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Review

Mitochondria and mammalian reproduction

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ABSTRACT

Mitochondria are cellular organelles with crucial roles in ATP synthesis, metabolic integration, reactive oxygen species (ROS) synthesis and management, the regulation of apoptosis (namely via the intrinsic pathway), among many others. Additionally, mitochondria in different organs or cell types may have distinct properties that can decisively influence functional analysis. In terms of the importance of mitochondria in mammalian reproduction, and although there are species-specific differences, these aspects involve both energetic considerations for gametogenesis and fertilization, control of apoptosis to ensure the proper production of viable gametes, and ROS signaling, as well as other emerging aspects. Crucially, mitochondria are the starting point for steroid hormone biosynthesis, given that the conversion of cholesterol to pregnenolone (a common precursor for all steroid hormones) takes place via the activity of the cytochrome P450 side-chain cleavage enzyme (P450scc) on the inner mitochondrial membrane. Furthermore, mitochondrial activity in reproduction has to be considered in accordance with the very distinct strategies for gamete production in the male and female. These include distinct gonad morpho-physiologies, different types of steroids that are more prevalent (testosterone, estrogens, progesterone), and, importantly, the very particular timings of gametogenesis. While spermatogenesis is complete and continuous since puberty, producing a seemingly inexhaustible pool of gametes in a fixed environment; oogenesis involves the episodic production of very few gametes in an environment that changes cyclically. These aspects have always to be taken into account when considering the roles of any common element in mammalian reproduction.

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1. Introduction

Mitochondria are usually mentioned primarily in terms of cellular ATP production by oxidative phosphorylation (OXPHOS) via the electron transport chain (ETC) located in the inner mitochondrial membrane. ETC activity generates a transmembrane proton gradient (Fig. 1), of which the mitochondrial membrane potential (MMP) is the main component, driving the ATP synthase (Kakkar and Singh, 2007; Newmeyer and Ferguson-Miller, 2003; Scheffler, 2001). A few components of this machinery are encoded by resident mitochondrial DNA (mtDNA) a prokaryotic-like genome that is inherited maternally (Jansen and de Boer, 1998; St John et al., 2010).

However, recent mitochondrial research focuses on other topics, such as the production of reactive oxygen species (ROS) by the ETC and their role(s) in both physiological cell signaling and pathological processes (related to oxidative stress); the regulation of the intrinsic apoptosis pathway and intracellular calcium levels; the production of steroid hormones; quality control of cellular mitochondria via autophagy/mitophagy pathways, or the central position of mitochondria in integrating several metabolic and signaling pathways, epigenetics and the cell cycle (Folmes et al., 2012; Kakkar and Singh, 2007; Nichols and Ferguson, 2002; Nunnari and Suomalainen, 2012).

Moreover, although previously mitochondria were thought to have a fixed and individual morphology, it is now known that changes in shape (both in terms of cristae structure and matrix texture), size (regulated by the fission/fusion machinery) and relationships with other cellular features (the cytoskeleton, the endoplasmic reticulum) can have important functional consequences (Bereiter-Hahn and Voth, 1994; Collins et al., 2002; Rowland and Voeltz, 2012). Indeed, studies of mitochondrial (dys)function related to aging, degenerative and metabolic disorders or cancer encompass several of these aspects, from abnormal OXPHOS activity and ROS production, to defective apoptosis and mitophagy/autophagy, to changes in mtDNA and mitochondrial structure (Amaral et al., 2008b; Amaral and Ramalho-Santos, 2009; Cereghetti and Scorrano, 2011; Correia et al., 2012; Dorn and Scorrano, 2010; Martinou and Youle, 2011; Nunnari and Suomalainen, 2012; Oettinghaus et al., 2012; Palmeira and Ramalho-Santos, 2011; Ramalho-Santos and Rodrigues, 2013; Ramalho-Santos et al., 2009; St John et al., 2010). In short, mitochondria are involved in many other duties while (also) making ATP.

In this review we will focus specifically on the role of mitochondria in gametogenesis, fertilization and early embryo development. It should noted that mitochondrial function is most often studied in terms of dysfunction induced by pathological conditions or toxic substances (pharmacological agents, environmental contaminants, distinct pathologies, etc.), and how these dysfunctions may ultimately affect the reproductive system (Aly and Khafagy, 2011; Amaral et al., 2008a, 2009; Banu et al., 2011; Miyamoto et al., 2010; Mota et al., 2011; Svechnikov et al., 2009; Wang et al., 2009, 2010). Using different aspects of mitochondrial function as damage indicators in several disease models and, conversely, as diagnostic tools in Assisted Reproductive Technologies (ART), has increased in recent years, in terms of functional sperm analysis (Aitken et al., 2012; Dorn and Scorrano, 2010; Gallon et al., 2006; Marchetti et al., 2002; Marchetti et al., 2012; Nakada et al., 2006; Ruiz-Pesini et al., 1998; Sanchez-Partida et al., 2008; Sousa et al., 2011), and oocyte quality assessment (Van Blerkom, 2011; Wang and Sun, 2007).

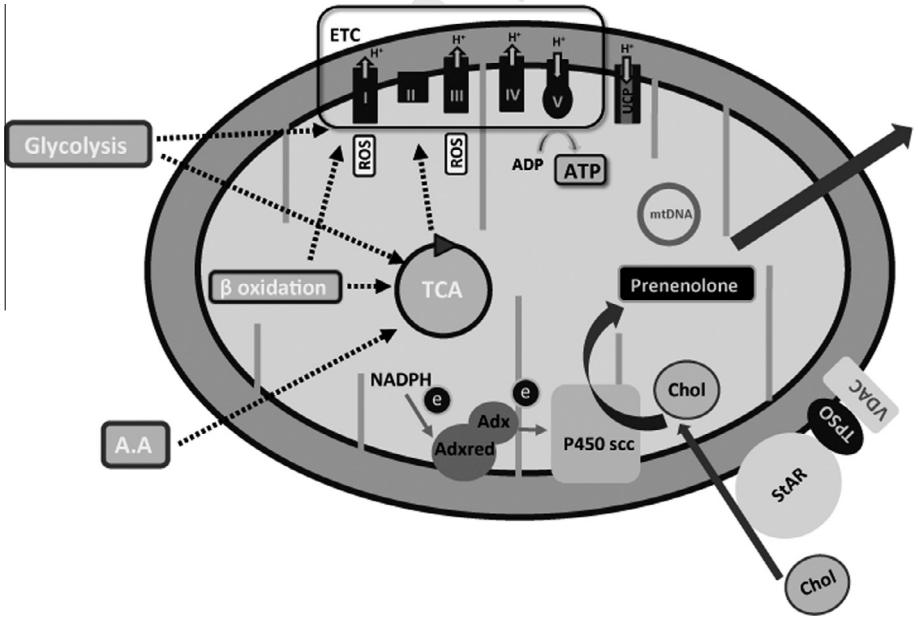

Fig. 1. Possible roles of mitochondria in reproduction. Mitochondria are double membrane organelles with their own genome (mtDNA). Mitochondrial substrates derived from glycolysis, beta-oxidation of fatty acids and the Krebs cycle (Tricarboxylic acid cycle- TCA) provide energy for ATP production through oxidative phosphorylation (OXPHOS) by the activity of the electron transfer chain (ETC) on the inner mitochondrial membrane, composed of four inner membrane (IMM)-associated enzyme complexes (I–IV), plus cytochrome c (Cytc) and the mobile electron carrier ubiquinone (Q). This electron transfer generates a proton gradient across the inner membrane that drives ATP synthase (often known as complex V). However, at several sites of the electron transport chain (mainly complexes I and III) electrons can react with oxygen forming ROS. The energy dissipation mechanism promoted by UCPs (uncoupling proteins) can reduce ROS formation. Both beta-oxidation of fatty acids and amino acid catabolism provide TCA intermediates. The initial step of steroidogenesis also takes place in mitochondria. The first step involves cholesterol (Chol) transport into the mitochondria facilitated by StAR protein via its interaction with Translocator protein (TSPO) and voltage dependent anion channel (VDAC) that constitute the transduceosome, located on the outer mitochondrial membrane (OMM). Once in the mitochondria, cholesterol will be converted to pregnenolone through the action of side chain cleavage cytochrome P450 (P450scc) that depends on the Adrenoxin reductase (AdxRed)–adrenoxin (Adx) system to receive electrons from NADPH. Pregnenolone then diffuses to the smooth endoplasmatic reticulum (SER) where it is further metabolized. See text for discussion.

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