughter cell. This is evidenced by the redox-sensitive fluorescent proteins targeted towards the mitochondrial matrix [40, 41]. If the mitochondria are heterogeneous, the daughter cell is more likely to inherit functional mitochondria, while the mother cell retains the non-functional ones [39]. However, the mechanisms behind the selectivity of mitochondrial anchoring and transport remain unclear.

Mitochondrial dysfunction begins to manifest in the mother cell after several consecutive rounds of asymmetrical divisions. Specifically, during the first ten cell cycles, transmembrane potential of the mother cell mitochondria decreases [42], and the mitochondrial network collapses [42, 43]. Factors such as protonophores [44] and oxidative stress [45, 46] can induce mitochondrial fragmentation. This leads to the assumption that age-related mitochondrial fragmentation is induced by age-dependent mitochondrial depolarization. Studies have shown that the deletion of *DNM1*, a gene that encodes the Dnm1p protein, which mediates mitochondrial fission, extends the replicative lifespan of yeast [47]. Thus, it can be concluded that mitochondrial fragmentation plays a causative role in detrimental processes in aging cells, and it cannot be considered as a mere side effect of the depolarization.

Furthermore, the age-dependent decrease in mitochondrial transmembrane potential ($\Delta\Psi$) contributes to a diminished efficiency of protein import into mitochondria [48]. While protein import through the outer membrane does not depend on the $\Delta\Psi$, protein translocation through the inner membrane stops when $\Delta\Psi$ is dissipated [48].

The inhibition of protein import into mitochondria has two unfavorable outcomes for the cell. Firstly, it can cause a deficiency in proteins vital for mitochondrial DNA (mtDNA) replication, as well as mitochondrial transcription and translation. It is noteworthy that yeast aging correlates with a drop in Mip1p levels, a mitochondrial DNA polymerase, an enzyme indispensable for mtDNA replication [49]. Interestingly, increased expression of the *TOM70* gene, encoding a component of the translocase of the outer mitochondrial membrane (TOM) complex, may partially offset this effect by activating protein import [49]. This finding suggests that compromised protein import is a contributing factor to replicative aging in yeast. Eventually, the inhibition of mitochondrial protein import culminates in the loss of mtDNA in replicatively aged cells [50] (Fig. 1).

Secondly, the inhibition of protein import into mitochondria results in the accumulation of the mitochondrial protein precursors in the cytoplasm. These precursors are known to be toxic to the cell. For example, the expression of "clogger" proteins, which block the mitochondrial protein import system, inhibits the growth of yeast cells [28]. Although *S. cerevisiae* cells can survive without mtDNA and oxidative phosphorylation (OxPhos) by relying on glycolysis, the deletion of TIM- (mitochondrial inner membrane translocase) or TOM-complex genes are usually lethal [51].

We propose that these two unfavorable phenomena – a reduction in the concentration of essential proteins in the mitochondria and proteotoxic stress induced by mitochondrial protein precursors in the cytosol – contribute to an extended cell cycle duration and, eventually, cell death. To our knowledge, there are no direct experimental assessments of the mitochondrial contribution to these two yeast aging scenarios. However, the second scenario is associated with mitochondrial network fragmentation [25] and a decrease in mitochondrial membrane potential, as evidenced by a reduction in DiOC6 staining of aging cells [27]. This implies that

mitochondrial dysfunction is more likely associated with the second scenario.

BIDIRECTIONAL EFFECT OF MITOCHONDRIAL DNA DEPLETION ON YEAST REPLICATIVE LIFESPAN

The mitochondrion, a semi-autonomous cellular organelle found in most eukaryotic species, retains its own DNA. This DNA encodes components of mitochondrial translation systems, as well as some respiratory chain proteins [52]. Therefore, mutations in mtDNA or its complete disappearance (denoted as *rho*^{0}) result in the loss of mitochondrial capacity to perform OxPhos.

In certain laboratory strains, such as *YPK9*, the elimination of mitochondrial DNA (*rho*^{0} mutation) triggers an increase in RLS [53-57]. However, this effect is not universal; in some strains, the *rho*^{0} mutations have the opposite effect [58], or no effect [53]. An example of this can be observed in the *W303-1A* strain, which is frequently used for studying OxPhos in yeast [53]. Furthermore, removal of mtDNA in strains based on *BY4742* – the genetic background for yeast mutant collections – does not induce an increase in RLS [59, 60].

We propose that the contrasting effects of the *rho*^{0} mutation can be attributed to the varying responses of different strains to mitochondrial dysfunction [53]. The complete depletion of mitochondrial DNA in yeasts alters both gene expression levels and protein concentrations [61-63]. Notably, *rho*^{0} mutation activates retrograde signaling cascade, which in turn activates genes that encode glycolysis and the glyoxylate cycle enzymes [61, 64]. This process enables cells to adapt their metabolic functions to conditions where OxPhos is unfeasible and reactions linked to respiration, such as succinate oxidation, are blocked.

At the same time, laboratory strains can react differently to the loss of mtDNA. For instance, the *W303-1A* strain, following the complete depletion of mtDNA, does not increase the expression of the *CIT2* gene, encoding citrate-synthase localized in peroxisomes [65]. Conversely, *YPK9 rho*^{0} cells, which exhibit a high RLS, upregulate this gene [53]. Furthermore, different laboratory strains can vary in rDNA array length [66], which is positively correlated with yeast RLS [67]. This correlation is attributed to the regulation of the histone deacetylase gene *SIR2*. Sir2p limits the formation of extrachromosomal rDNA circles (ERCs), identified as one of the factors contributing to aging. Concurrently, upstream activation factors (UAFs) bind to chromosomal rDNA and, when not bound, inhibit Sir2p. As a result, strains with a shorter rDNA array length possess a higher number of free UAFs, which inhibit Sir2p, induce ERC formation. ERCs accumulate in older cells, disrupting chromatin silencing and increasing the probability of cell death with age, leading to decreased RLS [67].

We suggest that the lifespan of yeast strains with shorter rDNA array lengths is primarily constrained by the activity of *SIR2*, the formation of ERCs, and the prevalence of aging through the second scenario. Therefore, mitochondrial dysfunction does not pose a limitation to the RLS in these strains. Conversely, in strains with a longer rDNA array, aging predominantly proceeds via the second scenario, which is linked to mitochondrial function. In this context, mitochondrial dysfunction accelerates the aging process and shortens RLS.

The strains' variability in the consequences of mtDNA depletion could also be explained by the dynamics of the cell adaptation to mtDNA loss, a process requiring tenth of generations [68]. Notably, newly formed *rho*^{0} cells exhibit a reduced lifespan, while adapted to the absence of mtDNA *rho*^{0} cells demonstrate an extended lifespan in comparison to the parental strain [68]. It could be hypothesized that this adaptation process unfolds at different speeds and follows distinct pathways in various laboratory strains. This, in turn, contributes to the observed variability in the impact of the *rho*^{0} mutation on RLS.

The loss of mtDNA could have differential effects on the two aging scenarios previously outlined. While it may accelerate aging in one scenario, it could potentially inhibit the aging process in the other. For instance, in the context of the second scenario, the *rho*^{0} mutation could help yeast cells in pre-adapting to the detrimental processes of aging, such as disruption of heme biogenesis. The variable proportions of cells in laboratory strains, which are presumed to age following one scenario or another, may contribute to the uncertainty regarding the effect of mtDNA loss on RLS.

THE ROLE OF NUCLEAR-ENCODED MITOCHONDRIAL PROTEINS IN YEAST REPLICATIVE LONGEVITY

The yeast mitochondrial proteome comprises ~900 proteins, the vast majority of these proteins are encoded within the nucleus and are imported into the mitochondria from the cytoplasm [69]. Therefore, mitochondrial dysfunction can arise not only from the loss of mtDNA but also from the inactivation of nuclear genes that encode these proteins. In a study involving whole-genome sequencing of an entire yeast knockout collection, it was revealed that the deletion of 129 out of roughly 5000 nonessential genes leads to the loss of mtDNA [70]. Intriguingly, several of these genes were also identified in a screen designed to uncover genes whose deletion results in an increased RLS of yeast [16]. This overlap is not likely to be random and suggests an interconnection between mitochondrial DNA maintenance and RLS (Fig. 2).

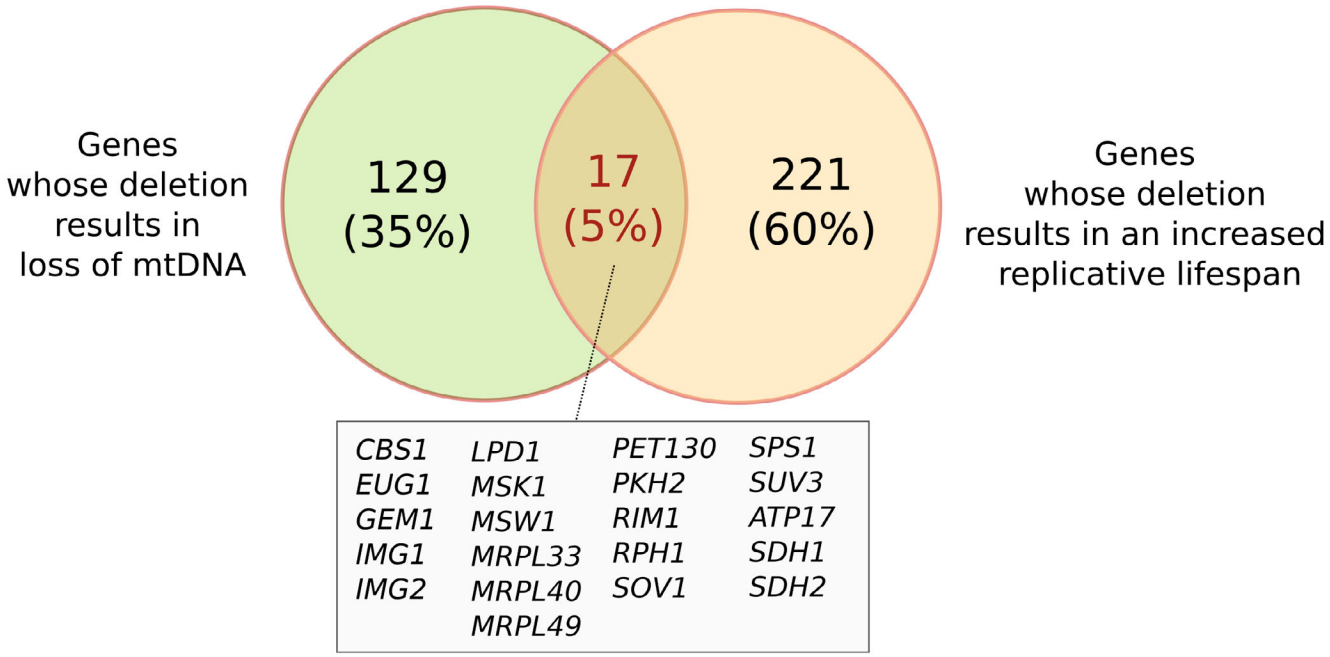

Fig. 2. The Venn diagram illustrates the intersection of two gene sets in yeast *S. cerevisiae*. One set includes genes whose deletion leads to mtDNA loss (Puddu et al. [70]), the other set comprises genes whose deletion results in an increased replicative lifespan (McCormick et al. [16]). The probability of a random overlap of 17 or more genes between these two samples is less than 0.1%.

However, it is important to note that not all genes, whose deletion results in mtDNA loss, necessarily lead to an increased lifespan. Among the genes encoding for mitochondrial proteins, whose deletion concurrently enhances yeast RLS, one category stands out: the genes encoding components of the mitochondrial ribosome. The Venn diagram depicted in Fig. 2 illustrates that the deletion of *MRPL33*, *MRPL40*, *MRPL49*, *IMG1*, and *IMG2* genes, which encode mitochondrial ribosomal proteins, leads to an increase in RLS. Furthermore, the deletion of another ribosomal protein gene, *MRPL25*, renders cell resistance to pro-oxidants and increases RLS, with the maximum lifespan of the deletion strain reaching 60 [71]. Additionally, the deletion of the *SOV1* gene, which is essential for mitochondrial ribosome assembly, has also been observed to increase yeast RLS [72].

The mitochondrial ribosome cannot be assembled irrespective of the reasons causing mtDNA loss because mtDNA encodes mitochondrial rRNA subunits [73], making it impossible for mitochondrial ribosomes to assemble in the absence of mtDNA. Thus, what makes protein components of mitochondrial ribosomes special remains uncertain. However, the import mechanism of mitochondrial ribosome proteins (MRPs) diverges from that of other mitochondrial proteins. A significant number of MRPs lack a distinctive mitochondrial address sequence, a phenomenon attributed to the conservative nature of their function, including the N-terminal region of these proteins [74]. Thus, deleting MRP genes could affect the mitochondrial import machinery in a unique way, distinct from the effect caused by the deletion of other mitochondrial proteins harboring a conventional N-end mitochondrial address. For instance, the deletion of MRP genes could potentially unburden a specific set of accessory TOM proteins. An alternative explanation for the unique phenotype associated with MRP deletion could be that the absence of rRNA in the mitochondria of *rho*^{0} cells can increase toxicity of some other MRP proteins, consequently accelerating the aging process in yeast mother cells. Caballero et al. suggested that the disappearance of certain mitochondrial translation machinery components could result in acquiring novel signaling functions by the remaining components. These functions could be related to chromatin silencing, potentially leading to an extended lifespan [72]. This hypothesis aligns with observations made regarding the Cbs2p protein, which possesses dual cytosol and mitochondrial localization. This protein appears to be essential for the life-extension effect of the mitochondrial translation activator gene, *CBS1*, deletion [72].

While the deletion of certain nuclear-encoded mitochondrial protein genes increases RLS, the deletion of some other genes substantially diminishes it. For instance, deleting the *MIP1* gene, which encodes mitochondrial DNA polymerase, results in a reduced yeast lifespan [72]. MtDNA replication is impossible without Mip1p. Similarly, a decrease in RLS is also noted upon the deletion of the *COX4*, *COX7* genes [72, 75], and cytochrome *c* heme lyase gene *CYC3* [76]. COX genes encode complex IV subunits of the respiratory chain. Their absence disrupts OxPhos, thereby rendering the utilization

of non-fermentable carbon sources impossible [77]. The deletion of *TOM70*, a gene that encodes a component of the TOM complex, reduces RLS [49]. Similarly, RLS is decreased upon the deletion of *PIM1*, a gene encoding mitochondrial matrix protease [78]. We propose that mitochondrial dysfunction may accelerate aging by inflating the number of cells that age by the second scenario. Meanwhile, the second scenario is characterized by a shortened yeast RLS, in comparison to the first scenario, which is associated with deregulation of chromatin silencing [25].

Mitochondrial dysfunction can be induced by mitochondrial inhibitors such as antimycin A or oligomycin D, as well as protonophores, which dissipate mitochondrial membrane potential. These interventions, similar to the *rho*^{0} mutation, exhibit bidirectional effects on RLS that can vary based on other factors [76, 79]. For instance, on the one hand, the "weak" protonophore dinitrophenol, when applied at a concentration of 5 mM, has been shown to slightly increase RLS [79]. This effect was likely mediated through the activation of the Rtg mitochondria-to-nucleus signaling pathway. Meanwhile, it has been shown that protonophores activate the *PDR5* gene, a known target of the Rtg pathway [80], and the Rtg pathway can trigger adaptive responses that extend the RLS of yeast [81].

On the other hand, the "strong" protonophore cyanide-p-trifluoromethoxy phenylhydrazone, FCCP, results in a significant decrease in RLS of *BY4741* cells [82]. How can protonophores contribute to this decrease in RLS? The diminished mitochondrial transmembrane potential, induced by protonophores, can exhibit selective toxicity towards cells with limited capacity to generate $\Delta\Psi$. Indeed, the protonophores are particularly toxic to *rho*^{0} cells, where the $\Delta\Psi$ is generated by the adenine nucleotide translocator, which appears to be not very effective [83, 84]. As the replicative age of a yeast cell advances, the likelihood of total loss of mtDNA and respiratory activity elevates. Therefore, high concentrations of protonophores might be selectively detrimental to older cells relative to younger ones, thereby reducing RLS [83, 84].

CONCLUSIONS

We hypothesize the following chain of events in aging yeast cells. The asymmetric distribution of mitochondria results in the accumulation of dysfunctional mitochondria in the mother cell. As a result, mitochondrial dysfunction emerges during the early stages of replicative aging. With age, the yeast cells experience a deficiency in nucleus-encoded mitochondrial proteins. This deficiency subsequently induces mutations or a complete loss of mtDNA. At the same time, toxic mitochondrial protein precursors are accumulated within the cytoplasm. Furthermore, as yeast cells age, they increasingly depend on oxidative metabolism, in contrast to younger cells that rely more heavily on glycolysis. Yeast replicative aging is associated with upregulated pentose phosphate pathway, tricarboxylic acid cycle and glycerol biosynthesis pathways, alongside with a decrease in cellular ATP concentration [85]. Thus, while mitochondrial dysfunction increases with age, the sequential metabolic adjustments in the cell render it increasingly reliant on OxPhos. This seeming paradox may contribute to a diminished growth rate of the old cells, ultimately leading to cell death.

The notion that mitochondrial dysfunction decreases viability of older cells implies that cells with initially compromised OxPhos may have a shortened lifespan. Furthermore, the way how yeast cells adapt to mitochondrial dysfunction, such as activating mitochondria-to-nucleus pathway targets, seems to be a crucial factor for yeast longevity. Taken together, the yeast aging model reveals a vulnerable system within eukaryotic cells, which appears susceptible to deregulation. This system, the coordination mechanism between the mitochondria and the nucleus, is an intricate machinery that has evolved over a billion years since the symbiogenesis of archaea and mitochondrial ancestors.

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