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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.

Contents

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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).

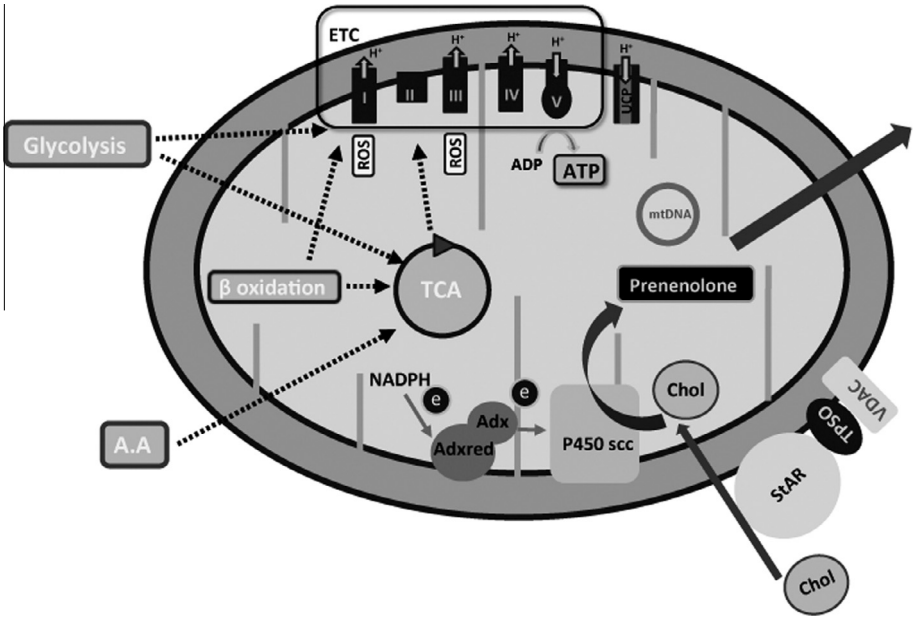

Fig. 1. Possible roles of mitochondria in reproduction. Mitochondria are double membrane organelles with their own genome (mtDNA). Mitochondrial substrates derived from glycolysis, beta-oxidation of fatty acids and the Krebs cycle (Tricarboxylic acid cycle- TCA) provide energy for ATP production through 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.

2. Mitochondria in gametogenesis and early embryo development

2.1. Primordial germ cells and gonad specification

Mammalian gametogenesis is commonly defined by important sex-specific differences, although the starting point is identical. Gonadal tissue derives from the mesoderm, into which primordial germ cells (PGCs) migrate from outside the developing embryo and are subjected to distinct sex determination signals. PGCs divide several times, and establish functional relationships with somatic cells that will have supportive, protective, nutritional, and endocrinal roles in gamete formation. In the testis these include Sertoli and Leydig cells, while their homologous equivalents in the ovary are granulosa and theca cells, respectively (Gilbert, 2010; Soder, 2007).

While PGCs that colonize the fetal testes ultimately differentiate into spermatogonial stem cells, which remain mostly quiescent, retinoic acid exposure causes ovarian oogonia to commit to meiosis in utero. Therefore, at puberty the testis still contains stem cells which can both self-renew and enter meiosis to form sperm, allowing for the continuous production of a large number of male gametes. On the other hand, the ovary contains only a finite amount of committed primary oocytes, which will mature cyclically until the gamete pool is exhausted, ultimately resulting in menopause (Gassei and Schlatt, 2007; Pereda et al., 2006; Soder, 2007). This is one of the main reasons why more information is available on male gametogenesis. Anatomical differences are also evident between gonads: the testis is comprised of an extensive duct system formed by seminiferous tubules onto which millions of small mature sperm are constantly released (ultimately maturing in the epididymis); while the ovary consists of a series of follicular structures embedded in the ovarian stroma, each containing one large female gamete which will be released upon ovulation, with the oocyte and follicle developing in unison (Gilbert, 2010; Holstein et al., 2003; McLaughlin and McIver, 2009). In terms of mitochondrial characteristics and metabolic activity there are also several sex- and stage-specific differences (Table 1).

2.2. Mitochondria in spermatogenesis

Besides providing support and assisting in sperm formation and transport Sertoli cells form the blood-testis barrier, creating a separate and immuneprivileged site (Meinhardt and Hedger, 2011; Smith and Braun, 2012). Testosterone-secreting Leydig cells are found in the intertubular tissue surrounding the capillaries and have a prominent role in spermatogenesis maintenance, the differentiation of male sexual organs and secondary sex characteristics (Ge et al., 2008). Testis-specific morphogenetic events in early gonad differentiation suggest that male gonads have a higher energy requirement than ovaries, and that these distinct metabolic features, focused on mitochondrial activity, might even have a role in sex determination itself (Matoba et al., 2008; Mittwoch, 2004).

Spermatogenesis takes place in the seminiferous tubules and is a highly dynamic and metabolically active biological process during which haploid spermatozoa are produced through a gradual transformation of an interdependent population of germ cells. These cells sequentially migrate from the basal compartment towards the luminal regions of the tubules, passing the blood-testis barrier (Holstein et al., 2003). The existence of numerous mitochondria in male germ cells (Meinhardt et al., 1999), as well as the presence of several testis-specific mitochondrial protein isoforms (Hess et al., 1993; Huttemann et al., 2003) highlights their importance in testicular metabolism. As a whole testis mitochondria have been shown to possess specific bioenergetical and controlled proton leak characteristics that distinguish them from mitochondria from other organs, consuming less oxygen in order to generate approximately the same maximum electric potential (Amaral et al., 2008a, 2009; Mota et al., 2009; Rodrigues et al., 2010). This suggests that, unlike what is usually the case, testicular mitochondria should be considered as the primary mitochondrial models to test the effect of distinct substances on male gametogenesis, and not be substituted by other *in vitro* models, such as commonly used liver mitochondria (Mota et al., 2011; Tavares et al., 2009).

Although descriptive studies, or those that consider cells outside of their biological context (isolated from tissue architecture, grown in nutrient-rich media, under normoxia), must be interpreted with caution, it is well known that different testicular cells have morphologically different mitochondria. These differences may be due to the mitochondrial fusion/fission machinery (Aihara et al., 2009), and could have functional consequences, as is the case in other systems (Bereiter-Hahn and Voth, 1994; Campello and Scorrano, 2010; Collins et al., 2002; De Martino et al., 1979; Hom and Sheu, 2009; Mannella, 2006, 2008). In fact both somatic (Sertoli, Leydig) and germline (spermatogonia, spermatocytes, spermatids, sperm) cells have distinct metabolic preferences and activities, which are translated into distinct mitochondrial contributions (Bajpai et al., 1998; De Martino et al., 1979; Grootegoed et al., 1984; Meinhardt et al., 1999; Nakamura et al., 1984; Robinson and Fritz, 1981) (Table 1). Interestingly, putative substrate availability does not fully explain the differences encountered in the testis, as spermatogonia on the basal membrane remain mostly glycolytic although they are closer to blood vessels (and therefore oxygen sources), while spermatocytes in the seminiferous tubules seem to rely more on OXPHOS, despite being farther away from the oxygen supply. This seems to be a peculiarity spermatogonia share with other stem cells (Ramalho-Santos and Rodrigues, 2013; Ramalho-Santos et al., 2009).

The importance of ATP formed via OXPHOS for spermatogenesis is exemplified by the meiotic arrest found in mice that do not express a testis-specific adenine nucleotide translocase (ANT4), essential for the translocation of ADP and ATP across the inner mitochondrial membrane (Brower et al., 2009). The regulation of apoptosis is also another aspect of mitochondrial function in the testis, both to ensure a manageable number of germ cells that can be supported by existing Sertoli cells (Ramalho-Santos et al., 2009), or as result of different environmental stimuli (Jia et al., 2010; Reyes et al., 2012; Shaha et al., 2010). The former aspect is highlighted by several experiments involving genetically modified mice that lack different components of the intrinsic apoptosis pathway. For example, the deletion of pro-apoptotic BCL-2 family proteins BAX, BAK, as well as the simultaneous deletion of BIM and BIK (possibly due to redundant functions), results in an excess of germ cells, increased mutagenesis and testicular tumorigenesis (Coultas et al., 2005; Katz et al., 2012; Knudson et al., 1995; Russell et al., 2002; Xu et al., 2010), a process somewhat mirrored following overexpression of the pro-survival BCL-W in the testis (Yan et al., 2003). On the other hand deletion of this protein also results in male infertility (Ross et al., 2001; Russell et al., 2001), and the same is true for BCL-2 (Yamamoto et al., 2001), although in the former this seems due to BAX-induced death of Sertoli cells, while in the latter germ cells were more affected. Mice devoid of apoptotic protease-activating factor-1 (Apaf-1), which is usually activated by cytochrome c, are also infertile, in this case due to degenerated spermatogonia leading to an almost absence of viable sperm in the seminiferous tubules (Honarpour et al., 2000). Additionally, mice lacking the testis-specific form of cytochrome c have impaired sperm function (Narisawa et al., 2002).

Pathophysiological processes such as mitochondrial ROS production may also have an (usually detrimental) effect on

Table 1
Mitochondrial characteristics and energy metabolism throughout mammalian gametogenesis and early embryo development.

Cell type	Mitochondria Morphology	Mitochondria Cellular localization	Energy source	Metabolic particularities
Male				
Spermatogonia	Ovoid shaped, lamellar cristae, electron translucent matrix – **Orthodox**	Scattered through the cytoplasm	Glycolysis	– Existence of the blood-testis barrier and Oxygen gradient in the seminiferous tubules
Primary spermatocyte	**Orthodox (Leptotene) → Condensed (Pachytene, Diplotene)** (round shaped, dense matrix, expansion of the intracristal spaces)	Around the nucleus (Zygotene, early Pachytene). Small cytoplasmic clusters with the nuage (intermitochondrial cement; late Pachytene)	Glycolysis	– Associations between germ cell mitochondrial morphology and metabolic status have been suggested in which condensed mitochondria are more efficient
			OXPHOS	– Germ cells have some pentose phosphate pathway activity, mainly spermatocytes
Secondary spermatocyte	**Condensed**	No cluster arrangement	OXPHOS	– There are several testis-specific mitochondrial protein isoforms
Spermatid	**Condensed (early Spermatid) → intermediate (late Spermatid)** (elongated, crescent shaped cristae, matrix less condensed)	No cluster arrangement. Start to localize close to plasma membrane	OXPHOS	
		In late spermatids localize close to the flagellum.		
Sperm	Intermediate	Arranged in the midpiece	Glycolysis OXPHOS β-oxidation	
Female/embryo				
Oogonia	Spherical-ovoid shape. Tubulo-vesicular cristae → lamellar cristae	Typically clustered in close association with the nuage (intermitochondrial cement)	Glycolysis	– Mitochondrial number increases throughout oocyte maturation
	Pale matrix			– Despite their primitive state, mitochondria are active in OXPHOS and are the primary source of ATP in the human oocyte and early embryo – The oocyte contains two populations of mitochondria; the more abundant mitochondria have low MMP and the smaller population is highly polarized. Mitochondrial MMP increases as the oocyte progress through meiotic maturation – Changes in mitochondrial distribution during oocyte growth may be a response to different energy demands. – Mammalian oocytes have limited ability in using glucose and therefore rely on cumulus cells. These cells convert glucose into readily utilizable substrates that enter the oocyte and are further metabolized via TCA followed by OXPHOS. The origin of these substrates may also be external (i.e. female reproductive tract) – While growing oocytes preferentially metabolize pyruvate over glucose, the somatic compartment of ovarian follicles is more gycolitic – The pentose phosphate pathway is important for oocyte development. -Triglycerides provide an additional rich energy supply for oocyte maturation through beta-oxidation – Mammalian oocytes may also utilize amino acids mainly via cumulus cells. Aminoacids serve as substrates for the synthesis of proteins, nucleotides, GSH, signaling molecules and provide substrates for the TCA cycle – Bioenergetic deficiencies have been associated with failure of oocyte maturation and fertilization and embryo demise during pre-implantation stages

(*continued on next page*)

Table 1 (*continued*)

Cell type	Mitochondria Morphology	Mitochondria Cellular localization	Energy source	Metabolic particularities
1^{ry} Oocyte	Spherical. Cristae with lamellar pattern (L,Z,P) → arch like pattern or disposed parallel to the outer membrane (D) Z,P-high dense matrix D-lighter matrix	Random cytoplasmic (L) perinuclear(Z) form a crescent shape mass near nucleus (D), in association with other organelles(balbiani's vitelline body)	OXPHOS	
Growing Oocyte	Spherical, cristae pattern change and increasingly dense matrix	Dispersed in cytoplasm	OXPHOS Beta-oxidation	
Preovulatory Oocyte (mature)	Round with arched cristae, dense matrix	In the ooplasm. Form voluminous aggregates with smooth endoplasmic reticulum tubules and vesicles.	OXPHOS	
Zygote	Round or oval with few cristae parallel to the outer mitochondrial membrane. Some dumb-bell shaped. Electrodense matrix.	Concentrated around pronuclei	OXPHOS	Although early embryos have poorly differentiated mitochondria, they are active and the main source of ATP. A more complex form is gradually achieved, matching increasing development energetic requirements. – A subset of high-polarized mitochondria is observed in zygotes and early embryos, and this population increases with cleavage state. – A transient increase in the ratio of high to low MMP was observed in 2-cell stage mouse embryos, synchronized with embryonic genome activation (maternal-embryonic transition)
2 cell	Round shape with few small peripheral cristae. Dense matrix	Uniformly dispersed in the blastomeres with a tendency towards perinuclear arrangement	OXPHOS	– In human 8-cell embryos an increased ratio of mitochondria with high- to low-MMP correlates with embryo fragmentation – It has been hypothesized that up regulation of beta-oxidation might result in increased availability of carbohydrates such as glucose for use in other pathways. This situation may also aid metabolic regulation and rapid cell proliferation via the Warburg effect
4 cell	More elongated with numerous transverse cristae. Lighter matrix	Dispersed in blastomeres	OXPHOS	
6-8 cell	Most with elongated shape	Associated with nuage (intermitochondrial cement)	Glycolysis	
Blastocyst				– Mitochondria in the trophoblast are more numerous and hyperpolarized.
Trophoblast	Orthodox-like Mitochondrial cristae transversely oriented.		OXPHOS Glycolysis	
ICM	Matrix less dense		Quiescent	

Information collected from the following sources: Amaral et al. (2013), Amaral et al. (2009), Bajpai et al. (1998), Bentov et al. (2011), Boussouar and Benahmed (2004), Collado-Fernandez et al. (2012), De Martino et al. (1979), Dumollard et al. (2009), Dunning et al. (2010), Hess et al. (1993), Meinhardt et al. (1999), Mota et al. (2009), Motta et al. (2000), Ramalho-Santos et al. (2009), Songsasen et al. (2012), Van Blerkom (2008), Van Blerkom (2009), Van Blerkom (2011), Wilding et al. (2001).

spermatogenesis and sperm quality (Agarwal et al., 2003; Tremellen, 2008). For example, mice with a mutation in the inner mitochondrial membrane peptidase 2-like (Immp2l) gene show impairment in processing of signal peptide sequences from mitochondrial cytochrome c and glycerol phosphate dehydrogenase 2, and this causes testicular damage and subfertility, possibly due to excessive ROS production (George et al., 2012).

2.3. Mitochondria in sperm

In the final step of sperm differentiation (spermiogenesis) most of the cytoplasm (including most mitochondria) is lost in the so-called residual bodies. The remaining 22–75 mitochondria rearrange end to end in the midpiece (Ho and Wey, 2007; Olson and Winfrey, 1990; Otani et al., 1988). The fact that some mitochondria are evolutionarily retained in a very specialized sperm region suggests that these organelles have a role in sperm function. Indeed the tight arrangement of mitochondria around the sperm midpiece often is used to exemplify a strategy to concentrate ATP production for a specific function, in this case sperm movement. In fact, mitochondrial parameters (MMP, ETC complex activity) correlate positively with sperm function (Gallon et al., 2006; Marchetti et al., 2002, 2012; Nakada et al., 2006; Ruiz-Pesini et al., 1998; Sousa et al., 2011), mitochondrial inhibition impairs sperm activity (Ruiz-Pesini et al., 2000; St John et al., 2005), and the introduction of a mutant mtDNA with a pathogenic 4696-bp deletion in mice resulted in male infertility (Nakada et al., 2006), with comparable data being reported in human patients (St John et al., 2005). However, this is probably not due to ATP production specifically directed to fuel movement, as other pathways (such as glycolysis) seem more prevalent in mammalian sperm for this specific purpose (Amaral et al., 2011; Nascimento et al., 2008). The available evidence seems to demonstrate that in the few days it can spend in the female reproductive tract mammalian sperm might be able to utilize both glycolysis and OXPHOS to produce ATP for different purposes. The balance between these (and other) metabolic pathways may vary between species, according to the substrates available during in the female reproductive tract and the specific function to be carried out (Amaral et al., 2013). Finally, the ability of sperm mitochondria to accumulate calcium has also been suggested to have a role in sperm signaling pathways (Publicover et al., 2008; Publicover et al., 2007).

2.4. Mitochondria in oogenesis

Essentially the same roles are postulated for mitochondria in female gametogenesis, adapted to the circumstances related to cyclic oogenesis/folliculogenesis. Oogenesis involves the production of very few gametes with high developmental competence, rather than millions of gametes with reduced (individual) potential, and, as in the testis, intrinsic apoptotic pathways involving mitochondria also seem to play a role in follicle survival and selection (Hunzicker-Dunn and Mayo, 2006). Indeed, recent mouse data suggests that the mitochondrial-dependent intrinsic apoptotic pathway is constitutively active in oocytes, and might help eliminate female gametes with meiotic defects (Ene et al., 2013). Interestingly there also seem to be sex-specific differences, as noted in mice devoid of BCL-2: while males show decreased spermatogenesis (as discussed above), folliculogenesis was increased and follicle apoptosis inhibited (Yamamoto et al., 2001). Female mice without BAX also had an increased number of ovarian follicles and extended fertility (Greenfeld et al., 2007; Perez et al., 2007), although this could be due to an indirect effect on PGC migration (Greenfeld et al., 2007). At any rate targeted expression of BCL-2 seemed to provide equivalent results (Morita et al., 1999). Using similar strategies other BCL-2 family proteins expressed in the ovary (BCL-X, BOK) were shown to have no apparent role (Ke et al., 2012; Riedlinger et al., 2002).

Mitochondria are the most abundant and prominent organelle in the oocyte and early embryo (Motta et al., 2000; Sathananthan and Trounson, 2000) (Table 1). Depending on the species, a mammalian oocyte contains around 10^5 to 10^8 mitochondria (Chen et al., 1995; Jansen and de Boer, 1998), descending from a restricted founder population in PGCs. Interestingly, female mice seem to select against mutated mtDNA that cause extensive damage and mitochondrial dysfunction, not including these mutations in ovulated oocytes (Fan et al., 2008). As noted previously, mitochondria are transmitted exclusively from the maternal gamete (Cummins, 2001; St John et al., 2010). Contradicting a common notion, in mammals the entire sperm enters the oocyte at fertilization however sperm mitochondria are diluted or destroyed inside the embryo (Ankel-Simons and Cummins, 1996; Ramalho-Santos, 2011). In rare cases where paternal mitochondria are not destroyed a mixture of mtDNA types in the embryo (mtDNA heteroplasmy) might result, and could impair development (St John et al., 2010). During oocyte maturation mitochondria are relocated to different regions, in response to localized energy demands (Bavister and Squirrell, 2000; Van Blerkom, 2011), and bursts on ATP production are correlated with mitochondrial redistribution and oocyte maturation (Yu et al., 2010).

Mitochondrial function may determine mammalian oocyte quality and mitochondrial activity, mtDNA copy number and mtDNA mutations, have been associated with fertilization rates, embryo development and maternal age, and proposed as bioindicators for oocyte competence (Wang and Sun, 2007). Additionally, mitochondria-related factors such as ATP, pyruvate dehydrogenase complex and ROS are necessary for correct spindle assembly and chromosome alignment in female meiosis (Choi et al., 2007; Johnson et al., 2007; Van Blerkom, 2011; Zhang et al., 2006). On the other hand the mitochondrial Immp2l mutation mentioned earlier in the context of spermatogenesis causes female infertility, by affecting MMP and ROS production (Lu et al., 2008). Finally, oocyte mitochondria also contribute in regulating calcium waves, essential for zygote activation (Dumollard et al., 2003; Dumollard et al., 2004).

2.5. Mitochondria in early embryo development

Similarly to what has been described for spermatogenesis, mitochondrial structure and metabolic activity seem to vary in distinct stages of oocyte and embryo development (Biggers et al., 1967; Gott et al., 1990; Harris et al., 2009; Houghton, 2006; Leese, 1995; Van Blerkom, 2009; Van Blerkom, 2011; Wycherley et al., 2005) (Table 1). Nevertheless, OXPHOS is clearly important at certain stages of follicular development/meiotic maturation, during fertilization, and in the first stages on embryo development.

In the final stage of pre-implantation development (i.e. the blastocyst stage) there is a clear division of cellular lineages, with a small cluster of Inner Cell Mass (ICM)/pluriblast cells, surrounded by a thin layer of trophoblast (called trophectoderm after implantation) cells. Interestingly, while ICM cells have low MMP and are almost quiescent in terms of mitochondrial activity, trophoblast cells are highly polarized and very active, producing more ATP and consuming more oxygen, and both aspects seem to be important for implantation (Houghton, 2006; Leese, 2012; Van Blerkom, 2009; Van Blerkom, 2011) (Table 1). Pluripotent embryonic stem cells (ESCs) isolated from the ICM maintain this characteristic, and favor aerobic glycolysis over OXPHOS in terms of ATP production (Ramalho-Santos et al., 2009; Van Blerkom, 2008; Varum et al., 2009). More importantly, somatic cell reprogramming to pluripotency to generate induced pluripotent stem cells (iPSCs) also involves a glycolytic shift away from OXPHOS, and concomitant

changes in mitochondrial function and morphology (Armstrong et al., 2010; Folmes et al., 2011; Prigione et al., 2010; Varum et al., 2011). As noted above some of these features are also found in spermatogonial stem cells, suggesting that they may be common to all cells with differentiation potential and roles in the transmission of information. The reasons for this remain unknown, although it has been suggested (Ramalho-Santos et al., 2009) that low mitochondrial activity would also prevent ROS-induced cell damage, which might be detrimental both to embryo development (ICM cells), and genetic transmission via the germline (spermatogonia).

3. The endocrine role of mitochondria in reproduction

3.1. The mitochondrial step in steroid biosynthesis

The initial enzymatic reaction in the biosynthesis of all steroids takes place in mitochondria, and involves the conversion of cholesterol to pregnenolone (Manna et al., 2009; Stouffer, 2006). This reaction is dependent on cytochrome P450 side-chain cleavage (P450scc; or CYP11A1), located on the matrix-facing side of the inner mitochondrial membrane (Fig. 1). In turn, P450cc activity is dependent on electron transfer from NADPH mediated by the adrenoxin-adrenoxin reductase system (Miller, 2005). Pregnenolone is exported from mitochondria (although it can also be further processed there in some cases) and can be converted to other compounds (progesterone, testosterone) by enzymes in the endoplasmic reticulum/microsomal system (Stocco and McPhaul, 2006). Other crucial factors for the mitochondrial step in steroid biosynthesis are the steroidogenic acute regulatory protein (StAR; (Stocco, 2001) and the transducesome complex, which includes components such as a 18 kDa translocator protein (TPSO), the voltage dependent anion channel (VDAC-1), TPSO-associated protein 7 and protein kinase A subunit 1a (Hauet et al., 2005; Li et al., 2001; Papadopoulos et al., 2007; Papadopoulos and Miller, 2012). Pregnenolone synthesis requires the processing of cholesterol by an inner mitochondrial membrane cytochrome, i.e., it takes place in a membrane devoid of cholesterol (Tuckey et al., 2002), possibly to avoid changes in membrane fluidity/functionality that might occur elsewhere. Although cholesterol sources for steroid biosynthesis may vary, a limiting step is the transport of this lipid from the outer to the inner mitochondrial membrane, a process catalyzed by StAR, and in which transduceosome also participates, although details regarding the interaction of StAR with this complex need to be further clarified (Manna et al., 2009).

3.2. Sex-specific steroidogenesis

Male steroidogenesis involves the final production of testosterone (or of the more potent testosterone-derived androgen dihydrotestosterone), and also of some estrogens. As noted previously this takes place mostly in Leydig cells (Ge et al., 2008). Although in the ovary theca cells are homologous to Leydig cells, steroidogenesis (notably the production of estrogens and progesterone) also occurs in granulosa cells, from androgens initially produced in theca cells, and varies (both in quantity and in quality) in conjunction with the folliculogenesis/ovulation cycle (Bjersing, 1968; Gelety and Magoffin, 1997). In fact, follicle growth is related to granulosa cell division, maturation and increased steroidogenic activity, which also influences/is influenced by oocyte growth and maturation within the follicle, due to gap junctions established between the gamete and its supporting cells (Albertini et al., 2001; Gilchrist et al., 2008). Following ovulation the ruptured follicle contains theca cells and granulosa cells that did not accompany the oocyte (surrounding it as cumulus cells). The extensive cellular remodeling that then takes place seems to include these different cell types, resulting in the formation of the corpus luteum, a transient endocrine gland crucial for the establishment of a viable pregnancy, and that produces mainly progesterone (Niswender, 2002; Stouffer, 2006). The continuous production of the same steroid hormones by a defined cell type in the male (following the continuous nature of spermatogenesis) is thus contrasted by the cyclic production of different steroid hormones by changing cell types in the female.

Several signaling pathways can regulate steroid production by activating/inactivating distinct factors, or changing their expression levels. This may take place under physiological circumstances (puberty in either sex, different stages of the ovarian cycle), or as a result of a pathological event. Molecular tools devised to specifically target the gonads have provided information focusing mostly downstream of initial mitochondrial intervention. Thus, ovarian StAR expression is upregulated during the periovulatory period in parallel with steroid biosynthesis. It is mainly present in the theca interna at the beginning of the ovulatory process, increasing in the granulosa layer when ovulatory follicles begin producing substantial amounts of progesterone, and continues to be prevalent in the corpus luteum (Richards and Pangas, 2010a, 2010b). Conversely in Leydig cells StAR and P450scc expression is reduced as a function of aging, and this might therefore compromise the early steps of steroidogenesis (Luo et al., 2001). Furthermore, the importance of StAR in this process was confirmed with KO mice, which showed undescended testicles, problems with sperm maturation, and premature ovarian failure (Hasegawa et al., 2000). Similar approaches had been employed to study the role of other participants in this process, such as the importance of VDAC and of the phosphate transporter in StAR function (Bose et al., 2008).

Additionally, different *in vitro* models have been used to study the role of mitochondria in steroidogenesis. For example, in Leydig cell models it has been convincingly shown that synthesis of pregnenolone from cholesterol via P450scc requires ETC activity, high MMP and the ability to produce ATP (Allen et al., 2006; Hales et al., 2005; Levine et al., 2007; Midzak et al., 2011; Stocco and McPhaul, 2006). However, these requirements may well vary with the system used (e.g. primary cells isolated from the testis, versus immortal Leydig cell lines), an important point that has been highlighted in a recent study (Midzak et al., 2011). Similar studies have also been developed in ovarian cells, mainly regarding the effects of different substances on mitochondrial function and associated steroidogenesis, including putative therapeutic agents (Ortega et al., 2012) and toxicants (Svechnikova et al., 2007). It has also been shown that P450cc induction takes place before steroidogenesis (Hanukoglu et al., 1990).

Such models should provide novel insights into the role of mitochondria in reproduction, although they must always accurately specify, and report back to, the particularities of gametogenesis in either sex. It should also be noted that gonad steroidogenesis may link back to other mitochondrial attributes, for example participating in the regulation apoptosis in both Sertoli cells and ovarian follicles (Simoes et al., 2013; Yacobi et al., 2007).

4. Conclusions and future perspectives

Although some reproductive processes are hard to model *in vitro*, or monitor *in vivo*, many studies have highlighted the several roles played by mitochondria in mammalian reproduction, as stressed by the fact that mitochondrial dysfunction has been linked to subfertility and infertility at distinct levels, including poor OXPHOS activity, changes in mtDNA, excessive ROS production, the abnormal triggering of apoptosis, or defects in steroidogenesis. These studies are extremely relevant, both in terms of fertility management and for reproductive toxicology. However, there are

a few other emerging topics where the study of mitochondrial function may also prove useful.

Although the mechanisms involved remain obscure, recent data showing a putative transgenerational (and sex-specific) influence of certain conditions (high fat or low protein diets), or even the use of modified ART, on offspring (Calle et al., 2012; Carone et al., 2010; Ng et al., 2010) is particularly interesting, and may also involve changes in mitochondrial function. Indeed, mitochondrial dysfunction in oocytes and cumulus cells cultured under diabetic or insulin-resistance conditions has been recently related to poor fertility, (Ou et al., 2012; Wang et al., 2009, 2010) and infertility in obese Leptin-deficient (ob/ob) mice has been linked to ovarian dysfunction, and notably to higher levels of apoptosis and decreased steroidogenesis (Serke et al., 2012).

The integration of mitochondrial functions (especially ETC and TCA) in the wider context of cell homeostasis has also been suggested (Folmes et al., 2012; Hitchler and Domann, 2009), as it pertains to signaling and epigenetic status (for example, with mitochondria providing intermediates for epigenetic post-translational modifications). This may provide novel insights into reproductive function, where both erasure of imprints in PGCs and the re-placing of sex-specific marks upon gonad colonization are well known phenomena (Abramowitz and Bartolomei, 2012).

Finally, mitochondrial function in gonads may also be unexpectedly related to regulatory RNA processing. Recently male (but not female) KO mice for the mitochondria-specific phospholipase D, were shown by two independent groups to be infertile due to meiotic arrest, and this was correlated with fission-fusion defects and, interestingly, also with impaired production of piRNAs that are crucial for proper spermatogenesis (Huang et al., 2011; Watanabe et al., 2011).

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References

Abramowitz, L.K., Bartolomei, M.S., 2012. Genomic imprinting: recognition and marking of imprinted loci. Curr. Opin. Genet. Dev. 22, 72–78.
Agarwal, A., Saleh, R.A., Bedaiwy, M.A., 2003. Role of reactive oxygen species in the pathophysiology of human reproduction. Fertil. Steril. 79, 829–843.
Aihara, T., Nakamura, N., Honda, S., Hirose, S., 2009. A novel potential role for gametogenetin-binding protein 1 (GGNBP1) in mitochondrial morphogenesis during spermatogenesis in mice. Biol. Reprod. 80, 762–770.
Aitken, R.J., Gibb, Z., Mitchell, L.A., Lambourne, S.R., Connaughton, H.S., De Iuliis, G.N., 2012. Sperm motility is lost in vitro as a consequence of mitochondrial free radical production and the generation of electrophilic aldehydes but can be significantly rescued by the presence of nucleophilic thiols. Biol. Reprod. 87, 110.
Albertini, D.F., Combelles, C.M., Benecchi, E., Carabatsos, M.J., 2001. Cellular basis for paracrine regulation of ovarian follicle development. Reproduction 121, 647–653.
Allen, J.A., Shankara, T., Janus, P., Buck, S., Diemer, T., Hales, K.H., Hales, D.B., 2006. Energized, polarized, and actively respiring mitochondria are required for acute Leydig cell steroidogenesis. Endocrinology 147, 3924–3935.
Aly, H.A., Khafagy, R.M., 2011. 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)-induced cytotoxicity accompanied by oxidative stress in rat Sertoli cells: Possible role of mitochondrial fractions of Sertoli cells. Toxicol. Appl. Pharmacol. 252, 273–280.
Amaral, S., Ramalho-Santos, J., 2009. Aging, mitochondria and male reproductive function. Curr. Aging Sci. 2, 165–173.
Amaral, S., Mota, P., Rodrigues, A.S., Martins, L., Oliveira, P.J., Ramalho-Santos, J., 2008a. Testicular aging involves mitochondrial dysfunction as well as an increase in UCP2 levels and proton leak. FEBS Lett. 582, 4191–4196.
Amaral, S., Oliveira, P.J., Ramalho-Santos, J., 2008b. Diabetes and the impairment of reproductive function: possible role of mitochondria and reactive oxygen species. Curr. Diabetes Rev. 4, 46–54.
Amaral, S., Mota, P.C., Lacerda, B., Alves, M., Pereira Mde, L., Oliveira, P.J., Ramalho-Santos, J., 2009. Testicular mitochondrial alterations in untreated streptozotocin-induced diabetic rats. Mitochondrion 9, 41–50.
Amaral, A., Paiva, C., Baptista, M., Sousa, A.P., Ramalho-Santos, J., 2011. Exogenous glucose improves long-standing human sperm motility, viability, and mitochondrial function. Fertil. Steril. 96, 848–850.
Amaral, A., Castillo, J., Estanyol, J.M., Ballesca, J.L., Ramalho-Santos, J., Oliva, R., 2013. Human sperm tail proteome suggests new endogenous metabolic pathways. Mol. Cell. Proteomics 12, 330–342.
Ankel-Simons, F., Cummins, J.M., 1996. Misconceptions about mitochondria and mammalian fertilization: implications for theories on human evolution. Proc. Natl. Acad. Sci. USA 93, 13859–13863.
Armstrong, L., Tilgner, K., Saretzki, G., Atkinson, S.P., Stojkovic, M., Moreno, R., Przyborski, S., Lako, M., 2010. Human induced pluripotent stem cell lines show stress defense mechanisms and mitochondrial regulation similar to those of human embryonic stem cells. Stem Cells 28, 661–673.
Bajpai, M., Gupta, G., Setty, B.S., 1998. Changes in carbohydrate metabolism of testicular germ cells during meiosis in the rat. Eur. J. Endocrinol. 138, 322–327.
Banu, S.K., Stanley, J.A., Lee, J., Stephen, S.D., Arosh, J.A., Hoyer, P.B., Burghardt, R.C., 2011. Hexavalent chromium-induced apoptosis of granulosa cells involves selective sub-cellular translocation of Bcl-2 members, ERK1/2 and p53. Toxicol. Appl. Pharmacol. 251, 253–266.
Bavister, B.D., Squirrell, J.M., 2000. Mitochondrial distribution and function in oocytes and early embryos. Hum. Reprod. 15 (Suppl. 2), 189–198.
Bentov, Y., Yavorska, T., Esfandiari, N., Jurisicova, A., Casper, R.F., 2011. The contribution of mitochondrial function to reproductive aging. J. Assist. Reprod. Genet. 28, 773–783.
Bereiter-Hahn, J., Voth, M., 1994. Dynamics of mitochondria in living cells: shape changes, dislocations, fusion, and fission of mitochondria. Microsc. Res. Tech. 27, 198–219.
Biggers, J.D., Whittingham, D.G., Donahue, R.P., 1967. The pattern of energy metabolism in the mouse oocyte and zygote. Proc Natl Acad Sci USA 58, 560–567.
Bjersing, L., 1968. On the morphology and endocrine function of granulosa cells in ovarian follicles and corpora lutea. Biochemical, histochemical, and ultrastructural studies on the porcine ovary with special reference to steroid hormone synthesis (Copenh). Acta Endocrinol. (Suppl. 12), 121–123.
Bose, M., Whittal, R.M., Miller, W.L., Bose, H.S., 2008. Steroidogenic activity of StAR requires contact with mitochondrial VDAC1 and phosphate carrier protein. J. Biol. Chem. 283, 8837–8845.
Boussouar, F., Benahmed, M., 2004. Lactate and energy metabolism in male germ cells. Trends Endocrinol. Metab. 15, 345–350.
Brower, J.V., Lim, C.H., Jorgensen, M., Oh, S.P., Terada, N., 2009. Adenine nucleotide translocase 4 deficiency leads to early meiotic arrest of murine male germ cells. Reproduction 138, 463–470.
Calle, A., Miranda, A., Fernandez-Gonzalez, R., Pericuesta, E., Laguna, R., Gutierrez-Adan, A., 2012. Male mice produced by in vitro culture have reduced fertility and transmit organomegaly and glucose intolerance to their male offspring. Biol. Reprod. 87, 34.
Campello, S., Scorrano, L., 2010. Mitochondrial shape changes: orchestrating cell pathophysiology. EMBO Rep. 11, 678–684.
Carone, B.R., Fauquier, L., Habib, N., Shea, J.M., Hart, C.E., Li, R., Bock, C., Li, C., Gu, H., Zamore, P.D., Meissner, A., Weng, Z., Hofmann, H.A., Friedman, N., Rando, O.J., 2010. Paternally induced transgenerational environmental reprogramming of metabolic gene expression in mammals. Cell 143, 1084–1096.
Cereghetti, G.M., Scorrano, L., 2011. Phagocytosis: coupling of mitochondrial uncoupling and engulfment. Curr. Biol. 21, R852–854.
Chen, X., Prosser, R., Simonetti, S., Sadlock, J., Jagiello, G., Schon, E.A., 1995. Rearranged mitochondrial genomes are present in human oocytes. Am. J. Hum. Genet. 57, 239–247.
Choi, W.J., Banerjee, J., Falcone, T., Bena, J., Agarwal, A., Sharma, R.K., 2007. Oxidative stress and tumor necrosis factor-alpha-induced alterations in metaphase II mouse oocyte spindle structure. Fertil. Steril. 88, 1220–1231.
Collado-Fernandez, E., Picton, H.M., Dumollard, R., 2012. Metabolism throughout follicle and oocyte development in mammals. Int. J. Dev. Biol. 56, 799–808.
Collins, T.J., Berridge, M.J., Lipp, P., Bootman, M.D., 2002. Mitochondria are morphologically and functionally heterogeneous within cells. EMBO J. 21, 1616–1627.
Correia, S.C., Santos, R.X., Perry, G., Zhu, X., Moreira, P.I., Smith, M.A., 2012. Mitochondrial importance in Alzheimer's, Huntington's and Parkinson's diseases. Adv. Exp. Med. Biol. 724, 205–221.
Coultas, L., Bouillet, P., Loveland, K.L., Meachem, S., Perlman, H., Adams, J.M., Strasser, A., 2005. Concomitant loss of proapoptotic BH3-only Bcl-2 antagonists Bik and Bim arrests spermatogenesis. EMBO J. 24, 3963–3973.
Cummins, J.M., 2001. Mitochondria: potential roles in embryogenesis and nucleocytoplasmic transfer. Hum. Reprod. Update 7, 217–228.

De Martino, C., Floridi, A., Marcante, M.L., Malorni, W., Scorza Barcellona, P., Bellocci, M., Silvestrini, B., 1979. Morphological, histochemical and biochemical studies on germ cell mitochondria of normal rats. Cell Tissue Res. 196, 1–22.
Dorn 2nd, G.W., Scorrano, L., 2010. Two close, too close: sarcoplasmic reticulum-mitochondrial crosstalk and cardiomyocyte fate. Circ. Res. 107, 689–699.
Dumollard, R., Hammar, K., Porterfield, M., Smith, P.J., Cibert, C., Rouviere, C., Sardet, C., 2003. Mitochondrial respiration and Ca^{2+} waves are linked during fertilization and meiosis completion. Development 130, 683–692.
Dumollard, R., Marangos, P., Fitzharris, G., Swann, K., Duchen, M., Carroll, J., 2004. Sperm-triggered [Ca^{2+}] oscillations and Ca^{2+} homeostasis in the mouse egg have an absolute requirement for mitochondrial ATP production. Development 131, 3057–3067.
Dumollard, R., Carroll, J., Duchen, M.R., Campbell, K., Swann, K., 2009. Mitochondrial function and redox state in mammalian embryos. Semin. Cell Dev. Biol. 20, 346–353.
Dunning, K.R., Cashman, K., Russell, D.L., Thompson, J.G., Norman, R.J., Robker, R.L., 2010. Beta-oxidation is essential for mouse oocyte developmental competence and early embryo development. Biol. Reprod. 83, 909–918.
Ene, A.C., Park, S., Edelmann, W., Taketo, T., 2013. Caspase 9 is constitutively activated in mouse oocytes and plays a key role in oocyte elimination during meiotic prophase progression. Dev. Biol..
Fan, W., Waymire, K.G., Narula, N., Li, P., Rocher, C., Coskun, P.E., Vannan, M.A., Narula, J., Macgregor, G.R., Wallace, D.C., 2008. A mouse model of mitochondrial disease reveals germline selection against severe mtDNA mutations. Science 319, 958–962.
Folmes, C.D., Nelson, T.J., Martinez-Fernandez, A., Arrell, D.K., Lindor, J.Z., Dzeja, P.P., Ikeda, Y., Perez-Terzic, C., Terzic, A., 2011. Somatic oxidative bioenergetics transitions into pluripotency-dependent glycolysis to facilitate nuclear reprogramming. Cell Metab. 14, 264–271.
Folmes, C.D., Dzeja, P.P., Nelson, T.J., Terzic, A., 2012. Metabolic plasticity in stem cell homeostasis and differentiation. Cell Stem Cell 11, 596–606.
Gallon, F., Marchetti, C., Jouy, N., Marchetti, P., 2006. The functionality of mitochondria differentiates human spermatozoa with high and low fertilizing capability. Fertil. Steril. 86, 1526–1530.
Gassei, K., Schlatt, S., 2007. Testicular morphogenesis: comparison of in vivo and in vitro models to study male gonadal development. Ann. N. Y. Acad. Sci. 1120, 152–167.
Ge, R., Chen, G., Hardy, M.P., 2008. The role of the Leydig cell in spermatogenic function. Adv. Exp. Med. Biol. 636, 255–269.
Gelety, T.J., Magoffin, D.A., 1997. Ontogeny of steroidogenic enzyme gene expression in ovarian theca-interstitial cells in the rat: regulation by a paracrine theca-differentiating factor prior to achieving luteinizing hormone responsiveness. Biol. Reprod. 56, 938–945.
George, S.K., Jiao, Y., Bishop, C.E., Lu, B., 2012. Oxidative stress is involved in age-dependent spermatogenic damage of Immp2l mutant mice. Free Radic. Biol. Med. 52, 2223–2233.
Gilbert, S., 2010. Developmental Biology, ninth ed.. Sinauer, New York.
Gilchrist, R.B., Lane, M., Thompson, J.G., 2008. Oocyte-secreted factors: regulators of cumulus cell function and oocyte quality. Hum. Reprod. Update 14, 159–177.
Gott, A.L., Hardy, K., Winston, R.M., Leese, H.J., 1990. Non-invasive measurement of pyruvate and glucose uptake and lactate production by single human preimplantation embryos. Hum. Reprod. 5, 104–108.
Greenfeld, C.R., Pepling, M.E., Babus, J.K., Furth, P.A., Flaws, J.A., 2007. BAX regulates follicular endowment in mice. Reproduction 133, 865–876.
Grootegoed, J.A., Jansen, R., Van der Molen, H.J., 1984. The role of glucose, pyruvate and lactate in ATP production by rat spermatocytes and spermatids. Biochim. Biophys. Acta 767, 248–256.
Hales, D.B., Allen, J.A., Shankara, T., Janus, P., Buck, S., Diemer, T., Hales, K.H., 2005. Mitochondrial function in Leydig cell steroidogenesis. Ann. N. Y. Acad. Sci. 1061, 120–134.
Hanukoglu, I., Suh, B.S., Himmelhoch, S., Amsterdam, A., 1990. Induction and mitochondrial localization of cytochrome P450scc system enzymes in normal and transformed ovarian granulosa cells. J. Cell Biol. 111, 1373–1381.
Harris, S.E., Leese, H.J., Gosden, R.G., Picton, H.M., 2009. Pyruvate and oxygen consumption throughout the growth and development of murine oocytes. Mol. Reprod. Dev. 76, 231–238.
Hasegawa, T., Zhao, L., Caron, K.M., Majdic, G., Suzuki, T., Shizawa, S., Sasano, H., Parker, K.L., 2000. Developmental roles of the steroidogenic acute regulatory protein (StAR) as revealed by StAR knockout mice. Mol. Endocrinol. 14, 1462–1471.
Hauet, T., Yao, Z.X., Bose, H.S., Wall, C.T., Han, Z., Li, W., Hales, D.B., Miller, W.L., Culty, M., Papadopoulos, V., 2005. Peripheral-type benzodiazepine receptor-mediated action of steroidogenic acute regulatory protein on cholesterol entry into leydig cell mitochondria. Mol. Endocrinol. 19, 540–554.
Hess, R.A., Miller, L.A., Kirby, J.D., Margoliash, E., Goldberg, E., 1993. Immunoelectron microscopic localization of testicular and somatic cytochromes c in the seminiferous epithelium of the rat. Biol. Reprod. 48, 1299–1308.
Hitchler, M.J., Domann, F.E., 2009. Metabolic defects provide a spark for the epigenetic switch in cancer. Free Radic. Biol. Med. 47, 115–127.
Ho, H.C., Wey, S., 2007. Three dimensional rendering of the mitochondrial sheath morphogenesis during mouse spermiogenesis. Microsc. Res. Tech. 70, 719–723.
Holstein, A.F., Schulze, W., Davidoff, M., 2003. Understanding spermatogenesis is a prerequisite for treatment. Reprod. Biol. Endocrinol. 1, 107.
Hom, J., Sheu, S.S., 2009. Morphological dynamics of mitochondria–a special emphasis on cardiac muscle cells. J. Mol. Cell. Cardiol. 46, 811–820.
Honarpour, N., Du, C., Richardson, J.A., Hammer, R.E., Wang, X., Herz, J., 2000. Adult Apaf-1-deficient mice exhibit male infertility. Dev. Biol. 218, 248–258.
Houghton, F.D., 2006. Energy metabolism of the inner cell mass and trophectoderm of the mouse blastocyst. Differentiation 74, 11–18.
Huang, H., Gao, Q., Peng, X., Choi, S.Y., Sarma, K., Ren, H., Morris, A.J., Frohman, M.A., 2011. PiRNA-associated germline nuage formation and spermatogenesis require MitoPLD profusogenic mitochondrial-surface lipid signaling. Dev. Cell 20, 376–387.
Hunzicker-Dunn, M., Mayo, K., 2006. Gonadotropin signaling in the ovary. In: Neill, J.e. (Ed.), Knobil and Neill's Physiology of Reproduction, third ed. Academic Press/Elsevier, St. Louis, MO, USA, pp. 547–592.
Huttemann, M., Jaradat, S., Grossman, L.I., 2003. Cytochrome c oxidase of mammals contains a testes-specific isoform of subunit VIb – the counterpart to testes-specific cytochrome c? Mol. Reprod. Dev. 66, 8–16.
Jansen, R.P., de Boer, K., 1998. The bottleneck: mitochondrial imperatives in oogenesis and ovarian follicular fate. Mol. Cell. Endocrinol. 145, 81–88.
Jia, Y., Lee, K.W., Swerdloff, R., Hwang, D., Cobb, L.J., Sinha Hikim, A., Lue, Y.H., Cohen, P., Wang, C., 2010. Interaction of insulin-like growth factor-binding protein-3 and BAX in mitochondria promotes male germ cell apoptosis. J. Biol. Chem. 285, 1726–1732.
Johnson, M.T., Freeman, E.A., Gardner, D.K., Hunt, P.A., 2007. Oxidative metabolism of pyruvate is required for meiotic maturation of murine oocytes in vivo. Biol. Reprod. 77, 2–8.
Kakkar, P., Singh, B.K., 2007. Mitochondria: a hub of redox activities and cellular distress control. Mol. Cell. Biochem. 305, 235–253.
Katz, S.G., Fisher, J.K., Correll, M., Bronson, R.T., Ligon, K.L., Walensky, L.D., 2012. Brain and testicular tumors in mice with progenitor cells lacking BAX and BAK. Oncogene.
Ke, F., Voss, A., Kerr, J.B., O'Reilly, L.A., Tai, L., Echeverry, N., Bouillet, P., Strasser, A., Kaufmann, T., 2012. BCL-2 family member BOK is widely expressed but its loss has only minimal impact in mice. Cell Death Differ. 19, 915–925.
Knudson, C.M., Tung, K.S., Tourtellotte, W.G., Brown, G.A., Korsmeyer, S.J., 1995. Bax-deficient mice with lymphoid hyperplasia and male germ cell death. Science 270, 96–99.
Leese, H.J., 1995. Metabolic control during preimplantation mammalian development. Hum. Reprod. Update 1, 63–72.
Leese, H.J., 2012. Metabolism of the preimplantation embryo: 40 years on. Reproduction 143, 417–427.
Levine, S.L., Han, Z., Liu, J., Farmer, D.R., Papadopoulos, V., 2007. Disrupting mitochondrial function with surfactants inhibits MA-10 Leydig cell steroidogenesis. Cell Biol. Toxicol. 23, 385–400.
Li, H., Degenhardt, B., Tobin, D., Yao, Z.X., Tasken, K., Papadopoulos, V., 2001. Identification, localization, and function in steroidogenesis of PAP7: a peripheral-type benzodiazepine receptor- and PKA (RIalpha)-associated protein. Mol. Endocrinol. 15, 2211–2228.
Lu, B., Poirier, C., Gaspar, T., Gratzke, C., Harrison, W., Busija, D., Matzuk, M.M., Andersson, K.E., Overbeek, P.A., Bishop, C.E., 2008. A mutation in the inner mitochondrial membrane peptidase 2-like gene (Immp2l) affects mitochondrial function and impairs fertility in mice. Biol. Reprod. 78, 601–610.
Luo, L., Chen, H., Zirkin, B.R., 2001. Leydig cell aging: steroidogenic acute regulatory protein (StAR) and cholesterol side-chain cleavage enzyme. J. Androl. 22, 149–156.
Manna, P.R., Dyson, M.T., Stocco, D.M., 2009. Regulation of the steroidogenic acute regulatory protein gene expression: present and future perspectives. Mol. Hum. Reprod. 15, 321–333.
Mannella, C.A., 2006. The relevance of mitochondrial membrane topology to mitochondrial function. Biochim. Biophys. Acta 1762, 140–147.
Mannella, C.A., 2008. Structural diversity of mitochondria: functional implications. Ann. N. Y. Acad. Sci. 1147, 171–179.
Marchetti, C., Obert, G., Deffosez, A., Formstecher, P., Marchetti, P., 2002. Study of mitochondrial membrane potential, reactive oxygen species, DNA fragmentation and cell viability by flow cytometry in human sperm. Hum. Reprod. 17, 1257–1265.
Marchetti, P., Ballot, C., Jouy, N., Thomas, P., Marchetti, C., 2012. Influence of mitochondrial membrane potential of spermatozoa on in vitro fertilisation outcome. Andrologia 44, 136–141.
Martinou, J.C., Youle, R.J., 2011. Mitochondria in apoptosis: Bcl-2 family members and mitochondrial dynamics. Dev. Cell 21, 92–101.
Matoba, S., Hiramatsu, R., Kanai-Azuma, M., Tsunekawa, N., Harikae, K., Kawakami, H., Kurohmaru, M., Kanai, Y., 2008. Establishment of testis-specific SOX9 activation requires high-glucose metabolism in mouse sex differentiation. Dev. Biol. 324, 76–87.
McLaughlin, E.A., McIver, S.C., 2009. Awakening the oocyte: controlling primordial follicle development. Reproduction 137, 1–11.
Meinhardt, A., Hedger, M.P., 2011. Immunological, paracrine and endocrine aspects of testicular immune privilege. Mol. Cell. Endocrinol. 335, 60–68.
Meinhardt, A., Wilhelm, B., Seitz, J., 1999. Expression of mitochondrial marker proteins during spermatogenesis. Hum. Reprod. Update 5, 108–119.
Midzak, A.S., Chen, H., Aon, M.A., Papadopoulos, V., Zirkin, B.R., 2011. ATP synthesis, mitochondrial function, and steroid biosynthesis in rodent primary and tumor Leydig cells. Biol. Reprod. 84, 976–985.
Miller, W.L., 2005. Minireview: regulation of steroidogenesis by electron transfer. Endocrinology 146, 2544–2550.
Mittwoch, U., 2004. The elusive action of sex-determining genes: mitochondria to the rescue? J. Theor. Biol. 228, 359–365.

Miyamoto, K., Sato, E.F., Kasahara, E., Jikumaru, M., Hiramoto, K., Tabata, H., Katsuragi, M., Odo, S., Utsumi, K., Inoue, M., 2010. Effect of oxidative stress during repeated ovulation on the structure and functions of the ovary, oocytes, and their mitochondria. Free Radic. Biol. Med. 49, 674–681.
Morita, Y., Perez, G.I., Maravei, D.V., Tilly, K.I., Tilly, J.L., 1999. Targeted expression of Bcl-2 in mouse oocytes inhibits ovarian follicle atresia and prevents spontaneous and chemotherapy-induced oocyte apoptosis in vitro. Mol. Endocrinol. 13, 841–850.
Mota, P., Amaral, S., Martins, L., de Lourdes Pereira, M., Oliveira, P.J., Ramalho-Santos, J., 2009. Mitochondrial bioenergetics of testicular cells from the domestic cat (Felis catus)-a model for endangered species. Reprod. Toxicol. 27, 111–116.
Mota, P.C., Cordeiro, M., Pereira, S.P., Oliveira, P.J., Moreno, A.J., Ramalho-Santos, J., 2011. Differential effects of p, p'-DDE on testis and liver mitochondria: implications for reproductive toxicology. Reprod. Toxicol. 31, 80–85.
Motta, P.M., Nottola, S.A., Makabe, S., Heyn, R., 2000. Mitochondrial morphology in human fetal and adult female germ cells. Hum. Reprod. 15 (Suppl. 2), 129–147.
Nakada, K., Sato, A., Yoshida, K., Morita, T., Tanaka, H., Inoue, S., Yonekawa, H., Hayashi, J., 2006. Mitochondria-related male infertility. Proc Natl Acad Sci USA 103, 15148–15153.
Nakamura, M., Okinaga, S., Arai, K., 1984. Metabolism of pachytene primary spermatocytes from rat testes: pyruvate maintenance of adenosine triphosphate level. Biol. Reprod. 30, 1187–1197.
Narisawa, S., Hecht, N.B., Goldberg, E., Boatright, K.M., Reed, J.C., Millan, J.L., 2002. Testis-specific cytochrome c-null mice produce functional sperm but undergo early testicular atrophy. Mol. Cell. Biol. 22, 5554–5562.
Nascimento, J.M., Shi, L.Z., Tam, J., Chandsawangbhuwana, C., Durrant, B., Botvinick, E.L., Berns, M.W., 2008. Comparison of glycolysis and oxidative phosphorylation as energy sources for mammalian sperm motility, using the combination of fluorescence imaging, laser tweezers, and real-time automated tracking and trapping. J. Cell. Physiol. 217, 745–751.
Newmeyer, D.D., Ferguson-Miller, S., 2003. Mitochondria: releasing power for life and unleashing the machineries of death. Cell 112, 481–490.
Ng, S.F., Lin, R.C., Laybutt, D.R., Barres, R., Owens, J.A., Morris, M.J., 2010. Chronic high-fat diet in fathers programs beta-cell dysfunction in female rat offspring. Nature 467, 963–966.
Nichols, D.G., Ferguson, S.J., 2002. Bioenergetics, third ed. Academic Press, Amsterdam.
Niswender, G.D., 2002. Molecular control of luteal secretion of progesterone. Reproduction 123, 333–339.
Nunnari, J., Suomalainen, A., 2012. Mitochondria: in sickness and in health. Cell 148, 1145–1159.
Oettinghaus, B., Licci, M., Scorrano, L., Frank, S., 2012. Less than perfect divorces: dysregulated mitochondrial fission and neurodegeneration. Acta Neuropathol. 123, 189–203.
Olson, G.E., Winfrey, V.P., 1990. Mitochondria-cytoskeleton interactions in the sperm midpiece. J. Struct. Biol. 103, 13–22.
Ortega, I., Cress, A.B., Wong, D.H., Villanueva, J.A., Sokalska, A., Moeller, B.C., Stanley, S.D., Duleba, A.J., 2012. Simvastatin reduces steroidogenesis by inhibiting Cyp17a1 gene expression in rat ovarian theca-interstitial cells. Biol. Reprod. 86, 1–9.
Otani, H., Tanaka, O., Kasai, K., Yoshioka, T., 1988. Development of mitochondrial helical sheath in the middle piece of the mouse spermatid tail: regular dispositions and synchronized changes. Anat. Rec. 222, 26–33.
Ou, X.H., Li, S., Wang, Z.B., Li, M., Quan, S., Xing, F., Guo, L., Chao, S.B., Chen, Z., Liang, X.W., Hou, Y., Schatten, H., Sun, Q.Y., 2012. Maternal insulin resistance causes oxidative stress and mitochondrial dysfunction in mouse oocytes. Hum. Reprod. 27, 2130–2145.
Palmeira, C.M., Ramalho-Santos, J., 2011. Mitochondrial dysfunction in reproductive and developmental toxicity. In: Gupta, C. (Ed.), Reproductive and Developmental Toxicology R. Elsevier, New York, pp. 815–824.
Papadopoulos, V., Miller, W.L., 2012. Role of mitochondria in steroidogenesis. Best Pract. Res. Clin. Endocrinol Metab. 26, 771–790.
Papadopoulos, V., Liu, J., Culty, M., 2007. Is there a mitochondrial signaling complex facilitating cholesterol import? Mol. Cell. Endocrinol. 265–266, 59–64.
Pereda, J., Zorn, T., Soto-Suazo, M., 2006. Migration of human and mouse primordial germ cells and colonization of the developing ovary: an ultrastructural and cytochemical study. Microsc. Res. Tech. 69, 386–395.
Perez, G.I., Jurisicova, A., Wise, L., Lipina, T., Kanisek, M., Bechard, A., Takai, Y., Hunt, P., Roder, J., Grynpas, M., Tilly, J.L., 2007. Absence of the proapoptotic Bax protein extends fertility and alleviates age-related health complications in female mice. Proc. Natl. Acad. Sci. USA 104, 5229–5234.
Prigione, A., Fauler, B., Lurz, R., Lehrach, H., Adjaye, J., 2010. The senescence-related mitochondrial/oxidative stress pathway is repressed in human induced pluripotent stem cells. Stem Cells 28, 721–733.
Publicover, S.J., Harper, C.V., Barratt, C., 2007. [Ca2+]i signalling in sperm–making the most of what you've got. Nat. Cell Biol. 9, 235–242.
Publicover, S.J., Giojalas, L.C., Teves, M.E., de Oliveira, G.S., Garcia, A.A., Barratt, C.L., Harper, C.V., 2008. Ca2+ signalling in the control of motility and guidance in mammalian sperm. Front. Biosci. 13, 5623–5637.
Ramalho-Santos, J., 2011. A sperm's tail: the importance of getting it right. Hum. Reprod. 26, 2590–2591.
Ramalho-Santos, J., Rodrigues., A.S., 2013. From oocytes and pluripotent stem cells to fully differentiated fates: (Also) a mitochondrial odyssey. In: St. John, J.C. (Ed.), Mitochondrial DNA Mitochondria Disease and Stem Cells. Humana Press/Springer-Verlag, New York, pp. 69–86.
Ramalho-Santos, J., Varum, S., Amaral, S., Mota, P.C., Sousa, A.P., Amaral, A., 2009. Mitochondrial functionality in reproduction: from gonads and gametes to embryos and embryonic stem cells. Hum. Reprod. Update 15, 553–572.
Reyes, J.G., Farias, J.G., Henriquez-Olavarrieta, S., Madrid, E., Parraga, M., Zepeda, A.B., Moreno, R.D., 2012. The hypoxic testicle: physiology and pathophysiology. Oxid. Med. Cell Longev. 2012, 929285.
Richards, J.S., Pangas, S.A., 2010a. New insights into ovarian function. Handb. Exp. Pharmacol., 3–27.
Richards, J.S., Pangas, S.A., 2010b. The ovary: basic biology and clinical implications. J. Clin. Invest. 120, 963–972.
Riedlinger, G., Okagaki, R., Wagner, K.U., Rucker 3rd, E.B., Oka, T., Miyoshi, K., Flaws, J.A., Hennighausen, L., 2002. Bcl-x is not required for maintenance of follicles and corpus luteum in the postnatal mouse ovary. Biol. Reprod. 66, 438–444.
Robinson, R., Fritz, I.B., 1981. Metabolism of glucose by Sertoli cells in culture. Biol. Reprod. 24, 1032–1041.
Rodrigues, A.S., Lacerda, B., Moreno, A.J., Ramalho-Santos, J., 2010. Proton leak modulation in testicular mitochondria affects reactive oxygen species production and lipid peroxidation. Cell Biochem. Funct. 28, 224–231.
Ross, A.J., Amy, S.P., Mahar, P.L., Lindsten, T., Knudson, C.M., Thompson, C.B., Korsmeyer, S.J., MacGregor, G.R., 2001. BCLW mediates survival of postmitotic Sertoli cells by regulating BAX activity. Dev. Biol. 239, 295–308.
Rowland, A.A., Voeltz, G.K., 2012. Endoplasmic reticulum-mitochondria contacts: function of the junction. Nat. Rev. Mol. Cell Biol. 13, 607–625.
Ruiz-Pesini, E., Diez, C., Lapena, A.C., Perez-Martos, A., Montoya, J., Alvarez, E., Arenas, J., Lopez-Perez, M.J., 1998. Correlation of sperm motility with mitochondrial enzymatic activities. Clin. Chem. 44, 1616–1620.
Ruiz-Pesini, E., Lapena, A.C., Diez-Sanchez, C., Perez-Martos, A., Montoya, J., Alvarez, E., Diaz, M., Urries, A., Montoro, L., Lopez-Perez, M.J., Enriquez, J.A., 2000. Human mtDNA haplogroups associated with high or reduced spermatozoa motility. Am. J. Hum. Genet. 67, 682–696.
Russell, L.D., Warren, J., Debeljuk, L., Richardson, L.L., Mahar, P.L., Waymire, K.G., Amy, S.P., Ross, A.J., MacGregor, G.R., 2001. Spermatogenesis in Bclw-deficient mice. Biol. Reprod. 65, 318–332.
Russell, L.D., Chiarini-Garcia, H., Korsmeyer, S.J., Knudson, C.M., 2002. Bax-dependent spermatogonia apoptosis is required for testicular development and spermatogenesis. Biol. Reprod. 66, 950–958.
Sanchez-Partida, L.G., Simerly, C.R., Ramalho-Santos, J., 2008. Freeze-dried primate sperm retains early reproductive potential after intracytoplasmic sperm injection. Fertil. Steril. 89, 742–745.
Sathananthan, A.H., Trounson, A.O., 2000. Mitochondrial morphology during preimplantational human embryogenesis. Hum. Reprod. 15 (Suppl. 2), 148–159.
Scheffler, I.E., 2001. A century of mitochondrial research: achievements and perspectives. Mitochondrion 1, 3–31.
Serke, H., Nowicki, M., Kosacka, J., Schroder, T., Kloting, N., Bluher, M., Kallendrusch, S., Spanel-Borowski, K., 2012. Leptin-deficient (ob/ob) mouse ovaries show fatty degeneration, enhanced apoptosis and decreased expression of steroidogenic acute regulatory enzyme. Int. J. Obes. (Lond.) 36, 1047–1053.
Shaha, C., Tripathi, R., Mishra, D.P., 2010. Male germ cell apoptosis: regulation and biology. Philos. Trans. Roy. Soc. Lond. B Biol. Sci. 365, 1501–1515.
Simoes, V.L., Alves, M.G., Martins, A.D., Dias, T.R., Rato, L., Socorro, S., Oliveira, P.F., 2013. Regulation of apoptotic signaling pathways by 5alpha-dihydrotestosterone and 17beta-estradiol in immature rat Sertoli cells. J. Steroid Biochem. Mol. Biol. 135, 15–23.
Smith, B.E., Braun, R.E., 2012. Germ cell migration across Sertoli cell tight junctions. Science 338, 798–802.
Soder, O., 2007. Sexual dimorphism of gonadal development. Best Pract. Res. Clin. Endocrinol. Metab. 21, 381–391.
Songsasen, N., Wesselowski, S., Carpenter, J.W., Wildt, D.E., 2012. The ability to achieve meiotic maturation in the dog oocyte is linked to glycolysis and glutamine oxidation. Mol. Reprod. Dev. 79, 186–196.
Sousa, A.P., Amaral, A., Baptista, M., Tavares, R., Caballero Campo, P., Caballero Peregrin, P., Freitas, A., Paiva, A., Almeida-Santos, T., Ramalho-Santos, J., 2011. Not all sperm are equal: functional mitochondria characterize a subpopulation of human sperm with better fertilization potential. PLoS ONE 6, e18112.
St John, J.C., Jokhi, R.P., Barratt, C.L., 2005. The impact of mitochondrial genetics on male infertility. Int. J. Androl. 28, 65–73.
St John, J.C., Facucho-Oliveira, J., Jiang, Y., Kelly, R., Salah, R., 2010. Mitochondrial DNA transmission, replication and inheritance: a journey from the gamete through the embryo and into offspring and embryonic stem cells. Hum. Reprod. Update 16, 488–509.
Stocco, D.M., 2001. StAR protein and the regulation of steroid hormone biosynthesis. Annu. Rev. Physiol. 63, 193–213.
Stocco, D.M., McPhaul, M.J., 2006. Physiology of testicular steroidogenesis. In: Neill, J.e. (Ed.), Knobil and Neill's Physiology Of Reproduction, third ed. Academic Press/Elsevier, St. Louis, MO, USA, pp. 977–1016.
Stouffer, R., 2006. Structure, function, and regulation of the corpus luteum. In: Neill, J.e. (Ed.), Knobil and Neill's Physiology of Reproduction, third ed. Academic Press/Elsevier, St. Louis, MO, USA, pp. 475–526.
Svechnikov, K., Spatafora, C., Svechnikova, I., Tringali, C., Soder, O., 2009. Effects of resveratrol analogs on steroidogenesis and mitochondrial function in rat Leydig cells in vitro. J. Appl. Toxicol. 29, 673–680.
Svechnikova, I., Svechnikov, K., Soder, O., 2007. The influence of di-(2-ethylhexyl) phthalate on steroidogenesis by the ovarian granulosa cells of immature female rats. J. Endocrinol. 194, 603–609.

Tavares, R.S., Martins, F.C., Oliveira, P.J., Ramalho-Santos, J., Peixoto, F.P., 2009. Parabens in male infertility-is there a mitochondrial connection? Reprod. Toxicol. 27, 1–7.
Tremellen, K., 2008. Oxidative stress and male infertility–a clinical perspective. Hum. Reprod. Update 14, 243–258.
Tuckey, R.C., Headlam, M.J., Bose, H.S., Miller, W.L., 2002. Transfer of cholesterol between phospholipid vesicles mediated by the steroidogenic acute regulatory protein (StAR). J. Biol. Chem. 277, 47123–47128.
Van Blerkom, J., 2008. Mitochondria as regulatory forces in oocytes, preimplantation embryos and stem cells. Reprod. Biomed. Online 16, 553–569.
Van Blerkom, J., 2009. Mitochondria in early mammalian development. Semin. Cell Dev. Biol. 20, 354–364.
Van Blerkom, J., 2011. Mitochondrial function in the human oocyte and embryo and their role in developmental competence. Mitochondrion 11, 797–813.
Varum, S., Momcilovic, O., Castro, C., Ben-Yehudah, A., Ramalho-Santos, J., Navara, C.S., 2009. Enhancement of human embryonic stem cell pluripotency through inhibition of the mitochondrial respiratory chain. Stem Cell Res. 3, 142–156.
Varum, S., Rodrigues, A.S., Moura, M.B., Momcilovic, O., Easley, C.A.t., Ramalho-Santos, J., Van Houten, B., Schatten, G., 2011. Energy metabolism in human pluripotent stem cells and their differentiated counterparts. PLoS ONE 6, e20914.
Wang, Q., Sun, Q.Y., 2007. Evaluation of oocyte quality: morphological, cellular and molecular predictors. Reprod. Fertil. Dev. 19, 1–12.
Wang, Q., Ratchford, A.M., Chi, M.M., Schoeller, E., Frolova, A., Schedl, T., Moley, K.H., 2009. Maternal diabetes causes mitochondrial dysfunction and meiotic defects in murine oocytes. Mol. Endocrinol. 23, 1603–1612.
Wang, Q., Frolova, A.I., Purcell, S., Adastra, K., Schoeller, E., Chi, M.M., Schedl, T., Moley, K.H., 2010. Mitochondrial dysfunction and apoptosis in cumulus cells of type I diabetic mice. PLoS ONE 5, e15901.
Watanabe, T., Chuma, S., Yamamoto, Y., Kuramochi-Miyagawa, S., Totoki, Y., Toyoda, A., Hoki, Y., Fujiyama, A., Shibata, T., Sado, T., Noce, T., Nakano, T., Nakatsuji, N., Lin, Sasaki, H., 2011. MITOPLD is a mitochondrial protein essential for nuage formation and piRNA biogenesis in the mouse germline. Dev. Cell 20, 364–375.
Wilding, M., Carotenuto, R., Infante, V., Dale, B., Marino, M., Di Matteo, L., Campanella, C., 2001. Confocal microscopy analysis of the activity of mitochondria contained within the 'mitochondrial cloud' during oogenesis in Xenopus laevis. Zygote 9, 347–352.
Wycherley, G., Kane, M.T., Hynes, A.C., 2005. Oxidative phosphorylation and the tricarboxylic acid cycle are essential for normal development of mouse ovarian follicles. Hum. Reprod. 20, 2757–2763.
Xu, G., Vogel, K.S., McMahan, C.A., Herbert, D.C., Walter, C.A., 2010. BAX and tumor suppressor TRP53 are important in regulating mutagenesis in spermatogenic cells in mice. Biol. Reprod. 83, 979–987.
Yacobi, K., Tsafriri, A., Gross, A., 2007. Luteinizing hormone-induced caspase activation in rat preovulatory follicles is coupled to mitochondrial steroidogenesis. Endocrinology 148, 1717–1726.
Yamamoto, C.M., Hikim, A.P., Lue, Y., Portugal, A.M., Guo, T.B., Hsu, S.Y., Salameh, W.A., Wang, C., Hsueh, A.J., Swerdloff, R.S., 2001. Impairment of spermatogenesis in transgenic mice with selective overexpression of Bcl-2 in the somatic cells of the testis. J. Androl. 22, 981–991.
Yan, W., Huang, J.X., Lax, A.S., Pelliniemi, L., Salminen, E., Poutanen, M., Toppari, J., 2003. Overexpression of Bcl-W in the testis disrupts spermatogenesis: revelation of a role of BCL-W in male germ cell cycle control. Mol. Endocrinol. 17, 1868–1879.
Yu, Y., Dumollard, R., Rossbach, A., Lai, F.A., Swann, K., 2010. Redistribution of mitochondria leads to bursts of ATP production during spontaneous mouse oocyte maturation. J. Cell. Physiol. 224, 672–680.
Zhang, X., Wu, X.Q., Lu, S., Guo, Y.L., Ma, X., 2006. Deficit of mitochondria-derived ATP during oxidative stress impairs mouse MII oocyte spindles. Cell Res. 16, 841–850.