Review

Nuclear receptors and other nuclear transcription factors in mitochondria: Regulatory molecules in a new environment

Anna-Maria G. Psarra [a], Constantine E. Sekeris [b],*

[a] *Biomedical Research Foundation, Academy of Athens, Center for Basic Research, 4 Soranou Efesiou, 11527, Athens, Greece*
[b] *National Hellenic Research Foundation, Institute of Biological Research and Biotechnology, Laboratory of Molecular Endocrinology, 48 Vas Constantinou Avenue, 11635, Athens, Greece*

Abstract

The mitochondrion is the major energy generating organelle of the cell and the site of other basic processes, including apoptosis. The mitochondrial functions are performed in concert with other cell compartments and are regulated by various extracellular and intracellular signals. Several nuclear receptors and other nuclear transcription factors, such as NF-κB, AP-1, CREB and p53, involved in growth, metabolic and developmental processes, have been detected in mitochondria. This finding raises the question as to the role of these regulatory molecules in their "new" environment. Experimental evidence supports the action of the mitochondrially localized transcription factors on mitochondrial transcription, energy yield and apoptosis, extending the known nuclear role of these molecules outside the nucleus. A principle of coordination of nuclear and mitochondrial gene transcription has been ascertained as regards the regulatory action of steroid and thyroid hormones on energy yield. Accordingly, the same nuclear receptors, localized in the two compartments–nuclei and mitochondria–regulate transcription of genes serving a common function by way of interaction with common binding sites in the two genomes. This principle is now expanding to encompass other nuclearly and mitochondrially localized transcription factors.
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1. Introduction

The molecular mechanisms of action and the role of nuclear transcription factors in their functional environment, the cell nucleus, have been intensively studied and partially revealed. This holds true in particular for steroid and thyroid hormone receptors, a major class of the superfamily of nuclear receptors, representing ligand activated transcription factors, involved in the regulation of metabolic, growth, developmental and immune processes [1]. In the ligand unbound, non-activated state, these receptors are components of a macromolecular complex with heat shock and other proteins. Upon binding with the cognate ligand, the receptors are released from the complex, form dimers and interact with hormone responsive elements (HREs) in the regulatory sites of the hormone modulated genes. This initiates a series of events involving several interacting proteins, e.g. transcription factors, coactivators and corepressors, histone modifying enzymes and the basal transcription machinery, leading to chromatin restructuring, culminating in the activation or repression of gene transcription [2]. In the case of action of thyroid hormones, the cognate receptor is found bound to chromatin, acting as a transcription repressor, from which it is released after interaction with the hormone, leading thus to transcription activation. Regulation of transcription can also be attained by interaction of the receptors as monomers, not directly with DNA, but with other transcription factors having direct access to respective DNA binding sequences [3]. Furthermore, hormones exert rapid, non-genomic effects [4] by way of classical receptors, G-protein associated receptors, or other still unidentified molecules [5,6] (Fig. 1). A host of other nuclear transcription factors has been characterized, e.g. NF-κB, AP-1, CREB and p53, activated by extracellular or intracellular regulatory molecules, involved in cell growth, differentiation,

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* Corresponding author. Tel.: +30 210 7273767; fax: +30 210 7273677.
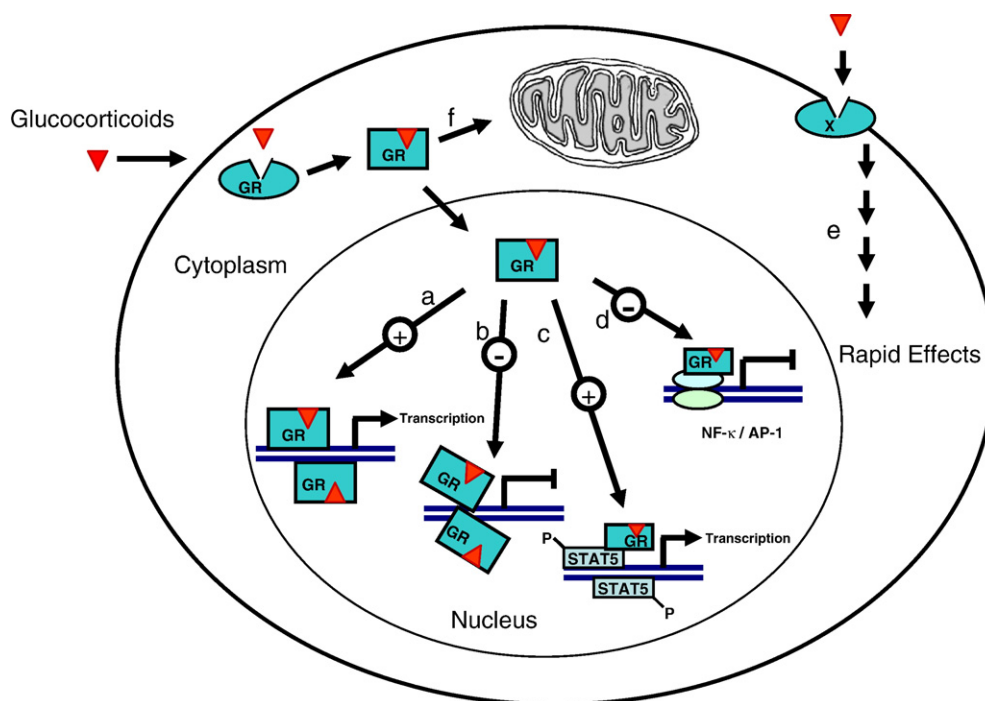*E-mail address:* csekeris@eie.gr (C.E. Sekeris).

Fig. 1. Mechanisms of action of steroid hormones in the example of glucocorticoids. The steroid hormones, by way of binding to cognate receptors and interaction with Hormone Responsive Elements, can (a) activate or (b) attenuate gene transcription. By protein–protein interaction of the hormone—receptor complex with other transcription factors the hormone can (c) activate, or (d) block gene transcription. The hormone can also lead to rapid, non-genomic effects (e) by way of classical receptor forms, G-protein coupled receptors or still unidentified molecules and signal transduction mechanisms. In mitochondria (f), the hormone—receptor complex, by interaction with the mitochondrial genome, can modulate mitochondrial transcription. GR, Glucocorticoid receptor; NF-κB, Nuclear Factor κB; AP-1, Activator Protein-1; STAT5, signal transducer and activator of transcription 5 [adapted from 5].

survival and apoptosis. Until recently, research on how the nuclear receptors and the other transcription factors exert their physiological functions was centered mainly on their action within the nuclear environment and their interaction with nuclear genes. The detection of steroid and thyroid hormone receptors in mitochondria of various cells and tissues raised the question of their role in this "new" environment, in particular their possible involvement in the regulation of mitochondrial transcription [5,7–11].

2. Nuclear receptors in mitochondria: Role in mitochondrial transcription and coordination of expression of genes encoding enzymes of oxidative phosphorylation (OXPHOS)

Receptors for glucocorticoids [12–18], estrogens [11,19–28], androgens [26], thyroid hormones [5,29–32], the retinoid receptor alpha (RXRα) [31,33], the retinoic acid receptor (RAR) [34], the orphan receptor Nur77/TR3 [35,36] and the peroxisome proliferator-activated receptor β- and γ2-coactivator (PPAR β- and γ2) related proteins [37], have been found in mitochondria of lymphocytes, of rat liver, brain, Mueller glia cells and periodontal ligament, of spermatocytes and of many cell lines [5,38].

Mitochondria are vital organelles, participating in important cellular functions [39]. They provide more than 90% of the energy requirements of the cell by way of oxidative phosphorylation in the respiratory chain (Fig. 2). Mitochondria are involved in many steps of intermediary metabolism, in urea production, heme

biosynthesis and β-oxidation of fatty acids. Furthermore, mitochondria are key components of the stress response [46], they play a central role in oxidative stress by way of reactive oxygen species (ROS) generation [27], in immunomodulation [47,48], in cell differentiation [49] and in ageing [50]. Derangements of mitochondrial functions have been etiologically correlated to neuromuscular degenerative diseases [51,52], such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and in cancer [53–55] (Fig. 2).

This central role of mitochondria in cell metabolism, necessitates an integration and coordination of their functions with those of other cell organelles, importantly with the cell nucleus [5,13,48,56–62]. Energy production by way of oxidative phosphorylation is such a function, in which both nuclear and mitochondrially encoded enzymes of oxidative phosphorylation (OXPHOS) are needed for the formation of active respiratory complexes [63]. The mitochondrion is a sensor of the energy requirements of the cell [64] attaining various levels of adaptive regulation of OXPHOS [57,64]. If the energy needs are not excessive, the respiratory chain increases the ATP yield by allosteric activation of the OXPHOS by metabolites, such as ADP. In cases of higher energy needs, such as evoked by glucocorticoid and thyroid hormones in target cells and during certain developmental periods [65,66], the cells react by increased biosynthesis of OXPHOS or, in extreme cases, by mitochondrial biogenesis, implicating increased transcription of nuclear and mitochondrial OXPHOS genes and increase in gene dosage [67].
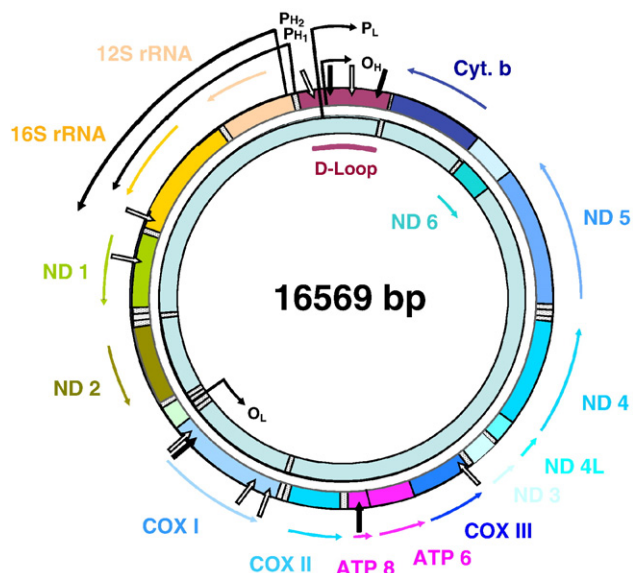
Fig. 2. The mammalian mitochondrial genome [40] and sites on the genome of sequences showing similarity to hormone responsive elements (HREs) for steroid and thyroid hormones. The mammalian mitochondrial genome is a circular double-stranded molecule of approximately 16 Kb (human: 16,569 bases). The two strands of the DNA have an asymmetric distribution of purines and pyrimidines, generating heavy (H) and light (L) strands. 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. The absence of intragenic space denotes that modulation of gene expression is confined to the D-loop, although the possible presence of intragenic regulatory sequences could offer possibilities of regulation of other stages of the transcription process. Transcription emanating from PH2 and PL generates long, polycistronic products, some of which are nearly full-genome length, subsequently processed at the sites of transfer RNA coding genes, liberating mature mRNAs and tRNAs. 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 1–6 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 ND6 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 [8,41] and experimentally verified [9,11,31,42,43] binding sites for steroid and thyroid hormones are depicted: Open arrows: HREs for class I receptors, Filled arrows: HREs for class II receptors [adapted from 5]. Several neurodegenerative diseases, e.g. Alzheimer's disease, Parkinson's disease and Huntington's chorea, appear to be etiologically correlated with mitochondrial DNA defects. In addition to mutations in the structural genes, with their known consequences on mitochondrial function, the role of defects in the mitochondrial genome regulatory sites should be considered in this respect. This has been previously stressed [5,13,40,44] and indeed experimentally demonstrated in the case of Alzheimer's disease, where mutations in the D-loop of brain mitochondria suppressed mitochondrial transcription and replication [45].

The coordination of OXPHOS gene transcription in the two cell compartments by the hormones emanates from the nucleus, where the hormone—receptor complex interacts with respective HREs to induce transcription of nuclear OXPHOS genes and also of transcription factors for these genes [58,68–70] (Fig. 3). In addition, mitochondrial transcription factors are induced

[56,70,77] which, translocate to the mitochondria. They thus achieve the required coordination of OXPHOS' gene transcription in the two cellular compartments [70]. The presence of steroid/thyroid hormone receptors in mitochondria and of HRE-like sequences in the mitochondrial genome [7,9,11,32,41–43] (Fig. 2) suggested an additional mode of coordination, by way of a direct effect of the mitochondrially localized receptor on mitochondrial transcription [5,7,9,11,13,33,61]. Accordingly, common transcription factors, the receptors, present in the nucleus and in the mitochondrion, activated by the same regulatory agent, the hormone, will ensure the coordination of a process requiring the parallel transcription of genes residing in the two cell organelles (Fig. 3).

Several studies in various systems supported an effect of nuclear receptors on mitochondrial transcription [5,11,65,55]. Direct experimental proof for the action of thyroid hormones on mitochondrial transcription was provided by the groups of Enriquez et al. [10] and Casas et al. [78] applying an organello mitochondrial system capable of sustaining faithful transcription for several hours [79]. The conclusion from these experiments was that the regulatory effect of T3 on mitochondrial transcription is exerted by a direct influence of the hormone on the mitochondrial transcription machinery, that it does not require the previous activation of nuclear genes, and that transcription initiation was the step affected by T3.

3. Nuclear receptors in mitochondria: Role in apoptosis

The unique role of mitochondria in supplying ATP to the cell by oxygen metabolism in the respiratory chain, a beneficial step in the evolutionary organismic explosion, leads invariably to the generation of reactive oxygen species (ROS), which represent major intrinsic apoptotic agents. Thus, the fluctuation of energy production by way of the respiratory chain can, in extreme cases, have deleterious consequences on cell viability [80,81]. Mitochondria receive and integrate several other intracellular and extracellular pro- and anti-apoptotic signals, therefore playing a decisive role in the cell's fate [35,62,82,83].

Steroid hormones are such major regulatory signals of apoptosis, inducing or inhibiting the process depending on the nature of the target cells and their mitochondria. These organelles demonstrate tissue specificity, as underlined by the fact that only a subset of their proteins are common in mitochondria of different cell types [84].

Estrogens are important anti-apoptotic signals for many cell types, such as breast cancer cells, endothelia and brain cells [25,85–87], whereas glucocorticoids are major apoptotic agents for thymocytes and leukemic cells [83,88]. A direct involvement of mitochondrial receptors in the apoptotic process in both cases is now emerging.

Estrogens promote the development, proliferation, migration and survival of breast cancer cells. The actions of estrogens are mediated by the two estrogen receptor forms, estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ). Studies in human hepatoma derived HepG2 and in human breast tumor MCF-7 cells, have demonstrated that 17β-estradiol administration leads to translocation of the two estrogen receptors into mitochondria
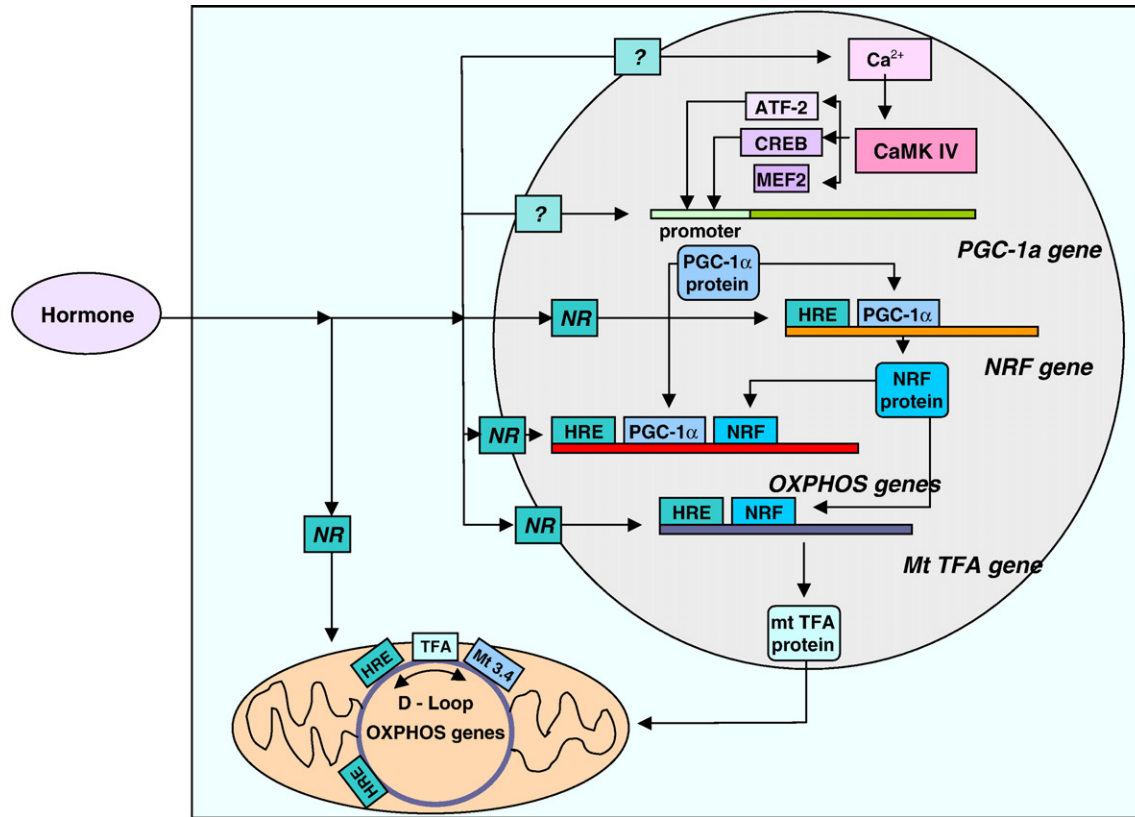
Fig. 3. Nuclear-cytoplasmic coordination of transcription of mitochondrial and nuclear genes encoding OXPHOS subunits by steroid/thyroid hormones. In the nucleus, the hormone—receptor complex (NR) can interact with hormone responsive elements (HREs) of oxidative phosphorylation (OXPHOS) genes, to directly activate them, and with HREs of nuclear respiratory factor (NRF) genes, to induce the respective transcription factors, which can then exert a positive effect on transcription of nuclear OXPHOS genes. By way of non-genomic modulation of intracellular $Ca2+$ concentration and activation of the calcium-calmodulin-dependent protein kinase IV (CaMKIV), the "master regulator" of mitogenesis, peroxisome proliferator-activated receptor γ-coactivator (PGC-1α) [71] is induced, which can directly and indirectly (be way of NRF induction) stimulate the transcription of nuclear OXPHOS genes and of the mitochondrial transcription factor A (mtTFA), which in mitochondria activates transcription. PGC-1α and PPARα can also be induced by thyroid hormones [72] and by glucocorticoids [73]. PCG1α/1β can also be induced by IFNγ by way of the JAK/STAT-1 pathway [74]. PCG1α/1β subsequently can activate the estrogen-related receptor α (ERRα), an orphan nuclear receptor [75], which by direct binding to promoters of genes important for mitochondrial functions, such as for oxidative phosphorylation or to promoters of factors controlling mitochondrial expression, lead to increased mitochondrial respiration and ROS production. In mitochondria, the hormones can directly affect transcription of the OXPHOS genes by way of cognate mitochondrial receptors and interaction with respective binding sites on the mitochondrial genome, ensuring an optimal coordination of OXPHOS gene transcription in the two genomes. The specific sequences Mt3 and Mt4, present in the 5′-flanking region of the genes encoding the cytochrome bcl complex and in the D-loop [76] are likely binding sites for still unknown coordinating regulatory factor(s). NRF, nuclear respiratoy factors 1,2; MEF2, Myocyte enhancer factor 2; ATF2, activating transcription factor 2; CREB, cAMP-response element-binding protein transcription factor; p53, tumor suppressive protein; NF-κB, Nuclear Factor κB; AP-1, Activator Protein 1 [adapted from 73].

[11,22]. Furthermore, 17β-estradiol increases the levels of mitochondrial encoded mRNAs for cytochrome oxidase subunits I, II, and III, and of respiratory enzyme activities [11,89,90]. As already mentioned, mitochondrial DNA contains sequences similar to nuclear Estrogen Response Elements (EREs), EMSA and surface plasmon resonance studies have demonstrated that the estrogen receptors bind to these sequences [11,89,90]. Therefore, the role of the mitochondrial estrogen receptors in mitochondrial transcription was considered in the protective effects of estrogens on apoptosis [90].

Experiments by Hsieh et al. [91,92] support the anti-apoptotic effect of the mitochondrial ERβ in the case of heart muscle of rats subjected to trauma and hemorrhage. Under such conditions, prolonged depression of cardiovascular functions, such as decreased cardiac output, occurs and the amount of ERβ in cardiac mitochondria decreases. 17β-estradiol and the ERβ agonist DPN, but not the agonist of the ERα PPT, restore cardiac

function and the amount of ERβ in mitochondria. Moreover, 17β-estradiol increases ERβ binding to mitochondrial DNA. Subsequently, the expression of COX I and COX II, the activity of the respiratory complex IV and the production of ATP increases, effects which underlie the cardioprotective effects of the hormone. A protective effect of estrogens on cerebral blood vessels and cultured endothelial cells, also supporting the involvement of mitochondrial estrogen receptors, has been reported by Stirone et al. [93], Duckles et al. [27] and Lu et al. [94]. In studies, focused on the regulation of vascular tone, O'lone et al. [95] applying gene expression profiling in mouse aorta, observed that ERα and ERβ regulate distinct and non-overlapping sets of genes. They showed, that ERβ is essential for most of the estrogen-mediated decrease, in gene expression. Among the genes attenuated are nuclear genes encoding subunits of the major respiratory complexes, presumably by direct binding of ERβ to the promoter of these genes. The downregulation of these genes in the aorta is in contrast to the

stimulatory effect of ERβ in other cell types and may reflect the biological consequences of estrogen in the different cell types.

Pedram et al. [25] also focused on the estrogen receptors as contributing to the mechanisms of cell survival. UV irradiation of MCF-7 cancer cells increases the mitochondrial generation of ROS, leading to translocation of the apoptotic factor Bax to mitochondria, to decrease of the mitochondrial membrane potential, to release of cytochrome *c* and finally to apoptosis. These effects are inhibited by estrogens. To show the direct anti-apoptotic involvement of the mitochondrial estrogen receptors, ER-negative breast cancer derived HCC-1569 cells and CHO cells were transfected with the E-domain (the ligand binding domain) of the estrogen receptor, specifically targeted either to the nucleus, or to the mitochondria by linking it with a mitochondrial localization signal. Targeting of the E-domain to the nucleus did not provide estrogen protection of the irradiated cells. However, the mitochondrially targeted E-domain of the receptor protected the cells from the UV induced cell death [25]. The applied estrogen receptor construct lacked the DNA binding domain of the receptor, therefore its anti-apoptotic effect does not seem to be mediated by a genomic action [25]. Similarly, estrogen protection from oxidative stress demonstrated by Razmara et al. [87] was in part due to activating the levels of manganese superoxide dismutase, the mitochondrial enzyme which catalyses superoxide radical breakdown. Effects of estrogens on this enzyme have been previously reported by Pedram et al. [25].

As regards glucocorticoids, the balance of hormone induced apoptosis versus apoptosis resistance depends on the cell lineage. The apoptotic effects of glucocorticoids are well documented on cells of the hematopoietic system, such as monocytes, macrophages, thymocytes and leukemic cells and require the presence of a functional glucocorticoid receptor [96]. In contrast, cells of epithelial origin, such as mammary gland cells, follicular cells and hepatocytes are protected by gluco-corticoids against apoptotic stimuli. The bulk of the extensive work concerning mechanisms of action of these hormones on apoptosis was centered on their transactivation and transrepression effects on nuclear apoptotic and anti-apoptotic genes, respectively. Many genes of the extrinsic and intrinsic death pathways are expressed in a pro-apoptotic manner upon treatment of sensitive lymphoid cells with glucocorticoids [97]. However, these effects alone are insufficient to elicit apoptotic death and additional signals are required to activate the apoptotic process.

Work by Sionov et al. [18,97] demonstrated the central role of the mitochondrial glucocorticoid receptor in the induction of apoptosis of leukemic cells. Using T-lymphoid cell lines varying in sensitivity towards glucocorticoids, these authors showed a rapid glucocorticoid induced translocation of GR in the mitochondria of sensitive cells, whereas in the resistant cells no such movement was evident. Furthermore, nuclear targeting of the receptor after hormone administration was similar in the two cell lines. Targeting the glucocorticoid receptor to mitochondria, by linking the receptor with the cytochrome oxidase mitochondrial localization signal, resulted in accumulation of the receptor in mitochondria and to apoptosis of the cells in a glucocorticoid independent manner. Thymic epithelial cells, which cause apoptosis of the PDI.6 T-cell line in a gluco-corticoid receptor dependent manner, induce translocation of the receptor to the mitochondria, but not to the nucleus, pointing also to the role of the mitochondrial receptor in eliciting apoptosis. These results are similar to the ones obtained by Li et al. [35], who targeted the nuclear orphan receptor TR3/Nur77 devoid of its DNA binding and transactivation domain to mitochondria and observed cytochrome *c* release and apoptosis and to those of Jeong et al. [36], who induced apoptosis by synthetic chenodeoxycholic acid derivatives in human cancer cell lines mediated by TR3/Nurr77 translocation into mitochondria. The experiments of Sionov et al. [18,97] demonstrate that the exclusive expression of GR in mitochondria is sufficient to induce apoptosis. The mechanism of action of the translocated receptor in mitochondria–whether the effects involve non-genomic or genomic actions or a combination of both–is being currently explored in the authors' laboratory.

3.1. Other nuclear transcription factor in mitochondria: Role in mitochondrial transcription and apoptosis

In addition to the nuclear family of receptors, several other transcription factors with well studied effects on the regulation of the activity of nuclear genes involved in cell proliferation, innate immunity and apoptosis, such as NF-κB, AP-1, CREB, p53, c-Myc [reviewed in 48], Wnt13 [98], Dok-4 [99], HMGA1 [100] and c-Src [101], have been detected in mitochondria (Fig. 4). Furthermore, binding sites in the mitochondrial genome for some of these molecules, homologous to their binding sites in the nuclear genome, have been determined by in silico methodology [102] and experimentally [103–108]. A role of these factors in mitochondrial transcription and energy metabolism in relation to apoptosis is now emerging [61,104–107,109,110]. In apoptosis, independent of the causative stimulus, these regulatory molecules in mitochondria mostly downregulate mitochondrial gene expression, intervening at various levels of this process.

NF-κB was detected in the intermembrane space of mitochondria of cells of the human leukemic T-cell line Jurkat, in association with I-κBα. Upon induction of apoptosis of these cells by engagement of the Fas surface molecule with a CH11 specific antibody, p65 was released from mitochondria together with I-κBα [111]. It was suggested, that the reservoir of I-κB and NF-κB in the intermembrane mitochondrial space could be involved in modulating apoptosis responses. NF-κB was also found in mitochondria of human fibroblast HT1080 cell lines, of human prostate LNCaP and PC3 cell lines [105] and of HeLa cells [112]. Cogswell et al. [113] reported the localization of NF-κB and I-κBα in mitochondria of U937 leukemia cells. Stimulation of the cells with TNFα led to degradation of I-κBα. Importantly, cytokine treatment reduced the expression of the mitochrondrially encoded cytochrome *c* oxidase III and cytochrome *b* mRNA. Blocking the activation of mitochondrial NF-κB by expression of the superrepressor form of I-κBα restored the expression of both cytochrome *c* oxidase III and cytochrome *b* mRNA. These results demonstrate that the
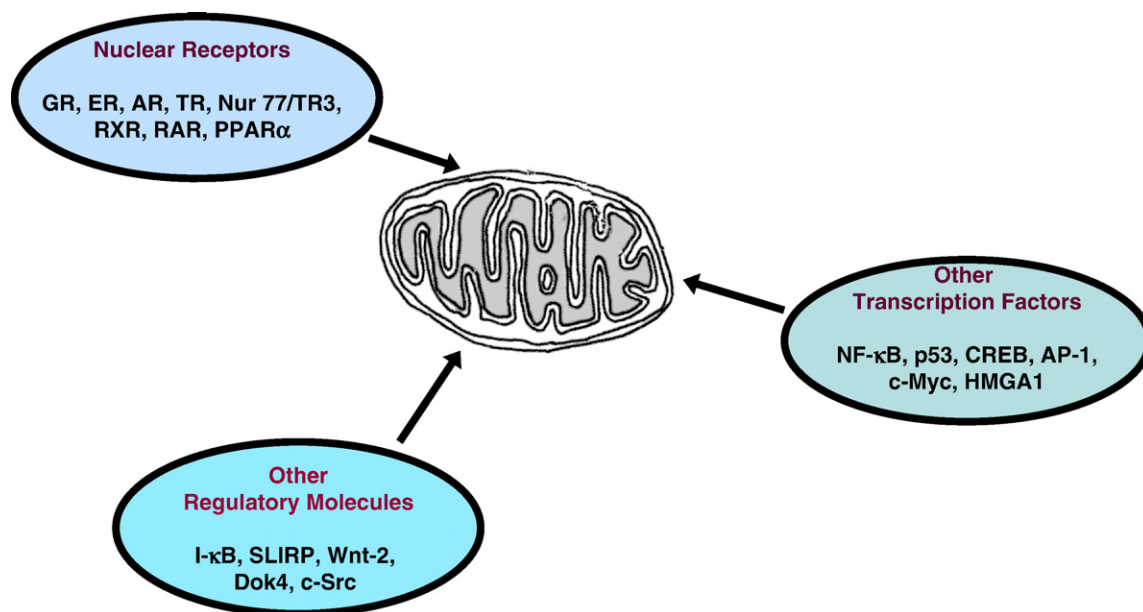
Fig. 4. Nuclear receptors, other transcription factors and regulatory molecules present in mitochondria. GR, Glucocorticoid receptor; ER, Estrogen receptor; AR, androgen receptor; TR, Thyroid receptor; NR77/TR3, orphan receptor NR77/TR3 [36]; RXR, Retinoid X Receptor; RAR, Retinoic Acid Receptor; PPARα, Peroxisome Proliferator-Activated Receptor α; NF-κB, Nuclear Factor κB; p53, tumor suppressive protein; CREB, cAMP-response element-binding protein transcription factor; AP1, Activator Protein 1; c-Myc, c-Myc oncogenes protein; I-κB, inhibitor of NF-κB; SLIRP, SRA stem–loop interacting RNA binding protein; Dok-4, downstream of tyrosine kinase adaptor protein 4 [99]; HMGA1, High Mobility Group A1 [100]; c-Src, cellular tyrosine kinase Src [101]; WNT2, Wingless-type MMTV integration site, family member 2.

NF-κB regulatory pathway exists in mitochondria and that this transcription factor negatively regulates mitochondrial mRNA expression.

The NF-κB p65 and p50 subunits detected in prostate LNCaP cell mitochondria, were in part bound to mitochondrial DNA [105]. This binding was increased by treatment of the cells with the TNF related apoptosis inducing ligand (TRAIL), without increasing the amount of NF-κB, suggesting activation of the transcription factor in the absence of additional translocation to the mitochondria. TRAIL treatment also led to decrease of mitochondrial encoded cytochrome oxidase III mRNA levels. The decrease was prevented by inhibiting NF-κB, pointing to the possible role of mitochondrial NF-κB in regulating mitochondrial gene transcription [106].

AP-1 is found in mitochondria of rat cerebral cortex cells and of dental granular cells [103,104] and its role there is currently being explored in relation to the action of glutamic acid and its agonist kainate. These excitatory agents participate in several neuronal functions by way of interaction with cognate receptors. In mice, they induce the expression of c-fos and c-jun and enhance binding of AP-1 to DNA both in nuclear and in mitochondrial extracts, as demonstrated by electrophoretic mobility shift assays (EMSA). This binding could be competed by oligonucleotides with sequence similarity to the AP-1 binding sites detected in the non-coding region of the mitochondrial DNA. The mitochondrial binding site of AP-1 was found to be localized in the D-loop region of the genome [104]. It was suggested, that kainate may facilitate the expression of the AP-1 complex and its subsequent translocation into mitochondria, where it could participate in mechanisms associated with regulation of mitochondrial DNA transcription. AP-1 has also

been detected in mitochondria of prostate LNCaP cancer cells and binding of the transcription factor to mitochondrial DNA was demonstrated. TRAIL treatment of the cells for 4 h led to maximal mitochondrial DNA binding activity of AP-1 and to decrease of mitochondrially encoded mRNA levels. This also suggested involvement of AP-1 in mitochondrial transcription in the TRAIL induced apoptosis of the cancer cells [105].

In studies dealing with the role of CREB in synaptic transmission, retrograde memory and brain function, this transcription factor was detected in rat brain mitochondria, concentrated in the inner membrane [109]. Mitochondrial CREB can be phosphorylated by a mitochondrially localized protein kinase A and can bind to double-stranded DNA containing the calcium-cyclic AMP-responsive element consensus sequence, as demonstrated by EMSA. These findings were confirmed by Schuh et al. [110]. Furthermore, both a phosphorylated and a non-phosphorylated form of CREB were found, as well as a calcium dependent phosphatase which regulates the phosphorylation state of the transcription factor [110]. CREB and protein kinase A were also found in the mitochondrial matrix of mouse neurons [108,109]. CREB-binding sites on the D-loop of the mitochondrial genome were also identified by CHIP analysis. Interestingly, dexerozamine, an antioxidant and iron chelator, known to inhibit oxidative stress-induced death, activated mitochondrial PKA, increased mitochondrial CREB phosphorylation and CREB binding to cognate responsive elements in the D-loop of the mitochondrial genome. It was suggested [107], that mitochondrial gene transcription modulation by CREB underlies the salutary effects of dexerozamine.

Several publications report the presence of p53 in mitochondria of various cell types (fibroblasts, human HT1080 cells,

murine C3H10T1/2 cells) and of PHA-stimulated peripheral blood mononuclear cells [114–123]. In apoptotic myeloid leukemia ML-1- and colorectal carcinoma RKO-cells, induced either by DNA damage or by hypoxia, a small but significant fraction of the stress-induced p53 was detected in the inner mitochondrial membrane, but also within the mitochondria, translocating from the cytoplasm [116]. The translocation of p53 in mitochondria is rapid and precedes the observed effects on mitochondrial membrane permeabilization and release of cytochrome *c*. These effects are blocked by overexpression of the anti-apoptotic protein Bcl-2 and BclX2 due to the formation of inhibitory complexes of these proteins with p53. Targeting of p53 linked to the mitochondrial leader sequence of ornithine transcarbamylase to mitochondria of p53-null SaOS-2 osteosarcoma cells, was sufficient to induce apoptosis in the tumor cells. Using deletion mutants of p53, the authors showed that the transactivation activity of p53 is fully dispensable for its mitochondrial action [116,120], pointing to a non-genomic action of mitochondrial p53 in apoptosis in this cell system. Similar findings have been reported in the irradiation induced apoptosis of mice thymocytes [118], in which also p53 was found in mitochondria. In irradiated thymocytes, p53 directly induces permeabilization of the outer mitochondrial membrane by forming complexes with protective BclXL through its DNA binding domain, resulting in cytochrome *c* release. Mutant p53 is unable to form BclXL complexes and does not lead to release cytochrome *c* from the mitochondria. However, a p53 binding motif within the 16S gene of the mitochondrion was found, conferring p53 responsiveness to a reporter gene in transfection experiments [106]. Furthermore, in hydrogen peroxide stressed HA-1 fibroblasts, a specific downregulation of mitochondrial RNA encoding OXPHOS, but not of nuclear RNA, was observed [117], as well as an inhibitory effect of a dominant-negative p53 mutant on the expression of mitochondrial 16S rRNA [121,122]. Also, p53 directly interacts with the mitochondrial transcription factor mtTFA [123]. These findings support a direct, negative effect of p53 on mitochondrial transcription in stress-related apoptotic states, in addition to its non-genomic actions.

3.2. The mitochondrion as a primary receiver and integrator of regulatory signal acting in cooperation with the nucleus

The recent explosion in the literature as regards the multiple functions of mitochondria, has exposed the role of these organelles not only as simple powerhouses and providers of the cell's energy requirements, but as a key site and important integrator of regulatory signals affecting the cell's fate—division, growth, differentiation, survival and apoptosis [5,52,57–62].

During the long history of symbiosis of the invading proteobacterium turned mitochondrion with its eukaryotic host [124], an adaptation of the functions of the new organelle to the regulatory mechanisms of the cell was necessary and apparently a prerequisite for the survival of both symbiont and host. Significantly, recent proteome analysis of the mitochondrion [84,125] has revealed proteins originally derived from the eubacterial ancestor and proteins that have been acquired from the host during the last two and a half billion years of symbiosis, some of which belong to the class of nuclear regulatory proteins.

As already presented, mitochondria host several transcription factors involved in the regulation of nuclear gene activity
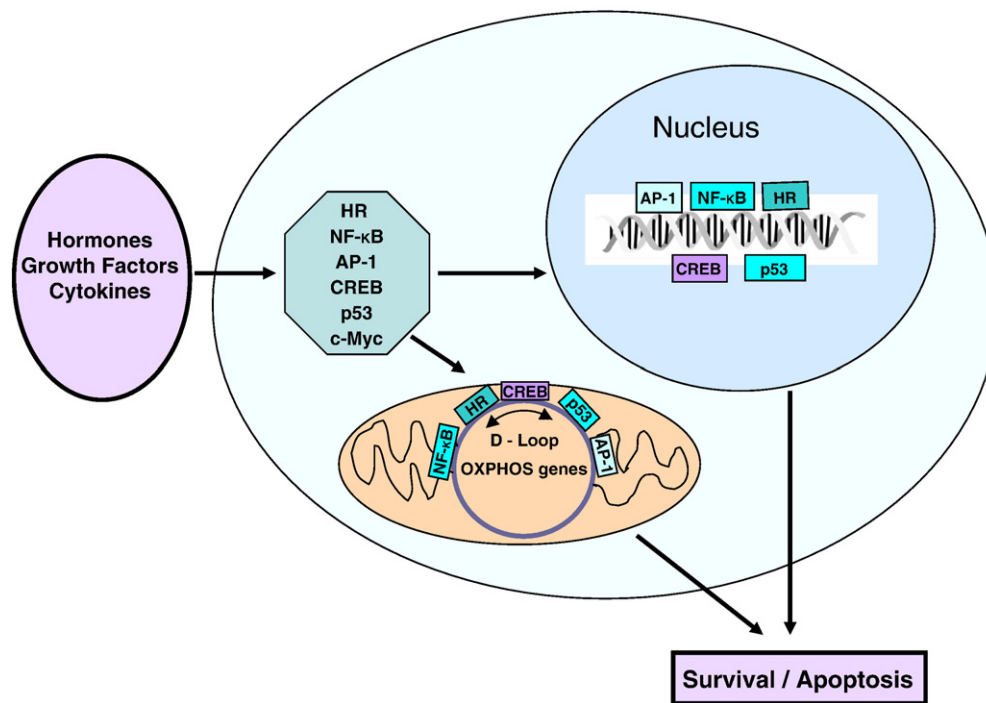

Fig. 5. The dual role of nuclear transcription factors on survival/apoptosis by way of nuclear and mitochondrial gene regulation. Nuclear transcription factors acting directly on both the nuclear and the mitochondrial genome in the process of apoptosis/survival induced by hormones, growth factors, cytokines and oxidative stress. AP-1, Activator Protein 1; NF-κB, Nuclear Factor κB; HR, Hormone Receptor; CREB, cAMP-response element-binding protein transcription factor; p53, tumor suppressive protein; OXPHOS, oxidative phosphorylation; c-Myc, c-Myc oncogenes protein.

pertaining to cell growth, differentiation, immune reactions and survival [reviewed in 5,61], whose role was previously regarded as solely nuclear. The mitochondrial localization of these transcription factors and the information obtained on their mechanism of action in mitochondria was instrumental in underlining the significant role of mitochondria as direct, primary receivers of regulatory signals, and in revealing their expanded and complex role in cell physiology (Fig. 5).

Regulation of energy production is one of the critical processes determining the cell's pathway towards survival and growth or apoptosis. It requires the participation of several mitochondrial and nuclear components, and, importantly, the coordination of the process in these two cell compartments. Indeed, oxidative phosphorylation, ATP production and its hormonal control can be viewed from the perspective of signal integration and coordination of gene activity carried out in different cell organelles as well as a paradigm of action of regulatory proteins undertaking a dual–in this case mitochondrial and nuclear–but common role. Thus, a hormone, steroid or thyroid, by way of common nuclear and mitochondrial transacting receptor proteins and common DNA binding sites for these receptors in the two genomes, can induce the expression of OXPHOS, providing coordinate transcription regulation.

Apoptosis is another vital cell process in which mitochondria play a major role. The mitochondria receive and integrate a series of apoptotic and survival signals, key among them the steroid hormones, with their demonstrable dual survival/apoptotic effects. In the apoptotic/anti-apoptotic action of these hormones in mitochondria, the role of mitochondrial receptors has been shown to be instrumental. Other nuclear regulatory proteins detected in mitochondria, such as the transcription factors NF-κB, AP-1, CREB and p53, have a well defined role within the nucleus—they participate in the regulation of genes, among them genes affecting apoptosis. Some of these transcription factors (NF-κB, AP-I and CREB) induce the expression of anti-apoptotic factors, others (p53), of apoptotic ones. In the mitochondrial environment their precise role is now beginning to be unraveled. Some bind to mitochondrial DNA sequences similar to cognate nuclear nucleotide sequences, and affect the mitochondrial transcription process, mostly attenuating mitochondrial gene expression, in contrast to their stimulatory effects on nuclear gene transcription. The precise mechanism of action of these transcription factors on mitochondrial gene expression, in relation to the apoptotic process, is a major field of further research. The detailed mechanism of the mitochondrial action of these transcription factors in the coordination of nuclear and mitochondrial apoptotic events is an expanding research field.

The catalogue of nuclear transcription factors detected in mitochondria is rapidly increasing. It is well known, that these factors show multiple interactions in their nuclear and cytoplasmic environment [126]. These interactions modify their DNA binding properties and their effects on transcription, thus increasing their regulatory possibilities on gene transcription. This could also be true as regards the mitochondrially localized transcription factors and their effects on mitochondrial transcription.

In this review, the emphasis was placed on the genomic actions of nuclear receptors and transcription factors in nuclei and in mitochondria, relative to OXPHOS gene expression and apoptosis. As already stressed, nuclear receptors and transcription factors also exert non-genomic, rapid effects and certainly such actions in mitochondria are important and could act in accord with the genomic role of these regulatory proteins.

Acknowledgements

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