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Review

Glucocorticoid receptors and other nuclear transcription factors in mitochondria and possible functions

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ABSTRACT

The central role of mitochondria in basic physiological processes has rendered this organelle a receiver and integrator of multiple regulatory signals. Steroid and thyroid hormones are major modulators of mitochondrial functions and the question arises as to how these molecules act at the molecular level. The detection in mitochondria of steroid and thyroid hormone receptors suggested their direct action on mitochondrial functions within the context of the organelle. The interaction of the receptors with regulatory elements of the mitochondrial genome and the activation of gene transcription underlies the hormonal stimulation of energy yield. Glucocorticoid activation of hepatocyte RNA synthesis is one of the experimental models exploited in this respect. Furthermore, the interaction of the receptors with apoptotic/antiapoptotic factors is possibly associated with the survival-death effects of the hormones. In addition to the steroid/thyroid hormone receptors, several other receptors belonging to the superfamily of nuclear receptors, as well as transcription factors with well defined nuclear actions, have been found in mitochondria. How these molecules act and interact and how they can affect the broad spectrum of mitochondrial functions is an emerging exciting field.

1. Introduction

Mitochondria are the powerhouses of the cell, generating over 90% of its energy requirements by way of oxidative phosphorylation in the respiratory chain. The mitochondria host several other important metabolic processes, e.g. the Krebs cycle, β-oxidation of fatty acids and heme biosynthesis, thus playing a central role in cellular events [1,2]. Furthermore, they are involved in oxidative stress by way of reactive oxygen species generation, in immunomodulation and in ageing [3–6]. Consequently, these unique organelles are rendered receivers and integrators of several regulatory signals, modulating metabolic, growth, developmental and apoptotic processes [3,7–10].

Steroid and thyroid hormones are major regulators of such processes and their multiple actions on mitochondria in this respect have been explored [11–16]. Well studied are the effects of these hormones on biogenesis of mitochondria in muscle, distal colon, kidney and liver [15–17], as well as the actions of glucocorticoids and estrogens on apoptosis and survival of various cells, such as lymphocytes and endothelia [18–21]. As regards biogenesis of mitochondria and the respiratory complexes, a central feature of the hormonal regulation of this process is the encoding of the subunits of the respiratory enzymes in two cell compartments, nuclei and mitochondria [22], necessitating the coordination of the hormonal induced gene activation in two different cell sites [23–28]. The presence of steroid and thyroid hormone receptors in mitochondria (Table 1) [29,30] implicated a direct action of the hormones by way of their cognate receptors on mitochondrial gene transcription [31–33], which, in the case of thyroid hormones, has been experimentally verified [34,35].

2. Action of glucocorticoids on RNA metabolism of hepatocytes

Glucocorticoids are major gluconeogenic agents, inducing liver enzymes involved in this process by way of cognate receptor activation of gene transcription [36]. Hormone administration to adrenalectomized rats markedly stimulates nuclear RNA synthesis, encompassing HnRNA containing the mRNAs of the induced enzymes, ribosomal RNA and tRNA [37–39]. Importantly, mitochondrial RNA synthesis is also activated by the hormones [37,40]. This intense nucleic acid stimulation requires a high expenditure of energy, which the cell must eventually replenish. The involvement of mitochondrial RNA synthesis in the hormonal response can be correlated to this energy regeneration process, as the sole functional role of the mitochondrial genome is to encode subunits of enzymes of oxidative phosphorylation (OXPHOS) and the RNAs participating in the protein synthetic machinery of the mitochondrion. Due to the fact that most of

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Table 1
Receptors of the superfamily of nuclear receptors found in mitochondria

Receptor	Cell type
Glucocorticoid	Rat liver
	HeLa, Hep-2, HepG2, SaOS-2
	Rat brain, C6-glioma
	Salamander Müller
	Thymic epithelial
Estrogen beta	HepG2, SaOS-2, MCF-7
	Rabbit ovarian, uteri
	Murine hippocampal
	Neurons
	Human lens epithelial
	Human spermatocytes
	Murine cardiomyocytes
	Endothelial
Androgen	Human spermatocytes, LNCaP
Thyroid	Rat liver, cardiac
RXR	Rat liver
RAR	Rat liver
Nur77/TR3	Gastric cancer cell lines
	T cells, LNCaP
PPARgamma2	Rat Liver

Reviewed in [14,29,30].

the OXPHOS subunits are nuclearly encoded and are required for the formation of active respiratory complexes, a hormonal coordination of nuclear and mitochondrial transcription is necessary. This coordination is realized by way of activation of nuclearly encoded mitochondrial transcription factors, whose subsequent increased presence in mitochondria can per se stimulate the organelles transcription machinery [23–25,28,41]. In addition, a direct action of glucocorticoids on mitochondrial transcription was suggested (Fig. 1). This was

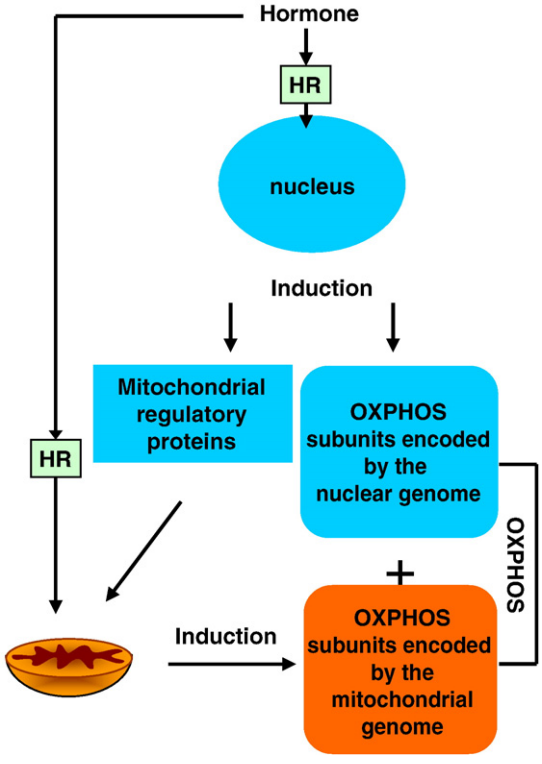

Fig. 1. Nuclear and mitochondrial action of steroid/thyroid hormones on OXPHOS biosynthesis by way of cognate receptors. In the nucleus, the hormone–receptor complex induces OXPHOS genes, and genes of mitochondrial transcription factors [13,14,29,30]. The mitochondrial transcription factors, subsequently, activate mitochondrial gene transcription. In addition, the hormone, can directly affect transcription of the mitochondrial OXPHOS genes by way of cognate mitochondrial receptors and their interaction with respective binding sites on the mitochondrial genome.

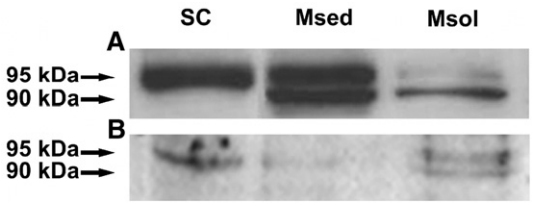

Fig. 2. Detection of a phosphorylated form of GR in mitochondrial extracts of HepG2 cells. Soluble cytosol (SC), mitochondrial membranous fraction (Msed) and mitochondrial soluble fraction (Msol) of HepG2 cells were isolated applying differential centrifugation and discontinuous sucrose gradient, as previously described [18]. Equal amounts of protein extracts from these fractions were submitted to electrophoresis and transferred to nitrocellulose membrane. Detection of the glucocorticoid receptor (A) and its phosphorylated form in Ser 211 (B) was achieved using specific antibodies recognizing the human GR and the phosphorylated glucocorticoid receptor (Ser 211) (provided by SantaCruz and cell signaling (# 4161), respectively).

based on studies of hormone distribution in liver cells, demonstrating a very rapid uptake of 3H-cortisol in mitochondria, with a similar kinetics as the uptake of the hormone in nuclei [42]. Furthermore, analysis of the radioactivity recovered from the liver cells revealed the bulk of the radioactivity in the cytosol, in form of metabolites, as the liver is not only a site of action of glucocorticoids but also of their metabolic transformation. However, the radioactivity recovered in the nuclear and mitochondrial fractions was mostly non-metabolized cortisol [42], suggesting that the mitochondrion, similarly to the nucleus, could be a direct site of action of glucocorticoids by way of the cognate receptor. Indeed, the glucocorticoid receptor (GR) was detected in liver mitochondria of adrenalectomized rats after hormonal induction of the animals, translocating from the cytoplasm [43]. Subsequently, the glucocorticoid receptor was detected in various other cell types [14,29,30] (Table 1). In our efforts to characterize the mitochondrial GR (mtGR) by Western blot analysis, we detected a 90 kDa GR isoform [18] which could correspond to the GRαB or GRαC isoform of the receptor [44]. This isoform, as it is previously suggested [45], may also represent a functional proteolytic product of an inducible cytosolic endoprotease activation, which leads to uncovering cryptic mitochondrial targeting signals and to mitochondrial translocation of the product [45]. Lower molecular weight GR fragments, predominantly found in liver mitochondria, could correspond to other GRα isoforms or represent proteolytic fragments of the receptor. The mitochondrial GR is present in a phosphorylated form (Fig. 2). These findings supported the suggestion, that the receptor could have direct effects on mitochondrial transcription, similarly as its action on nuclear genes.

3. Effects and molecular mechanisms of glucocorticoid action on RNA synthesis of hepatocyte mitochondria

Analysis of mitochondrial DNA of humans and rodents revealed the presence of nucleotide sequences with high similarity to glucocorticoid responsive elements (GREs) within the regulatory sites (D-loop) of the genome [46] (Fig. 3). In addition, potential GREs were also found within structural genes, e.g. of cytochrome oxidase I, ND I and 12S RNA [46]. Some of these sequences were shown to interact with the glucocorticoid receptor, as demonstrated in gel shift assays [49], and were able to confer hormone inducibility to reporter genes in transfection assays [50]. ChIP analysis of isolated mitochondria from hepatocarcinoma HepG2 cells verified binding sites for the glucocorticoid receptor in the D-loop of the mitochondria and in the genes ND I and 12S RNA (Psarra A-M.G., in preparation), supporting a direct action of the receptor on mitochondrial transcription.

If the coordination of mitochondrial transcription by glucocorticoids is solely accomplished indirectly by way of nuclear gene activation of mitochondrial transcription factors, then inhibition of nuclear RNA synthesis would block the activation of mitochondrial

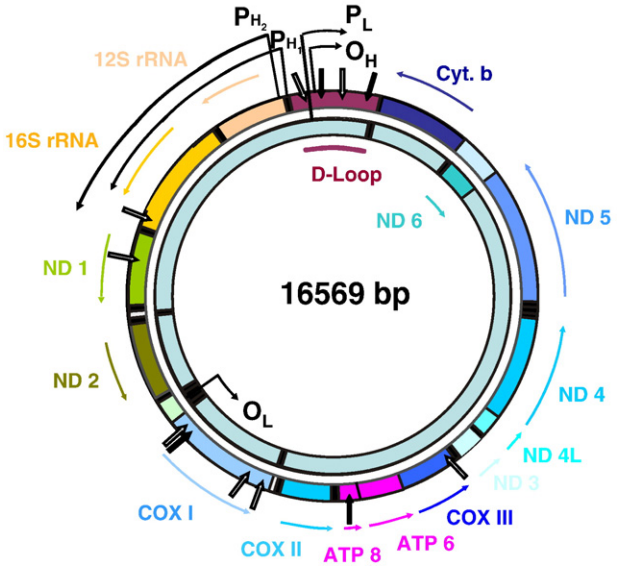

Fig. 3. The mammalian mitochondrial genome [47] and sites showing sequence similarity to hormone responsive elements (HREs) for steroid and thyroid hormones. The mammalian mitochondrial genome is a circular double stranded molecule of approximately 16 kb (human: 16,569 bases) composed of a heavy (H) and a light (L) strand. The L strand is transcribed from one predominant promoter (PL), whereas the H strand is transcribed from two adjacent promoters (PH1 and PH2), located in the control region, which includes a displacement (D) loop. Transcription emanating from PH2 and PL generates long, polycistronic products, subsequently processed at the sites of transfer RNA coding genes, liberating mature mRNAs and t-RNAs. Transcription from PH1 produces a short message containing the two rRNAs, terminating at a specific site on the tRNA-Leu gene. A transcription terminating factor (mTERF) promotes the termination of transcription initiated at the PH1 site. The mRNAs encode three subunits of cytochrome oxidase (I, II and III, COX I, COX II, COX III), seven of NADH-CoQ-reductase (ND I–VI and ND4L), one of cytochrome *b* (Cyt-*b*), two of ATP-synthase (ATP 6, 8), two ribosomal RNAs (12S and 16S rRNA) and 22 tRNAs. Only ND VI and the Gln, Ala, Asn, Cys, Tyr, Ser, Glu and Pro-tRNAs are generated from the light strand transcript. Three transcription factors have been characterized, mTFA, mTFB1 and mTFB2. The sites on the genome of the predicted [32,46] and experimentally verified [33, 48–51] binding sites for steroid and thyroid hormones are depicted: Open arrows: HREs for class I receptors, filled arrows: HREs for class II receptors [from Psarra and Sekeris [14]].

transcription. In case the hormone acts additionally by directly stimulating mitochondrial transcription, RNA synthesis in mitochondria would continue to proceed, perhaps somewhat attenuated, even in the presence of inhibitors of nuclear RNA synthesis. To this end, experiments with α-amanitin, a direct inhibitor of Pol II [52,53] and indirectly, of Pol I mediated transcription [54], were performed.

Indeed, various cell lines, e.g. HEK 293, HepG2 and HeLa cells, transfected with a construct carrying a mitochondrial targeted GR gene, reacted to the addition of an inducing dose of glucocorticoids by increased transcription of mitochondrial genes, among them ND I, ND II, ATP 8, Cyt *b*, COX I, COX II, COX III, 12S and 16S RNA, even in the presence of α-amanitin, whereas the induction of the nuclearly encoded COX IV gene was inhibited by the amatoxin (Fig. 4).

To provide further support for the direct activation by glucocorticoids of mitochondrial transcription, experiments are under way to study the import mechanism of the receptor and the consequence of this translocation for mitochondrial functions, in an in organello mitochondrial system derived from rat liver cells [55].

4. Other nuclear transcription factors in mitochondria

The detection of receptors for steroid and thyroid hormones in mitochondria (Table 1) initiated research towards elucidating their function within the confines of this organelle. As regards the thyroid hormone receptor, Enriquez et al. [34] and Casas et al. [35] have demonstrated a direct effect of the cognate receptor on mitochondrial transcription. A series of publications have strongly supported similar effects of the estrogen receptors on mitochondrial transcription of several target tissues [20,21,56]. Furthermore, apoptotic and anti-apoptotic actions of mitochondrial glucocorticoid and estrogen receptors, respectively, have been reported [14,19–21,57–60].

In previous publications and in the work presented here, a stimulatory action of glucocorticoids on mitochondrial transcription has been shown [37,40]. These findings support the concept whereby coordination of OXPHOS biosynthesis by steroid and thyroid hormones can be achieved by the direct effects of their cognate nuclear and mitochondrially localized receptors on nuclear and

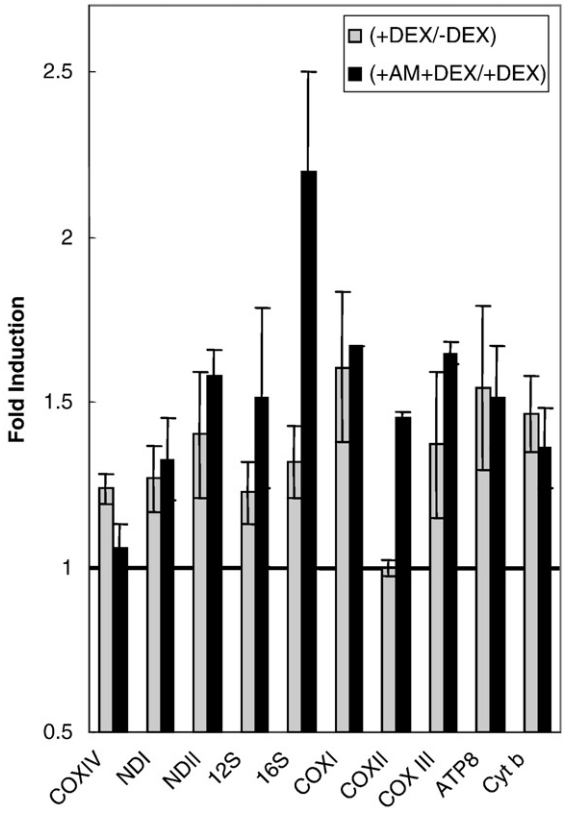

Fig. 4. Effect of mtGR on mitochondrial RNA synthesis in the presence of α-amanitin in HEK 293 cells. HEK 293 cells, grown in DMEM supplemented with 10% FBS, 2 mM L-glutamine and penicillin/streptamycin on 6 well plates, were transiently transfected with a pIRES vector carrying a mitochondria targeted GR. Cells were treated with 10 μg/ml α-amanitin, for 5 h, at 37 °C. α-Amanitin treated as well as non treated cells was further incubated in the presence of 10^{-6} DEX, for 1 h. Subsequently, cells were washed with phosphate buffer saline and total RNA was extracted using Trizol, followed by DNase treatment (Promega) and reverse transcription into cDNA, using random primers and superscript II reverse transcriptase (Invitrogen). Expressed levels of mRNA were quantitated using real-time RCR, which was performed after mixing the cDNA with SYBR GreenER qPCR super mix Universal (Invitrogen) and appropriate primers. Products were quantitated with a Chromo4 Real-Time System (Bio-Rad). Conditions for PCR were: 52 °C for 2 min, 95 °C for 2 min, 35 cycles of 95 °C for 15 s and 60 °C for 40 s, followed by 60 °C for 10 min. Primers for cytochrome oxidase subunits I–IV (COX I, COX II, COX III, COX IV), cytochrome *b* (Cyt *b*), NADH dehydrogenase subunits I, II, (ND I, ND II),12S and 16S ribosomal RNA (12S, 16S), and ATP synthase subunit 8 (ATP 8), glyceraldehyde 3-phosphate dehydrogenase (GAPDH, reference gene), were: COX I forward: ccctagaccaaacctacgccaaa; COX I reverse: aggccgagaaagtgttgtgggaa; COX II forward: acagatgcaattcccggacgtcta; COXII reverse: ggcatgaaactgtggtttgctcca; COX III forward: tcacttccactccataacgctcct; COX III reverse: gtgttacatcgcgccatcattggt; Cyt *b* forward: agtcccaccctcacacgattcttt; Cyt *b* reverse: agtaagcc-gagggcgtctttgatt; ND I forward: atggccaacctcctactcctcatt; ND I reverse: ttatggcgtcagc-gaagggttgta; ND II forward: ccatctttgcaggcacactcatca; ND II reverse: attatggatgcggttgcttgcgtg; 12S forward: aaactgctcgccagaacactacga; 12S reverse: tgagcaa-gaggtggtgaggttgat; 16S forward: taccctcactgtcaacccaacaca; 16S reverse: ttaaacatgtgt-cactgggcaggc; ATP 8 forward: accgtatggcccaccataattacc; ATP 8 reverse: tttatgggctttggtgagggaggt; COX IV forward: agaaagtcgagttgtatcgcatt; COX IV reverse: gataacgagcgcggtgaaac; GAPDH forward: catgagaagtatgacaacagcct; GAPDH reverse: agtcctttccacgataccaaagt.

Table 2
Nuclear transcription factors found in mitochondria

Receptor	Cell type
NF-κB	Jurkat T cells
	Human fibroblast HT1080
	Prostatic carcinoma cell lines
	U937 leukemic
	HeLa
AP-1	Murine brain
	Murine hippocampal
CREB	Brain neurons, dentral granular
p53	Human skin fibroblasts
	Rat embryo fibroblasts
	HA-1 hamster fibroblasts
	Human HT1080
	Thymocytes
	MRC-5, 32D, BAF-3
	Human ML-1, MCF-7
	Mouse liver
	KB human epidermoid

Reviewed in [14,30,61].

mitochondrial OXPHOS transcription, respectively [33,34,55]. This, in addition to the well established mechanism of coordination through hormonal activation of nuclearly encoded mitochondrial transcription factors [16,23,24,26–28,30,61–63].

The central role of mitochondria in several basic functions necessitates coordination with the functions of other involved cellular organelles by a variety of regulatory molecules. One such category is the superfamily of nuclear receptors, many of which have been localized in mitochondria from various sources [30]. Recently, the catalogue of regulatory molecules found in mitochondria has been enriched [14,64,65] (Table 2). Many of these molecules represent transcription factors with important role in nuclear gene regulation and their role in mitochondrial functions is now beginning to be revealed, particularly as regards cell survival and apoptosis [14,64,65]. Some of these factors seem to act on mitochondrial gene expression, others in a non-genomic manner, interacting directly with other regulatory molecules.

AP-1, NF-κB, CREB and p53 are among the major nuclear transcription factors detected in mitochondria of various cell types. AP-1 has been found in mitochondria of rat cerebral cortex and dental granular cells [66,67] and in mitochondria of prostate LNCaP cancer cells [68]. Binding of this factor to mitochondrial DNA, in the regulatory (D-loop) region, has been shown and associated with the regulation of mitochondrial DNA transcription [67]. Similarly, NF-κB has been localized in mitochondria of human leukemic Jurkat [69,70], fibroblast and prostate cancer [68,71] cell lines, whereas CREB has been found in brain mitochondria [72–74]. ChIP analysis identified CREB binding to cognate responsive elements in the D-loop. The antioxidant dexerozamine, which inhibits stress induced death, increased DNA-binding of CREB suggesting that modulation of mitochondrial transcription could underlie the salutary effect of dexerozamine. Several publications demonstrate the presence of p53 in mitochondria of many cell types [75–93]. The majority of the results point to an apoptotic action of p53 by way of a non-genomic mechanism and interaction with apoptotic factors [77,79,81,88,89]. Thus, targeting of p53 to mitochondria of p53-null SaOS-2 osteosarcoma cells is sufficient to induce apoptosis, furthermore the transactivation region of p53 is not needed for this effect [77,81]. However, some publications suggest a parallel genomic role of p53 in mitochondria [78,82–85].

5. Perspectives

The wealth of information amassed concerning the presence in mitochondria of regulatory molecules regarded as solely involved in nuclear actions increases the regulatory potential of mitochondria and opens perspectives in deepening our knowledge on the physiology of mitochondria and on recognizing and understanding the complexity of this organelle's interaction with the other cell compartments. An intriguing facet of this research is the mode of interaction of eukaryotic regulatory factors with the prokaryotic transcriptosome and with bona fide mitochondrial components. The new knowledge will be instrumental in delineating the aetiopathology of mitochondria related diseases and in designing therapeutic strategies.

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