The effect of Mitochondria, in biosynthesis of Sex Steroid Hormones, as Heme biosynthesis, and Hormones regulate mitochondrial as a Potential Target in Aging, Cancer and Autoimmunity Treatment and Prevention

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Abstract

On top of oxidative phosphorylation (OXPHOS), mitochondria perform other functions such asheme biosynthesis and oxygen sensing and mediate calcium homeostasis, cell growth, and cell death.

The genetic and biochemical heterogeneity of these states is remarkably similar to those of certain acquired diseases characterized by metabolic and oxidative stress and displaying wide variability.

However, emerging concepts of mitochondrial turnover and dynamics along with new mitochondrial disease models are providing opportunities to develop and evaluate mitochondrial based therapies.

Furthermore, Mitochondria play important roles in biosynthesis of sex steroid hormones, and these hormones can also regulate mitochondrial function. Understanding the cross talk between mitochondria and sex steroid hormones may provide insights into the pathologies associated with aging.

The effect of mitochondria on sex steroid hormone production in the gonads, and then enumerates the contribution of sex steroid hormones on mitochondrial function in hormone responsive cells.

In this article, I discuss Mitochondria and sex steroid hormone Biosynthesis, Mitochondrial damage in promote menopause and partial androgen deficiency, Sex steroid hormones and mitochondrial function, and Sex steroid hormone membrane receptors protect against mitochondrial oxidative damage

Key Word: Mitochondria, Sex steroid hormone, Androgen, Oxidative damage, Cancer, and Autoimmunity

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1. Introduction

Reflecting the fact that mitochondria have received increasing attention in recent decades, biomedical scientistsacross disciplines frequently appear to 'fortuitously' encounter mitochondria at one point or another through the natural development of their research program. Likewise, recent discoveries of unsuspected pathophysiological mechanisms involving this organelle abound acrossmedical disciplines (1),(2),(3). Is attributable to the convergence of key signaling pathways and biological processes onto the mitochondrion; As life evolved from unicellular organisms over the last 1.2–1.5 billion years, mitochondria played a permissive role in the evolution of multicellular organisms (4),(5), eventhough the exact timing of endosymbiosis is under debate (6). Most likely as a result of this evolutionary connectionto the basic cellular circuitry (7), mitochondria are intimatelylinked to a number of basic cellular and physiological functions(8). The present article focuses on classical and emerging aspects of mitochondrial biology and their relevance to specific areas of medicine, including inherited genetic disorders, neurology, oncology, immunology, endocrinology, and critical care medicine.Cases are outlined where considering emerging facets of mitochondrial biology has yielded new opportunities for diagnosis and/or therapy.

2. Mitochondria and sex steroid hormone Biosynthesis

2.1. Sex steroid hormone biogenesis

Mitochondria play an essential role during the initial steps of sex steroid hormone biosynthesis, particularly by producing the sex steroid hormone precursor pregnenolone. Import of cholesterol from the outer to the inner mitochondrial membrane is a rate limiting step during the initial biosynthesis of sex steroid hormones(9)Cholesterol transport involves interaction betweenthe steroidogenic acute regulatory protein (StAR) and a multi-component molecular complex, which is composed of an 18 kDatranslocator protein (TSPO), the voltage dependent anion channel, TSPO-associated protein 7, and protein kinase A subunit 1a(10). Once imported, cholesterol is converted to pregnenolone by the cytochrome P450 side-chain cleavage (P450scc; or CYP11A1) enzyme, located on the inner membrane of the mitochondria, involving the oxidation of nicotinamide adenine dinucleotide phosphate (NADPH) (11).Pregnenolone can then be exported out of the mitochondria and converted by specific microsomal P450 enzymes into the different sex steroid hormones(12). In males, testosterone biogenesis mostly occurs in Leydig cells through the sequential conversion of pregnenolone to 17α-hydroxypregnenolone, dehydroepiandrosterone (DHEA), androstenedione, and testosterone (11). In females, however, estrogen and progesterone biosynthesis occurs through the crosstalk between the granulosa and theca cells of the ovarian follicle. Pregnenolone in granulosa cells can diffuse to theca cells and be converted into androstenedione, which then re-diffuses back to granulosa cells and is eventually processed to estrogen. In some instances, androstenedione produced by the theca cells can also be immediately converted to testosterone in these cells. During the luteal phase of the menstrual cycle, progesterone is produced in luteinized granulosa cells by direct conversion from pregnenolone.

2.2. Mitochondrial damage may promote menopause and partial androgen deficiency

Mitochondria can produce reactive oxygen species (ROS) at multiple sites of the electron transport chain (13). During mitochondrial respiration, the electron transport chain generates a flux of electrons, capable of establishing a proton gradient within the mitochondria. While this proton gradient is necessary for ATP production, electrons produced during oxidative phosphorylation need to be completely neutralized to water upon reaction with oxygen at complex IV (that is, cytochrome c oxidase). However, partial reduction of oxygen can occur upstream of complex IV, resulting in production of superoxides. These superoxides are normallyeliminated by antioxidants (that is, superoxide dismutases, SOD) in the mitochondria. However, in certain conditions, some superoxides are thought to escape the mitochondrial antioxidant system and cause damage to mitochondrial proteins and DNA. Damaged mitochondriabecome less efficient in transferring electrons across the respiratory chain, rendering more electrons to be converted to superoxides. This positive feedback loop of mitochondrial
superoxide (ROS) production and mitochondrial damage was proposed to cause aging, a theory known as the free radical theory of aging (14),(15). Consistent with this theory, damage to mitochondrial DNA, lipids, and proteins increases with age, and is accompanied by decreased mitochondrial membrane potential and impaired mitochondrial (16),(17). In women, drop in sex steroid hormones during menopause is mainly attributed to loss of ovarian follicles. Continuous ovulation and follicular atresia, plus inability of follicles to naturally regenerate, eventually lead to reduced sex steroid hormone production. Aside from this progressive decline in follicle numbers, it is suggested that excessive oxidative damage in the ovaries,due to a decrease in the levels of antioxidants, may be a potential contributing factor for reproductive

aging(18). While it is yet to be shown whether mitochondrial ROSgeneration promotes mitochondrial damage in ovarian follicles, increased number of damaged mitochondria have been observed in ovarian follicles of aged women (19),(20), and the proportion of granulosa cells with ruptured mitochondrial membranes significantly increasewith age(19). While human studies only reveal correlations between mitochondrial damage and loss of ovarian follicles, mouse studies show that mitochondrial damage can contribute to reproductive aging. Mitochondrial DNA damage in a mouse model with defective mitochondrialDNA polymerase can reduce female fertility (21). Mitochondrial dysfunction in a mouse model with high mitochondrial ROS generation also results in infertility, defective folliculogenesis, and impaired ovulation (22). Hence, mitochondrial damage may potentially accelerate the decline in ovarian follicles and partly contribute to reproductive aging in females. In men, drop of testosterone levels during aging is associated with decreasing supply of mitochondrial steroidprecursors by Leydig cells(23),(24). In male rats, testosterone levels have also been shown to decline with age(25). This age-related decline in testosterone steroidogenesis is consistent with decreased mitochondrial expression of StAR and CYP11A1 in Leydig cells of old versus youngrats(26). While the cause of this decline in StAR and CYP11A1 expression is still unclear, it has been proposed that ROS may contribute to this effect. Increased mitochondrial ROS was observed in Leydig cells of old versus young rats(27). Transient elevation of ROS productionafter luteinizing hormone treatment caused more DNA damage in aged versus young Leydig cells (28). Moreover, ROS (that is, H2O2) can inhibit testosteronebiosynthesis in the mouse Leydig cell line MA-10 and a primary rat Leydig cell line(29),(30). But becausethe concentration used is relatively high (100 to 250 μM), the physiological relevance of this ROS-inhibition to steroidogenesis remains questionable. Nevertheless, while the biological impact of mitochondrial ROS on steroidogenesis needs further validation, the role ofmitochondria in producing steroid precursors suggests that properly functioning mitochondria are important to maintain sex steroid hormone levels. Hence, there is a need to critically evaluate the contribution of mitochondrial damage on sex steroid hormone production during aging.

2.3. Sex steroid hormones and mitochondrial function

Sex steroid hormone nuclear receptors regulate mitochondrial gene expressionWhile mitochondria mediate sex steroid hormone production, sex steroid hormones can also regulate mitochondrial function. Sex steroid hormones estrogen, progesterone, and testosterone classically function by binding to their nuclear receptors: estrogen receptors (ERα and ERβ1-6), progesterone receptors (PR-A and PR-B), and androgen receptors (AR1 and AR2), respectively. These receptors along with specific nuclear receptor co-regulators can directly or indirectly bind to nuclear DNA regulatory elements and influence gene expression(31). While the direct contributions of testosterone and progesterone on mitochondrial function are less studied, the effect of estrogen on mitochondrial function and biosynthesis is more evident. Estrogen, through its receptor, can directly modulate expression of genes important for mitochondrial function (Figure 1). Estrogen can directly up-regulate transcription of nuclear respiratory factor-1 (NRF1), a key transcription factor necessary for regulating expression of most of the mitochondrial respiratory chain complex proteins(32). NRF1 promoter contains putative estrogen receptor response elements capable of binding both ERs(32),(33). ERα can also interact with peroxisome proliferator-activated receptor gamma co-activator 1 (PGC-1), another important transcription factor that promotes transcription of NRFs and other mitochondrial proteins(34). Regulation of NRFs and PGC-1 by estrogen is thought to play an important role

in modulating overall mitochondrial biogenesis and function (35).

2.4. Sex steroid hormone membrane receptors protect against mitochondrial oxidative damage

Aside from the function of sex steroid hormones in the nucleus, sex steroid hormones can also have rapid, non-genomic actions by activating plasma membrane-associated receptors, leading to intracellular protein kinase-mediated phosphorylation signaling cascades(36). While studies regarding the contribution of plasma membrane-associated receptors on mitochondrial function are very limited, some reports suggest a role for this signaling in mitochondria. Estrogen, by acting on plasma membrane-associated ER, is thought to trigger a phosphorylation cascade and limit mitochondrial oxidative damage. One of the early studies suggesting this phenomenon was when a BSAconjugated form of estrogen, which is membraneimpermeable, was able to undergo rapid internalization and translocation into mitochondria but not the nucleus (37),(38). Estrogen, acting through intracellular phosphorylation cascades, may protect mitochondria from oxidative damage. One study shows that estrogen can activate the MAP kinase and NF-kB pathways to reduce cellular levels of hydrogen peroxides by stimulating the nuclear transcriptionof mitochondrial antioxidant enzyme Sod2(39). However, it remains to be confirmed whether this estrogenmediated Sod2 mRNA regulation is necessary to protect against mitochondrial oxidative damage. Another study also shows that estrogen can activate ERK, permit its translocation to the mitochondria, and enhance cytochrome c oxidase complex IV activity(40). Whether these estrogen actions are due to plasma membrane-associated receptors and whether they play a significant role in protecting mitochondria against oxidative damage needs furtherinvestigation.

2.5. Mitochondria-associated sex steroid hormone receptors protect against mitochondrial oxidative damage

Sex steroid hormone receptors, particularly ERs, have been observed to localize in mitochondria and contribute to mitochondrial function. Despite the controversy regarding mitochondrial localization of ERs (41),(42), accumulating evidence suggest that both ERα and ERβ are indeed present in the mitochondria, depending on cell type(43),(44),(45),(46), ERβ seems to be the ER that is more frequently present in mitochondria of most cell types (47),(48),(49),(50),(51). Knockdown of the ERβ1 isoform, which predominantly localizes to mitochondria, eliminates estrogen-dependent protection against peroxideinduced mitochondrial membrane depolarization(52). Using a targeting vector containing mitochondrial or nuclear localization sequences, ER can be efficiently targeted to mitochondria or nucleus(50). Expression of a mitochondrial-targeted, but not a nuclear-targeted ER, confers estrogen-dependent inhibition of UV-induced mitochondrial depolarization in a breast cancer cell line MCF-7 by enhancing mitochondrial SOD2 protein activity, independent of its transcriptional regulation(50). However, the mechanism of ER in regulating SOD2 protein activity remains unclear and needs further confirmation. Sex steroid hormone receptors in the mitochondria can regulate transcription of mitochondrial encoded genes(53). Mitochondrial DNA contains hormone response elements, which allow binding of steroid hormone receptors. Indeed, ER in the mitochondria can bind to estrogen response elements (ERE) located in mitochondrial DNA (54). This estrogenmediated ER binding to mitochondrial DNA is thought to increase expression of mitochondrial-encoded mitochondrial genes associated with the electron transport

Chain(55). Aside from regulating transcription of mitochondrial encoded genes, sex steroid hormone receptors have been suggested to bind to mitochondrial proteins. For example, ERβ has been shown to coimmunoprecipitate with the mitochondrial protein ATP synthase(55). However, whether this interaction is functional remains to be addressed. Hormone replacements improve mitochondrial function in healthy cells Estrogen can inhibit mitochondrial ROS generation in primary cells, such as endothelial cells, cardiomyocytes, and epithelial lens cells (52),(55),(56),(57). Animal experiments also demonstrate that estrogen can reduce mitochondrial ROS production and enhance mitochondrial respiration in normal brains of male and female rats(58),(59). Estrogen seems to limit mitochondrial ROS production in cell types, which are predominantly expressing ERβ, but a few studies have also supported a protective role of ERα (60). While estrogen replacement seems to provide overall beneficial effects on mitochondrial function, timing of treatment and type of cell may be important for this phenomenon. Estrogen can decrease mitochondrial ROS production in non-cancer primary cells, but it can also increase ROS production in damaged estrogenresponsive cancer cells (61),(62),(63). This suggests that while estrogen can protect normal cells from oxidative stress, it exacerbates oxidative stress in damaged cells, that is, cancer cells. While it remains unclear what mechanisms regulate this contradictory effect of estrogen on mitochondrial ROSproduction, the contribution of damaged versus healthy cell on estrogen action is consistent with the critical window and healthy cell hypothesis of estrogen replacement therapy (64),(65). This hypothesis proposes that estrogen replacement is only beneficial if performed at the appropriate time of a woman's life, before she accumulates a certain threshold of cellular damage. Indeed, estrogen replacement therapies seem to be more beneficial in younger versus older women(66). This is one of the rationales for the current KEEPS and ELITE studies on estrogen replacement therapies (67). Results from these studies will hopefully addresssome of these questions. The effect of testosterone replacement on mitochondrialfunction is less well understood. Low levels of testosterone in males seem to be associated with reduced expression of mitochondrial respiratory genes and activity (68). Orchiectomyin young male mice decreases expression of genes associated with energy metabolism, oxidative phosphorylation, and ubiquinone pathways (69). AR overexpression in myocytes increases mitochondrial enzyme activities and oxygen consumption (70),(71). Testosterone therapy potentiates the effect of low-intensity physical training in old male mice by increasing mitochondrial biogenesis, improving mitochondrial quality, and increasing spontaneousphysical activity, respiration, muscle mass, and grip strength (72). However, testosterone has also been shown to reduce mitochondrial function (73). Whether or not testosterone play a major role in mitochondrial function needs further investigation.

3. Conclusion

Mitochondrial functions respond to a number of genetic, metabolic, neuroendocrine signals by undergoing functional and morphological changes, and in turn generate signals that influence a large number of cellular functions contributing to disease complexity. For mitochondrial medicine, discoveries that mtDNA defects are at the origin of certain human diseases contributed novel diagnostic information for rare inherited monogenic metabolic disorders. Besides the well-established nuclear pathway involving the c-ErbA receptors, it appears that a recently identified direct mitochondrial pathway also plays a significant role by stimulating mitochondrial genome transcription with a very short latency period.In association with more delayed responses through the nuclear pathway leading to a stimulation of mitochondriogenesis, these mechanisms provide an efficient mitochondrial response to abrupt

and/or prolonged changes in physiological conditions.Moreover, currently studies show that mitochondria are important for the initial step of steroidogenesis, and sex steroid hormones (estrogens) are capable of regulating mitochondrial biogenesis and function. Dysregulation of mitochondrial function and sex steroid hormone action may compromise cellular integrity and lead to progressive decline in tissue function. Finally, no agent can rescue every cell or tissue, but a measurable impact on a subset of cells and conditions depending on the type of mitochondrial defect and the pathologic phenotype could be beneficial to tissue repair.

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