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Are mitochondria the Achilles' heel of the Kingdom Fungi?

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A founding event in the origin of eukaryotes is the acquisition of an extraordinary organelle, the mitochondrion, which contains its own genome. Being linked to energy metabolism, oxidative stress, cell signalling, and cell death, the mitochondrion to a certain extent controls life and death in eukaryotic cells. The large metabolic diversity and living strategies of the Kingdom Fungi make their mitochondria of particular evolutionary interest. The review focuses first on the characteristics of mitochondria in the Kingdom Fungi, then on their implications in the organism survival, pathogenicity and resistance, and finally on proposing unconventional strategies to investigate the biology of fungal mitochondria, unveiling the possibility that mitochondria play as the Achilles' heel of this kingdom.

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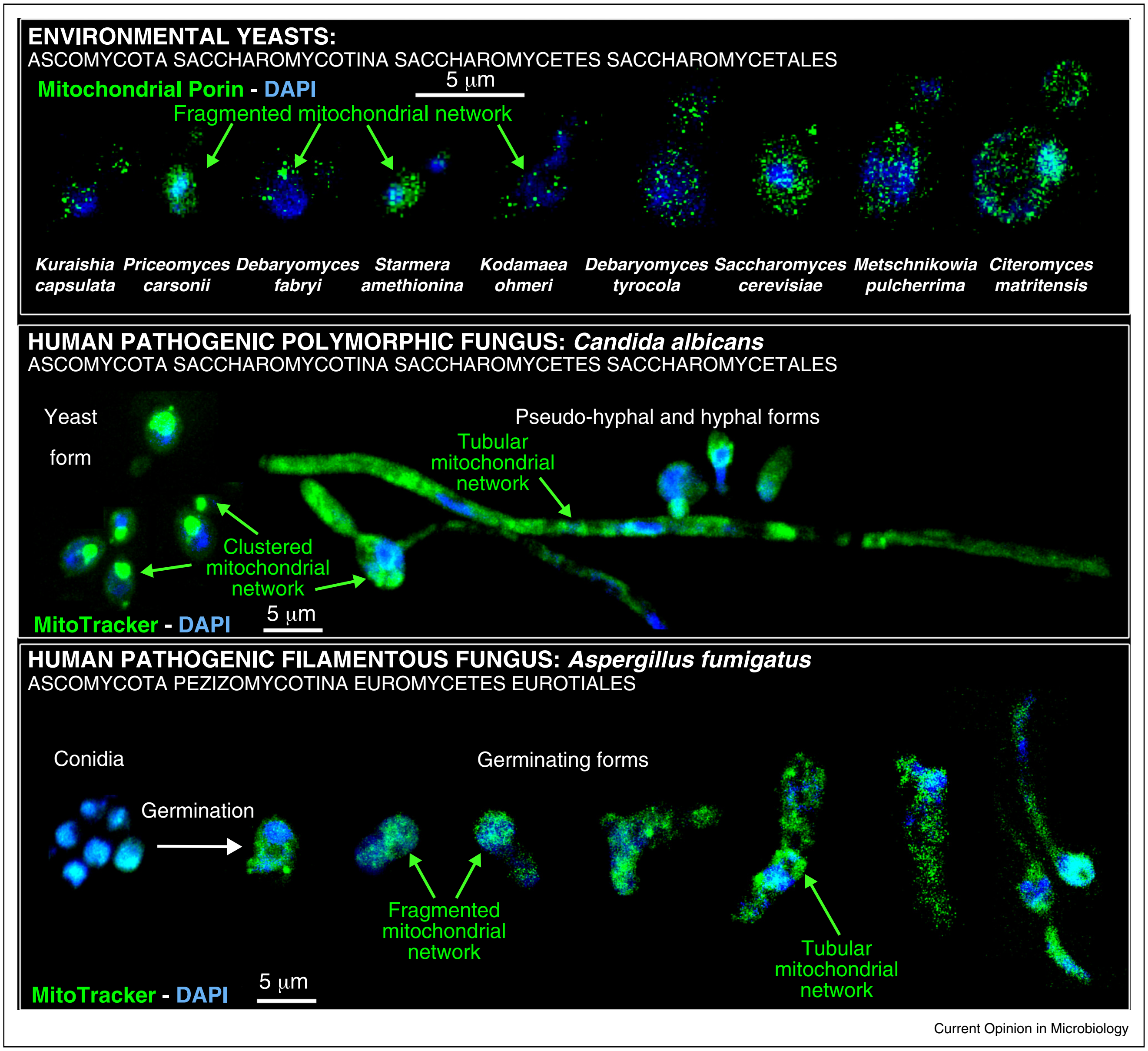
Introduction

Eukaryotic cells contain in multiple copies an amazing organelle, the mitochondrion, which originated from the engulfment and progressive transformation of free-living bacteria by another free-living cell. The potential of endosymbiosis for the origin of chloroplasts was first described in 1883 by the French botanist Andreas Franz Schimper, followed by Mereschkowsky in 1905 [1••], and became an impactful theory to explain the origin of chloroplasts and mitochondria thanks to Lynn Margulis in 1970 [2••]. The proto-mitochondrion likely originated from a α-proteobacteria [1••,3]. The next step is currently explained by two alternative models: (1) an obligate aerobe bacteria was engulfed by an anaerobic amitochondrial nucleus-bearing cell host or (2) a facultative anaerobe was engulfed by an archaebacteria-like host cell [1••]. This happened in a nearly anaerobic time, between 1.5 and 2.0 billion years ago, in a period where eukaryotic cells appeared on the young Earth in the presence of low oxygen and high sulfide levels in the atmosphere and ocean waters [4]. Interestingly, it is suggested that fungi are among the earliest-branching eukaryotes [4]. The Kingdom Fungi includes more than 100 000 described species ranging from multicellular mushrooms to unicellular yeasts [5]. Mitochondria have highly differed in fungi as in other eukaryotes, essentially by distinct loss of the coding content and increased dependence on nuclear factors. Moreover some fungi that live in anoxic environments do not contain mitochondria but carry double-membrane-bound organelles, with no DNA but either the ability to produce ATP generated from pyruvate (hydrogenosomes) or not (mitosomes that seem able to generate iron–sulphur (Fe–S) clusters) [3,6]. In this review are first summarized the characteristics of fungal mitochondria, followed by an overview of implications of mitochondria in fungal physiology, and by the proposal of strategies of investigation aiming to better understand the role of mitochondria in fungal biology.

Characteristics of mitochondria

To date, PubMed-NCBI searches result in 55 564 hits for 'human mitochondria', and only about one-fifth and one-fourth of hits for 'plant mitochondria' and 'fungi mitochondria', respectively. In the last category, about two-third of hits concern 'yeast mitochondria' and one half '*Saccharomyces cerevisiae* mitochondria'. This rapid overview shows that fungal mitochondria are intensely studied in the budding yeast *S. cerevisiae*, but much less in other fungal species. Mitochondria are dynamic organelles that range from 0.35 to 1 μm in diameter and are present in almost all eukaryotic cells with few exceptions, like mature red blood cells in mammals. Typically, the double-membrane enclosed mitochondria fuse and divide to generate functional structures ranging from an interconnected tubular network to individual units [7]. A comprehensive view of the heterogeneous mitochondrial morphology and distribution in several fungal species is shown in Figure 1. Mitochondria are central players in the energy metabolism *via* respiratory chain complexes (Oxidative Phosphorylation or OXPHOS) and in apoptosis [8,9], which plays a role in the development and response to cell damage in higher eukaryotes. In fungi apoptotic-like cell death occurs in response to environmental stress and during ageing, and through factors that display modest conservation compared to the higher eukaryotes counterparts [10]. Mitochondria are also implicated in calcium homeostasis and represent the major source of reactive oxygen species (ROS), which act as signalling molecules but may also generate oxidative stress [11]. Mitochondria carry several copies of their own compact

Figure 1



Mitochondrial morphology and distribution in different fungal species. Note the heterogeneity of mitochondrial morphology from fragmented (diffuse small and big punctuate structures) to clustered and tubular networks. Cells were stained with the mitochondrial marker MitoTracker® Green FM (Life Technologies) (green) or immunostained with yeast mitochondrial Porin (Life Technologies) (green), and DAPI (Sigma–Aldrich) (blue, nuclei). High-resolution three-dimension confocal acquisition with spinning-disc, 100× objective, 200-nm optical slices and 1.024/1.024 pixels resolution (Imagopole, PFID, Institut Pasteur). 3D reconstruction: IMARIS (Bitplane). Post-acquisition analysis: ImageJ 1.47 *K. capsulata*, *P. carsonii*, *D. fabryi*, *S. amethionina*, *K. ohmeri*, *D. tyrocola*, *S. cerevisiae*, *M. pulcherrima* and *C. matritensis* — generous gifts from Dr. Lucia Morales and Prof. Bernard Dujon, Institut Pasteur; *C. albicans* — generous gifts from Murielle Chauvel and Dr. Christophe d'Enfert, Institut Pasteur; *A. fumigatus* — generous gifts from Dr. Vishu Aimanianda and Prof. Jean-Paul Latgé, Institut Pasteur.

double-stranded circular mitochondrial DNA (mtDNA) that is autonomously replicated and transcribed and is mostly dedicated to mitochondrial respiration [12]. Alternative configurations of mitochondrial genomes, which include linear DNAs have been described [6]. Fungal mtDNA range from 19.4 kb (*Schizosaccharomyces pombe*) to ~170 kbp (*Agaricus bitorquis*). Importantly, the mtDNA is associated with proteins to form dynamic mitochondrial nucleoids [12]. Fungal mitochondria display several differences compared to the mitochondria of other organisms. For example, yeasts are facultative anaerobes and can survive without a functional OXPHOS [13]; mtDNA can be found as concatemers in *S. cerevisiae* [12]; and yeasts Saccharomycetaceae have entirely lost