



Contents lists available at ScienceDirect

The International Journal of Biochemistry
& Cell Biologyjournal homepage: www.elsevier.com/locate/biociel

1 Organelles in focus

2 Mitochondria: Participation to infertility as source of energy and
3 cause of senescence4 Q2 Moncef Benkhalifa^{a,*}, Yannick J. Ferreira^b, Hikmat Chahine^c, Nouredine Louanjli^d,
5 Pierre Miron^b, Philippe Merviel^a, Henri Copin^a6 Q3 ^a Reproductive Medicine & Medical Cytogenetics, Centre of Obstetrics and Gynecology, Regional University Hospital and School of Medicine, Picardie

7 University Jules Verne, Amiens, France

8 ^b Fertily Inc., Laval, Québec QC, Canada9 ^c Andrology unit, ForteBio Laboratory, Dax, France10 ^d IVF & Genetics Laboratory, LaboMac, Clinique des Iris, Casablanca, Morocco11
12
13
14
15
16
17
18
19
20
21
22
23
24
ARTICLE INFO

Article history:

Received 18 June 2014

Accepted 13 August 2014

Available online xxx

Keywords:

Mitochondria

Reactive oxygen species

Fertility potential

Reproductive pathology

Infertility

ABSTRACT

Mitochondria is a powerhouse organelle involved in ATP synthesis, calcium signaling, reactive oxygen species (ROS) by oxidative stress production, cell cycle arrest via apoptosis and sex steroid hormones biosynthesis. Improvement of sperm parameters such as motility, capacitation, acrosome reaction, and oocyte interaction, involve regulation of ROS levels by the mitochondria. In human, the relation between the quantitative level of mitochondrial DNA (mtDNA), oocyte cytoplasm maturation and fertilization potential, is not clear. It has been hypothesized that oocytes without sufficient wild type mtDNA and therefore able to generate ATP, would not normally be ovulated. This is reflected in the low numbers of mtDNA observed in degenerate oocytes obtained through super ovulation protocols during assisted reproductive technology programs. Different theories place mitochondria in a central role of oxidative damage to cells and tissues related to infertility declining and aging. Mitochondria-dependent apoptosis seems to be responsible for the pre and post-natal decline in germ cells, embryo development, implantation failure, and miscarriages.

© 2014 Published by Elsevier Ltd.

25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
Organelle facts

- Manages membrane potential, ATP, and oxidative metabolism. (Hua et al., 2012; Vadnais et al., 2014).
- Involved in abortive gametogenesis by playing a role in steroid hormones biosynthesis, germ cells genome decays and aging (George et al., 2011; Kasashima et al., 2014; Miller, 2013).
- Related with oocyte maturation and developmental potential in mammals. (Lee et al., 2014)
- Linked with oocyte activation (Wakai et al., 2013).
- Can mediate cell apoptosis and might be involved in implantation failure and reactivation of diapause blastocysts (Fu et al., 2014; Yang et al., 2014).
- Via the oxidative stress can be the origin of abortion and abnormal birth (Simmons, 2012; Tang et al., 2014).

* Corresponding author. Tel.: +33 685137369.

E-mail address: benkhalifamoncef78@gmail.com (M. Benkhalifa).<http://dx.doi.org/10.1016/j.biociel.2014.08.011>

1357-2725/© 2014 Published by Elsevier Ltd.

1. Introduction

Mitochondria participates in numerous processes in eukaryotic cells. Among these, the production of ATP via oxidative phosphorylation (OXPHOS) is certainly the most extensively described. Measuring between 0.5–1 μm in diameter by 7 μm long, this organelle although it can present different shapes (spheres or rods) it has a consistent architecture (Fig. 1). It is the only human organelle containing a distinct genome. The mitochondrial DNA (mtDNA) (Fig. 2) consists of a double-stranded molecule containing 37 genes encoding for 13 proteins, 2 rRNAs and 22 tRNAs. The 13 proteins are the constituents of the electron chain transport (ETC) complexes sub-units (Table 1). Depending on the cells, 2–10 molecules of mtDNA can be present in one mitochondria and 100–1000 mitochondria per cell. It was originally thought that mtDNA repair activity was inexistent but multiple mtDNA repair pathways have been revealed. These include base excision, single-strand break, mismatch repairs, and possibly homologous recombination. These pathways are similarly observed in the nucleus.

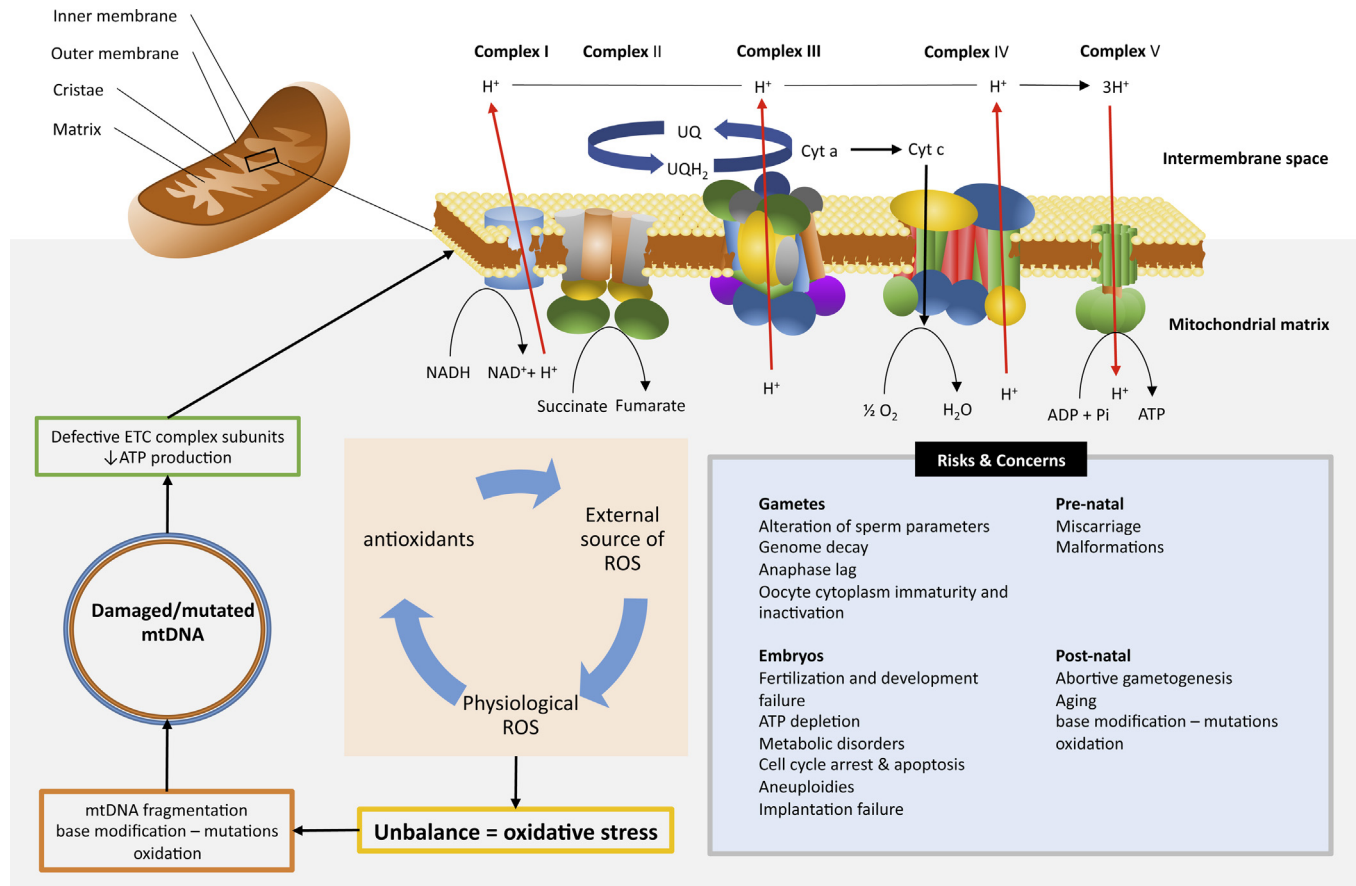


Fig. 1. Schematic of the electron transfer chain (ETC) and the effect of oxidative stress. Representation of the impact of oxidative stress on physiological balance of reactive oxygen species (ROS) over the mtDNA and consequently on the ATP production by oxidative phosphorylation. List of risks and concerns of the impact of oxidative stress on the gametes, embryos, pre-natal and post-natal stage of development. Structural scheme of human mitochondria.

Mitochondrial dysfunction has been associated with a large variety of disorders, such as, infertility, aging, and cancer diseases (Amaral et al., 2013b; Edeas and Weissig, 2013). In Functional Biology, the mitochondria play a fundamental role in oxidative metabolism by producing non-useful forms of adenosine triphosphate (ATP). Moreover, it has an important role during apoptosis, calcium homeostasis, and many anabolic pathways such as

proteins, nucleotides, and steroids synthesis (Pfeiffer et al., 2013). Different theories place mitochondria in a central role of cellular events related to aging by the accumulation of ROS and oxidative damage to cells and tissues. Mitochondrial defects are known to cause physio-pathological disorders including infertility and reproductive pathology. Different studies reported a clear relation between the qualitative abnormalities of mtDNA and infertility (Gabriel et al., 2012). Indeed, patients having specific mutations or deletions of mtDNA were identified as oligoasthenospermia (Lestienne et al., 1997).

Calcium oscillations are described as an essential step of oocyte activation leading to the completion of meiosis (Kashir et al., 2010). During oogenesis, oocytes with low levels of ATP production due to low levels of mitochondria and mtDNA may be unable to maintain the Ca²⁺ wave pacemaker, activating the apoptotic pathway. It has been hypothesized that oocytes without sufficient wild type mtDNA, and therefore the capacity to generate

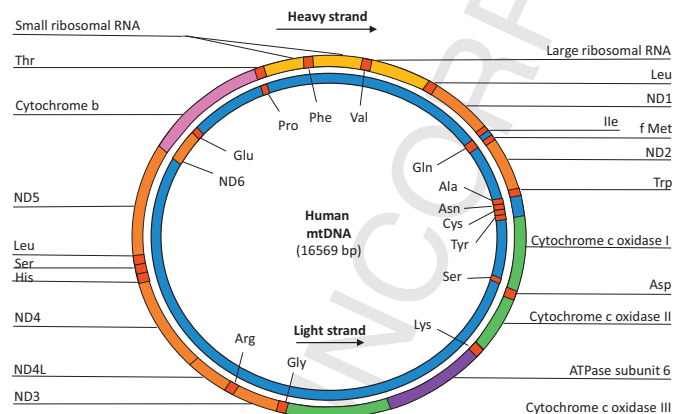


Fig. 2. Representation of the human mtDNA with respective gene locations. Scheme of the double-stranded molecule of mtDNA. In orange, the genes encoding for the subunits of the complex I from the electron transfer chain (ETC); in pink, the gene encoding for the subunit of the complex III; genes coding for the subunits of complex IV are represented in green; in violet, the gene encoding for the protein of the complex V.

Table 1
Electron transport chain link between mtDNA genes and ETC complex proteins.

ETC complex	Protein/encoding gene
Complex I	ND1; ND2; ND3; ND4; ND5; ND6
Complex III	Cytochrome b
Complex IV	CO1; CO2; CO3
Complex V	ATPase 6; ATPase 8

ATP, would not be ovulated (St John, 2002). This is reflected in the low numbers of mtDNA observed in degenerate oocytes after ovarian stimulation protocols (Duran et al., 2011). During early embryo development, unequal numbers of mitochondria and/or mtDNA molecules among blastomeres have been reported in pig and human embryos (El Shourbagy et al., 2006; Van Blerkom et al., 2000). This may result in some blastomeres with reduced ATP-generating capacity and leading to embryo arrest or low blastocyst development and implantation potential. Moreover, mitochondria have become an interesting target for drug discovery and therapeutics medicine (Edeas and Weissig, 2013). This review will focus on the potential contribution of mitochondria to infertility and reproductive pathology.

2. Organelle function

Mitochondria is a powerhouse organelle involved in ATP synthesis, calcium signaling, reactive oxygen species (ROS) by oxidative stress management and cell cycle arrest via apoptosis. In human cells, the number of mitochondrial DNA copies varies in relation with the cell type. Mitochondrial genome is a circular double-stranded DNA with main genes coding for ribosomal RNAs, transfer RNAs, and respiratory protein chains. Different theories place mitochondria in a central role of cellular events related to fertility declining (Buzadzic et al., 2014), aging (Kong et al., 2014), and reproductive pathology in general (Mando et al., 2014). Due to the production, accumulation, and damage of ROS to cells and tissues, the mitochondrial disorders seem to be responsible for the pre and post-natal declining of germ cells quality (Perez et al., 2000), embryo development potential (Acton et al., 2004) and pregnancy loss (Pang et al., 2013).

3. Cell physiology

Normal function of mitochondria plays an essential role in enabling reproductive capacity. To date, few studies have investigated the role of promoting mitochondrial health in relation to fertility in humans (Shaum and Polotsky, 2013). During spermatogenesis there is a significant reduction of mitochondria number per cell due to mtDNA replication arrest. Mitochondria may supply sperm with energy for several purposes, including motility. It is known that sperm is also responsible for reactive oxygen species (ROS) production (Agarwal et al., 2014). It was reported that regulation of ROS levels is involved in sperm capacitation, motility acquisition, and acrosome reaction (Ramalho-Santos et al., 2009). In human sperm, there is clear evidence that alterations in the mitochondrial genome can compromise spermatogenesis efficiency (Amaral et al., 2013a). Another issue relates to protein synthesis, it is generally accepted that gene expression in mature sperm is restricted to the mitochondria. In fact, mammalian sperm seem to be able to synthesize both mitochondria-encoded RNAs.

During oocyte maturation and early embryo stage, mitochondria are distributed to different regions in the cytoplasm and probably in response to localized energy needs. Mitochondria are the most abundant and prominent organelle in the early embryo (Sathananthan and Trounson, 2000) and are thought to be exclusively derived from the oocyte (Cummins, 2000). During oogenesis, the oocyte cytoplasm diameter increases from 30 to 120 μm and accumulate a large number of metabolic substrates and mitochondria changes. The oogonia contain nearly a dozen of mtDNA copies, whereas the mature oocytes contain thousands. There is a clonal expansion from a very small number of selected mtDNA, allowing the oocyte to transmit to the new individual homoplasmic population of mtDNA (Van Blerkom et al., 2004). In human oocytes collected from IVF attempts, it was observed between 50,000 and

100,000 copies of mtDNA. But there is a large variability in copies numbers of mtDNA between oocytes of the same patient, including those from the same cohort (Duran et al., 2011). However, it is now established that the cohorts of oocytes with fertilization and activation failures are significantly less rich in mtDNA than those with a normal rate of fertilization and activation. The rate of mtDNA can thus be considered (like the sperm, but in reverse) as a good cytoplasmic maturation marker (Reynier et al., 2001). Oocyte mitochondrial dysfunction, expressed through declined cell respiration and electron transport, may contribute to diminished fertility, and is the cause of development delay and arrest in human preimplantation embryos (Thouas et al., 2004).

Oocyte mitochondria play a key role for the regulation of sperm-triggered Ca^{2+} waves essential for zygote activation by acting as a Ca^{2+} reservoir (Dumollard et al., 2003). The Ca^{2+} wave pacemaker that is necessary for meiosis ending at fertilization is maintained by mitochondrial uptake of Ca^{2+} . Oocytes with low levels of ATP production due to low levels of mitochondria and mtDNA may be unable to maintain the Ca^{2+} wave pacemaker, resume meiosis after fertilization. Indeed, failure to maintain the Ca^{2+} wave pacemaker can be triggered by oocyte apoptosis (Tripathi and Chaube, 2012).

Following fertilization, only the mitochondria from the oocytes are kept and serve as main early embryo mitochondria reservoir. These maternally inherited mitochondria, initially dispersed in the oocyte cytoplasm, are redistributed in the zygote. Significantly different numbers of copies were also observed between arrested 2-cell human embryos and those that developed further. The specific elimination of paternal mitochondria in the oocyte and the absence of replication of mtDNA in the fertilized egg are mechanisms, which can explain the very low presence and transmission of paternal mtDNA. The recognition and destruction of paternal mitochondria is based on the ubiquitination process of mitochondrial membrane protein (prohibitin) and initiates during spermatogenesis. When sperm decondensation starts in the oocyte cytoplasm, the ubiquitinated sites of paternal mitochondrial membranes (protected initially by disulfide bonds during epididymal transit) are exposed and targeted by proteolytic enzymes from the oocyte cytoplasm (Piko and Taylor, 1987). It has been reported, in 2013, that the uniparental inheritance of mtDNA results in a selection of asymmetric mutations that only affects male genotype which will not overcome natural selection, imposing a male-specific mitochondrial mutation load (Wolff and Gemmell, 2013).

It has been shown that oocyte ATP reduction can harm the kinetics of the embryo development, the blastulation rate and the implantation ability. Thus, ATP content is a good indicator of the vitality of the embryo (Brison and Leese, 1991). It has been hypothesized that oocytes without sufficient wild type mtDNA and therefore the capacity to generate ATP would not normally be ovulated also the failure to regulate mtDNA replication and mtDNA transmission during development is disadvantageous (St John, 2014). The disproportionate quantity of mitochondria and/or mtDNA molecules among blastomeres has been reported in the pig and human (El Shourbagy et al., 2006; Van Blerkom et al., 2000). This may result in blastomeres with reduced ATP-generating capacity. If this occurs early during development, blastomeres may fragment, resulting in embryo arrest or less competent blastocysts with fewer cell number. The production of ATP through glycolysis is far less efficient than through OXPHOS. It is therefore vital that sufficient mtDNA molecules are present at fertilization to maintain embryo survival until mtDNA replication (Margineantu et al., 2002).

With a better understanding of the role of this organelle in zygotes, blastocysts and ultimately on the offspring. Mitochondria distribution and number increasing assessment can be considered as a method to improve oocyte quality (Chappel, 2013). Mitochondria-dependent apoptosis seems to be responsible for

Table 2
Organelle pathology mutations related with mitochondria.

Localization	Mutation/gene	References
Sperm	ATPase 6; ATPase 8 ND2; ND3; ND5; CO II CO III (m.9588G > A)	Kumar et al., 2009 Shamsi et al., 2008 Baklouti-Gargouri et al., 2013
Unfertilized oocytes; 3 pro-nuclei zygote; arrested embryos	ATPase 6 CO III ND3	Hsieh et al., 2004
Low fertilization oocyte cohorts	ΔmtDNA5286	Yesodi et al., 2002

the pre- and post-natal decline in germ cells, embryo development, implantation failure and miscarriages and mitochondria constitute a common link between aging and fertility loss (Amaral et al., 2013b). It is possible that a sex-specific selective sieve in mitochondrial genome evolution is a contributing factor to sexual dimorphism in aging, commonly observed across species (Camus et al., 2012).

4. Organelle pathology

Mitochondria has a maternally inherited genome (mtDNA) and the accumulation of multiple mtDNA rearrangements is associated with loss of sperm function (St John et al., 2001). Moreover, DNA variations and high rate of mutations in D-loop of mtDNA was observed in maternal blood, a fact that may have a direct or indirect role in inducing oocyte maturation defect, early embryo cell death and repeated pregnancy loss (Seyedhassani et al., 2010; Vanniarajan et al., 2011). Furthermore, there is evidence that mtDNA mutations can have a striking impact on the viability of gametes and human embryos (Table 2). The effect of these mutations on the ETC (electron chain transport) can range from a decrease in ATP production up to cell cycle arrest and apoptosis (Fig. 1). Indeed, mutations on the ATPase and nicotinamide adenine dinucleotide dehydrogenase (ND) group of genes were identified in sperm from oligo-asthenozoospermic patients, resulting from oxidative stress (Kumar et al., 2009). Nonetheless, inhibiting mitochondrial metabolic activity during oocyte maturation has a negative impact on oocyte maturation and subsequent embryo developmental competence (Ge et al., 2012). Also, the possibility that defects in mitochondrial calcium regulation or bioenergetics homeostasis could have negative downstream development consequences, including imprinting disorders, can be considered in the

The mitochondria: Source of energy and cause of senescence

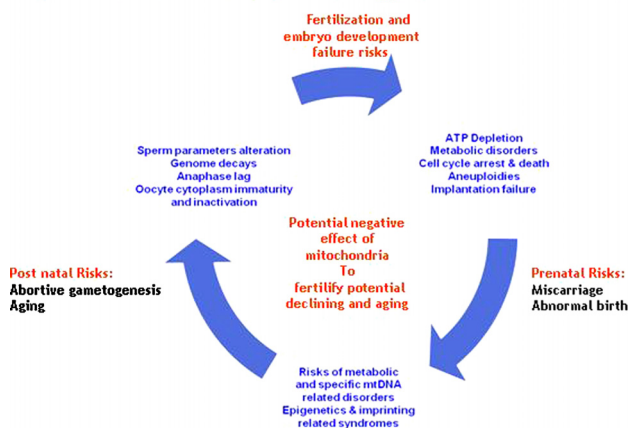


Fig. 3.

context of signaling pathways and cytoplasmic redox state (Van Blerkom, 2011).

5. Future outlook

There is clear contribution of mitochondria to infertility and reproductive pathology as source of energy and cause of senescence (Fig. 3). In clinical setting and during infertility management mitochondrial medicine should be considered during investigation and for potential treatment such as mitochondria transfer or disorder diagnostic. More research is needed to evaluate the potential of mitochondria mutation index as a diagnostic tool for patients undergoing assisted reproductive technology treatments.

References

- Acton BM, Jurisicova A, Jurisica I, Casper RF. Alterations in mitochondrial membrane potential during preimplantation stages of mouse and human embryo development. *Mol Human Reprod* 2004;10(1):23–32.
- Agarwal A, Tvrda E, Sharma R. Relationship among teratozoospermia, seminal oxidative stress and male infertility. *Reprod Biol Endocrinol: RB&E* 2014;12(1):45. <http://dx.doi.org/10.1186/1477-7827-12-45>.
- Amaral A, Lourenco B, Marques M, Ramalho-Santos J. Mitochondria functionality and sperm quality. *Reproduction* 2013a;146(5):R163–74. <http://dx.doi.org/10.1530/REP-13-0178>.
- Amaral S, Amaral A, Ramalho-Santos J. Aging and male reproductive function: a mitochondrial perspective. *Front Biosci* 2013b;5:181–97.
- Baklouti-Gargouri S, Ghorbel M, Ben Mahmoud A, Mkaouer-Rebai E, Cherif M, Chakroun N. A novel m.6307A>G mutation in the mitochondrial COXI gene in asthenozoospermic infertile men. *Mol Reprod Dev* 2013;80(7):581–7. <http://dx.doi.org/10.1002/mrd.22197>.
- Brison DR, Leese HJ. Energy metabolism in late preimplantation rat embryos. *J Reprod Fertil* 1991;93(1):245–51.
- Buzadzic B, Vucetic M, Jankovic A, Stancic A, Korac A, Korac B<ET AL>. New insights into male (in) fertility: the importance of NO. *Br J Pharmacol* 2014. <http://dx.doi.org/10.1111/bph.12675>.
- Camus MF, Clancy DJ, Dowling DK. Mitochondria, maternal inheritance, and male aging. *Curr Biol: CB* 2012;22(18):1717–21. <http://dx.doi.org/10.1016/j.cub.2012.07.018>.
- Chappel S. The role of mitochondria from mature oocyte to viable blastocyst. *Obstet Gynecol Int* 2013;2013:183024. <http://dx.doi.org/10.1155/2013/183024>.
- Cummins JM. Fertilization and elimination of the paternal mitochondrial genome. *Hum Reprod* 2000;15(Suppl 2):92–101.
- Dumollard R, Hammar K, Porterfield M, Smith PJ, Cibert C, Rouviere C<ET AL>. Mitochondrial respiration and Ca²⁺ waves are linked during fertilization and meiosis completion. *Development* 2003;130(4):683–92.
- Duran HE, Simsek-Duran F, Oehninger SC, Jones HW Jr, Castora FJ. The association of reproductive senescence with mitochondrial quantity, function, and DNA integrity in human oocytes at different stages of maturation. *Fertil Steril* 2011;96(2):384–8. <http://dx.doi.org/10.1016/j.fertnstert.2011.05.056>.
- Edeas M, Weissig V. Targeting mitochondria: strategies, innovations, and challenges: the future of medicine will come through mitochondria. *Mitochondrion* 2013;13(5):389–90. <http://dx.doi.org/10.1016/j.mito.2013.03.009>.
- El Shourbagy SH, Spikings EC, Freitas M, St John JC. Mitochondria directly influence fertilization outcome in the pig. *Reproduction* 2006;131(2):233–45. <http://dx.doi.org/10.1530/rep.1.00551>.
- Fu Z, Wang B, Wang S, Wu W, Wang Q, Chen Y<ET AL>. Integral proteomic analysis of blastocysts reveals key molecular machinery governing embryonic diapause and reactivation for implantation in mice. *Biol Reprod* 2014;90(3):52. <http://dx.doi.org/10.1095/biolreprod.113.115337>.
- Gabriel MS, Chan SW, Alhathal N, Chen JZ, Zini A. Influence of microsurgical varicocelelectomy on human sperm mitochondrial DNA copy number: a pilot study. *J Assist Reprod Genet* 2012;29(8):759–64. <http://dx.doi.org/10.1007/s10815-012-9785-z>.
- Ge H, Tollner TL, Hu Z, Dai M, Li X, Guan H<ET AL>. The importance of mitochondrial metabolic activity and mitochondrial DNA replication during oocyte maturation in vitro on oocyte quality and subsequent embryo developmental competence. *Mol Reprod Dev* 2012;79(6):392–401. <http://dx.doi.org/10.1002/mrd.22042>.
- George SK, Jiao Y, Bishop CE, Lu B. Mitochondrial peptidase IMMP2L mutation causes early onset of age-associated disorders and impairs adult stem cell self-renewal. *Aging Cell* 2011;10(4):584–94. <http://dx.doi.org/10.1111/j.1474-9726.2011.00686.x>.
- Hsieh RH, Au HK, Yeh TS, Chang SJ, Cheng YF, Tzeng CR. Decreased expression of mitochondrial genes in human unfertilized oocytes and arrested embryos. *Fertil Steril* 2004;81(Suppl 1):912–8. <http://dx.doi.org/10.1016/j.fertnstert.2003.11.013>.
- Hua S, Zhang H, Song Y, Li R, Liu J, Wang Y<ET AL>. High expression of Mfn1 promotes early development of bovine SCNT embryos: improvement of mitochondrial membrane potential and oxidative metabolism. *Mitochondrion* 2012;12(2):320–7. <http://dx.doi.org/10.1016/j.mito.2011.12.002>.

- 315 Kasashima K, Nagao Y, Endo H. Dynamic regulation of mitochondrial
316 genome maintenance in germ cells. *Reprod Med Biol* 2014;13:11–20,
317 <http://dx.doi.org/10.1007/s12522-013-0162-0>.
- 318 Kashir J, Heindryckx B, Jones C, De Sutter P, Parrington J, Coward K. Oocyte
319 activation, phospholipase C zeta and human infertility. *Hum Reprod Update*
320 2010;16(6):690–703, <http://dx.doi.org/10.1093/humupd/dmq018>.
- 321 Kong Y, Trabucco SE, Zhang H. Oxidative stress, mitochondrial dysfunction and
322 the mitochondria theory of aging. *Interdiscip Top Gerontol* 2014;39:86–107,
323 <http://dx.doi.org/10.1159/000358901>.
- 324 Kumar R, Venkatesh S, Kumar M, Tanwar M, Shamsi MB, Kumar R. Oxidative stress
325 and sperm mitochondrial DNA mutation in idiopathic oligoasthenozoospermic
326 men. *Indian J Biochem Biophys* 2009;46(2):172–7.
- 327 Lee SK, Zhao MH, Kwon JW, Li YH, Lin ZL, Jin YX. The association of mitochon-
328 drial potential and copy number with pig oocyte maturation and developmental
329 potential. *J Reprod Dev* 2014.
- 330 Lestienne P, Reynier P, Chretien MF, Penisson-Besnier I, Malthiery Y, Rohmer V.
331 Oligoasthenospermia associated with multiple mitochondrial DNA rearrange-
332 ments. *Mol Hum Reprod* 1997;3(9):811–4.
- 333 Mando C, De Palma C, Stampalija T, Anelli GM, Figus M, Novielli C<ET AL>.
334 Placental mitochondrial content and function in intrauterine growth restric-
335 tion and preeclampsia. *Am J Phys Endocrinol Metab* 2014;306(4):E404–13,
336 <http://dx.doi.org/10.1152/ajpendo.00426.2013>.
- 337 Margineantu DH, Gregory Cox W, Sundell L, Sherwood SW, Beechem JM, Capaldi
338 RA. Cell cycle dependent morphology changes and associated mitochon-
339 drial DNA redistribution in mitochondria of human cell lines. *Mitochondrion*
340 2002;1(5):425–35.
- 341 Miller WL. Steroid hormone synthesis in mitochondria. *Mol Cell Endocrinol*
342 2013;379(1–2):62–73, <http://dx.doi.org/10.1016/j.mce.2013.04.014>.
- 343 Pang W, Zhang Y, Zhao N, Darwiche SS, Fu X, Xiang W. Low expression of
344 Mfn2 is associated with mitochondrial damage and apoptosis in the pla-
345 cental villi of early unexplained miscarriage. *Placenta* 2013;34(7):613–8,
346 <http://dx.doi.org/10.1016/j.placenta.2013.03.013>.
- 347 Perez GI, Trbovich AM, Gosden RG, Tilly JL. Mitochondria and the death of oocytes.
348 *Nature* 2000;403(6769):500–1, <http://dx.doi.org/10.1038/35000651>.
- 349 Pfeiffer NV, Dirndorfer D, Lang S, Resenberger UK, Restelli LM, Hemion C<ET
350 AL>. Structural features within the nascent chain regulate alternative tar-
351 getting of secretory proteins to mitochondria. *EMBO J* 2013;32(7):1036–51,
352 <http://dx.doi.org/10.1038/emboj.2013.46>.
- 353 Piko L, Taylor KD. Amounts of mitochondrial DNA and abundance of some mitochon-
354 drial gene transcripts in early mouse embryos. *Dev Biol* 1987;123(2):364–74.
- 355 Ramalho-Santos J, Varum S, Amaral S, Mota PC, Sousa AP, Amaral A. Mitochon-
356 drial functionality in reproduction: from gonads and gametes to
357 embryos and embryonic stem cells. *Hum Reprod Update* 2009;15(5):553–72,
358 <http://dx.doi.org/10.1093/humupd/dmp016>.
- 359 Reynier P, May-Panloup P, Chretien MF, Morgan CJ, Jean M, Savagner F<ET AL>.
360 Mitochondrial DNA content affects the fertilizability of human oocytes. *Mol Hum
361 Reprod* 2001;7(5):425–9.
- 362 Sathananthan AH, Trounson AO. Mitochondrial morphology during preimplanta-
363 tional human embryogenesis. *Hum Reprod* 2000;15(Suppl 2):148–59.
- 364 Seyedhassani SM, Houshmand M, Kalantar SM, Modabber G, Aflatoonian
365 A. No mitochondrial DNA deletions but more D-loop point mutations
366 in repeated pregnancy loss. *J Assist Reprod Genet* 2010;27(11):641–8,
367 <http://dx.doi.org/10.1007/s10815-010-9435-2>.
- 368 Shamsi MB, Kumar R, Bhatt A, Bamezai RN, Kumar R, Gupta NP<ET AL>. Mitochon-
369 drial DNA mutations in etiopathogenesis of male infertility. *Indian J Urol*
2008;24(2):150–4.
- Shaum KM, Polotsky AJ. Nutrition and reproduction: is there evidence to
support a “Fertility Diet” to improve mitochondrial function? *Maturitas*
2013;74(4):309–12, <http://dx.doi.org/10.1016/j.maturitas.2013.01.011>.
- Simmons RA. Developmental origins of diabetes: The role of oxidative stress.
Best practice and research. *Clin Endocrinol Metab* 2012;26(5):701–8,
<http://dx.doi.org/10.1016/j.beem.2012.03.012>.
- St John J. The control of mtDNA replication during differentiation
and development. *Biochim Biophys Acta* 2014;1840(4):1345–54,
<http://dx.doi.org/10.1016/j.bbagen.2013.10.036>.
- St John JC. Ooplasm donation in humans: the need to investigate the trans-
mission of mitochondrial DNA following cytoplasmic transfer. *Hum Reprod*
2002;17(8):1954–8.
- St John JC, Jokhi RP, Barratt CL. Men with oligoasthenoteratozoospermia harbor
higher numbers of multiple mitochondrial DNA deletions in their spermatozoa,
but individual deletions are not indicative of overall etiology. *Mol Hum Reprod*
2001;7(1):103–11.
- Tang C, Liang J, Qian J, Jin L, Du M, Li M<ET AL>. Opposing role of JNK-p38 kinase and
ERK1/2 in hydrogen peroxide-induced oxidative damage of human trophoblast-
like JEG-3 cells. *Int J Clin Exp Pathol* 2014;7(3):959–68.
- Thouas GA, Trounson AO, Wolvetang EJ, Jones GM. Mitochondrial dysfunction in
mouse oocytes results in preimplantation embryo arrest in vitro. *Biol Reprod*
2004;71(6):1936–42, <http://dx.doi.org/10.1095/biolreprod.104.033589>.
- Tripathi A, Chaube SK. High cytosolic free calcium level signals apoptosis through
mitochondria-caspase-mediated pathway in rat eggs cultured in vitro. *Apopto-
sis* 2012;17(5):439–48, <http://dx.doi.org/10.1007/s10495-012-0702-9>.
- Vadnais ML, Cao W, Aghajanian HK, Haig-Ladewig L, Lin AM, Al-Alao
O<ET AL>. Adenine nucleotide metabolism and a role for AMP in
modulating flagellar waveforms in mouse sperm. *Biol Reprod* 2014.,
<http://dx.doi.org/10.1095/biolreprod.113.114447>.
- Van Blerkom J. Mitochondrial function in the human oocyte and embryo and
their role in developmental competence. *Mitochondrion* 2011;11(5):797–813,
<http://dx.doi.org/10.1016/j.mito.2010.09.012>.
- Van Blerkom J, Davis P, Alexander S. Differential mitochondrial distribution in
human pronuclear embryos leads to disproportionate inheritance between
blastomeres: relationship to microtubular organization, ATP content and com-
petence. *Hum Reprod* 2000;15(12):2621–33.
- Van Blerkom J, Davis P, Alexander S. Occurrence of maternal and paternal spindles
in unfertilized human oocytes: possible relationship to nucleation defects after
silent fertilization. *Reprod Biomed Online* 2004;8(4):454–9.
- Vanniarajan A, Govindaraj P, Carlus SJ, Aruna M, Aruna P, Kumar A<ET
AL>. Mitochondrial DNA variations associated with recurrent preg-
nancy loss among Indian women. *Mitochondrion* 2011;11(3):450–6,
<http://dx.doi.org/10.1016/j.mito.2011.01.002>.
- Wakai T, Zhang N, Vangheluwe P, Fissore RA. Regulation of endoplasmic reticu-
lum Ca(2+) oscillations in mammalian eggs. *J Cell Sci* 2013;126(Pt 24):5714–24,
<http://dx.doi.org/10.1242/jcs.136549>.
- Wolff JN, Gemmell NJ. Mitochondria, maternal inheritance, and asym-
metric fitness: why males die younger. *Bioessays* 2013;35(2):93–9,
<http://dx.doi.org/10.1002/bies.201200141>.
- Yang T, Li MH, Liu J, Huang N, Li N, Liu SN<ET AL>. Benzimidazole derivative,
BMT-1, induces apoptosis in multiple myeloma cells via a mitochondrial-
mediated pathway involving H+/K+-ATPase inhibition. *Oncol Rep* 2014.,
<http://dx.doi.org/10.3892/or.2014.3122>.
- Yesodi V, Yaron Y, Lessing JB, Amit A, Ben-Yosef D. The mitochondrial DNA mutation
(deltamtDNA5286) in human oocytes: correlation with age and IVF outcome. *J
Assist Reprod Genet* 2002;19(2):60–6.