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The role of mitochondria in fungal aging

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Time-dependent impairments of mitochondrial function play a key role in biological aging. Work on fungal aging models has been instrumental in unraveling basic mechanisms leading to mitochondrial dysfunction and the identification of different pathways active in keeping mitochondria 'healthy' over time. Pathways including those involved in reactive oxygen scavenging, repair of damage, proteostasis, mitochondrial dynamics, and biogenesis, are interconnected and part of a complex quality control system. The individual components of this network are limited in capacity. However, if the capacity of one pathway is overwhelmed, another one may be activated. The mechanisms controlling the underlying cross-talk are poorly understood and subject of intensive investigation.

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Introduction

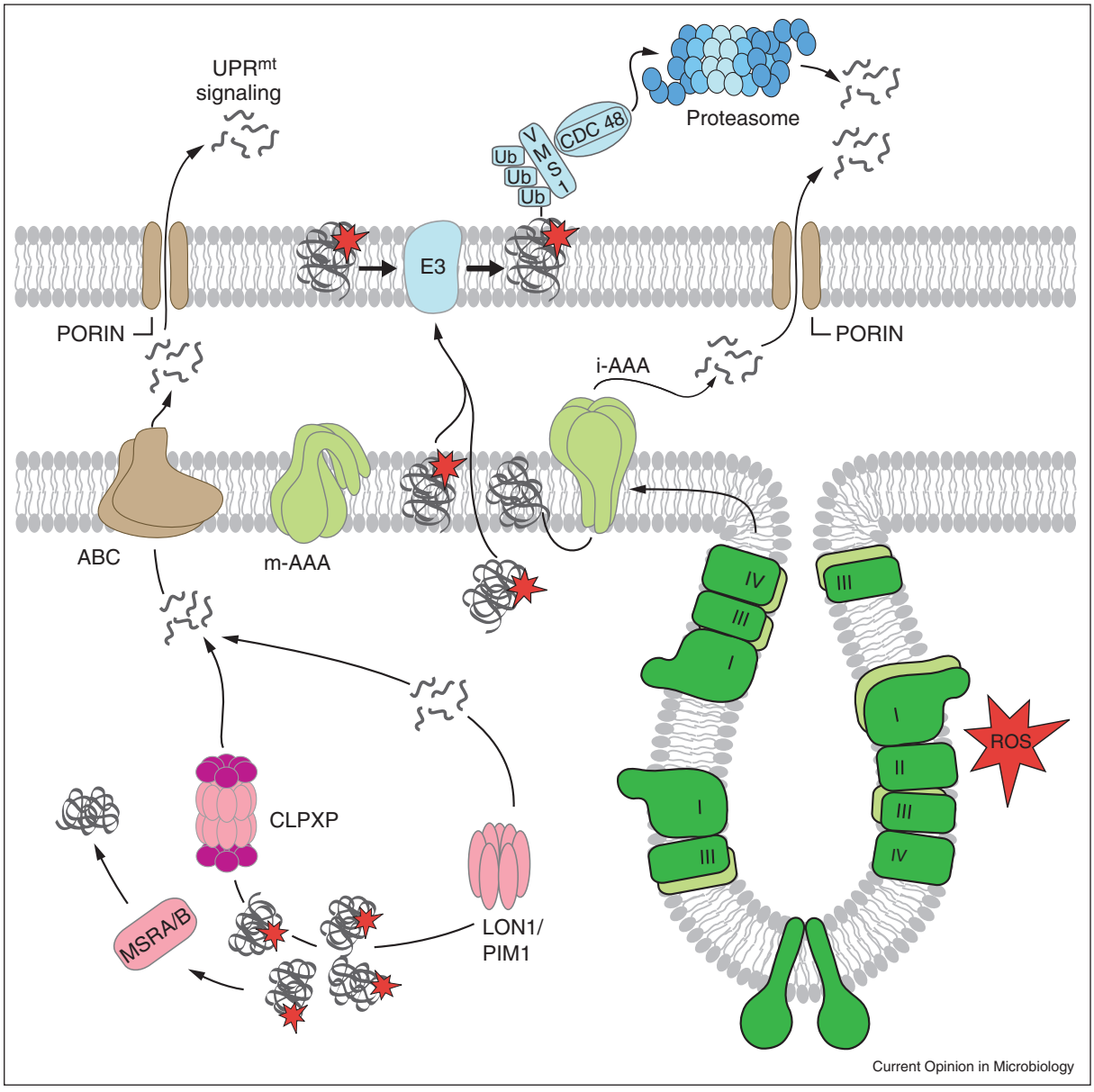
It is widely thought that fungi propagate indefinitely and may give rise to huge individual colonies, like it has been reported for a mycelium of *Armillaria bulbosa*, with an estimated weight of at least 10,000 kg and an age of approximately 1500 years [1]. This view is currently changing. More and more fungi with a limited vegetative growth have been described. Historically, the first description of limited fungal growth dates back to a study of George Rizet in the early 1950s [2]. He observed that, during vegetative growth, cultures of the filamentous ascomycete *Podospora anserina* show characteristic time-related changes which he collectively described as 'senescence syndrome'. Finally, the peripheral hyphae die. Only a few years later, another type of fungal aging was described by Mortimer and Johnston [3], the finite number of daughter cells an individual mother cell of *Saccharomyces cerevisiae* can generate. This number is now defined as the replicative lifespan and the process is termed replicative aging [4,5]. Subsequently, strains of the genus *Neurospora* and *Aspergillus* with a limited replicative capacity were described and analyzed (reviewed in [6]). More recent surveys identified rapid senescence to occur frequently in species of coprophilous Sordariomycetes [7]. Apart from replicative aging, another type of aging was identified and studied in yeast. This process, termed chronological aging, describes the period of time a non-dividing yeast cell can survive. Both processes are controlled by common but also different traits and pathways.

Here we specifically focus on replicative aging (also referred to as 'proliferative' or 'mitotic' aging). Our emphasis lies on genetic traits and molecular pathways that affect the pace of aging. More specifically, we concentrate on the role of mitochondria, which have been identified as key determinants of fungal aging and have stimulated aging research in other organisms.

Respiratory metabolism

The best known function of mitochondria is oxygenic energy conservation: the generation of adenosine triphosphate from energy-rich compounds. Since it is known that part of this process relies on electron transport at the respiratory chain and that the majority of all cellular reactive oxygen species (ROS) are generated by this process, a link of mitochondria to aging has been conceptionalized in the 'mitochondrial free radical theory of aging' (MFRTA) [8]. This theory states that aging is caused by the accumulation of ROS-induced damage of biomolecules including nucleic acids, lipids, and proteins and the resulting adverse effects. In fungi, this link is well demonstrated. In particular in *P. anserina* which, in contrast to yeast, contains a standard respiratory chain organized in different supercomplexes (Figure 1) and additional, alternative respiratory components, an impact of respiration on aging has been demonstrated. In different mutants with impaired respiratory complex III or IV, an alternative terminal oxidase (PaAOX) is induced. Compared to standard respiration, the alternative respiration generates less ROS and the corresponding strains are characterized by an increased lifespan [9–12]. Also in yeast, which lacks complex I and alternative oxidase, a connection between ROS, lifespan, and respiration has been observed. Caloric restriction was found to lead to a decreased ROS release per consumed O_2. This decrease in ROS levels is thought to be responsible for lifespan extension and can be mimicked by artificially increased respiration via uncouplers [13].

Figure 1



Mitochondrial protein quality control. A number of different proteolytic pathways are active to keep mitochondria functional. LON/PIM1 and CLPXP are matrix protease complexes involved in the degradation of damaged proteins, which cannot be repaired by the methionine sulfoxide reductases MSRA and MSRB. The peptides generated by these proteases are delivered to the cytosol via ABC transporters and PORIN. In the cytosol they induce the mitochondrial 'unfolded protein response' (UPR^{mt}), signaling mitochondrial dysfunction to the nucleus. In the inner mitochondrial membrane proteases like i-AAA/YME1, m-AAA and others are involved in protein processing. In yeast, YME1 is also active in the degradation of access, non-assembled subunit 2 of the cytochrome *c* oxidase (COX2) of the respiratory chain complexes and supercomplexes. Also in yeast, m-AAA is active in the assembly of F_1F_0-ATP synthase (V). Damaged proteins from inside the mitochondrion can be retro-translocated to the outer membrane. These and other outer membrane proteins become ubiquitinated by E3 ligases. CDC48 and adaptor proteins like VMS1 deliver the ubiquitinated protein to the proteasome. Respiratory chain supercomplexes ($I_2II_1III_2IV$, $I_1III_2IV_2$, I_1III_2, III_2) as they were described in mitochondria of *P. anserina* are indicated. IM: inner mitochondrial membrane, MM: mitochondrial matrix.

Mitochondrial protein quality control (PQC)

Apart from reduced ROS production, scavenging of these molecules affects cellular ROS levels and can reduce oxidative stress and molecular damage. Mitochondrial superoxide dismutase and peroxidases are part of a cellular scavenging network and specifically involved in mitochondrial ROS balancing. Protein damage can also be repaired by methionine sulfoxide reductases (MSRA/