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Review

Particularities of mitochondrial structure in parasitic protists (Apicomplexa and Kinetoplastida)

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ABSTRACT

Without mitochondria, eukaryotic cells would depend entirely on anaerobic glycolysis for ATP generation. This also holds true for protists, both free-living and parasitic. Parasitic protists include agents of human and animal diseases that have a huge impact on world populations. In the phylum Apicomplexa, several species of *Plasmodium* cause malaria, whereas *Toxoplasma gondii* is a cosmopolite parasite found on all continents. Flagellates of the order Kinetoplastida include the genera *Leishmania* and *Trypanosoma* causative agents of human leishmaniasis and (depending on the species) African trypanosomiasis and Chagas disease. Although clearly distinct in many aspects, the members of these two groups bear a single and usually well developed mitochondrion. The single mitochondrion of Apicomplexa has a dense matrix and many cristae with a circular profile. The organelle is even more peculiar in the order Kinetoplastida, exhibiting a condensed network of DNA at a specific position, always close to the flagellar basal body. This arrangement is known as Kinetoplast and the name of the order derived from it. Kinetoplastids also bear glycosomes, peroxisomes that concentrate enzymes of the glycolytic cycle. Mitochondrial volume and activity is maximum when glycosomal is low and vice versa. In both Apicomplexa and trypanosomatids, mitochondria show particularities that are absent in other eukaryotic organisms. These peculiar features make them an attractive target for therapeutic drugs for the diseases they cause.

Contents

1. Introduction

The metabolic role of mitochondria places them among the most important organelles in eukaryotic cells. This is reflected in their wide distribution, number, and size in organisms above a certain level of complexity (review in Kakkar and Singh, 2007). Mitochondria house systems for energy production through oxidative phosphorylation, synthesis of key metabolites, and iron–sulfur clusters. In higher eukaryotes, the mitochondrial respiration

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occurs via an electron transport chain (ETC) which is constituted by four integral enzyme complexes in the mitochondrial inner membrane: NADH-ubiquinone oxidoreductase (Complex I), succinate-ubiquinone oxidoreductase (Complex II), ubiquinol-cytochrome *c* oxidoreductase (Complex III or cytochrome *bc*1) and cytochrome oxidase (Complex IV or cytochrome *a*3) with ubiquinone (coenzyme Q) and cytochrome *c* functioning as electron carriers between the complexes (Chance and Williams, 1956). Complexes I, III and IV function as H^+ pumps generating a proton electrochemical gradient that drives ATP synthesis via the reversible mitochondrial ATP synthase (Complex V), which couples the processes of respiration and phosphorylation (Schagger, 2001). In trypanosomatids, the presence of the complexes was already revealed using cytochemical detection for the cytochrome oxidase as observed in Fig. 1. In addition, the mitochondria are also a reservoir for factors involved in programmed cell death (PCD) (review in Kakkar and Singh, 2007). Parasitic protists, the main subject of this article, exhibit wide variation in the development of this organelle, as described below.

Some important organisms, such as *Giardia lamblia* (the agent of giardiasis), *Entamoeba histolytica* (the agent of amoebiasis), and members of the microsporida group, which comprise agents of important parasitic diseases, do not present mitochondria. However, genes coding for mitochondrial proteins have been found in these protists. These proteins include the chaperonins Cpn6O and Hsp7O and a single type of MCF protein which transports ATP and ADP via a mechanism that does not depend on membrane potential. More recently, genes coding for a protein containing Fe–S centers (e.g., the soluble enzyme cysteine desulphurase (IscS), a central component of the Fe–S assembly system) have been identified in protists. These proteins are widely distributed in nature and operate in metalloenzyme catalysis and electron transport in mitochondria (Tovar et al., 2003). In the case of microsporida, it has been estimated, based on the whole genome sequence of *Encephalitozoon cuniculi* that about 21 putative mitochondrial proteins exist. These proteins include those involved in protein and metabolite import, as well as ISC assembly and export (Burri et al., 2006). Using an immunocytochemical approach, these proteins have been localized in cytoplasmic structures called mitosomes that are found in protists like *E. histolytica* (Mai et al., 1999; Tovar et al., 1999), *G. lamblia* (Arisue et al., 2002; Hashimoto et al., 1998; Lill and Kispal, 2000; Morrison et al., 2001; Roger et al., 1998; Tachezy et al., 2001), *Blastocystis hominis* (León-Avila and Tovar, 2004; Nasirudeen and Tan, 2004), and several species of microsporida that are now considered to be fungi and believed to have undergone reductive evolution (Burri et al., 2006; Fast and Keeling, 2001; Germont et al., 1997; Hirst et al., 1997; Peyretailade et al., 1998; Williams et al., 2002). By immunofluorescence microscopy using confocal laser scanning microscopes, labeling of several structures distributed throughout the cytoplasm has been observed. In the case of *E. histolytica* trophozoites, the first studies showed the presence of one or two labeled structures (Tovar et al., 1999; Mai et al., 1999). In the case of *G. lamblia*, between 25 and 100 small structures (Tovar et al., 2003) were labeled and distributed throughout the protists. Using both antibodies and epitope-tagged mitochondrial proteins conditionally expressed in transgenic parasites, it was shown that a single central mitosome actively divides and segregates during mitosis of *G. lamblia*. This mitosome is tightly associated with the microtubular cytoskeleton (Fig. 2a and b). Other mitosomes, which were dispersed throughout the cell, replicated and segregated into daughter cells stochastically (Regoes et al., 2005). Using this approach, it was also shown that Cpn60 and IscS are localized in the mitosomes; this finding stands in contrast to a previous report showing that they did not co-localize to the same organelle (Tovar et al., 2003). A recent review by Burri and Keeling (2007) analyzes the process of protein import into mitosomes. Transmission electron microscopy

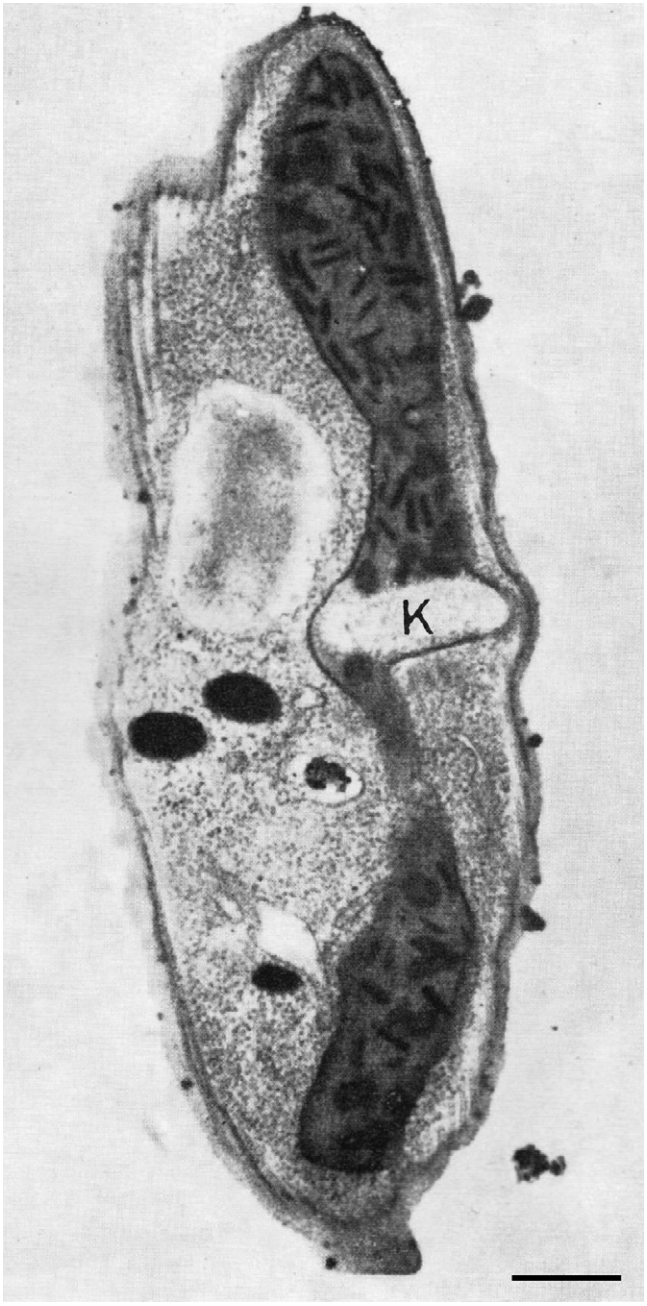

Fig. 1. Enzyme cytochemistry showing the localization of cytochrome oxidase in the whole mitochondrion of *Herpetomonas samuelpessoai*. K, kinetoplast. Bar, 500 nm. After de Souza et al. (1977).

has shown that the mitosomes containing these proteins correspond to a small organelle (140 nm × 65 nm) surrounded by two unit membranes that display a rounded or elongated shape (Tovar et al., 2003). The mitosome does not contain a genome, thus preventing a direct genetic demonstration of its mitochondrial ancestry. In addition, the organelle apparently is not involved in the generation of ATP. However, cytochemical studies have shown that *G. lamblia* possesses structures that selectively partition the cationic, membrane-potential sensitive dye rhodamine 123 (Lloyd et al., 2002). Additionally, the presence of DNA in the mitosomes of *B. hominis* has been reported (Loftus et al., 2005; Xu et al., 2004).

Mitochondria from *B. hominis* were recently characterized. Morphological studies revealed the presence of a rounded, double membrane-surrounded organelle with a mean diameter of 1 μm