Glucocorticoids and their receptors: Insights into specific roles in mitochondria

ARTICLE *in* PROGRESS IN BIOPHYSICS AND MOLECULAR BIOLOGY · APRIL 2013

Impact Factor: 2.27 · DOI: 10.1016/j.pbiomolbio.2013.04.001 · Source: PubMed

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Progress in Biophysics and Molecular Biology 112 (2013) 44–54

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Review

Glucocorticoids and their receptors: Insights into specific roles in mitochondria

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ARTICLE INFO

Article history:
Available online 16 April 2013

Keywords:
Glucocorticoid
Glucocorticoid receptor
Glucocorticoid response element
Mitochondria
Genomic
Non-genomic

ABSTRACT

Glucocorticoids (GCs) affect most physiological systems and are the most frequently used drugs for multiple disorders and organ transplantation. GC functions depend on a balance between circulating GC and cytoplasmic glucocorticoid receptor II (GR). Mitochondria individually enclose circular, double-stranded DNA that is expressed and replicated in response to nuclear-encoded factors imported from the cytoplasm. Fine-tuning and response to cellular demands should be coordinately regulated by the nucleus and mitochondria; thus mitochondrial–nuclear interaction is vital to optimal mitochondrial function. Elucidation of the direct and indirect effects of steroids, including GCs, on mitochondria is an important and emerging field of research. Mitochondria may also be under GC control because GRs are present in mitochondria, and glucocorticoid response elements (GREs) reside in the mitochondrial genome. Therefore, mitochondrial gene expression can be regulated by GCs via at least two different mechanisms: direct action on mitochondrial DNA and oxidative phosphorylation (OXPHOS) genes, or by an indirect effect through interaction with nuclear genes. In this review, we outline possible mechanisms of regulation of mitochondrial genes in response to GCs in view of translocation of the GR into mitochondria and the possible regulation of OXPHOS genes by GREs in the mitochondrial genome.

Contents

Abbreviations: AF, activation function (domain); AMP, adenosine monophosphate; ATP, adenosine triphosphate; COX, cytochrome c oxidase; D-loop, displacement loop (of mitochondrial genome); DBD, DNA-binding domain; LBD, (C-terminal) ligand-binding domain; GC, glucocorticoid; GR, glucocorticoid receptor II; GRE, glucocorticoid response element; mtDNA, mitochondrial DNA; mRNA, messenger RNA; nDNA, nuclear DNA; NLS, nuclear localizing sequence; NO, nitric oxide; NOS, nitric oxide synthase; NRF, nuclear respiratory factors; NTD, N-terminal domain; OXPHOS, (mitochondrial) oxidative phosphorylation; PGC-1, peroxisome proliferator-activated receptor (PPAR)-γ coactivator 1; PPAR, peroxisome proliferator-activated receptor; rRNA, ribosomal RNA; TFAM, mitochondrial transcription factor A; tRNA, transfer RNA; UCP-1, (mitochondrial) uncoupling protein-1.

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http://dx.doi.org/10.1016/j.pbiomolbio.2013.04.001

1. Introduction

Our understanding of the multiple effects of steroid hormones continues to advance (Hammes and Levin, 2011). Glucocorticoids (GCs; cortisol in humans and corticosterone in rodents) control approximately 20% of the expressed human genome, targeting almost all organs and tissues (Chrousos and Kino, 2005). GCs are crucial to life because they regulate and support an array of vital cardiovascular, metabolic, immunologic, and homeostatic functions. Although cortisol secretion varies diurnally (Dallman et al., 1993; Walker et al., 2012), its release also fluctuates depending on traumatic stress, as well as other types of stress, including illness, surgery, extreme temperatures, and psychological stress (Barnes, 2011; Biddie et al., 2012). GC participates in the establishment of a hypermetabolic state linked to physical or mental stress and trauma, and accompanied by an increased metabolic rate, skeletal muscle protein metabolism, liver gluconeogenesis, and hyperglycemia with insulin resistance (Brillon et al., 1995). GC deficiency or insufficiency is uncommon; for example, cortisol deficiency due to adrenocortical insufficiency rarely occurs, but may lead to hypotension, weight loss, asthenia, hypoglycemia, and secondary endocrine effects, including GC-reversible hypothyroidism, hyperprolactinemia, and hypercalcemia (Burke, 1985). Clinically, under- or over-production of GCs, as seen in Addison's (cortisol deficiency) or Cushing's (cortisol excess) syndrome, may result in adverse reactions or even death (Burke, 1985; Whitworth et al., 2000). As in the case of adrenalectomy, although GC insufficiency leads to upregulation of the glucocorticoid receptor II (GR), the GR does not function properly in the absence of GC (Gregory et al., 1976). Similarly, GC alone does not have significant effects on the cardiovascular or other organ systems. Therefore, the actions of GCs and the functional receptor system, the GR, are tightly coupled, and over- or under-stimulation of GC signaling may evoke pathological changes.

Mitochondria are integral to adenosine triphosphate (ATP) production, apoptosis (Fosslien, 2001; Green and Kroemer, 2004; Jeong and Seol, 2008), and production of biomolecules such as amino acids, lipids, hemes, purines, and steroid hormones (Miller, 2011). Intracellular cholesterol is ultimately converted to GC in the mitochondria (Miller, 2011) and the secretion of synthesized GC is tightly controlled by a specific mechanism in the adrenal gland (Rosol et al., 2001). Mitochondria also participate in intracellular calcium homeostasis; however, exposure to excessive Ca^{2+} levels causes massive swelling of the mitochondrial matrix, leading to necrotic cell death (Green and Kroemer, 2004). Furthermore, mitochondria are first-line responders to different stresses (Ryan and Hoogenraad, 2007) and can adjust bioenergetics, thermogenesis, and oxidative stress and/or apoptotic responses in response to perturbed homeostasis (Lesnefsky et al., 2001; Manoli et al., 2007). Consequences of mitochondrial damage include various diseases associated with multiple organ failure, which often precipitates the death of critical care patients (Kozlov et al., 2011). The concept that the nucleus is the domain of steroid receptor action has become controversial with the discovery of steroid hormone receptors and the GR in mitochondria and the identification of glucocorticoid response elements (GREs) in the mitochondrial genome (Demonacos et al., 1995, 1996; Martinus et al., 1996; Tsiriyotis et al., 1997). The consensus sequence of a positive GRE is 5′-GGTACAnnnTGTTCT-3′ (Gruber et al., 2004), whereas a negative GRE has a more variable sequence (Adcock, 2000). Based on these findings, exploration of the direct and rapid effects of steroid hormones on mitochondria is a novel field worthy of investigation (Gavrilova-Jordan and Price, 2007).

The dual localization of proteins in mitochondria and the nucleus, and the involvement of these proteins in control of gene expression or post-transcriptional processes, is also a common phenomenon among plants and higher eukaryotes (Duchene and Giege, 2012). It has been strongly postulated that the significance of the GR and GRE in mitochondria is crucial to understanding the effect of GCs on this organelle and the possibility of genomic interplay between the nucleus and mitochondria (Ioannou et al., 1988). Cytoplasmic GRs, which share no sequence homology with other known mitochondrial localization signals, can translocate into the liver (Demonacos et al., 1993; Psarra and Sekeris, 2011) and lymphoid cell mitochondria (Boldizsar et al., 2010), or move out of brain mitochondria (Demonacos et al., 1995), in response to dexamethasone (DEX) treatment or acute stress, implying that the mitochondrial GR is not static but is dynamically regulated in response to GCs. Simoes et al. (2012) also demonstrated that asthma, an inflammatory disease, reduces mitochondrial GR and OXPHOS enzyme biosynthesis in mouse lung epithelial cell monolayers. Although mitochondrial gene expression has been less well characterized than that of nuclear genes, there is a strong possibility that the GR also plays a role in mitochondrial gene expression. Because mitochondria also possess functional GREs, these organelles are not simply regulated by the nucleus; rather, the regulation of expression of some genes is finely and rapidly coordinated by translocation of the GR between the nucleus and mitochondria. Thus, the regulatory role of GC and GR on mitochondrial gene expression may take place through at least two different mechanisms: a direct effect on mitochondrial DNA (mtDNA) or an indirect effect via interaction with nuclear genes (e.g., those encoding mitochondrial RNA-processing enzymes, mitochondrial transcription factors, and nuclear respiratory factors). In this review, we outline the possible effects of GCs on regulation of mitochondrial gene expression in view of the localization of the GR in mitochondria and possible impacts on regulation of mitochondrial proteins.

2. Glucocorticoid receptor

The action of GCs is dependent on the expression of the GR, and, in turn, the functions of the GR in gene regulation are affected by chromatin structure, epigenetic factors, genetic variation, and the pattern of GC secretion (Biddie et al., 2012; John et al., 2011; Nicolaides et al., 2010). In addition, the GR can be also influenced by ligand binding, chemical compounds, post-translational modification, chaperones (or co-chaperones), GR isoforms, transcriptional co-regulators, transcription factors, and other proteins (Chrousos and Kino, 2005, 2007; Lu and Cidlowski, 2004). Therefore, complex GC–GR signaling activity contributes to the intricate nature of human physiology and pathophysiology.

The human GR is encoded by nine exons of a single gene located on chromosome 5 (Fig. 1). The protein consists of a variable N-terminal domain (NTD), two hormone-independent activation function domains (AF; AF1 and 2), a DNA-binding domain (DBD) with two zinc finger motifs, a hinge (H) region, and a C-terminal ligand-binding domain (LBD). The human GR also contains two nuclear localization sequences (Savory et al., 1999). Sumoylation sites are present in AF1. In the absence of ligand, newly synthesized GR is phosphorylated at three sites (S203, S221, and S226) and then rapidly dephosphorylated by protein phosphatase(s) associated with the LBD. Several post-translational modifications of GR-α, including phosphorylation, sumoylation, and ubiquitination, can modify aspects of signaling, such as subcellular localization, interaction with other proteins, and degradation (Anbalagan et al., 2012; Ismaili and Garabedian, 2004). The GR-α is a classical glucocorticoid receptor and has eight isoforms, with NTDs of different lengths, that are produced by alternative translation initiation from a single GR mRNA species. GR-α isoforms have different cellular distributions and gene regulatory profiles (Lu and Cidlowski, 2005; Oakley

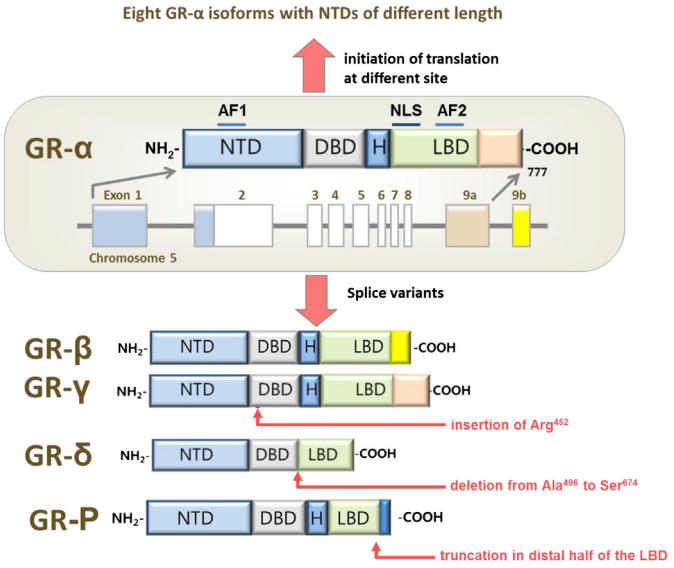

Fig. 1. Structure of the human GR. A single GR gene resides on human chromosome 5. Alternative splicing of nine exons produces the GR-α and GR-β isoforms. GR-α has an NTD, DBD with two zinc finger motifs, H region, and C-terminal LBD. GR-β has no LBD and acts as a dominant-negative form of GR-α (Yudt et al., 2003). The NLS and domains AF1 and AF2 are shown. Multiple GR-α isoforms are produced by initiation of translation of the NTD at alternative sites. Other GR variants, including GR-γ (arginine insertion between the two zinc fingers of the DBD), GR-δ (deletion of the proximal 185 amino acids of the LBD, encoded by exons 5–7), and GR-P (a truncated receptor mutant lacking the distal half of the LBD) have been reported in cancer, but exact functions of these variants are still unknown (McMaster and Ray, 2007). AF, hormone-independent activation function domain; DBD, DNA-binding domain; GR, glucocorticoid receptor II; LBD, ligand-binding domain; H, hinge; NLS, nuclear localizing sequence; NTD, N-terminal domain.

and Cidlowski, 2011). The splice variant GR-β is expressed at a lower level than GR-α (Pujols et al., 2002), and exerts a dominant-negative effect on the GR-α isoforms due to the absence of the LBD (Yudt et al., 2003). Other GR splice variants, including GR-γ, GR-δ, and GR-P, have been reported in some types of cancer (Fig. 1). GR-γ, an integral splice variant of GR-α, has an extra arginine in the DBD and shows reduced transcriptional activity compared with GR-α (Krett et al., 1995; Moalli et al., 1993; Rivers et al., 1999). However, the exact functions of these variants are still under investigation (McMaster and Ray, 2007). Mutations in the human GR gene can impair GC signal transduction by altering tissue reactivity to the GR, and can have various outcomes, ranging from asymptomatic to extreme cases of hyperandrogenism, fatigue, and/or mineralocorticoid excess (Charmandari and Kino, 2007). The GR is primarily metabolized via the ubiquitin/proteasome-dependent protein degradation pathway (Wallace and Cidlowski, 2001; Weber et al., 2002).

Insight into the pathophysiological role of the GR was gained in research using transgenic animal models (Cole et al., 2001; Goodwin et al., 2011; Sainte-Marie et al., 2007). The events of embryonic development were less affected in GR-deficient mice, but neonatal mortality was attributed to retarded lung maturation and lung collapse (Cole et al., 1995). In addition, these mice had decreased ability to induce expression of major gluconeogenic enzymes (i.e., those that affect mitochondrial function indirectly in the liver) (Cole et al., 1995), but showed markedly elevated plasma adrenocorticotropic hormone and corticosterone (Cole et al., 1995, 2001). Additionally, knockout of GR genes can increase secretion of corticosteroid-binding globulin (CBG), a 50–60-kDa glycoprotein with a single steroid-binding site. CBG is a primary glucocorticoid transporter in the blood stream (Gagliardi et al., 2010; Perogamvros et al., 2010) and, thereby, suppresses GC availability in the circulation (Cole et al., 1999). In mice with a partially deleted GR gene, both fetuses and adults showed profound resistance to DEX-mediated functional activation or repression (Cole et al., 2001). Surprisingly, when the point mutation A458T was introduced into the GR D-loop region, resulting in defective DNA binding, this mutant had normal local and systemic anti-inflammatory responses (Reichardt et al., 2001). This implies that the anti-inflammatory effect of GCs is not solely dependent on GC-mediated genomic effects.

3. Mitochondria

Mitochondria individually encapsulate their own genome (Fig. 2), which is expressed and replicated by the action of nuclear-encoded factors exported to the cytoplasm. Although there are large differences between tissues, a cell may contain several thousand mitochondria, and each mitochondrion contains 1–10 copies of mtDNA (Bogenhagen and Clayton, 1974; Garesse and Vallejo, 2001). Mitochondrial morphology is not static, but is dynamically maintained through the processes of fission and fusion (Frazier et al., 2006). In humans, the maternally-inherited mtDNA consists of circular, double-stranded DNA containing 37 genes. The genes encode 13 proteins of the mitochondrial respiratory chain, two ribosomal RNAs (rRNAs; 12S and 16S), and 22 transfer RNAs (tRNAs) (Bonawitz et al., 2006). Mitochondrial integrity is essential for the function and survival of cells. Surprisingly, in rho-0 mitochondria, which have little or no mtDNA, the formation and function of mitochondrial respiratory complexes is inhibited; however, these mitochondria have a proton gradient required for importing protein and preventing apoptosis (Zamzami and Kroemer, 2001). Moreover, the content of mitochondrial proteins, including respiratory complexes, catabolic proteins, transport proteins, and the mitochondrial translational system, are dramatically changed in rho(0) mitochondria (Chevallet et al., 2006; Jeon et al., 2011). This implies that mitochondrial protein functional networks can be reorganized to respond to the physiological status of the cell, and that alterations in mtDNA can lead to pleiotropic effects on the mitochondrial architecture.

A noncoding sequence of mtDNA, the D-loop or hypervariable region, serves as a control region for both DNA transcription and replication (Scarpulla, 2012; Scarpulla et al., 2012). Unlike the nuclear genome, all mitochondrial genes are expressed together, primarily from three promoters, the L-strand promoter (LSP), and H-strand promoters (HSPs) 1 and 2. These promoters are located in the regulatory D-loop (Montoya et al., 1982) and are recognized by the mitochondrial basal transcriptional machinery, which is comprised of the mitochondrial RNA polymerase and mitochondrial transcription factors (mtTFAs) (Bonawitz et al., 2006; Scarpulla, 2008; Scarpulla et al., 2012). Mitochondrial RNAs are produced from polycistronic transcripts and undergo processing and modification to produce mature mRNA (polyadenylation), rRNA (nucleotide modification), and tRNA (addition of CCA). However, the abundance of each mRNA, rRNA, and tRNA is highly variable, possibly due to further post-transcriptional modifications that affect transcript processing, maturation, stability, and degradation (Rackham et al., 2012). Although mitochondrial transcription has been intensively studied, the mechanism of mitochondrial translation remains, for the most part, unknown (Bonawitz et al., 2006; Rackham et al., 2012).

The basal metabolic rate of resting hepatocytes is controlled by energy from non-mitochondrial processes (10%) and mitochondrial proton leak (20%); the greatest proportion of the metabolic rate is dependent on mitochondrial ATP production (70%) (Hulbert and Else, 2000). The maintenance of mitochondrial function requires a delicate balance between continuous protein synthesis and degradation, i.e., protein turnover. Recent metabolic labeling

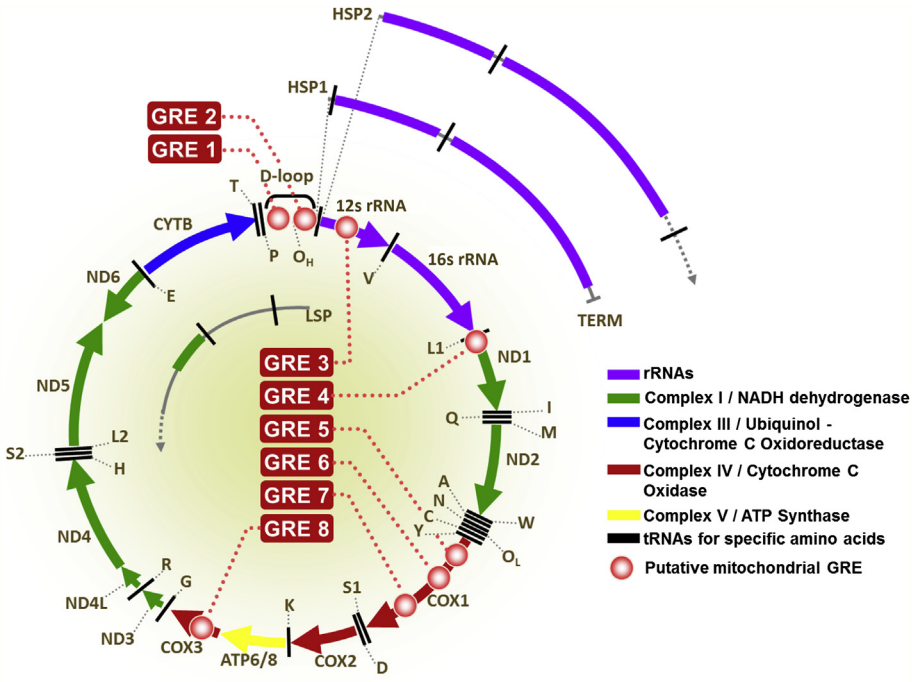

Fig. 2. Location of putative GREs in the mitochondrial genome. The mitochondrial genome is circular and composed of heavy (H) and light (L) strands. The displacement loop (D-loop) is the major noncoding region of the genome and is a stable, triple-stranded structure that harbors the L-strand promoter (LSP), one of the H-strand promoters (HSPs), and the origin of replication of the H-strand (O_H) found in many mtDNA molecules *in vivo*. The major L-strand origin (O_L) is located in the "WANCY" cluster of tRNAs. The consensus GRE is 5′-GGTACAnnnTGTTCT-3′, wherein "n" indicates any base. The putative GREs in the mitochondrial genome are located in the D-loop and within the structural genes, and their role could be in transcription initiation. In the mouse mitochondrial genome, there are at least eight GRE-like elements. GRE 1 and 2 are found in the D-loop region and contain the mitochondrial promoters. These two GREs are involved in the regulation of mitochondrial transcription, and the same transcription factor (GR) regulates nuclear and mitochondrial gene transcription in a similar manner (Demonacos et al., 1996). The 12S rRNA gene and the $tRNA^{Leu}$ gene contain GRE 3 and 4, respectively. Three putative GREs (GRE 5, 6, and 7) are located within the COX1 subunit, and GRE 8 is present within the COX3 gene (Demonacos et al., 1996; Sekeris, 1990). The putative GREs were arbitrarily named for the purpose of this review. tRNAs are denoted with capital letters for specific amino acids according to the standard one-letter nomenclature code. There are two tRNAs for serine and leucine, which are labeled S1 and S2 or L1 and L2, respectively (Bonawitz et al., 2006). COX, cytochrome c oxidase; GRE, glucocorticoid response element; ND, NADH dehydrogenase; TERM, specific termination site.

studies determined the turnover rates of at least 458 proteins in mouse cardiac and hepatic mitochondria; respective median rates of 0.0402 and 0.163 per day were calculated, corresponding to median half-lives of 17.2 and 4.26 days (Kim et al., 2012). The mitochondrial proteome shows significant heterogeneity among tissues, based on mitochondrial functional requirements (Johnson et al., 2007; Mootha et al., 2003); examples include enhancements of fatty acid oxidation for ATP production in the heart, specific aspects of the urea cycle and biosynthesis in liver, uncoupled respiration in adipose tissue, coupled and uncoupled respiration in skeletal muscle, metabolism of reabsorbed amino acids (e.g., tryptophan) in kidney, and specialized neurotransmitter metabolism and some aspects of reactive oxygen species (ROS) inactivation in brain. Thus, individual tissues have specific protein requirements that are provided by nuclear-encoded proteins.

4. GCs and mitochondrial biogenesis

Mitochondria are not produced *de novo*, but duplicate by a mechanism involving recruitment of proteins and replication of mtDNAs, which are added to preexisting subcompartments. Biogenesis and proliferation of mitochondria are influenced by external factors, such as nutrients, hormones, temperature, exercise, hypoxia, and aging (Ryan and Hoogenraad, 2007), which modify mitochondrial bioenergetics, thermogenesis, and oxidative stress and/or apoptotic responses (Manoli et al., 2007). Mitochondrial biogenesis and metabolism require the coordinated expression of multiple genes in two organelles, the nucleus and the mitochondrion. It has been proposed that, in the mitochondrial respiratory chain, mtDNA-encoded proteins serve constitutive functions and nuclear-encoded proteins have regulatory roles (Kelly and Scarpulla, 2004; Scarpulla, 2012). However, changes in mitochondrial activity can alter nuclear gene expression, a process known as retrograde communication (Finley and Haigis, 2009). Depletion of mtDNA sends signals to the nucleus, which, in turn, compensates by modifying expression of multiple genes (Liu and Butow, 2006; Park et al., 2006). For example, cardiomyocytes with low mtDNA content and/or decreased mitochondrial membrane potential generate a complex nuclear response, possibly through Ca^{2+} signaling, which results in the alteration of signaling pathways involving the transcription factors calcineurin-dependent nuclear factor of activated T-cells cytoplasmic 1, c-Jun N-terminal kinase (JNK)-dependent ATF2, and nuclear factor-kappa B (NF-κB), and enhances transcription of the gene encoding cytochrome c oxidase (COX) Vb (Biswas et al., 1999). In addition, cell proliferation and differentiation are closely related in terms of the status of mitochondria in myoblasts (Herzberg et al., 1993; Rochard et al., 2000). The regulation of mtDNA copy number, which is believed to be influenced, at least, by nuclear-encoded mtTFAs, is multifaceted, with different pathways influencing mtDNA replication and stability; and together, these pathways determine the specific amount and dynamic regulation of mtDNA *in vivo*. However, genetic mutation in mtDNA does not eventually induce mitochondrial biogenesis (Moraes et al., 1992). The contribution of mutations in mtDNA to carcinogenesis has been scrutinized using various approaches, but the conclusions remain controversial.

It is assumed that the main effect of GCs is the activation of nuclear-encoded genes, leading to enhanced mitochondrial

biogenesis and increased mitochondrial mass and respiration (Goffart and Wiesner, 2003). The impairment of GC production by adrenalectomy does not interfere *per se* with mitochondrial oxidation; rather, it alters the oxidative phosphorylation process in mitochondria and decreases ADP/O coefficient values and respiratory control (Kittas et al., 1984). In fetal adrenalectomized rats, COX mRNA level and mtDNA content were unchanged by GCs in heart, whereas mitochondrial maturation and differentiation were subject to the regulatory effect of GCs (Prieur et al., 1998). Mitochondrial biogenesis is sensitive to ROS (Scarpulla, 2012) and is precisely orchestrated by nuclear respiratory factors (NRFs) 1 and 2, mitochondrial transcription factors (TFAM A and B), and the integrative activity of coactivators, such as the peroxisome proliferator-activated receptor (PPAR)-γ coactivator 1 (PGC-1) family (PGC-1α, PGC-1β, and PRC) (Finley and Haigis, 2009; Scarpulla et al., 2012). GCs are essential for the rise in expression of oxidative phosphorylation enzymes and the development of the inner mitochondrial membrane, but do not regulate postnatal changes in mitochondrial density and mtDNA content in kidney or other tissues (Djouadi et al., 1994), with the exception of skeletal muscle (Weber et al., 2002).

5. GCs, the GR, and mitochondria

Circulating GC levels are regulated by CBG (Perogamvros et al., 2010). Tissue sensitivity can also be controlled by the enzyme 11β-hydroxysteroid dehydrogenase 1 (converts inactive cortisone into active cortisol), 11β-hydroxysteroid dehydrogenase 2 (a cortisol-degrading enzyme), or 5α-reductase (converts GC into tetrahydrocortisol or allodihydrocortisol). It should be mentioned that 11-ketometabolites (cortisone, 11-dehydrocorticosterone) produced in degradative pathways have some additional effects, such as reducing the response to aldosterone (Odermatt et al., 2001), and some products of GC metabolism have the potential for activation (McInnes et al., 2004). The GR is a ligand-regulated transcription factor, located primarily in the cytoplasm in its inactive form as a multimeric complex (Fig. 3). The GR is also a target of multiple kinases, and post-translational modifications, including sumoylation and ubiquitination, can affect subcellular localization, interaction with other proteins, and degradation (Anbalagan et al., 2012; Ismaili and Garabedian, 2004). Several protein kinases phosphorylate the GR at specific sites. Phosphorylation of the GR may affect its transcriptional activation in response to hormone stability, receptor stability, subcellular localization, regulation of transcription, and interactions with co-regulators (Ismaili and Garabedian, 2004; Weigel and Moore, 2007). Mitogen-activated protein kinase (MAPK) phosphorylates the GR residues T171 and S246, whereas multiple cyclin-dependent kinase complexes modify S224 and S232 (Krstic et al., 1997). The GR undergoes cyclic phosphorylation by one of these kinases and dephosphorylation, by protein phosphatase 5, at three sites (S203, S221, and S226), which serves to maintain steady-state receptor phosphorylation at a low

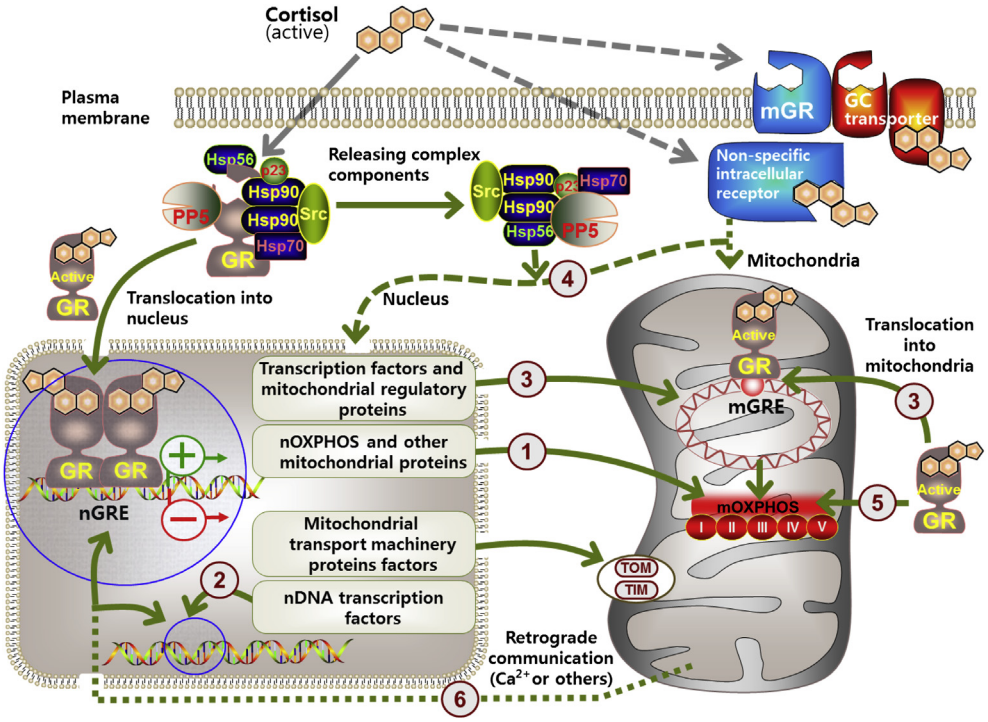

Fig. 3. Functional modulation of the mitochondrion by GCs and the GR. GC binding to the GR releases GC–GR from the cytoplasmic inactive GR complex. ① Active GR translocates into the nucleus and alters expression (transactivation or transrepression) of nuclear genes encoding OXPHOS and other mitochondrial proteins. ② The GR influences the expression of transcription factors for control of nDNA-encoded mitochondrial proteins. ③ Mitochondrial regulatory factors from the nucleus control transcription and mitochondrial gene expression. After binding GC, the GR translocates into the mitochondrion and regulates mitochondrial gene expression via mGREs. Because the mitochondrial genome contains putative GREs, transcription of mitochondrial genes encoding the OXPHOS proteins and other proteins required for protein synthesis can be initiated or suppressed. This kind of direct action of the GR on the mitochondrial genome may be faster than that of nDNA-encoded regulatory proteins due to the time lag associated with expression and transport into the mitochondrion. ④ Components released from the cytoplasmic GR complex, a non-specific intracellular receptor, and the GR and a GC transporter in the plasma membrane rapidly initiate cytosolic signaling, leading to non-genomic and genomic activity in both nucleus and mitochondrion. ⑤ The GR can affect OXPHOS activity directly or indirectly through cellular signaling in mitochondria. In addition, ⑥ The mitochondrial products or other cellular messengers, including ADP, Ca^{2+}, and NAD^{+}, derived from mitochondria, can regulate nuclear gene expression (Liu and Butow, 2006). These changes eventually affect mitochondrial functions. Therefore, non-classical GC activities evoked in mitochondria, together with classical activities in the nucleus, add complexity to the physiological phenomenon. "+" and "−" indicate transactivation and transrepression of genes, respectively. Solid arrows and dashed arrows indicate possible genomic and non-genomic actions, respectively. GC, glucocorticoid; GR, glucocorticoid receptor; GRE, glucocorticoid response element; mGR, membrane-bound GR; mGRE, mitochondrial GRE; mOXPHOS, mitochondrial DNA-encoded OXPHOS; nDNA, nuclear DNA; nOXPHOS, nuclear DNA-encoded OXPHOS; nGRE, nuclear glucocorticoid response element; OXPHOS, oxidative phosphorylation system.

basal level in the absence of ligand. Inhibition of protein phosphatase affects retention of the GR in the nucleus and transcriptional activation (Wang et al., 2007; Zuo et al., 1999).

Detection of the GR in mitochondria stimulated research to elucidate its specific role in this organelle and broaden the understanding of the actions of GCs in mitochondria. The activity of the respiratory chain depends on the expression of hundreds of nuclear-encoded genes and 13 genes encoded by the mitochondrial genome. In addition, nuclear DNA (nDNA)-encoded mitochondrial proteins for protein import and assembly, such as the transporter inner membrane and transporter outer membrane complexes, are important factors in mitochondrial biogenesis or homeostasis (Tome et al., 2012). GCs have diverse genomic effects in the nucleus through regulation of transcription factors. Apart from nuclear-encoded mitochondrial transcriptional regulators, it was recently discovered that human and rat mitochondrial genomes contain sequences similar to that of the nuclear GREs (Demonacos et al., 1995; Gregory et al., 1976; Gruber et al., 2004). Among mtDNA genes, those encoding COX subunits I and III, 12S and 16S rRNA, NADH dehydrogenase subunit I, and $tRNA^{Leu}$, as well as the D-loop (promoter region) of the mitochondrial genome (Demonacos et al., 1995; Ioannou et al., 1988; Tsiriyotis et al., 1997), contain putative GREs (Fig. 2). Considering the presence of GREs in both the nucleus and mitochondria, it is reasonable to postulate that expression of mitochondrial components can be tightly controlled temporally. Possible mitochondrial functions influenced by the GR can be categorized as 1) transcriptional control of mitochondrial proteins encoded by nDNA, 2) transcriptional control of nuclear-encoded transcription factors affecting nDNA-encoded mitochondrial proteins, 3) transcriptional control of mitochondrial proteins encoded by mtDNA, 4) activation of cytosolic signaling proteins by plasma membrane receptors or cytosolic steroid receptors that subsequently affect the mitochondria, and 5) non-genomic effects of mitochondrial membrane-bound GR or GCs through cognate mitochondrial receptors and the interaction of these receptors with binding sites in the mitochondrial genome (Fig. 3). These categories are briefly discussed in a separate section. It should be mentioned that the activities of mitochondrial OXPHOS proteins are regulated by protein level, as well as by post-translational modifications; however, this aspect will not be considered here.

5.1. Transcriptional control of mitochondrial proteins encoded by nDNA: nucleus to mitochondria

In cardiomyocytes from chronically restraint-stressed rats, mitochondrial proteomic analysis revealed that differentially expressed proteins were all nuclear-encoded (i.e., carnitine palmitoyltransferase 2, mitochondrial acyl-CoA thioesterase 1, isocitrate dehydrogenase3 [NAD1] alpha, fumarate hydratase 1, pyruvate dehydrogenase beta, creatine kinase, and prohibitin) and, at the same time, mitochondrial respiration capacity was impaired (Liu et al., 2004). It has been reported that among the genes whose expression was increased (140 genes) or decreased (108 genes) by corticosterone treatment (Chen et al., 2005), there were 15 signaling molecules, eight transcription factors, three chromatin- or DNA-binding proteins, and 11 enzymes involved in energy production or nucleic acid, lipid, or steroid metabolism. Thus, these modulated genes can indirectly or directly influence mitochondrial function, but whether the effect enhances or suppresses mitochondrial function is not easily determined. The pyruvate dehydrogenase complex (PDC) is a key regulatory enzyme in the oxidation of glucose to acetyl-CoA. Pyruvate dehydrogenase kinase 4 (PDK4) phosphorylates PDC, thereby reducing its activity. GCs contribute to the initiation of PDK4 gene transcription in fasting and diabetes, reinforced in part by GREs in the distal promoter (Connaughton et al., 2010).

Expression of proteins in the respiratory apparatus relies largely on gene-specific regulatory mechanisms. Chromatin accessibility is a primary factor in GR binding to chromatin and may determine cell- and gene-specific activities of the GR (John et al., 2011). GC-mediated transactivation can be achieved by translocation of the GR into the nucleus followed by interaction with regulatory regions (e.g., GREs), whereas transrepression of target genes (Santos et al., 2011) can be accomplished by binding to a negative GRE, counteracting the transactivating effects of other general transcription factors, or repression of inflammatory responses without binding of GCs to the GR. It has been proposed that the GR interacts directly with NF-κB or one of several AP-1 components (Schacke et al., 2002), and thereby suppresses the activity of these transcription factors. In addition, GRE tethering has been proposed, whereby, instead of binding directly to the DNA to achieve an effect, the GR binds to DNA-bound transcription factors in a regulatory complex to assist in transactivation or transrepression (Schoneveld et al., 2004). The action of GCs on RNA metabolism has been relatively well studied in the liver (Psarra and Sekeris, 2009), but little information is available for the heart or cardiovascular system. Regarding the inflammatory response, signaling pathways, including the extracellular signal-regulated kinase, JNK/SAPK, and P38/SAPK2 pathways, are involved in the control of mRNA turnover, and translation of mRNAs of proinflammatory proteins can be inhibited by GCs (Stellato, 2004). This raises the possibility that mitochondrial proteins can also be targets of GC–GR through modulation of mRNA stability or translation, although there is no direct evidence for this.

GCs may attenuate apoptosis caused by serum deprivation in rat hepatoma cells (Evans-Storms and Cidlowski, 2000). In addition, the GC agonist DEX can prevent cardiac injury caused by ischemia/reperfusion damage through transcriptional activation of the Bcl-xL gene, which prevents mitochondrial release of cytochrome c, in mouse heart (Xu et al., 2011). This GC-induced activation may be related to the presence of hormone response element-like sequences (e.g., GRE) in the promoter region of the Bcl-xL gene (Xu et al., 2011).

5.2. Transcriptional control of nDNA-encoded transcription factors that affect nDNA-encoded mitochondrial proteins

The ligand-activated GR-α is able to regulate gene expression without binding to GREs, perhaps by acting as a monomer to influence the capacity of other transcription factors to enhance or depress the transcription rates of target genes (Gottlicher et al., 1998; Nicolaides et al., 2010). The GR can also influence the expression of transcription factors controlling nDNA-encoded mitochondrial proteins. The general transcription factor Sp1 is crucial in the expression of a multitude of genes implicated in various constitutive and tissue-specific cellular activities (Suske, 1999). NRF-1 and NRF-2 play critical roles in transcription of nuclear-encoded mitochondrial proteins (Kelly and Scarpulla, 2004). NRF-1 is a 68-kD polypeptide with a C-terminal transcriptional activation domain comprised of glutamine-containing clusters of hydrophobic amino acid residues. NRF-1 participates in transcriptional control of genes encoding cytochrome c, proteins in five respiratory complexes, proteins involved in assembly of the respiratory apparatus, constituents of the mtDNA transcription and replication machinery, mitochondrial and cytosolic enzymes of the heme biosynthetic pathway, and proteins involved in mitochondrial protein import (Kelly and Scarpulla, 2004). However, regulation of most nuclear genes encoding mitochondrial enzymes upstream of the respiratory chain is not dependent on NRF-1/NRF-2 (Kelly and Scarpulla, 2004).

PGC-1α, which serves as a master regulator in the transcriptional control of mitochondrial biogenesis and respiratory functions (Scarpulla, 2011), can be induced by GCs in liver tissue, potentiating expression of gluconeogenic genes. The actual interaction of mammalian PGC-1α with the LBD of the GR serves as an effective stimulator of GR-mediated transcription in cells (Knutti et al., 2000). PGC-1α also plays a role in thermogenesis by the activation of mitochondrial uncoupling protein-1 (UCP-1), which promotes mitochondrial uncoupled respiration in brown adipose tissue (Puigserver et al., 1998). In human tissues, expression of PGC-1α is tissue-specific and at a high level in skeletal muscle, heart, kidney, and liver (Knutti et al., 2000). This suggests that the action of GCs can vary or is related to the differential responsiveness of GC–GR according to preexisting conditions in tissues. Nitric oxide (NO) can affect mitochondrial function directly or indirectly; PGC-1α is modulated in a cGMP-dependent manner, as demonstrated by the observation that the mitochondrial thermogenic response is significantly altered in mice lacking endothelial nitric oxide synthase (eNOS) (Kelly and Scarpulla, 2004). GCs can rapidly induce NO production by activation of eNOS by a non-genomic mechanism (Hafezi-Moghadam et al., 2002); however, in the long term, NO production is decreased by reduction of levels of inducible NOS (Simmons et al., 1996) and eNOS (Akaike and Matsumoto, 2007; Duckles and Miller, 2010; Wallerath et al., 2004), eventually reducing the level of bioavailable NO. It should be noted that cellular and mitochondrial NO levels or antioxidative status (Psarra et al., 2009) can impair GC–GR action. Nitrosative stress, such as septic shock, can decrease binding of GC to its receptor as a result of S-nitrosylation of critical –SH groups, and thus suppresses GR-hsp90 heterocomplex dissociation (Galigniana et al., 1999).

5.3. Transcriptional control of mitochondrial proteins encoded by mtDNA

Mitochondrial gene expression is largely influenced by the abundance of mtDNA, transcriptional activity of mitochondrial RNA polymerase, activities of mitochondrial transcription factor B (TFB) and TFAM, and RNA stability and translation efficiency (Fernandez-Vizarra et al., 2008). The bulk of mitochondrial regulatory proteins is nuclear-encoded and recruited to the D-loop regulatory region of mtDNA. TFAM is an NRF-1 target gene and is required for mtDNA replication and maintenance. Increased NRF-1 and TFAM mRNAs in mtDNA-deficient cells or defective mitochondria due to lipopolysaccharide-induced oxidative damage might constitute a coping mechanism for cellular stress. PGC-1α and TFAM are direct transcriptional coactivators of PPAR-γ in the mitochondrial biogenetic regulatory cascade (Puigserver and Spiegelman, 2003).

Recently, PPAR-γ and the heterodimeric transcription factor AP-1 has been identified in mammalian mitochondria. It is evident that binding of GR and AP-1 to the mitochondrial genome could potentially regulate mitochondrial gene expression (Leigh-Brown et al., 2010). For the GR to induce a genomic effect in mitochondria, translocation of the GR to mitochondria would be a prerequisite, but the underlying molecular mechanism remains unclear. It has been suggested that the GR may possess cryptic mitochondrial targeting signals in the C-terminal region, similar to the estrogen and androgen receptors (Psarra et al., 2005), although no known classical mitochondrial import sequences have been identified in the GR. It has also been noted that the GR/Bcl-2 complex is similar to estrogen receptors with regard to mitochondrial protein translocation via binding to heat shock protein 70/90 chaperone proteins (Du et al., 2009a). Direct activation of mitochondrial transcription by GCs has been proposed in various cell lines. In the presence of α-amanitin, a specific inhibitor of nuclear RNA polymerase II (Lindell et al., 1970), mitochondrial genes, such as those encoding COX I–III and 12S and 18S rRNAs, but not the nuclear COX IV gene, are upregulated by GCs (Psarra and Sekeris, 2009). DNA–RNA hybridization analysis showed that hydrocortisone (cortisol) administration induces expression of all mitochondrial genes simultaneously in rat liver, and does not selectively enhance individual gene transcription (Minchenko, 1989). However, treatment with the GC analog DEX increased the transcript levels of COX II and III and 12S RNA in skeletal muscle, but not in the colon, liver, or kidney (Weber et al., 2002). In addition, several nuclear transcription factors, including AP-1, NF-κB, cyclic-AMP response element-binding protein (CREB), T3 receptor p43 (activated by ligand binding), signal transducer and activator of transcription (STAT)3 (stimulated by growth hormone signaling), the estrogen receptor, and tumor suppressor p53 (activated in response to stress) were identified in mitochondria in various cell lines and tissues, with different localization (Psarra and Sekeris, 2009). Among these, mitochondrial STAT3 serves as a subunit of mitochondrial complex I, which directly regulates mitochondrial function via its effect on the electron transport chain (Wegrzyn et al., 2009). Mitochondrial p43 and CREB bind to mtDNA to regulate gene expression (Leigh-Brown et al., 2010). The presence of nuclear transcription factors in mitochondria and their interplay with GCs in regulation of mitochondrial gene expression should be further investigated to gain insight into the activities of GC and the GR.

5.4. Activation of cytosolic signaling proteins by plasma membrane or cytosolic steroid receptors

After GC binding, the multimeric GR complex undergoes a conformational change, generating a heteromeric complex and GR dimerization. Upon ligand activation, the GR is actively imported into the nucleus and mitochondria, where it influences gene regulation (Fig. 3). Apart from GC–GR, various components released from the cytosolic complex, including heat shock protein 90, heat shock protein 70, Src tyrosine kinase, serine/threonine protein phosphatase type 5 (Hinds and Sanchez, 2008), and heat shock protein 56 (Buttgereit et al., 2004; McMaster and Ray, 2007) can independently induce cell signaling (Fig. 3). The GR interacts with diverse cytosolic proteins, such as tubulin, actin, and other proteins involved in various signal transduction pathways (i.e., AP-1, NF-κB, Stat5, 14-3-3, HOP, p23, FKBP51, FKBP52, and Raf-1) (Hedman et al., 2006). Although further investigation is required, 27 putative GR-interacting proteins were newly identified, including PP63 (a protease inhibitor and tyrosine kinase inhibitor), major vault protein, TATA-binding interacting protein 49a, transcription elongation factor B, and hypoxanthine-guanine phosphoribosyltransferase. Activation of cellular signaling by these proteins can produce rapid non-genomic action. In HepG2 hepatoma cells, DEX significantly suppressed the activities of mitochondrial complexes I and II, whereas complex III activity was enhanced by a p38 MAPK-dependent mechanism (Desquiret et al., 2008). These cell signaling events initiated by the GR can eventually impact mitochondrial function.

5.5. Non-genomic effect of GCs on mitochondria

In the cell, complete synthesis and post-translational modification of a protein requires 15 min to hours; nuclear translocation takes 10–30 min and transcription, 5–120 min (Haller et al., 2008). Thus, achievement of the GC-mediated genomic effect is a more time-consuming process than that required to effect non-genomic changes, which occur within several minutes in the absence of transcriptional changes (Hafezi-Moghadam et al., 2002; Haller et al., 2008). These rapidly-occurring non-genomic effects of steroids are established and have been extensively described (Billing

et al., 2012; Haller et al., 2008; Lee et al., 2012; Samarasinghe et al., 2011; Song and Buttgereit, 2006; Zhang et al., 2006; Zhou et al., 2011). Non-genomic effects include hormone–ligand activity involving nuclear receptor proteins in the cytoplasm, which are stimulated either at the cell surface within mitochondria or by binding to other cytoplasmic receptors. In isolated kidney and brain mitochondria, low doses of GCs cause a decrease in state 3 respiration, which may affect the activity of COX, F_0F_1-ATPase, or complex IV (Katyare et al., 2003; Morin et al., 2000; Simon et al., 1998). Similar to what has been observed on the plasma membrane and nuclear pores (Losel and Wehling, 2003), GCs may directly modulate mitochondrial function by interpolating in the mitochondrial membrane, which may result in compromised ATP production due to increased proton leakage from the mitochondrion (Song and Buttgereit, 2006). In isolated rat brain mitochondria, a physiological dose of corticosterone non-specifically inhibits mitochondrial ATP production by suppressing electron transfer from NADH to the electron transfer chain through complex I (Fujita et al., 2009). Long-term administration of varying doses (100 nM–1 μM) of corticosterone dynamically modulates major functional indicators of mitochondria, including mitochondrial oxidation, membrane potential, and mitochondrial Ca^{2+} level, in cortical neurons (Du et al., 2009b). These findings imply that GC can directly modulate mitochondrial functions, such as ATP production, but the possibility of GC action through the GR cannot be completely excluded. The synthetic GC DEX can directly bind and activate both conventional PKCs and atypical PKC isoforms, and this activation is not blocked by the GR antagonist RU38486 (Alzamora and Harvey, 2008). This direct and non-genomic activation of PKC signaling by GC binding may further influence mitochondrial activity.

As the result of a variety of apoptotic stimuli, mitochondrial membrane potential can be changed by genomic and non-genomic actions of the GR (Kfir-Erenfeld et al., 2010; Sionov et al., 2006). Recently, it has been suggested that novel ligand-induced translocation of GC into mitochondria can initiate the apoptotic cascade in thymocytes by decreasing mitochondrial transmembrane potential (Buttgereit et al., 2000; Palinkas et al., 2008) or interacting with mitochondrial proteins that regulate apoptosis (Boldizsar et al., 2010; Psarra and Sekeris, 2009; Sionov et al., 2006). However, the exact mechanism underlying induction of the apoptotic cascade by the translocated GC–GR complex in mitochondria is still under investigation. The proposed mechanisms underlying GR-mediated apoptosis are 1) interaction with Bcl-2 family members (Thompson and Winoto, 2008), 2) promotion of Bax/Bak apoptotic oligomer formation by the GR (Brunelle and Letai, 2009), and 3) regulation of the activity of members of the pro-apoptotic Bcl-2 family of proteins via a genomic effect on Src tyrosine kinase (Herr et al., 2007).

GCs and the GR are responsible for multiple complex actions that are initiated both in the nucleus and mitochondria. The physiological status of cells and mitochondria play integral roles in determining the actions of GCs, rendering a complex and dynamic environment in which GC activity takes place (Pandya et al., 2007). In addition, the interactions of GR signaling pathways with other signaling pathways, and the existence of multiple coactivators contribute to an intricate, tightly regulated network, and represent phenomena central to gaining an understanding of hormone responsiveness and resistance.

6. Concluding remarks

GC–GR interactions modulate expression of OXPHOS and mitochondrial proteins directly and indirectly. In the present review, we have briefly outlined the specific roles of GCs and their receptors in mitochondria. Mitochondrial genes are under the tight control of nuclear-encoded structural and transcriptional regulatory proteins. However, the translocation of the GR into mitochondria and the existence of GRE-like elements in the mitochondrial genome provide evidence of highly ordered behavior of GCs and the GR in these organelles. In addition, the biological effects of GC–GR interactions vary, but are highly dependent on ligand specificity and availability, which, in turn, are influenced by the physiological status of the cell and mitochondria. For appropriate regulation of mitochondrial activities, the mitochondria should send signals to the nucleus indicating the nature of the stimuli so that the cell can adapt and respond accordingly. Understanding the mechanisms underlying retrograde signaling between mitochondria and the nucleus following the GC–GR response and the regulatory roles of GCs in mitochondria will be valuable for understanding GC activity and necessary for basic and clinical application of GCs.

Conflict of Interest

The authors declare no conflicts of interest.

Acknowledgments

This work was supported by the Priority Research Centers Program (2010-0020224) and the Basic Science Research Program (2010-0025855 and 2012R1A2A1A03007595) through the National Research Foundation of Korea (NRF), funded by the Ministry of Education, Science, and Technology.

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