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Review

Mitochondrial Nuclear Receptors and Transcription Factors: Who's Minding the Cell?

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Mitochondria are power organelles generating biochemical energy, ATP, in the cell. Mitochondria play a variety of roles, including integrating extracellular signals and executing critical intracellular events, such as neuronal cell survival and death. Increasing evidence suggests that a cross-talk mechanism between mitochondria and the nucleus is closely related to neuronal function and activity. Nuclear receptors (estrogen receptors, thyroid (T3) hormone receptor, peroxisome proliferators-activated receptor gamma2) and transcription factors (cAMP response binding protein, p53) have been found to target mitochondria and exert prosurvival and prodeath pathways. In this context, the regulation of mitochondrial function via the translocation of nuclear receptors and transcription factors may underlie some of the mechanisms involved in neuronal survival and death. Understanding the function of nuclear receptors and transcription factors in the mitochondria may provide important pharmacological utility in the treatment of neurodegenerative conditions. Thus, the modulation of signaling pathways via mitochondria-targeting nuclear receptors and transcription factors is rapidly emerging as a novel therapeutic target.

Key words: mitochondria; neurodegeneration; transcription regulation

Mitochondria provide energy synthesis in the form of ATP by passing electrons derived from the oxidation of nutrients down the respiratory chain to react with oxygen, using redox energy to translocate protons across the mitochondrial inner membrane (Saraste, 1999). A proton electrochemical potential gradient is generated across the inner membrane consisting of a membrane potential (negative inside) and a pH gradient (basic inside) that drives ATP synthesis through F_0F_1-ATP synthase (Nicholls and Ferguson, 1992). The established roles of mitochondria and its dysfunction in terms of energy deficiency and oxidative stress are of importance in characterizing the pathogenesis of neurodegenerative disorders (Beal et al., 1993; Albers and Beal, 2000; Zamzami and Kroemer, 2001). Mitochondrial DNA defects or mutations are also closely linked to neurological disorders. Excitotoxicity is a well-established mechanism of neuronal cell death in neurodegenerative disorders. N-methyl-D-aspartate (NMDA) stimulation induces the decrease of the mitochondrial membrane potential associated with neuronal excitotoxicity. Mitochondria play an indirect role as executioner in the excitotoxic pathway. Mitochondria are the source of 80% or more of the reactive oxygen species generated in neurons. Neuronal toxins and stress-blocking mitochondrial functions cause excessive neuronal damage and cell death by the dysregulation of oxyradicals. The mitochondrial toxins malonate and 3-nitropropionic acid produce striatal lesions that mimic Huntington's disease (HD) and are mediated by excitotoxic mechanisms. Consistent with this finding, mitochondrial electron transport enzymes are altered in HD. Mitochondria in HD lymphoblasts and fibroblasts show an increased susceptibility to depolarization, which directly correlates with CAG repeat length (Sawa et al., 1999). The maximal rate of mitochondrial ATP generation in muscle is significantly reduced both in symptomatic HD patients and in presymptomatic HD gene carriers. There has been some debate regarding the vulnerability of transgenic HD

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TABLE I. Nuclear Receptors and Transcription Factors That Are Translocated and Found in Mitochondria

Mitochondria targeting proteins	Reference
Nuclear receptors	
Estrogen receptors (α and β)	Yang et al., 2004; Chen et al., 2004a,b
c-ErbAα1 (thyroid hormone receptor)	Wrutniak et al., 1995, 2001
Glucocorticoid receptor (GR)	Ioannou et al., 1988; Demonacos et al., 1996
Nur 77	Liu et al., 1994; Li et al., 2000; Lin et al., 2004
PPARγ2	Casas et al., 2000; Smith and Muscat, 2005
Transcription factors	
AP1 (c-fos/c-jun)	Ogita et al., 2002, 2003
CREB	Cammarota et al., 1999; Lee et al., 2005; Ryu et al., 2005
NF-κB	Cogswell et al., 2003
p53	Marchenko et al., 2000
TFAM (mt-TFA)	Parisi et al., 1991
TFB1M	Falkenberg et al., 2002
TFB2M	Falkenberg et al., 2002

mice to neurotoxins. It has been reported that both R6/1 and R6/2 mice are resistant to excitotoxic lesions (Hansson et al., 1999, 2001). In contrast, we have shown that R6/2 mice are more susceptible to the mitochondrial toxin 3-nitropropionic acid (Bogdanov et al., 1998). The discrepancy in the findings may be methodological with regard to periodicity and dosage of injections. It is of interest, however, that YAC mice containing full-length huntingtin are more susceptible to excitotoxicity (Zeron et al., 2001). In addition, the fact that NMDA antagonists prolong survival in R6/2 mice clearly implicates excitotoxicity (Schiefer et al., 2002; Ferrante et al., 2002). Rotenone and MPTP/MPP^+ also induce mitochondrial dysfunction that is relevant to Parkinson's disease (PD). Thus, although a role for mitochondrial dysfunction has been proposed in neurodegenerative diseases, the exact mechanism of mitochondrial pathogenesis is unclear. Identification of specific molecules and signaling cascades, which may ultimately lead to neuronal dysfunction and/or cell death, may provide important clues in understanding the pathogenesis of neurological disorders. Recent findings have suggested a paradigm shift in which nuclear receptors and transcription factors target mitochondria and modulate molecular mechanisms to mediate mitochondria-dependent cellular events (Table I). In this Mini-Review, we address what nuclear receptors and factors target mitochondria and how they may trigger mitochondrial signaling pathways.

NUCLEAR RECEPTORS AND TRANSCRIPTION FACTORS ARE PRESENT IN MITOCHONDRIA

Mitochondrial CREB

The cAMP response element binding protein (CREB) is a transcription factor known to activate genes that are critical for plasticity, memory, and survival of neurons (Mayr and Montminy, 2001; Lonze and Ginty, 2002). CREB proteins are ubiquitously expressed 38-kDa and 43-kDa proteins. CREB activates transcription by binding to cAMP response elements upstream of the target gene, CRE; 5′-TGACGTCA-3′. CREB proteins belong to the leucine zipper class of proteins, which form heterodimers in specific combinations. The carboxyl terminus of CREB contains a leucine zipper that is required for dimerization and DNA binding (Meyer and Habener, 1993). The transactivation domain contains several motifs, including a kinase-inducible domain containing phosphorylation sites for several kinases, including protein kinase A. The involvement of CREB in cell death has been demonstrated in several, non-neuronal paradigms. For example, overexpression of a dominant negative form of CREB, KCREB, in melanoma cells enhanced apoptosis induced by thapsigargin (Jean et al., 1998). Furthermore, transgenic mice overexpressing KCREB show increased thymoctye apoptosis. One mechanism by which CREB proteins may inhibit apoptosis is through the up-regulation of Bcl-2 expression (Wilson et al., 1996). This has been shown to be the result of CREB binding to a CRE element in the Bcl-2 promoter. Despite these intriguing observations, CREB's role in regulating oxidative stress-induced apoptosis in HD is not well understood. A number of stimuli, including growth factors, neuropeptides, and neurotransmitters, alter intracellular second messengers in neurons, such as cAMP and calcium, and activate CREB by phosphorylation at serine133. Whereas wild-type CREB prevents cell death induced by growth factor deprivation, the overexpression of a dominant negative form of CREB (A-CREB) in sympathetic neurons leads to three changes: decreased Bcl-2 expression, a loss of cytochorome c from the mitochondria, and activation of apoptotic pathways. Recent reports by our group and others show that phosphorylated CREB (pCREB) is present and active in mitochondria and raise the possibility that pCREB may mediate neuronal survival in response to various stimuli by regulating mitochondrial gene expression (Bevilaqua et al., 1999; Lee et al., 2005; Ryu et al.,

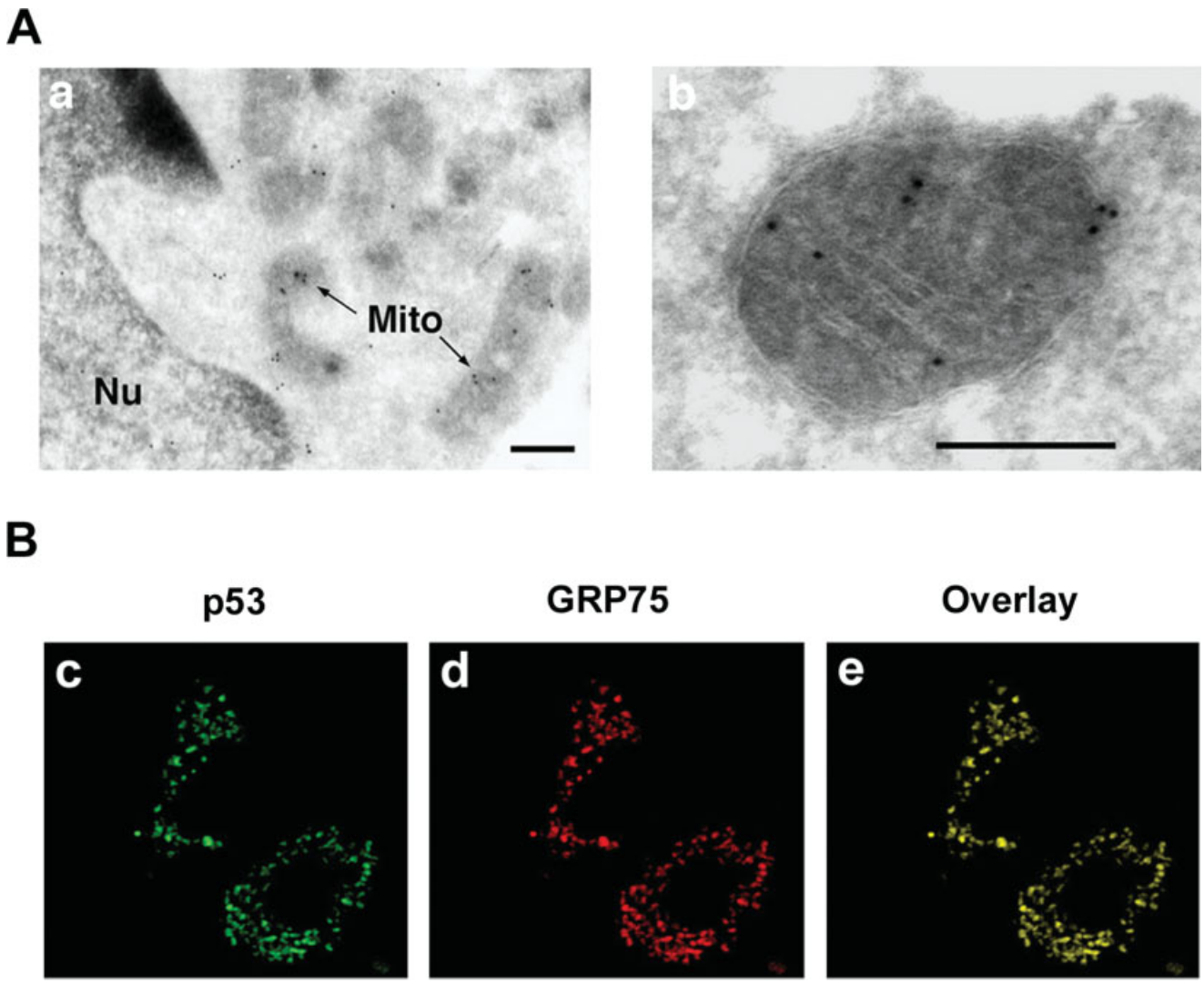

Fig. 1. Mitochondrial localization of nuclear transcription factors. **A:** CREB is presented in the mitochondrial matrix of primary cortical neuron (a,b; Lee et al., 2005). **B:** p53 (c) Colocalizes with mitochondrial heat shock protein 70 (mtHsp70/GRP75; d) in human striatal neurons; e is an overlay image of c and d. Scale bars = 200 nm in a; 10 μm in b. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

2005; Table I, Fig. 1). CREB may protect striatal neurons by up-regulating mitochondrial genes and interacting with antiapoptotic molecules that enhances neuronal survival.

Mitochondrial p53

p53 Is a nuclear transcription factor and a tumor suppressor protein. Exposure of cells to DNA-damaging agents induces accumulation of p53 protein along with a half-life lengthened by four- to fivefold, without significant changes in its mRNA level (Halaby and Yang, 2007). p53 Has a short half-life in normal cells, and it has been found that an efficient steady-state ubiquitination system for p53 is constitutively operating. Interestingly, p53 localizes to the mitochondria under conditions that provoke apoptosis, and mitochondria-localized p53 is sufficient to launch cell death via the release of cytochrome c (Marchenko et al., 2000; Sansome et al., 2001; Table I, Fig. 1). Mitochondrially localized p53 achieves this through direct molecular interaction via its DNA-binding domain with the antiapoptotic Bcl-2 and Bcl-xL proteins (Mihara et al., 2003). We also found that p53 is continually localized in mitochondria of neuronal cells (Fig. 1B), even in the absence of a death stimulus, which coincides with a recent report (Mahyar-Roemer et al., 2004). In spite of the abundance of p53 in the mitochondria in neurons and its importance in neurodegenerative disorders, the exact functions of p53 remain to be determined. It has recently been found that p53 plays a specific role in the

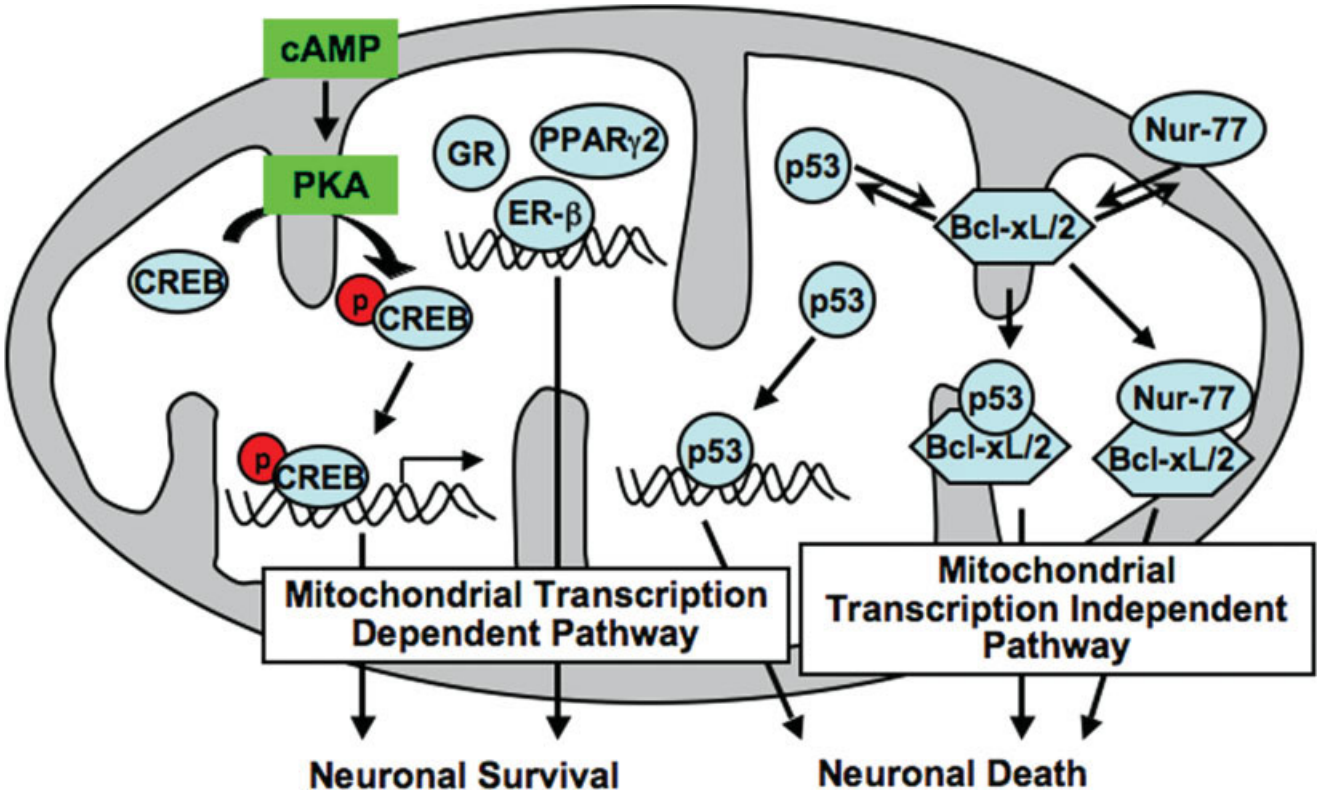

Fig. 2. The proposed scheme depicts the mitochondrial transcription-dependent and transcription-independent pathways for neuronal survival and death. The transcriptional regulation of mitochondrial gene expression by CREB, ER, GR, and PPARγ2 have been reported. PKA-mediated phosphorylation of CREB leads to CREB binding to cyclic AMP response elements (CREs) within the mitochondrial genome that promotes neuronal survival. p53-Dependent transcription from mitochondrial genome may also result in neuronal cell death. It is well established that p53 and Nur-77 complexes with Bcl-xL and Bcl-2 present on mitochondrial membrane, which subsequently triggers the downstream cascade of apoptosis via mitochondrial transcription-independent pathway. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

mitochondria-associated cellular dysfunction and behavioral abnormalities of HD mice (Bae et al., 2005). Mutant huntingtin (MtHtt) binds to p53 and up-regulates p53 transcriptional activity (Bae et al., 2005). This study suggests that p53, in part, links nuclear and mitochondrial pathological features of HD. Furthermore, it is proposed that mitochondrial translocalization of p53 by mtHtt and other cellular stresses may trigger or accelerate the apoptotic cascade in striatal neurons. In spite of the abundance of p53 in neuronal mitochondria and its importance in neurodegenerative disorders, the exact functions of p53 remain to be determined.

Mitochondrial Estrogen Receptor

There are two distinct estrogen receptor (ER) subtypes that mediate physiological responses to estrogen. ER alpha and ER beta are encoded by a unique gene, differing in the C-terminal ligand-binding domain and the N-terminal *trans*-activation domain. Both ERs are expressed in neurons in various stages of development and mediate direct effects of estrogen on brain. Recent findings on the mitochondrial localization of ERs raise question of how these mitochondrial hormone receptors regulate the transcription of the mitochondrial genome (Yang et al., 2004; Chen et al., 2004a; Table I). Mitochondrial ERs bind to estrogen response elements (EREs) or ERE-like sites in the noncoding region of the mitochondrial genome (Chen et al., 2004b; Chen and Yager, 2004). Based on previous findings, it is proposed that mitochondrial ERs may act through several different scenarios of mitochondrial transcription pathways (Fig. 2). First, mitochondrial ERs can activate the transcription of mitochondrial genes directly through binding to ERE-like sites, which is the mitochondrial ERE-dependent transcription pathway. The classical mode of ERs that target estrogen receptor-responsive areas in the promoter regions of nuclear genes could be applied to mitochondrial gene activation. Second, mitochondrial ERs may trigger other mitochondrial transcription factors such as CREB and cross-talk with other intracellular signaling pathways, which is transcription-dependent but not through binding to ERE-like sites.

Mitochondrial PPARγ2

The peroxisome proliferator-activated receptors (PPARs) are members of the nuclear hormone receptor superfamily and are involved in the regulation of lipid

metabolism. Three distinct subtypes have been identified: PPARα, PPARγ, and PPARδ. While PPARδ is ubiquitously expressed, PPARα is predominantly expressed in the liver and PPARγ in the adipose tissue. PPARα regulates fatty acid catabolism; PPARγ regulates adipocyte differentiation; and PPARδ regulates cholesterol efflux, lipid catabolism, and energy expenditure (Smith and Muscat, 2005). Casas et al. (2000) have found that a 45-kDa protein (mitochondrial PPAR) related to PPARγ2 isoform is located in the mitochondrial matrix and binds specifically in the D-loop region of mitochondrial DNA, which suggests that mitochondrial PPAR might also serve to regulate mitochondrial gene expression (Fig. 2).

Mitochondrial Nuclear Orphan Receptor-77

The nuclear-orphan receptor Nur-77 (also known as *TR3*) has been identified as an immediate early gene induced by serum and growth factors (Hazel et al., 1988). The most fascinating aspect regarding Nur-77 is that it can exhibit differential functions of cell survival or cell death. Although overexpression of Nur-77 in cancer cells is linked to survival, suppression of the expression is associated with inhibition of the transformation phenotype (Ke et al., 2004; Moll et al., 2006). Studies on apoptotic thymocytes and T-cell hybridomas demonstrate that high levels of Nur-77 in these cells are correlated with apoptotic function (Liu et al., 1994; Woronicz et al., 1994). Transactivation of nuclear gene expression by Nur-77 is thought to play a part in its apoptotic function. It is also emerging from recent studies that Nur-77 mediates apoptosis by translocating from the nucleus to the mitochondria, where it interacts with Bcl-2 and induces cytochrome c release (Jeong et al., 2003; Lin et al., 2004; Fig. 2).

Other Mitochondrial Nuclear Receptors and Transcription Factors

Glucocorticoid receptor (GR) and c-ErbAα1 [triiodothyronine (T3) receptor] have been found in the mitochondria (Table I). On the basis of these findings, glucocorticoid and thyroid hormones affect directly the mitochondrial genes concomitant with the effects on nuclear genes involving molecular mechanisms similar to those mediating glucocorticoid and thyroid hormone actions on nuclear gene transcription (Ioannou et al., 1988; Demonacos et al., 1996). c-ErbAα1 specifically binds to a direct repeat 2 sequence located in the D-loop of the mitochondrial genome. Moreover, expression of a truncated form of the c-ErbAα1 nuclear receptor is associated with a mitochondrial localization and a stimulation of mitochondrial activity. These results supply evidence of the localization of a member of the nuclear receptor superfamily in the mitochondrial matrix involved in the regulation of mitochondrial activity that could act as a mitochondrial T3-dependent transcription factor. However, the T-binding 43-kDa protein related to c-ErbA1 is not detectable in adult rat brain mitochondria, in agreement with the previously reported lack of T receptors in these mitochondria (Sterling et al., 1977; Wrutniak et al. , 1995). Thus, the mitochondrial presence of other c-Erb subunits in neurons remains to be investigated.

Ogita and colleagues (2002, 2003) have found that kainate injection increases AP-1 complex (c-fos and c-jun) translocation into mitochondria, followed by enhanced DNA-binding activity to mitochondrial AP-1-like sites in mouse hippocampus (Table I). They have demonstrate that AP-1-like sites, but not the genuine AP-1 site (5′-TGAGTCA-3′), are found in the noncoding region (D-loop) of the mitochondrial genome.

It has emerged from recent studies that nuclear factor-κB (NF-κB) and IκB localize in the mitochondria and NF-κB also regulates the mitochondrial gene expression (Cogswell et al., 2003; Table I). The NF-κB family comprises five members: NF-κB1 (p500), RelA (p65), NF-κB2 (p52), RelB, and c-Rel. The NF-κB resides predominantly in the cytoplasm complexes with inhibitor proteins (members of the IκB family). Activation of NF-κB occurs upon release from the inhibitor complex by phosphorylation and subsequent degradation of IκB proteins, mostly by IκB kinase (IKK). NF-κB exerts its antiapoptotic effects by inducing antiapoptotic genes, thereby promoting cell survival and proliferation. Thus, it antagonizes the proapoptotic functions of p53. NF-κB has been shown to regulate p53 stability negatively by modulating the p53 E3 ubiquitin ligase Mdm2 levels (Tergaonkar et al., 2002). NF-κB was shown to regulate negatively the mitochondrially encoded cytochrome c oxidase III and cytochrome b in response to tumor necrosis factor-α (TNF-α) stimulation (Cogswell et al., 2003).

TRAVELING MECHANISMS OF NUCLEAR TRANSCRIPTION FACTORS TO MITOCHONDRIA

Mitochondrial DNA (mtDNA) encodes only a small fraction of the mitochondrial proteins, with the vast majority being nuclearly encoded and thus having to be imported into mitochondria. Mitochondria are bound by two membranes: the outer mitochondrial membrane (OMM) and the inner mitochondrial membrane (IMM). Whereas the outer membrane is highly permeable and nonselective, the inner membrane has a limited permeability. The voltage-dependent anion channel (VDAC) in the OMM, a large water-filled pore, allows polar molecules up to 5-kDa to pass freely (Lee and Thevenod, 2006). In contrast, the inner membrane allows only a few molecules to pass freely. with the majority of the small molecules requiring specific transporters.

The nuclearly encoded mitochondrial proteins contain signal sequences either at the N-terminus or within their sequences that target them to the mitochondria. The proteins are synthesized on ribosomes in the cytosol and associate with chaperones that help in their mito-

chondrial translocation. One of the major chaperones in this category is the mitochondrial heat shock protein 70 (mtHsp70)/GRP75. Interestingly, p53 has been shown to localize to the mitochondria by associating with mtHsp70 at the onset of p53-dependent apoptosis. Based on the signal information in the precursor protein, it could be targeted to any of the four locations: the mitochondrial outer membrane, inner membrane, the intermembrane space, or the mitochondrial matrix. This signal also determines the translocation pathway and the energy requirement (Hood and Joseph, 2004). Furthermore, it is now being increasingly suggested in the literature that the translocation process happens cotranslationally (Ni et al., 1999; Mukhopadhyay et al., 2004). This process is mediated by translocases present in the mitochondrial outer and inner membranes. These comprise the translocase of the outer membrane (TOM) complex, which is the entrance gate for almost all mitochondrial proteins from the cytosol, and the TIM complex of the inner membrane for transporting proteins into/across the inner membrane. These translocases are multisubunit protein assemblies utilizing ATP and the membrane potential as energy sources (Neupert and Herrmann, 2007). After the initial entry through the TOM complex, distinct pathways sort proteins into different mitochondrial compartments, such as sorting and assembly machinery complex (SAM) for the β-barrel proteins of the outer membrane, the mitochondrial intermembrane space import and assembly (MIA) pathway for intermembrane space proteins bearing cysteine motifs, and the TIM 22/TIM 23 complexes for targeting to inner membrane or mitochondrial matrix (Bohnert et al., 2007). Further study is necessary to elucidate whether TOM/TIM complexes are involved in importation of nuclear receptors and transcription factors into mitochondria.

NOVEL ROLES OF NUCLEAR RECEPTORS AND TRANSCRIPTION FACTORS IN MITOCHONDRIA

Mitochondrial Transcription-Dependent Pathway

Mitochondrial DNA translates 37 genes: 22 tRNA genes, 2 rRNA genes, and 13 polypeptide encoding genes. All 13 mitochondrially encoded proteins are mainly components of the respiratory chain or the F_0F_1-ATP synthase (Wallace, 1999). Many subunits of mitochondrial oxidative phosphorylation enzymes are encoded by nuclear DNA, translated on cytoplasmic ribosomes, imported into mitochondria, and assembled there into functional complexes along with mitochondrially encoded proteins (Schatz, 1996; Neupert, 1997). The two strands of the mammalian mtDNA, named on the basis of their buoyant density heavy (H) and light (L) strand, are replicated asynchronously and asymmetrically (Clayton, 1982, 1987). The mammalian mtDNA contains three promoters (L, H1, and H3) located in the noncoding D-loop region. The transcription of the H-strand starts at two sites, IT_{H1} and IT_{H2}, whereas L strand transcription starts at a single site, IT_{L1} (Montoya et al., 1983). Transcripts synthesized from IT_{L1} and IT_{H2}, which is located within the $tRNA^{phe}$ gene, are polycistronic, and their corresponding transcription units encompass the complete L and H DNA strands, respectively (Taanman, 1999). IT_{H1} is placed just before the $tRNA^{phe}$ gene, and the transcription unit ends in a strong termination signal located downstream of the 16S rRNA gene. The termination signal is evolutionarily conserved (Valverde et al., 1994) and binds a *trans*-acting factor called *mTERF* (Fernandez-Silva et al., 1997, 2003). Therefore, the main function of the H1 promoter is to regulate synthesis of the two mitochondrial rRNAs. The primary polycistronic transcripts are further processed to monocistronic or bicistronic mRNAs, with the tRNAs acting as punctuation signals (Ojala et al., 1981). The enzymatic activities responsible for the 5′ and 3′ processing of tRNAs have been characterized (Rossmanith et al., 1995), but the genes encoding the mitochondrial RNase P and precursor tRNA 3′ endonuclease remain to be identified (Garesse and Vallejo, 2001). Despite the fact that mitochondrial mRNAs are polyadenylated, the mitochondrial poly(A) polymerase and potential associated factors also remain to be further characterized. The mitochondrial transcriptional machinery is relatively simple compared with the nuclear machinery and consists of a single, nonspecific RNA polymerase that is evolutionarily conserved to bacteriophage T7, T3 and SP6 RNA polymerases, and at least a specificity factor, mitochondrial transcription factor A (mtTFA/TFAM), a small protein that belongs to the family of high-mobility group (HMG) DNA-binding factors (Dairaghi et al., 1995). Not only does mtTFA play a role as a transcription factor but it also is essential for mtDNA maintenance in yeast (Diffley and Stillman, 1991) and most likely in mammals (Larsson et al., 1998), because of its binding capacity to nonspecific DNA. Thus, mtTFA shows a dual role as a mitochondrially specific factor/transcriptional activator and in mitochondrial genome packaging. Although it has been proposed that mtTFA may interact with the mitochondrial transcription factor B (mtTFB), the mitochondrial transcription machinery and mechanisms are poorly characterized (Shadel and Clayton, 1997).

CREB and ERs are nuclear transcription factors that have been shown to act in the nucleus to regulate gene expression. We and others provide evidence supporting the hypothesis that CREB and ERs also target mitochondrial DNA (Yang et al., 2004; Chen et al., 2004a,b; Lee et al., 2005; Ryu et al., 2005). These studies suggest that some nuclear transcription factors may participate in regulating mitochondrial function through transcriptional regulation of mitochondrial DNA (Fig. 2). For example, CREB is localized in the mitochondrial matrix as well as nuclei in rat hippocampus (Cammarota et al., 1999; Lee et al., 2005; Fig. 1). Mitochondrial CREB is phosphorylated on its serine-133 after one trial of inhibitory avoidance training procedures in rat hippocampus (Bevilaqua et al., 1999). Although direct evi-

dence that CREB regulates mitochondrial gene expression has been lacking, we have demonstrated that CREB is present in the inner mitochondrial matrix of neurons and directly binds to cAMP response elements (CREs) in the promoter (D-loop) regions of rodent mitochondrial DNA (mtDNA). Putative mitochondrial CRE-like sites have been found by chromatin immunoprecipitation (ChIP), EMSA, and DNAse footprint analysis (Lee et al., 2005; Ryu et al., 2005). It seems likely that the secondary structure of mitochondrial D-loop DNA is important for its occupancy by mitochondrial CREB when long D-loop template DNA is used for baiting CREB. Our group has shown that disruption of CREB activity in the mitochondria decreases the expression of a subset of mitochondrial genes, including the ND5 subunit of complex 1; reduces mitochondrial respiration; and increases susceptibility to 3-nitropropionic acid, a mitochondrial toxin known to induce a clinical and pathological phenotype similar to HD (Lee et al., 2005). In addition, transgenic HD mice contain decreased levels of mitochondrial CREB, correlating with lowered mitochondrial ND5 gene expression. These results show that CREB is transcriptionally active in mitochondria (Fig. 2). It further suggests that regulation of mitochondrial gene expression by mitochondrial CREB may underlie some of the established protective effects of CREB and raises the possibility that decreased mitochondrial CREB activity contributes to the mitochondrial dysfunction and neuronal loss in HD as well as in other neurodegenerative conditions.

Mitochondrial Transcription-Independent Pathway

The transcription-independent pathway of p53-mediated apoptosis has been proposed because studies showed that p53-dependent apoptosis proceeded in the absence of transcription or protein synthesis (Caelles et al., 1994; Marchenko et al., 2000; Fig. 2). Studies with p53 mutants that are inactive in transcription but capable of inducing apoptosis also support a mechanism that is independent of transcription (Haupt et al., 1995). Marchenko and coworkers (2000) have shown that a fraction of stress-induced p53 protein rapidly localizes to mitochondria at the onset of p53-dependent apoptosis that precedes the release of cytochrome c and procaspase-3 activation.

The antiapoptotic proteins Bcl-xL and Bcl2 present at the outer mitochondrial membrane (OMM) stabilize the mitochondrial membrane. Interestingly, p53 destabilizes the membrane by complexing with these proteins. Furthermore, p53 directly activates the cytoplasmic proapoptotic protein Bax, inducing Bax oligomerization and permeabilization of the outer membrane (Mihara et al., 2003). Permeabilization of the mitochondrial outer membrane leads to release of cytochrome c along with other apoptogenic factors that activate the caspase leading to apoptosis. These studies have also demonstrated that p53 interacts with Bcl-xL and Bcl2 through its DNA binding domain. Studies with tumor-derived mutants of p53 showed that these mutant proteins lose or are severely compromised in their abilities to form inhibitory complexes with Bcl-xL or Bcl-2 (Mihara et al., 2003; Tomita et al., 2006; Fig. 2). Chipuk et al. (2005) have shown that the p53/Bcl-xL complex requires an additional "p53 up-regulated modifier of apoptosis" (PUMA) to displace p53 from Bcl-xL and engage cell death, thus coupling the nuclear and cytoplasmic proapoptotic functions of p53.

THERAPEUTIC REGULATION OF MITOCHONDRIAL FUNCTION

Mitochondria as a Therapeutic Target

Mitochondria are thread-shaped organelles consisting of several compartments each with different compositions and functions (Murphy and Smith, 2000). Therefore, mitochondria have been considered as intracellular targets for small compounds (Murphy, 1997). The porous mitochondrial outer membrane is permeable to molecules smaller than ~5 kDa. The mitochondrial intermembrane space contains many specific proteins but is continuous with the cytoplasm for small molecules. The mitochondrial inner membrane with a convoluted and invaginated structure contains oxidative phosphorylation enzymes and a series of metabolic pathways. Mitochondrial membrane damage contributes to the pathogenesis of many neurodegenerative diseases. Neuronal cell fate is dependent on mitochondria that play key roles in apoptotic and necrotic cell death. Necrotic neuronal cell death occurs in response to acute damage and insults and results in rapid, uncontrolled death with subsequent cell lysis and an inflammatory response. Necrotic cell death follows ATP depletion and cellular calcium overloading, with extensive mitochondrial damage leading to necrotic cell death (Nicotera et al., 1998). Otherwise, apoptotic neuronal cell death accompanies the activation of cell death program that causes the ordered self-destruction of the cell, ending with phagocytosis without leakage of damaging contents and thus no inflammatory response. The difference between apoptotic and necrotic neuronal death is rather arbitrary, insofar as completion of the apoptotic program requires ATP, and if ATP levels drop lower than a critical threshold after initiation of apoptosis, apoptosis is aborted and neurons die by necrosis (Leist and Nicotera, 1998).

Mitochondrial CREB regulation by antioxidants

The catalytic subunit of protein kinase A (PKA) is found in the mitochondrial matrix to phosphorylate mitochondrial CREB in neurons (Ryu et al., 2005). The therapeutic approaches increasing mitochondrial PKA and mitochondrial CREB activity may provide a novel direction in both preclinical and human trials. Deferoxamine (DFO), an antioxidant and iron chelator known to inhibit oxidative stress-induced cell death, activates mitochondrial PKA and increased mitochondrial CREB phosphorylation (Ser 133; Ryu et al., 2005). DFO increases CREB binding to CRE in the mitochondrial D-loop

DNA and D-loop CRE-driven luciferase activity. In contrast, KT5720, a specific inhibitor of PKA, reduces DFO-mediated neuronal survival against oxidative stress induced by glutathione depletion. Neuronal survival by DFO may be, in part, mediated by the mitochondrial PKA-dependent pathway. These results suggest that the regulation of mitochondrial function via the mitochondrial PKA and CREB pathways may underlie some of the salutary effects of DFO in neurons. Taken together, the idea of targeting biologically active molecules to the mitochondria is to modulate selective mitochondrial functions in a specific manner. Therapeutic strategies will allow mitochondria to cope better with oxidative stress and mitochondrial damage by excitotoxicity and maintain efficient oxidative phosphorylation and respiratory function. This study provides a novel mechanism for preventing mitochondrial transcriptional dysfunction in neurodegenerative conditions and in the design of applicable therapeutic treatments to modulate mitochondrial hormone receptors and transcription factors.

Specific ER Modulators (SERMs) to Target Mitochondria

Estrogen attenuates NMDA receptor-mediated excitotoxic neuronal death and oxidative neuronal death (Weaver et al., 1997; Montal, 1998; Kajta et al., 2002; Linford et al., 2002; Dribben et al., 2003; Xue and Hay 2003). Estrogen has a number of neurotrophic effects mediated via different signaling pathways, including activation of PKA, ERK, and phosphatidylinositol 3-kinase (PI3K) cascades and inactivation of glycogen synthase kinase 3beta (GSK3 beta; Mendez et al., 2003; Yu et al., 2004). PKA localizes to the matrix of mitochondria in neurons. Thus, it has been proposed that estrogen- and agonist-dependent mitochondrial transcription is, in part, mediated via the mitochondrial PKA signaling pathways.

The important structural motif that elicits estrogenic effects is a phenol ring that is relatively unhindered and attached to a bulky hydrophobic structure (Schultz et al., 2002). The phenolic A ring is related to its neuroprotective function (Green et al., 1997). Steroids with a hydroxyl group in the C3 position of the A ring provides an antioxidant property. E2 can suppress intracellular ROS and prevent neurons from oxidative stress-induced cell death. However, the antioxidant property requires a higher concentration of E2 (10–100 μM). Furthermore, antiapoptotic neuroprotection may be blocked by ICI 182,720, which has hydroxyl group in C3 (Murashov et al., 2004; Stroppolo et al., 2004). Therefore, it is unlikely that the anticell death effect is due solely to the antioxidant property of E2. As neuroprotective molecules, SERMs may act through both the mitochondria-dependent and -independent signaling pathway. First, they may activate the transcription of mitochondrial genes directly through binding to mitochondrial ERs and subsequently to ERE in mitochondrial genome, which is the mitochondrial transcription-dependent pathway (Yager and Chen, 2007). This classical mode of estrogen action works through the activation of ERs that target ER-responsive areas in the promoter regions of mitochondrial genomes. Therefore, mitochondrial ERs that are activated by estrogen directly act as mitochondrial transcription factors (Chen et al., 2004a,b; Yang et al., 2004). Second, SERMs directly regulate gene expression through ERs and ERE as well as indirectly activating gene transcription by performing a cross-talk with various intracellular signaling pathways (Leong et al., 2004). In this case, it is predicted that estrogenic compounds bind to ERs that do not directly bind to the mitochondrial ERE but rather interact with other signaling cascades in the mitochondrial matrix. Such signaling partners of interaction may include the mitochondrial PKA and the CREB-signaling processes. Third, SERMs may directly effect mitochondrial membranes by modulating Ca^{2+} fluxes and protect neurons through their antioxidant effects, which promote the transcription-independent pathway (Farhat et al., 1996).

CONCLUSIONS

The extraordinary dependence of neurons on the energy provided by mitochondrial oxidative metabolism is directly linked to neurodegenerative conditions. The central role of mitochondria in neurodegeneration has become apparent over the last decade as the molecular mechanisms causing neuronal cell death have been underscored. Previous findings on the mitochondrial localization and function of nuclear receptors and transcription factors have unraveled interesting mechanisms in the mitochondria. The effectiveness of drug treatment may depend on targeting bioactive molecules to the appropriate organ, cell type, and subcellular organelle. Therefore, future studies using small compounds to target the mitochondria directly or to modulate nuclear receptors and transcription factors that subsequently convey the signal to the mitochondria may contribute to improve mitochondrial functions in a specific manner. We expect that novel therapeutic strategies will enable nuclear receptors and transcription factors via mitochondria to cope better with oxidative stress, excitotoxicity, and transcriptional dysfunction as well as maintain efficient respiratory function in neurons.

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