ANTIOXIDANTS & REDOX SIGNALING
Volume 20, Number 2, 2014

DOI: 10.1089/ars.2012.4774

Therapeutics

FORUM REVIEW ARTICLE

Mitochondrial Energy Metabolism and Redox Signaling in Brain Aging and Neurodegeneration

Fei Yin,[1] Alberto Boveris,[2] and Enrique Cadenas[1]

Abstract

Significance: The mitochondrial energy-transducing capacity is essential for the maintenance of neuronal function, and the impairment of energy metabolism and redox homeostasis is a hallmark of brain aging, which is particularly accentuated in the early stages of neurodegenerative diseases. ***Recent Advances:*** The communications between mitochondria and the rest of the cell by energy- and redox-sensitive signaling establish a master regulatory device that controls cellular energy levels and the redox environment. Impairment of this regulatory devise is critical for aging and the early stages of neurodegenerative diseases. ***Critical Issues:*** This review focuses on a coordinated metabolic network—cytosolic signaling, transcriptional regulation, and mitochondrial function—that controls the cellular energy levels and redox status as well as factors which impair this metabolic network during brain aging and neurodegeneration. ***Future Directions:*** Characterization of mitochondrial function and mitochondria-cytosol communications will provide pivotal opportunities for identifying targets and developing new strategies aimed at restoring the mitochondrial *energy-redox axis* that is compromised in brain aging and neurodegeneration. *Antioxid. Redox Signal*. 20, 353–371.

Introduction

THE BRAIN, SIMILAR TO MOST ORGANS, undergoes a gradual decline in energy metabolism during aging (30, 68, 170, 223). Since neurons require large amounts of energy for the firing of action potential, neurotransmission, and other processes, the age-related decline in metabolism contributes to the cognitive declines associated with aging (22, 30). Clinically, age-dependent reduction of glucose utilization was observed in most human brain regions (185). Similarly, an age-dependent decrease in O_2 uptake was observed in the rodent brain (171). Aging is also a risk factor for age-associated diseases such as neurodegenerative disorders. These diseases may occur when neurons fail to respond adaptively to an age-related decline in basal metabolic rates and in energy-driven tasks, such as neuromuscular coordination, cognitive performance, and environmental awareness (222). In human beings, cerebral glucose hypometabolism is an early and consistent event in the progression of Alzheimer's disease, Parkinson's disease, Huntington's disease, and mild cognitive impairment, before the onset of pathologies in the brain (9, 59, 73, 83, 120). Decreased frontal cortex O_2 uptake has been reported in Parkinson's disease and in dementia with Lewy bodies (172).

The energy-transducing capacity of mitochondria meets the cellular energy demands, thus supporting metabolic, osmotic, and mechanical functions. Mitochondria are sources of H_2O_2, and play a pivotal role as mediators of the intrinsic apoptotic pathway. Thus, they play significant roles in the function and plasticity of neurons and are implicated in the pathogenesis of a variety of neurological disorders (155). The most prominent metabolic process carried out by mitochondria is oxidative phosphorylation (OXPHOS) that generates ATP, the universal energy currency. On the other hand, high levels of H_2O_2 have been associated with mitochondrial redox changes and macromolecule oxidation during aging and are believed to mediate the detrimental effects associated with mitochondrial dysfunction in brain aging (14) and neurodegenerative disorders (18, 20, 214). The cellular composition of the brain consists mainly of terminally differentiated neurons, its regenerative capacity is relatively reduced as compared with other organs, and a dramatic decline in neurogenesis with age and in neurodegenerative diseases may contribute to the impairment of learning and memory (140). Thus, the brain is highly susceptible to neuronal loss due to hypometabolic states and the impairment of redox homeostasis. Age-related changes in energy production and redox status cannot be viewed as independent variables, but rather as an interdependent relationship reflected in the mitochondria energy-redox axis that represents a dual pronged approach to assess the changes in mitochondrial function as a function of age and disease (250).

[1]Department of Pharmacology and Pharmaceutical Sciences, School of Pharmacy, University of Southern California, Los Angeles, California.
[2]Institute of Biochemistry and Molecular Medicine (UBA-CONICET), University of Buenos Aires, Buenos Aires, Argentina.

The generation of H_2O_2 by mitochondria depends on the respiratory state (faster rates of H_2O_2 release in state 4 respiration and slower rates in state 3 respiration) and shows an exponential dependence on the mitochondrial membrane potential (32, 132). Mitochondrial H_2O_2 is implicated in the regulation of the cellular redox status, thus transducing redox signals into a wide variety of responses, such as proliferation, adaptation, differentiation, and cellular death pathways (199). Low to intermediate levels of H_2O_2 are involved in the regulation of redox-sensitive signaling and transcription, whereas high levels are involved in oxidative damage to cell constituents. The release of oxidants from mitochondria as a function of the mitochondrial metabolic and redox states serves as a coordinated response between these seemingly autonomous organelles and the rest of the cell through the modulation of redox-sensitive signaling and transcription pathways. Conversely, mitochondria are the recipients of cytosolic signaling, such as mitogen-activated protein kinases (MAPKs) and the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) pathway of insulin signaling, which elicit profound changes in the mitochondrial energy-transducing capacity.

This review focuses on the role of a coordinated metabolic triad (Fig. 1) entailing a regulatory devise encompassed by mitochondrial function (maintenance of the energy-redox axis), cytosolic kinase signaling, and transcriptional pathways.

The Mitochondrial Energy-Redox Axis

Mitochondria provide most of the energy needed for cellular functions by the metabolism of fuel molecules into ATP through OXPHOS. The generation of ATP entails the oxidation of acetyl-CoA in the tricarboxylic acid (TCA) cycle with the concomitant generation of reducing equivalents (NADH, $FADH_2$) that flow through the respiratory chain, generating a proton motive force (154); electron leakage leads to the generation of $O_2^{\cdot -}$, which is further disproportionate to H_2O_2, either catalyzed by the superoxide dismutases (matrix Mn-SOD and intermembrane space Cu, Zn-SOD) or, secondarily, through spontaneous dismutation (161). Steady-state levels of mitochondrial H_2O_2 are determined by both energy metabolism and the redox systems. A decrease in the mitochondrial energy-transducing capacity is a common feature of brain aging and neurodegeneration and is associated with a progressive increase of H_2O_2 steady-state concentrations that can shift the cell from a reduced state to an oxidized state. Thus, the maintenance of mitochondrial redox homeostasis becomes crucial for cell function.

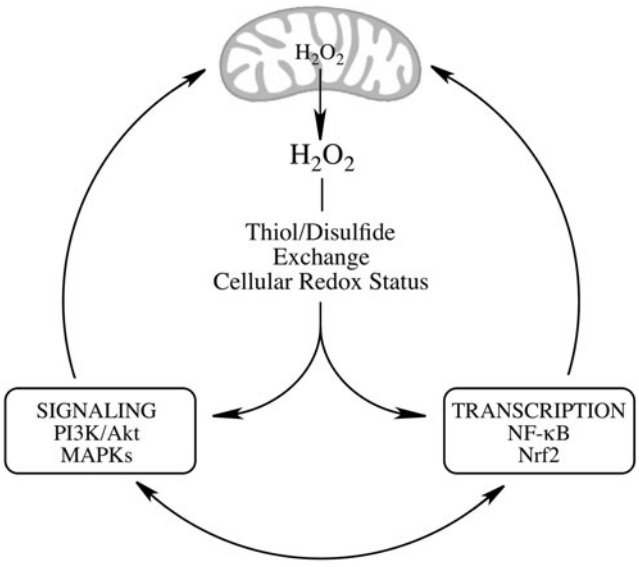

FIG. 1. Regulatory device encompassing the coordinated interactions of mitochondrial function and redox-sensitive signaling and transcription. PI3K, phosphatidylinositol 3-kinase; Akt, Protein kinase B; MAPK, mitogen-activated protein kinases; Nrf2, nuclear factor erythroid 2-related factor.

Mitochondrial energy metabolism

The effects of aging on mitochondrial energy metabolism are tissue specific and are more prominent in tissues whose parenchyma contains mostly postmitotic cells such as brain, heart, and skeletal muscle. Partial loss of the energy-transducing capacity has been documented in mitochondria isolated from aged animals and attributed to changes in protein expression and activities. Glucose is the primary fuel for brain, whereas metabolism of ketone bodies represents an alternative fuel source during glucose deprivation (89) (Fig. 2). Pyruvate, generated from glycolysis, undergoes oxidative decarboxylation by the pyruvate dehydrogenase (PDH) complex to acetyl-CoA that feeds into the TCA cycle. PDH activity in the brain was found to decrease with age (263, 264). In addition, there is an age-dependent decrease in succinyl-CoA:3-oxoacid Co-A transferase (SCOT) activity (137), a key mitochondrial matrix enzyme that metabolizes ketone bodies to acetyl-CoA (Fig. 2); the decreased SCOT activity as a function of age was due to irreversible protein post-translational modifications (137). In a triple transgenic mouse model of Alzheimer's disease, ketone body metabolism is a temporary mechanism that prevents the further decline of brain mitochondrial bioenergetic capacity (248) which is associated with decreased activities of PDH and cytochrome oxidase. 2-Deoxy-D-glucose treatment induced ketogenesis in the same mouse model, and this resulted in increased ketone body metabolism in the brain and a significant reduction of both amyloid precursor protein and amyloid-β (248). The activities of TCA enzymes, such as aconitase and α-ketogluterate dehydrogenase (α-KGDH), also decline as a function of age (251) and the activities of PDH, α-KGDH, and isocitrate dehydrogenase (IDH) are also lower in Alzheimer's disease (37, 249). It may be surmised that alterations in the activities of TCA cycle enzymes and of enzymes controlling the entry of acetyl-CoA into the TCA cycle, such as PDH and SCOT, affect NADH levels and contribute significantly to the decline in mitochondrial bioenergetics during aging and neurodegeneration.

Mitochondrial OXPHOS is a process that encompasses electron transfer through the complexes I, II, III, and IV of the respiratory chain; this exergonic electron transfer is the driving force for the vectorial H^+ release into the inter-membrane space and for the H^+ re-entry to the matrix through F_0 of complex V with ATP synthesis by F_1-ATP synthase. Electron transfer in mitochondria decreases in the aged brain (21, 170), with more marked changes in complexes I, III, and IV (135, 168, 169, 173). The inhibition of complex I activity on aging

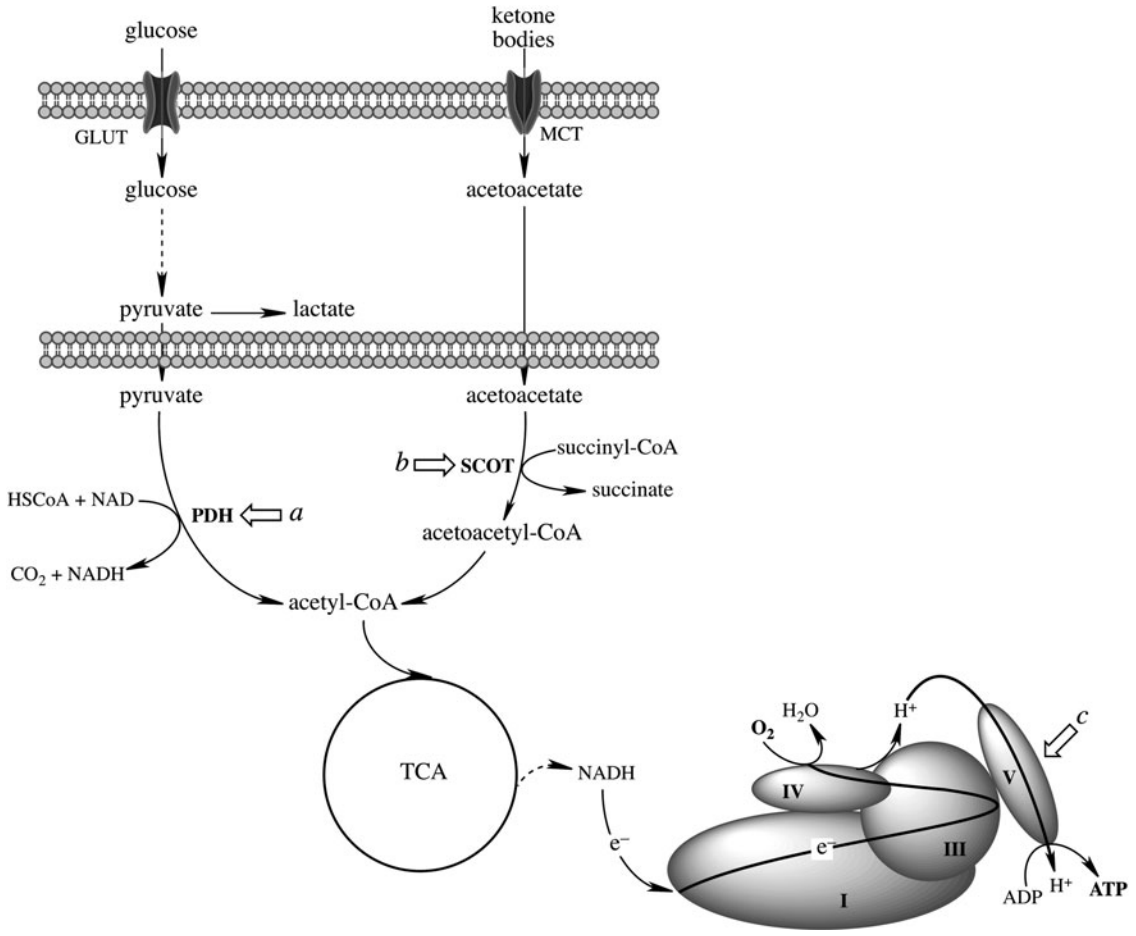

FIG. 2. Metabolism of pyruvate and ketone bodies by brain mitochondria. Glucose is the primary fuel for the brain and the secondary fuel for ketone bodies; metabolism of pyruvate (from glucose) is regulated by the PDH complex; metabolism of ketone bodies requires the activity of succinyl-CoA transferase (SCOT) (which is expressed in brain mitochondria). Acetyl-CoA, generated by PDH or SCOT activities, is further oxidized in the tricarboxylic acid cycle with the formation of NADH. The arrows indicate protein post-translational modifications found in the brain as a function of age: (*a*) phosphorylation (inactivation) of PDH on the translocation of JNK to the outer mitochondrial membrane (263, 264); (*b*) and (*c*) the nitration of SCOT and F_1-ATPase, respectively on the diffusion of ·NO to the mitochondria due to the increased expression and activity of nNOS as a function of age (137). PDH, pyruvate dehydrogenase; SCOT, succinyl-CoA:3-oxoacid Co-A transferase.

occurs with a decrease in NAD^+ levels (26) that leads to the impairment of the turnover efficiency of the TCA cycle, irrespective of the presence of acetyl-CoA. Moreover, reduced electron transfer can also lead to decreased mitochondrial inner membrane potential, which is observed in the aged rat brain (136, 205). The F_1-ATPase activity of complex V also decreases with age due to the nitration of Tyr^{269} close to the Mg^{++} binding site of the F1β subunit (137).

The operational concepts of mitochondrial metabolic states and respiratory control are defined as state 4 (resting or proton motive force controlled-respiration), with the availability of respiratory substrates but not ADP, and state 3 (active respiration) with ample respiratory substrate and ADP availability (45). Mitochondrial active respiration decreases in aging in terms of a marked decline in state 3 respiration and the related respiratory control ratio and membrane potential, as well as an increase in state 4 respiration (29, 137, 173), all of which indicate a lower energy-transducing efficiency.

Components of the electron transport chain (ETC) exist as large macromolecular assemblies or so-called supercomplexes (208), the ultra-structure of which determines the activity of mitochondrial OXPHOS and, therefore, plays a vital role in mitochondrial phenotype in aging and neurodegeneration (84, 211). The supramolecular architecture of OXPHOS complexes in rat brain cortex is affected by aging: The largest decreases were observed with supercomplexes I_1III_2, $I_1III_2IV_2$, and $I_1III_2IV_1$ (80).

Mitochondrial function is also regulated by ·NO, largely on reversible binding to cytochrome oxidase (36), and at higher concentrations, it inhibits electron transfer at the bc_1 segment of the respiratory chain (190–192). Although not free of discrepancy (236), multiple studies have shown the occurrence of a mitochondrial nitric oxide synthase (mtNOS) in several tissues [including brain (233) and with a function in rat brain development (200)] by its biochemical activity and by the inhibition of mitochondrial respiration elicited by NOS substrates and inhibitors (167, 171, 172). Mitochondrial metabolic states regulate the diffusion of both ·NO and H_2O_2 from mitochondria to cytosol (32, 200). Interestingly, the tissue levels of mtNOS have been reported to decrease with age,

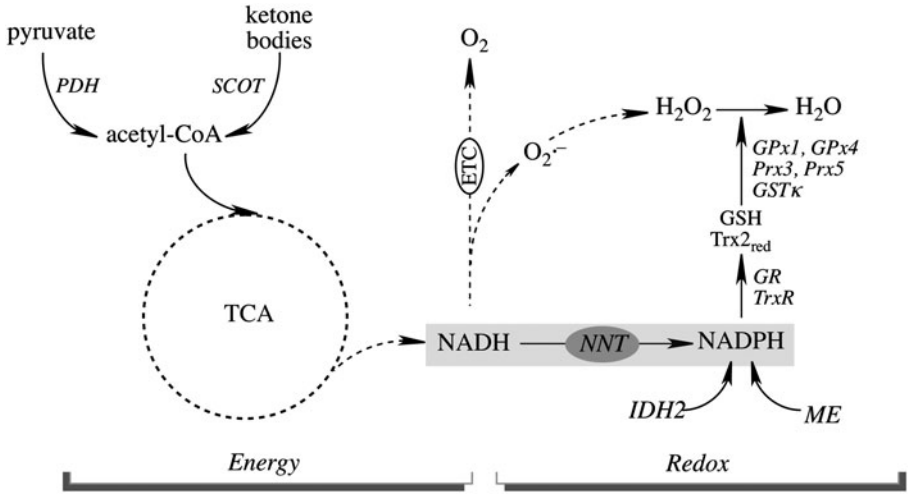

FIG. 3. The mitochondrial energy-redox axis. Energy–The energy-transducing capacity of mitochondria entails the flow of reducing equivalents (NADH) through the ETC to generate a proton motive force and ATP; the electron leak accounts for 2%–3% of O_2 consumed in the form of $O_2^{\cdot-}$ and H_2O_2. *Redox*–Reduction of H_2O_2 to H_2O (and maintenance of a mitochondrial $[H_2O_2]_{ss}$ is accounted for by thiol-based systems, for which the ultimate reductant is NADPH. Sources of NADPH in brain mitochondria: NNT, IDH2, and ME. GPx1, glutathione peroxidase-1; GPx4, glutathione peroxidase-4 or phospholipid hydroperoxides glutathione peroxidase (in intermembrane space); GR, glutathione reductase; GSTκ, glutathione transferase class kappa; IDH2, isocitrate dehydrogenase-2; ME, malic enzyme; NNT, nicotinamide nucleotide transhydrogenase; Prx3, peroxiredoxin 3; Prx5, peroxiredoxin 5; TCA, tricarboxylic acid; TrxR, thioredoxin reductase.

particularly in the brain, and it has been suggested to be a biomarker of brain aging. ·NO can signal through the cGMP-PKG pathway to activate Sirt1 and PGC1α (33, 171, 175).

The levels of neuronal NOS (nNOS) in the rat brain increase with age (137), and this is associated with the S-nitrosylation of cytosolic proteins and the nitration of a discreet set of mitochondrial proteins (40, 137). Excessive production of ·NO in the brain has been implicated in a number of neurodegenerative diseases, including Alzheimer's and Parkinson's disease (156, 247). Thus, during brain aging and neurodegeneration, the physiological regulation of mitochondrial function by lower concentrations of ·NO appears to decrease due to declined mtNOS and, in a separate phenomenon, increased pathophysiological levels of ·NO (generated by nNOS and inducible NOS [iNOS]) lead to the replacement of specific ·NO signaling by random ·NO-mediated modifications to proteins.

Mitochondrial redox homeostasis

After the initial reports on intact heart and liver mitochondria as an active source of H_2O_2 by Chance and Boveris (28, 31), further work established that superoxide anion ($O_2^{\bullet-}$) was the stoichiometric precursor of mitochondrial H_2O_2 and that it was primarily generated during ubisemiquinone auto-oxidation (25, 27, 39) and, secondarily, by reverse electron transfer at the NADH-dehydrogenase segment (229). Components of complex I and complex III were reported to generate $O_2^{\bullet-}$ (38, 228). Since the activities of complexes I, III, and IV decrease during aging, higher oxidant production is observed: The rates of $O_2^{\bullet-}$ and H_2O_2 formation increase with age and are higher in mitochondria from tissues of *ad libitum*-fed mice than in those on caloric-restricted diets (139, 215). $O_2^{\bullet-}$, formed on oxidation of the outer UQ pool (UQ_O), can be vectorially released into the cytosol, in part, through a voltage-dependent anion channel (91). Thus, cytosolic levels of H_2O_2 reflect the mitochondrial energy status, for mitochondrial H_2O_2 generation in state 4 respiration is about 4–5 times higher than that during effective OXPHOS (state 3 respiration) (29). A comprehensive review conducted by Murphy points out the difficulties in the determination of the rates of $O_2^{\bullet-}$ and H_2O_2 generation *in vivo* and under physiological conditions and recognizes four main determining factors: the ratios $NADH/NAD^+$ and UQH_2/UQ, the local mitochondrial $[O_2]$, and the $\Delta\psi$ of the inner membrane (164).

In brain mitochondria, H_2O_2 is eliminated mainly by glutathione (GSH)- or thioredoxin (Trx)-driven catalysts that depend on NADPH as ultimate electron donors (Fig. 3).

GSH-based systems

GSH, synthesized in the cytosol from glycine, glutamate, and cysteine in a two-step process by the enzymes γ-glutamylcysteine synthetase and GSH synthase (87), is imported into the mitochondria through the dicarboxylate- and oxoglutarate carriers on the inner mitochondrial membrane (88, 262). The role of mitochondrial thiols in redox signaling (165) and cell death pathways (252) has been recently reviewed. The redox potential—which is calculated of the mitochondrial GSH/glutathione disulfide (GSSG) or $Trx2_{red}/Trx2_{ox}$ couples—is ∼–300 and –340 mV (116, 124), respectively. The mitochondrial GSH pool can apparently function autonomously from the cytosolic GSH pool in response to local changes in the production of mitochondrial oxidants (107).

Mitochondrial GSH protects against oxidative stress largely as a cofactor for glutathione peroxidases (GPxs), glutathione-S-transferases, sulfiredoxins, and glutaredoxins (Grxs) (152, 197). GPx1 localizes mainly in the mitochondrial matrix, whereas GPx 4 (also referred to as phospholipid hydroperoxide GPx) (210, 232) occurs in the inner mitochondrial membrane; the latter detoxifies mainly phospholipid hydroperoxides, and its significance is underscored by the embryonic lethality that follows systemic ablation of GPx4, which is

explained in part by studies conducted on the expression of GPx4 in the embryonic brain and its role in organogenesis (24). The mouse brain showed a decreased GSH/GSSG ratio and a slight shift toward a more pro-oxidizing redox potential with regard to age (195, 196). Among the glutathione S-transferases (GST), the GST class κ is mitochondrion specific and also exhibits some selenium-independent peroxidase activity; in addition to the GST class κ, the α, π, and μ classes have also been reported in brain mitochondria (85, 194); however, the specific function of these GST classes in brain mitochondria is not clear, except as a response to xenobiotic inducers. It is worth noting that in a cross-species comparison study on the conservation of longevity assurance mechanisms, GST was the common denominator in *Caenorhabditis elegans*, *Drosophila*, and mice (158), thus supporting the hypothesis that detoxification reactions, such as those catalyzed by GSTs, are an important part of longevity assurance mechanisms (265).

Protein thiols are sensitive to changes in the redox environment (57): the GSH/GSSG redox couple regulates protein function through the reversible formation of mixed disulfides between protein cysteine sulfhydryls and GSH in a process termed S-glutathionylation. Mixed-disulfide formation affects the activity of enzymes, transcription factors, and transporters, thus enabling them to respond to the redox environment by reversible activation/inactivation (78, 227, 261). Thus, S-glutathionylation reflects the redox status of the mitochondria (207) and is viewed as a regulatory device for the proteins involved in energy metabolism, redox signaling, and cell function (61, 62, 99, 130, 162). A number of proteins have been identified to be S-glutathionylated during oxidative conditions, including components of the energy metabolism: (a) SCOT and the E_2 subunit of PDH (82, 107); (b)TCA cycle enzyme such as aconitase (92), α-KGDH (177), and IDH (126), and (c) complexes I (226), II (50), and V (82, 240). S-glutathionylation of SCOT and ATP synthase (F_1 complex, α-subunit) in brain mitochondria resulted in a decrease of activity and a reduction potential of -171 mV; supplementation of mitochondria with respiratory substrates to complex I or complex II increased NADH and NADPH levels, restored GSH levels through a reduction of GSSG, elicited deglutathionylation of mitochondrial proteins, and resulted in a more reducing mitochondrial environment (-291 mV) (82). Complex I is persistently glutathionylated under conditions of oxidative stress, and this resulted in increased generation of $O_2^{\cdot -}$ and decreased mitochondrial function (226). Conversely, S-glutathionylation of adenine nucleotide translocase (ANT) protects against mitochondrial membrane permeabilization and apoptosis (193). These data provide evidence of mitochondrial redox changes that modulate energy metabolism through protein thiol modifications.

The reversible formation of protein-GSH mixed disulfides has been suggested as a protective mechanism that masks critical sulfhydryls from irreversible oxidation; the reversibility of this process acquires further significance because of its involvement in the redox regulation of signal transduction (98, 130). Protein-mixed disulfides are specifically reduced by Grxs (Grx2 is the mitochondrial isoform) through a monothiol mechanism (102). Oxidized Grx2 is reduced by GSH, which is regenerated from GSSG by NADPH-supported glutathione reductase (GR). Grx2 is constitutively expressed in neurons and glia in mouse and human brain (122), and the knockdown of cytosolic Grx1 is associated with a loss of mitochondrial membrane potential (203) and is essential for maintaining the functional integrity of brain mitochondrial complex I (125). Grx2 protects cells against oxidative damage (72) involving Akt signaling and the redox-sensitive transcription factor NF-κB and anti-apoptotic Bcl-2 (166). In addition, Grx2 has been characterized as being a part of an iron-sulfur cluster that senses redox changes and controls the activation of Grx2 during conditions of oxidative stress (103), thus expanding the interaction between oxidants, mitochondrial redox status, and protein glutathionylation.

Trx-based systems

The reducing power for peroxiredoxins (Prx) is transmitted through thiols of the Trx system: NADPH → Thioredoxin reductase (TrxR) → Trx → Prx (257). A comprehensive study on immunohistochemical mapping of all six Prx subtypes in the mouse brain revealed that astrocytes and microglia were reactive to Prx6 and Prx1, respectively; immunoreactivity for Prx1 and Prx4 in the nuclei of oligodendrocytes; in neurons, Prx3 and Prx5 were found in the stratum lucidum of the hippocampus and Prx2 in the habenular nuclei (115). Of these Prxs, Prx2 was critical for the maintenance of hippocampal synaptic plasticity against age-associated oxidative damage (129) by a mechanism entailing the oxidant- and age-dependent mitochondrial decay of hippocampal neurons; in addition, the expression of Prx2 in hippocampal neurons increased as a function of age.

Mitochondrial Prx3 and Prx5 (Fig. 3) are involved in the enzymatic degradation of H_2O_2; Prx5 can also reduce $ONOO^-$ (69, 183). Trx2 is highly efficient at reducing disulfides in proteins (163), thus impacting cellular functions such as antioxidant defenses and the redox control of transcription and signal transduction (8, 101). Using a polarographic method for real-time detection of H_2O_2, it was concluded that the removal of H_2O_2 by energized brain mitochondria was largely dependent on the Trx/Prx system with a modest contribution by the GSH/GPx system (66). Prx3 and Prx5 are constitutively expressed in human neuroblastoma Sh-SY5Y cells, and their silencing by small hairpin RNAs renders the cells more susceptible to oxidative damage and apoptosis (63). Prx3 protects hippocampal neurons against excitotoxicity, and its up-regulation prevented or reduced gliosis, that is, proliferation of astrocytes in certain areas of the brain (96). The overexpression of Prx-3 reduces H_2O_2 production and lipid peroxidation and protects cells from hypoxia-, TNFα-, cadmium-, and oxidant-induced cell death (46, 49, 176, 243), and a neuroprotective effect was observed when administered into ischemic brains (108). The increased Prx3 (along with TrxR2 and Trx2) immunoreactivity in the hippocampus of aged dogs as compared with adult dogs was interpreted as a reduction of neuronal damage (against oxidative stress) during aging (3). Prx3 levels are found to be significantly lower in the brains of Alzheimer's disease patients (128), and a deficiency in Prx3 is also associated with multiple neurodegenerative disorders such as amyotrophic lateral sclerosis, Parkinson's disease, and Down syndrome (133, 244). $Trx2^{+/-}$ mice show reduced ATP production and electron-transport chain rates (184); this notion is further supported by the increased apoptosis in early embryos of $Trx2^{-/-}$ mice (embryonic lethal) with mitochondria

maturation. The systemic ablation of mitochondrial TrxR-2 also yielded embryonic lethal phenotypes (54). The levels of TrxR2 decrease with age in different tissues and is accompanied by enhanced susceptibility to apoptosis (201), also suggesting that NADPH supply and TrxR activity rather than activities of Trx2 may be rate limiting for the protection against oxidants and be of importance in dysregulated redox status during aging and neurodegeneration (182). The significance of the redox couples and redox catalysts for brain aging and age-related neurodegeneration just mentioned is underscored by the highly oxidized mitochondrial and cellular redox environment that is involved in these processes (146, 168, 252).

Interdependence of energy- and redox components—role of nicotinamide nucleotide transhydrogenase

The ultimate reductant of mitochondrial redox systems is NADPH (supporting the activities of GR and of TrxR) (Fig. 3). The age-dependent decrease in the ratio of $NADPH/NADP^+$ in kidney mitochondria (251) indicates that NADPH deficiencies are another factor in mediating mitochondrion-dependent aging. Mitochondrial NADPH is mainly formed through three pathways: $NADP^+$-dependent IDH_2, malic enzyme, and nicotinamide nucleotide transhydrogenase (NNT) (Fig. 3). Of these pathways, 50% of the mitochondrial NADPH pool is uncoupler sensitive, thus suggesting that the NNT-catalyzed reduction of $NADP^+$ accounts for more than 50% of the mitochondrial NADPH pool (202). NNT, a nuclear encoded mitochondrial 110 kDa protein located on the inner mitochondrial membrane (100), catalyzes the reversible reduction of $NADP^+$ to NADPH coupled to the oxidation of NADH to NAD^+. The proton gradient across the mitochondrial inner membrane strongly stimulates the forward reaction, that is, the generation of NADPH and the subsequent capacity for H_2O_2 reduction (255). NNT plays an important role in regulating cellular redox homeostasis, energy metabolism, and apoptotic pathways (150, 253). Knockdown of NNT in PC12 cells results in an altered redox status encompassed by decreased cellular NADPH levels and GSH/GSSG ratios and increased H_2O_2 levels, as well as an impaired mitochondrial energy-transducing capacity. The activation of redox-sensitive signaling (c-Jun N-terminal kinase, JNK) by H_2O_2 after NNT suppression induces mitochondrion-dependent intrinsic apoptosis and results in decreased cell viability (253). NNT activity provides a link between the mitochondrial metabolic function (energy-transducing activity) and redox homeostasis by coupling NADPH generation to the TCA cycle and active respiration (Fig. 3). This supports the notion that changes in cellular bioenergetics and changes in the redox status of the cell cannot be viewed as independent events, but rather as an interdependent relationship established by the mitochondrial energy-redox axis (250). Disruption of electron flux from fuel substrates to redox components due to NNT suppression not only compromises mitochondrial dysfunction, including energy-transducing capacity and redox homeostasis, but also affects cellular functions through interactive communication between mitochondrion-generated second messengers and cytosolic redox-sensitive signaling (see section III). The modulation of NNT function could be considered important in the collective impairments of the interdependent mitochondrial energy-redox axis and the regulation of cytosolic redox-sensitive signaling that is inherent in several pathophysiological situations. This study (253) potentially explains the underlying mechanisms of the poor response of $NNT^{-/-}$ C57Bl/6J mice to glucose (79). It also explains the shortened life span of mice when the SOD2 deficiency (lethal with $\sim$3 weeks life span) is combined with NNT deletion ($\sim$1 week life span) (106, 141, 143). NNT activity decreases during brain aging in rats and mice and is up-regulated on caloric restriction. Investigations of the physiological and pathological roles of NNT expands the understanding of the mechanisms that support energy- and/or redox deficits in the early or late stages of neurodegenerative diseases (146, 249, 264), diabetes (119, 149), cardiovascular disease (213), and aging (156, 169, 235).

Mitochondrial dynamic remodeling

Mitochondria are highly dynamic organelles and undergo continuous fusion and fission throughout their life cycle (44). These processes regulate not only mitochondrial morphology, but also their biogenesis, transportation, cellular localization, quality control, and degradation (mitophagy) (44, 231). Mitochondrial fusion is regulated by GTPases optic atrophy-1 (OPA1) and mitofusin-1/2 (Mfn1/Mfn2), which are responsible for the fusion of outer- and inner mitochondrial membranes, respectively (216). Mitochondrial fission is controlled by dynamin-related protein 1 (Drp1) and fission protein 1 homolog (Fis1), with the former as scissors of the mitochondrial membrane and the latter probably as a recruiter of Drp1 to mitochondria (110, 121, 256).

Mitochondrial dynamics are closely related to the energy-redox axis. A coordinated balance between fission and fusion is essential for cell function, and its perturbation is associated with pathologies (43, 47, 48, 144). OPA1 deficiency has been associated with decreased mitochondrial ATP production, increased oxidant production, mitochondrial fragmentation, decreased life span, and neurodegeneration (47, 53, 225, 258). The suppression of Mfn2 results in a loss of mitochondrial membrane potential, reduced OXPHOS complexes expression, and decreased glucose oxidation and respiration (13, 187). Similar effects on mitochondrial metabolism are shown when mitochondrial fission is inhibited: The down-regulation of Drp1 leads to a loss of mitochondrial membrane potential and DNA content, a decrease of mitochondrial respiration and cellular ATP levels, as well as an oxidized cellular redox status and cytochrome *c* release (77, 181). Repression of Fis1 decreases mitochondrial respiration with the accumulation of oxidized mitochondrial proteins (230). Conversely, the mitochondrial dynamics machinery could also be regulated by the energy and redox change: The energy-consuming OPA1 cleavage reflects the mitochondrial energy-transducing capacity and the inner membrane potential (70). It is also recognized that nitrosative stress activates mitochondrial fission through the S-nitrosylation of Drp1 (SNO-Drp1) by $\cdot$NO and further induce synaptic loss and neuronal damage (52), and levels of active forms (S-nitrosylated and phosphorylated forms) of Drp1 are higher in brains of Alzheimer's patients than in control subjects (238). It has also been shown that increased generation of mitochondrial $O_2^{\bullet -}$ or H_2O_2 induced by respiratory chain inhibitors or ionizing radiation enhances mitochondrial fragmentation (fission) and cell death (131, 147, 189), which is proposed to be due to an oxidative

stress-induced transcriptional regulation of fusion and fission proteins (114). Accordingly, the overexpression of Mfn2 or OPA1 inhibits H_2O_2-induced mitochondrial fission and cell death (112, 113). The inter-regulation between mitochondrial dynamics machinery and the energy-redox axis, therefore, allows the mitochondria to meet various specialized and localized metabolic needs in a timely and positional manner.

The Energy-Redox Axis with Cytosolic Signaling

The energy-transducing and redox-regulation capacity of mitochondria are highly affected in aging and age-related neurodegeneration. Mitochondria generate second messengers (redox: H_2O_2 and·NO; energy: ATP) that are involved in the regulation of redox/energy sensitive cell signaling pathways, thus coordinating functional responses between mitochondria and other cellular processes. Conversely, mitochondria are the recipients of cytosolic signaling molecules, which translocate to mitochondria under specific conditions and elicit profound metabolic or redox effects in the organelles. The communication between mitochondria and other components of the cell establishes a regulatory device that controls cellular energy levels and the redox environment (Fig. 1); impairment of this regulatory device may serve as the basis for the mechanisms which are inherent in aging and age-related degenerative disorders.

Mitochondrial regulation of cytosolic signaling

Mitochondrial-generated oxidants regulate important signaling pathways such as the insulin and insulin-like growth factor (IGF-1) signaling (IIS) and the MAPK (*e.g.*, JNK) pathways. The PI3K/Akt route of IIS in the brain (Fig. 4) is implicated in neuronal survival and synaptic plasticity *via*, among other effects, maintenance of the metabolic function of mitochondria. Aging is associated with decreases in the levels of both insulin/IGF-1 and their receptor (81). Mitochondrial H_2O_2 is involved in the regulation of insulin signaling, which is not surprising given the large quantity of redox-sensitive cysteine residues on the insulin and IGF1 receptors and insulin receptor substrates (IRS): Oxidation of specific cysteine residues promote tyrosine autophosphorylation of the insulin receptor (219) and inhibition of phosphatases (PTEN and PTP1B) involved in the IRS node of insulin signaling on the oxidation of critical cysteines to disulfides (151). Aged cells are more vulnerable to H_2O_2-induced apoptosis, which is accompanied by reduced activation of Akt, and caloric restriction can prevent this loss of Akt activation (109). In addition, Akt activation is also inhibited by nitrosative stress through tyrosine nitration (55). Akt inhibits GSK-3β on phosphorylation at Ser,[9] thereby protecting cell against apoptosis, because activated GSK3β stimulates phosphorylation of the anti-apoptotic member of the Bcl-2 family, Mcl-1, thus leading to its degradation and the ensuing cytochrome *c* release and apoptosis (157, 180).

The MAPKs are also sensitive to oxidative or nitrosative stress conditions, entailing an enhanced generation of H_2O_2 or peroxynitrite, which results in their activation (174, 188, 253, 263) (Fig. 5); H_2O_2 may act at multiple levels to activate JNK (and p38): dissociation of thioredoxin from the ASK-1 complex (204), disruption of the glutathione transferase (GT)-JNK complex (1), or inhibition of MAPK phosphatase activity (76). Basal JNK activity, but not its protein levels, is increased in mouse brain and liver, rat kidney and splenic lymphocytes, and human skeletal muscle during aging (105, 127, 142, 221, 242). Basal activities of ERK and p38 kinase, but not their protein levels, are reported to decrease in the brain cortex during aging, a phenomenon that was prevented by caloric restriction (259); conversely, basal p38 and ERK activities were increased in mouse liver, rat kidney, and human skeletal muscle (104, 127, 242). It is unclear whether or not these discrepancies are due to tissue specificity of p38 and ERK responses to the aging process. Nevertheless, the activation of ERK in response to epithelial growth factor is decreased in cortical brain slices and hepatocytes from old rats (148, 259), indicating reduced sensitivity to stimuli in these tissues during aging.

In addition, JNK also plays a central role in the progression of insulin resistance; a likely mechanism that entails the phosphorylation of the IRS-1 at Ser^{307}, leading to inhibition of the insulin-promoted tyrosine phosphorylation of IRS (2). Conversely, the MLK3-mediated JNK activation is inhibited by Akt on the phosphorylation of MLK3 both *in vitro* and *in vivo* (19). Due to the distinct downstream signaling between PI3K/Akt and JNK (survival *vs.* apoptosis; growth *vs.*

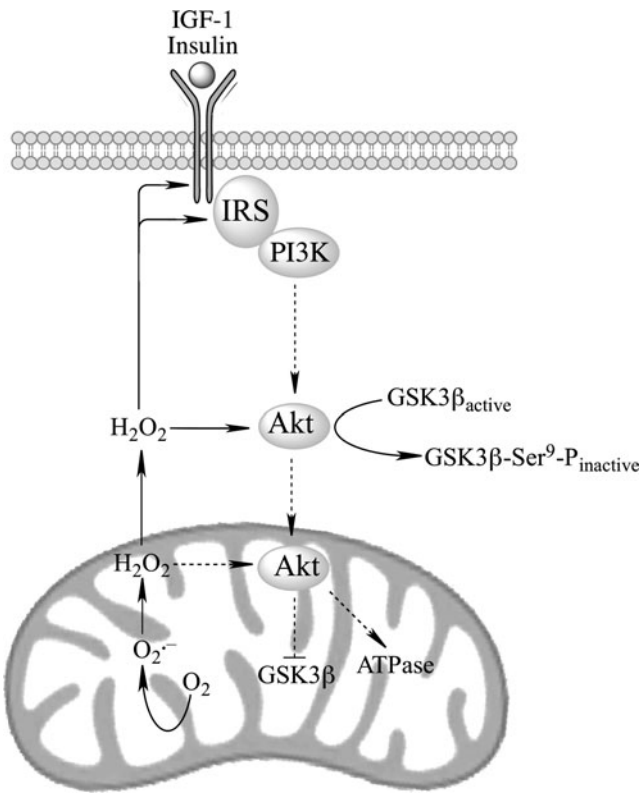

FIG. 4. Oxidative conditions and the PI3K/Akt pathway of insulin signaling. The large number of cysteinyl moieties in the IR and IRS renders them susceptible to oxidation (and activation) by H_2O_2; Akt is also redox sensitive. In NIH/3T3 cell lines, Akt translocation to the mitochondria is associated with a second phosphorylation, which is dependent on the mitochondrial $[H_2O_2]_{ss}$ (7); in neuroblastoma cells, the translocation of Akt to mitochondria resulted in the phosphorylation of a mitochondrial constitutive form of GSK3β and of ATPase (23). IGF-1, insulin-like growth factor-1; IRS, insulin receptor substrate.

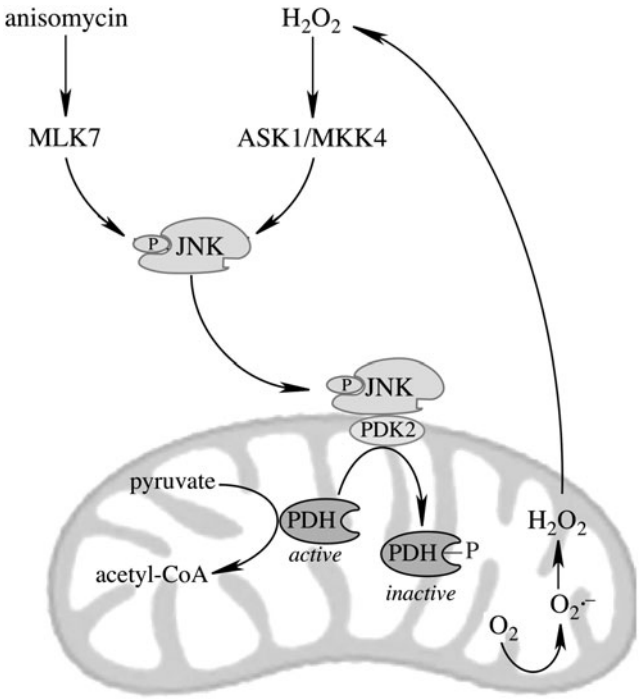

FIG. 5. Oxidative stress-induced activation (bisphosphorylation) of JNK and its translocation to the mitochondrion. Anisomycin or H_2O_2 (*via* MLK7 or MKK4, respectively) leads to the bisphosphorylation of JNK, which translocates to the outer mitochondrial membrane and triggers a phosphorylation cascade (including PDK2 activity) that results in phosphorylation (inactivation) of the pyruvate dehydrogenase complex (PDH) (263, 264). JNK, c-Jun N-terminal kinase.

differentiation), the counterbalance of the IIS and JNK pathways induced by different concentrations of H_2O_2 is expected to determine the coordinated response of the cell. These disparate effects of mitochondrial H_2O_2 are important, as they refer to a healthy aging or accelerated aging, and they need to be assessed in terms of the cellular peroxide tone, that is, a quantitative assessment of a mitochondrial steady-state concentration of H_2O_2 in connection with domain-specific signaling. Hence, the mitochondrial energy-redox axis is one of the factors that regulate the peroxide tone of the cell in a domain-specific signaling fashion.

Despite its role in regulating the activities of kinases, phosphatases, and other redox-sensitive enzymes on the time scale of minutes to hours, dynamic H_2O_2 signaling is also involved in sub-second signaling *via* ion channel activation in neuronal cells (198). In dopamine neurons of the *substantia nigra*, mitochondrial H_2O_2 inhibits neuron firing by activating ATP-sensitive K (K_{ATP}) channels, thus linking metabolic state to cell excitability (10, 15). The mitochondrial energy and redox status are also connected with suppressed dopamine release in the striatum through the activation of K_{ATP} channels by glutamatergic AMPA receptor-induced H_2O_2 generation (11, 12). False regulation of H_2O_2 signaling due to mitochondrial dysfunction could compromise striatal dopamine release and, thus, be implicated in nigrostriatal degeneration and Parkinson's disease (16). H_2O_2 can also activate the transient receptor potential (TRP) channels that increase the excitability of striatal GABAergic medium spiny neurons (16). The expression of the redox-sensitive ion channels, either inhibitory (K_{ATP}) or excitatory (TRP), in coordination with cell-specific mitochondrial metabolic and redox regulation, defines the specificity of dynamic neurotransmission (198).

Cytosolic regulation of mitochondrial function

Mitochondria are also important targets of cytosolic signaling molecules. It was shown that the expression and activation of JNK1 increases in the brain as a function of age and that active (bisphosphorylated) JNK translocates to the mitochondrion, where it triggers a phosphorylation cascade which results in phosphorylation (inhibition) of PDH, a key mitochondrial enzyme complex that bridges anaerobic and aerobic brain energy metabolism. PDK2 is an essential intermediate in this phosphorylation cascade. The outcome is a bioenergetic crisis translated into decreased cellular ATP and an increase in lactate levels (anaerobic glycolysis as a compensatory mechanism) (263, 264) (Fig. 5).

The PI3K/Akt pathway promotes neuronal survival and synaptic plasticity (234) by mechanisms entailing the phosphorylation of proapoptotic Bcl-2 family members (Bad) of GSK3β (thus inhibiting tau hyperphosphorylation) and of FoxO factors (that drives nuclear FoxO factors to the cytosol, thus inhibiting the transcription of some apoptotic genes and those involved in heme degradation) (51). In NIH/3T3 cell lines, mitochondrial H_2O_2 modulates the entrance of cytosolic Akt (phosphorylated at Ser^{473}) to the mitochondria and induces the further phosphorylation at Thr^{308} that is required for nuclear translocation (7). Akt translocates to the mitochondrion in human neuroblastoma cells, and its phosphorylation targets are a constitutive form of GSK3β in the mitochondrion and the β-subunit of ATPase (23) (Fig. 4).

ATP is the universal energy currency in the cell, and mitochondrial produced by ATP is transported to the cytosol by ANT in exchange with ADP. The cytosolic ADP/ATP ratio is an important parameter of not only the cellular consumption of ATP but also ATP synthesis as a reflection of mitochondria bioenergetic profile. The ubiquitously expressed adenylate kinases in all cell types, which catalyzed the inter-conversion of adenine nucleotides ($2ADP \leftrightarrow ATP + AMP$), make AMP/ATP another important indicator of energy status. 5′ adenosine monophosphate-activated protein kinase (AMPK) is a kinase with its activity controlled by intracellular AMP/ATP ratio and, therefore, rendered a sensor of cellular energy status. In fact, recent studies have suggested that AMPK activity can also be regulated by ADP (178, 246). AMPK is activated on various stress conditions, including glucose deprivation, ischemia, and hypoxia, and is also a key player involved in the cellular response to exercise (218). Moreover, AMPK is redox sensitive (237) and interacts with mitochondrial redox status through the mitochondrial aldehyde dehydrogenase (ALDH-2) (60). On activation, AMPK induces multiple responses, including enhanced glucose metabolism and fatty acid oxidation, to switch cellular metabolism from anabolism to catabolism by (a) increasing glucose uptake by stimulating glucose transporters expression (260) and its translocation to the plasma membrane (17, 134); (b) enhancing glycolysis by activating 6-phosphofructo-2-kinase (PFK2) (153); and (c) simultaneously inhibiting fatty acid synthesis and activating mitochondrial β-oxidation by blocking acetyl-CoA carboxylase

(ACC1/2) activity (95). AMPK is regarded a central regulator of the pathways that are implicated in aging and a potential longevity regulator in worms (86), and it is also involved in the beneficial effects of caloric restrication (118). Mixed results were reported regarding the change of AMPK activity during aging in different tissues, but growing evidence suggests that decreased AMPK activity and/or decreased responsiveness to AMPK activity is associated with declined mitochondrial function as a function of age (75), thus indicating an interrelationship between mitochondrial energy status and AMPK activity.

It may be surmised that the cross-talk between IIS, JNK, and AMPK signaling in the brain, their modulation by mitochondrial signaling molecules, and how these signaling impinge on mitochondrial function is of importance in understanding the process of aging and their relevance for some neurodegenerative disorders. Since active JNK can also initiate mitochondrion-dependent apoptosis, impairment of the communication between mitochondrion-supported redox signaling and cytosolic signaling pathways may serve as the basis for the mechanisms inherent in cell death pathways and the loss-of-cell function that is associated with aging and age-related degenerative disorders.

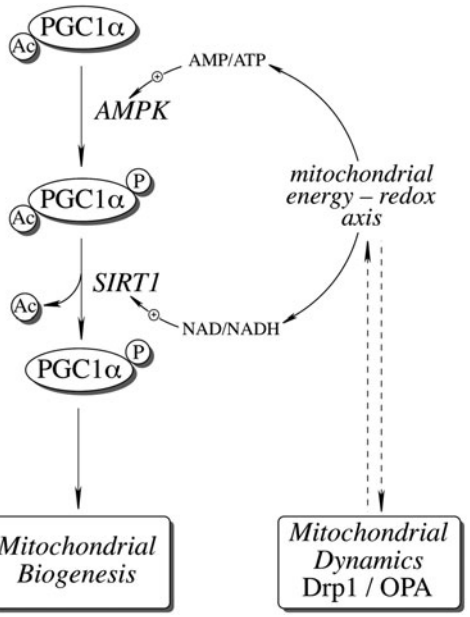

FIG. 6. The mitochondrial energy-redox axis in mitochondrial biogenesis and mitochondrial dynamics. Activation of the co-activator PGC1α requires phosphorylation and deacetylation, pathways involving AMPK and Sirt1; the former is sensitive to the energy levels (expressed as [ATP]/[AMP]+[ADP], whereas the latter requires NAD^+ as a co-substrate. Changes in the regulators of fission/fusion impinge on the mitochondrial energy-transducing capacity (see text). AMPK, 5′ adenosine monophosphate-activated protein kinase; Drp1, dynamin-related protein 1; OPA, optic atrophy; PGC-1, peroxisome-proliferator-activated receptor γ coactivator-1.

The Energy-Redox Axis and Nuclear Transcriptional Pathways

Transcriptional control of mitochondrial biogenesis

The majority of the mitochondrial proteins are nuclear encoded and cytosol synthesized before being transported to mitochondria (186), and mitochondrial DNA encodes 13 subunits of the complexes in the electron transport chain. The transcription of mtDNA is primarily controlled by mitochondrial transcription factor A (TFAM), while the coordinated expression of nuclear-encoded mitochondrial proteins involves multiple transcription factors such as Sp-1, YY-1, CREB, MEF-2, and nuclear respiration factors (NRFs) such as NRF-1, NRF-2, ERRα, and REBOX/OXBOX, among others (75, 206). The coordination of these transcriptional pathways is integrated by the peroxisome-proliferator-activated receptor γ coactivator-1 (PGC-1) family of transcriptional coactivators, and PGC-1α is currently the best-characterized member (93). The ability of PGC-1α in regulating the transcription of mtDNA by coactivating NRF-1 on the promoter of TFAM and mitochondrial transcription specificity factors TFB1M and TFB2M, as well as its role as a co-activator of major transcription factors involved in nuclear-encoded mitochondrial gene expression, renders PGC-1α the master regulator of mitochondrial biogenesis (Fig. 6). ·NO can signal through cGMP-PKG pathway to activate Sirt1 and PGC1α (33, 171, 175).

The decline of mitochondrial function with age and in neurodegeneration is associated with reduced mitochondrial biogenesis and decreased activity of its major regulator, PGC-1α. PGC-1α levels were found to be decreased with age, and the decline was rescued by caloric restriction in skeletal muscle (97); PGC-1α levels and mitochondrial function were positively linked to lifespan extension in several rodent genetic models (4, 123). Overexpression of PGC-1α in a model of mitochondrial myopathy significantly prolonged lifespan (239). PGC-1α knockout mice are more sensitive to the neurodegenerative effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and kainic acid; conversely, increased PGC-1α levels protect neurons against oxidative stress-mediated death by inducing expression of antioxidant genes (217). Mitochondria from a Huntington's disease transgenic mouse brain show reduced PGC-1α levels and OXPHOS gene expression (241), and PGC-1α null mice also show increased degeneration of striatal neurons and lesions in the striatum, which is the primary brain region affected by Huntington's disease (145). Conversely, the overexpression of PGC-1α in the striatum provides neuroprotection by reversing the toxic effects of mutant huntingtin (56). Notably, despite its major role in modulating mitochondrial function, the impact of PGC-1α activity modulation is stimulus- and tissue dependent (5).

As a key regulator of mitochondrial biogenesis and function, PGC-1α is regulated at multiple levels, including its transcription, post-translational modification, localization, and degradation. The regulation of PGC-1α expression involves CREB (245) and mTOR-YY1 (58) pathways, making them important modulators of mitochondrial metabolic function in aging (209). Post-translationally, PGC-1α is activated by Sirt1 by deacetylation after the translocation of the former into the nucleus during stress conditions (6). AMPK is another regulator of PGC-1α activity either by direct phosphorylation of PGC-1α (111) or by indirectly enhancing Sirt1 activity (42) (Fig. 6). The regulation of PGC-1α turnover by GSK3β phosphorylation and subsequent degradation (6) provides an additional layer of control on PGC-1α function.

Taken together, the spatiotemporal regulation of PGC-1α at multiple levels and time points enables the fine tuning of mitochondria activity and energy homeostasis by integrating transcriptional pathways driven by Sirt1, AMPK, and mTOR in response to extracellular signals and specific cell demands.

Mitochondrial regulation of transcriptional pathways

The signal communications between the nucleus and mitochondria are not unidirectional. Perturbations of mitochondrial energy and redox status can also be transmitted to the nucleus to induce cellular adaptive or compensatory responses. This process involves several mitochondrion-generated second messengers, such as ATP, H_2O_2, ·NO, and processes involved in the dysregulation of Ca^{2+} homeostasis and the maintenance of cytosolic NAD^+/NADH ratios. As the primary indicator of mitochondrial metabolic status, altered ATP levels in the cells affect AMPK activity and positively modulate energy-consuming anabolic processes through mTOR either directly (64) or indirectly (90, 212) involving a variety of transcription factors, such as p300, HNF4α, MEF-2C, and p53 (94, 159). ATP signaling is also involved in the regulation of mitochondrial biogenesis through the AMPK-PGC1α pathway (41, 111) (Fig. 6). Hence, the mitochondrial bioenergetic state is an important modulator of cell growth and proliferation. It is still controversial whether ATP levels or ATP production rate declines with age (67, 135, 138); thus, future studies should focus more on the sensitivity of these adenine nucleotides signaling pathways to altered mitochondrial energy status during aging.

As important intermediate metabolites, both NAD^+ and NADH, and their ratio, affect mitochondrial function by modulating mitochondrial permeability transition pore and Ca^{2+} homeostasis (254). Cytosolic/nuclear NAD^+ can serve as a substrate of Sirt1 to regulate mitochondria biogenesis by the deacetylation of PGC1α (42) and as a substrate of poly (ADP-ribose) polymerase, which is an important DNA nick sensor. The age-dependent decline in intracellular NAD^+ levels and NAD^+/NADH ratio were observed in parallel with decreased Sirt1 activity (34). Although the inner mitochondrial membrane is impermeable to NAD^+ and NADH, it was found that the malate-aspartate NADH shuttle could play a critical role in the activation of the downstream targets of caloric restriction, such as sir2 (Sirt1 homolog), and is required for caloric restriction-mediated lifespan extension in yeast (71). This indicates that alterations in the mitochondrial energy status are capable of influencing the cytosolic and nuclear NAD^+/NADH pool and further affecting the NAD^+-dependent sirtuin pathways (Fig. 6).

A variety of transcriptional pathways are redox sensitive and can be activated on extracellular stimuli or intracellular redox changes (35). Transcription factors, such as HSF-1, p53, and NF-κB, can be directly activated on oxidative stress (74), while some other factors, including NRF-1, NRF-2, and FoxO, can be activated/inhibited indirectly *via* redox-sensitive kinase signaling pathways such as JNK, ERK, p38, and PI3K/Akt (35) (see Section III). The role of H_2O_2 in NF-κB activation has been critically reviewed (179), and it was concluded that H_2O_2 does not function as an inducer of NF-κB but it is largely involved in the regulation of NF-κB-related pathways. Another redox-sensitive transcription factor is nuclear factor erythroid 2-related factor (Nrf2), which on its dissociation from Keap1, activates antioxidant responses. Altered redox status leads to the oxidation of Keap1 (*via* thiol/disulfide exchange) and the release of Nrf2; the latter translocates to the nucleus and activates the antioxidant response element-mediated Phase II enzyme expression (65). Multiple key endogenous antioxidant enzymes that are involved in GSH synthesis and reduction and $O_2^{\bullet -}/H_2O_2$ homeostasis are regulated by Nrf2 (117); the levels of Nrf2 and the expression of its downstream genes decrease with age (220), suggesting the potential role of the Nrf2 pathway in the age-related decline of redox capacity.

Mitochondria are also important regulators of Ca^{2+} storage and homeostasis. Ca^{2+} signaling is involved in cell- and stimuli-specific responses through various transcriptional networks such as NFAT, MEF2, TORC, CREB, and NF-κB (160). A comprehensive study on the role of mitochondrial Ca^{2+} in the regulation of cytosolic and nuclear redox signaling is previously reviewed (224).

Conclusions and Perspectives

Aging and neurodegeneration are associated with declines in energy production in the brain as well as parallel changes in redox status with a pro-oxidant shift that may be due in part through the mitochondrial generation of $O_2^{\bullet -}$ and H_2O_2. Mitochondria regulate distinct cytosolic signaling pathways and have vital roles: (*a*) They are the cellular organelles that generate ATP, which supports the cellular energy demands; (b) generate second messengers, such as H_2O_2 and ·NO, that are implicated in the modulation of redox-sensitive kinase signaling and transcriptional pathways; and (c) are involved in the regulation of NAD^+/NADH homeostasis, which, in turn, influence mitochondrial biogenesis and dynamic remodeling. Conversely, mitochondria are targets and recipients of cytosolic redox-sensitive signaling and nuclear transcriptional pathways. The pathways discussed in this review are part of an intricate signaling network that has evolved around mitochondrial metabolism, generation of H_2O_2, and cellular responses, further supporting the link between the mitochondrial formation of signaling molecules, the rate of aging, and the course of age-related diseases. Characterization of the signaling events originating from mitochondria and converging on mitochondria might unravel the molecular links between strategies aimed at restoring the mitochondrial energy-redox axis that is compromised in brain aging and neurodegeneration.

Acknowledgments

This review was supported by NIH grants RO1AG016718 to E.C. and PO1AG026572 (to Roberta Díaz Brinton; E.C. as co-investigator in Project 1).

References

1. Adler V, Funchs SY, Benezra M, Rosario L, Tew KD, Pincus MR, Sardana M, Henderson CJ, Wolf CR, Davis RJ, and Ronai Z. Regulation of JNK signaling by GSTp. *EMBO J* 18: 1321–1234, 1999.
2. Aguirre V, Uchida T, Yenush L, Davis R, and White MF. The c-Jun NH(2)-terminal kinase promotes insulin resistance during association with insulin receptor substrate-1 and phosphorylation of Ser(307). *J Biol Chem* 275: 9047–9054, 2000.

3. Ahn JH, Choi JH, Song JM, Lee CH, Yoo KY, Hwang IK, Kim JS, Shin HC, and Won MH. Increase in Trx2/Prx3 redox system immunoreactivity in the spinal cord and hippocampus of aged dogs. *Exp Gerontol* 46: 946–952, 2011.
4. Al-Regaiey KA, Masternak MM, Bonkowski M, Sun L, and Bartke A. Long-lived growth hormone receptor knockout mice: interaction of reduced insulin-like growth factor i/insulin signaling and caloric restriction. *Endocrinology* 146: 851–860, 2005.
5. Anderson R and Prolla T. PGC-1alpha in aging and anti-aging interventions. *Biochim Biophys Acta* 1790: 1059–1066, 2009.
6. Anderson RM, Barger JL, Edwards MG, Braun KH, O'Connor CE, Prolla TA, and Weindruch R. Dynamic regulation of PGC-1alpha localization and turnover implicates mitochondrial adaptation in calorie restriction and the stress response. *Aging Cell* 7: 101–111, 2008.
7. Antico Arciuch VG, Galli S, Franco MC, Lam PY, Cadenas E, Carreras MC, and Poderoso JJ. Akt1 intramitochondrial cycling is a crucial step in the redox modulation of cell cycle progression. *PLoS One* 4: e7523, 2009.
8. Aslund F and Beckwith J. Bridge over troubled waters: sensing stress by disulfide bond formation. *Cell* 96: 751–753, 1999.
9. Atamna H and Frey WH, 2nd. Mechanisms of mitochondrial dysfunction and energy deficiency in Alzheimer's disease. *Mitochondrion* 7: 297–310, 2007.
10. Avshalumov MV, Chen BT, Koos T, Tepper JM, and Rice ME. Endogenous hydrogen peroxide regulates the excitability of midbrain dopamine neurons via ATP-sensitive potassium channels. *J Neurosci* 25: 4222–4231, 2005.
11. Avshalumov MV, Chen BT, Marshall SP, Pena DM, and Rice ME. Glutamate-dependent inhibition of dopamine release in striatum is mediated by a new diffusible messenger, H_2O_2. *J Neurosci* 23: 2744–2750, 2003.
12. Avshalumov MV and Rice ME. Activation of ATP-sensitive K^+ (K(ATP)) channels by H_2O_2 underlies glutamate-dependent inhibition of striatal dopamine release. *Proc Natl Acad Sci U S A* 100: 11729–11734, 2003.
13. Bach D, Pich S, Soriano FX, Vega N, Baumgartner B, Oriola J, Daugaard JR, Lloberas J, Camps M, Zierath JR, Rabasa-Lhoret R, Wallberg-Henriksson H, Laville M, Palacin M, Vidal H, Rivera F, Brand M, and Zorzano A. Mitofusin-2 determines mitochondrial network architecture and mitochondrial metabolism. A novel regulatory mechanism altered in obesity. *J Biol Chem* 278: 17190–17197, 2003.
14. Balaban RS, Nemoto S, and Finkel T. Mitochondria, oxidants, and aging. *Cell* 120: 483–495, 2005.
15. Bao L, Avshalumov MV, Patel JC, Lee CR, Miller EW, Chang CJ, and Rice ME. Mitochondria are the source of hydrogen peroxide for dynamic brain cell signaling. *J Neurosci* 29: 9002–9010, 2009.
16. Bao L, Avshalumov MV, and Rice ME. Partial mitochondrial inhibition causes striatal dopamine release suppression and medium spiny neuron depolarization via H_2O_2 elevation, not ATP depletion. *J Neurosci* 25: 10029–10040, 2005.
17. Barnes K, Ingram JC, Porras OH, Barros LF, Hudson ER, Fryer LG, Foufelle F, Carling D, Hardie DG, and Baldwin SA. Activation of GLUT1 by metabolic and osmotic stress: potential involvement of AMP-activated protein kinase (AMPK). *J Cell Sci* 115: 2433–2442, 2002.
18. Barnham KJ, Masters CL, and Bush AI. Neurodegenerative diseases and oxidative stress. *Nat Rev Drug Discov* 3: 205–214, 2004.
19. Barthwal MK, Sathyanarayana P, Kundu CN, Rana B, Pradeep A, Sharma C, Woodgett JR, and Rana A. Negative regulation of mixed lineage kinase 3 by protein kinase B/AKT leads to cell survival. *J Biol Chem* 278: 3897–3902, 2003.
20. Beal MF. Aging, energy, and oxidative stress in neurodegenerative diseases. *Ann Neurol* 38: 357–366, 1995.
21. Beckman KB and Ames BN. The free radical theory of aging matures. *Physiol Rev* 78: 547–581, 1998.
22. Biessels GJ and Kappelle LJ. Increased risk of Alzheimer's disease in Type II diabetes: insulin resistance of the brain or insulin-induced amyloid pathology? *Biochem Soc Trans* 33: 1041–1044, 2005.
23. Bijur GN and Jope RS. Rapid accumulation of Akt in mitochondria following phosphatidylinositol 3-kinase activation. *J Neurochem* 87: 1427–1435, 2003.
24. Borchert A, Wang CC, Ufer C, Schiebel H, Savaskan NE, and Kuhn H. The role of phospholipid hydroperoxide glutathione peroxidase isoforms in murine embryogenesis. *J Biol Chem* 281: 19655–19664, 2006.
25. Boveris A and Cadenas E. Mitochondrial production of superoxide anions and its relationship to the antimycin-insensitive respiration. *FEBS Lett* 54: 311–314, 1975.
26. Boveris A and Cadenas E. Mitochondrial production of hydrogen peroxide regulation by nitric oxide and the role of ubisemiquinone. *IUBMB Life* 50: 245–250, 2000.
27. Boveris A, Cadenas E, and Stoppani AOM. Role of ubiquinone in the mitochondrial generation of hydrogen peroxide. *Biochem J* 156: 435–444, 1976.
28. Boveris A and Chance B. The mitochondrial generation of hydrogen peroxide. General properties and effect of hyperbaric oxygen. *Biochem J* 134: 707–716, 1973.
29. Boveris A, Costa LE, and Cadenas E. The mitochondrial production of oxygen radicals and cellular aging. In: *Understanding the Process of Aging. The Roles of Mitochondria, Free Radicals, and Antioxidants.* Cadenas E and Packer L (Eds.). New York: Marcel Dekker, Inc.; 1999, pp. 1–16.
30. Boveris A and Navarro A. Brain mitochondrial dysfunction in aging. *IUBMB Life* 60: 308–314, 2008.
31. Boveris A, Oshino N, and Chance B. The cellular production of hydrogen peroxide. *Biochem J* 128: 617–630, 1972.
32. Boveris A, Valdez LB, Zaobornyj T, and Bustamante J. Mitochondrial metabolic states regulate nitric oxide and hydrogen peroxide diffusion to the cytosol. *Biochim Biophys Acta* 1757: 535–542, 2006.
33. Boyd CS and Cadenas E. Nitric oxide and cell signaling pathways in mitochondrial dependent apoptosis. *Biol Chem* 383: 411–423, 2002.
34. Braidy N, Guillemin GJ, Mansour H, Chan-Ling T, Poljak A, and Grant R. Age related changes in NAD^+ metabolism oxidative stress and Sirt1 activity in wistar rats. *PLoS One* 6: e19194, 2011.
35. Brigelius-Flohe R and Flohe L. Basic principles and emerging concepts in the redox control of transcription factors. *Antioxid Redox Signal* 15: 2335–2381, 2011.
36. Brown GC. Nitric oxide regulates mitochondrial respiration and cell functions by inhibiting cytochrome oxidase. *FEBS Lett* 369: 136–139, 1995.
37. Bubber P, Haroutunian V, Fisch G, Blass J, and Gibson G. Mitochondrial abnormalities in Alzheimer brain: mechanistic implications. *Ann Neurol* 57: 695–703, 2005.

38. Cadenas E. Mitochondrial free radical production and cell signaling. *Mol Aspects Med* 25: 17–26, 2004.
39. Cadenas E, Boveris A, Ragan CI, and Stoppani AO. Production of superoxide radicals and hydrogen peroxide by NADH- ubiquinone reductase and ubiquinol-cytochrome c reductase from beef- heart mitochondria. *Arch Biochem Biophys* 180: 248–257, 1977.
40. Calabrese V, Sultana R, Scapagnini G, Guagliano E, Sapienza M, Bella R, Kanski J, Pennisi G, Mancuso C, Stella AM, and Butterfield DA. Nitrosative stress, cellular stress response, and thiol homeostasis in patients with Alzheimer's disease. *Antioxid Redox Signal* 8: 1975–1986, 2006.
41. Canto C and Auwerx J. PGC-1alpha, SIRT1 and AMPK, an energy sensing network that controls energy expenditure. *Curr Opin Lipidol* 20: 98–105, 2009.
42. Canto C, Gerhart-Hines Z, Feige JN, Lagouge M, Noriega L, Milne JC, Elliott PJ, Puigserver P, and Auwerx J. AMPK regulates energy expenditure by modulating NAD^+ metabolism and SIRT1 activity. *Nature* 458: 1056–1060, 2009.
43. Cerveny KL, Tamura Y, Zhang Z, Jensen RE, and Sesaki H. Regulation of mitochondrial fusion and division. *Trends Cell Biol* 17: 563–569, 2007.
44. Chan DC. Mitochondria: dynamic organelles in disease, aging, and development. *Cell* 125: 1241–1252, 2006.
45. Chance B and Williams GR. Respiratory enzymes in oxidative phosphorylation. *J Biol Chem* 217: 383–427, 1955.
46. Chang TS, Cho CS, Park S, Yu S, Kang SW, and Rhee SG. Peroxiredoxin III, a mitochondrion-specific peroxidase, regulates apoptotic signaling by mitochondria. *J Biol Chem* 279: 41975–41984, 2004.
47. Chen H and Chan DC. Mitochondrial dynamics—fusion, fission, movement, and mitophagy—in neurodegenerative diseases. *Hum Mol Genet* 18: R169–R176, 2009.
48. Chen H and Chan DC. Physiological functions of mitochondrial fusion. *Ann N Y Acad Sci* 1201: 21–25, 2010.
49. Chen L, Na R, Gu M, Salmon AB, Liu Y, Liang H, Qi W, Van Remmen H, Richardson A, and Ran Q. Reduction of mitochondrial H_2O_2 by overexpressing peroxiredoxin 3 improves glucose tolerance in mice. *Aging Cell* 7: 866–878, 2008.
50. Chen YR, Chen CL, Pfeiffer DR, and Zweier JL. Mitochondrial complex II in the post-ischemic heart: oxidative injury and the role of protein S-glutathionylation. *J Biol Chem* 282: 32640–32654, 2007.
51. Cheng Z, Tseng Y, and White MF. Insulin signaling meets mitochondria in metabolism. *Trends Endocrinol Metab* 21: 589–598, 2010.
52. Cho DH, Nakamura T, Fang J, Cieplak P, Godzik A, Gu Z, and Lipton SA. S-nitrosylation of Drp1 mediates beta-amyloid-related mitochondrial fission and neuronal injury. *Science* 324: 102–105, 2009.
53. Cho DH, Nakamura T, and Lipton SA. Mitochondrial dynamics in cell death and neurodegeneration. *Cell Mol Life Sci* 67: 3435–3447, 2010.
54. Conrad M. Transgenic mouse models for the vital selenoenzymes cytosolic thioredoxin reductase, mitochondrial thioredoxin reductase, and glutathione peroxidase 4. *Biochim Biophys Acta* 1790: 1575–1585, 2009.
55. Csibi A, Communi D, Muller N, and Bottari SP. Angiotensin II inhibits insulin-stimulated GLUT4 translocation and Akt activation through tyrosine nitration-dependent mechanisms. *PLoS One* 5: e10070, 2010.
56. Cui L, Jeong H, Borovecki F, Parkhurst CN, Tanese N, and Krainc D. Transcriptional repression of PGC-1alpha by mutant huntingtin leads to mitochondrial dysfunction and neurodegeneration. *Cell* 127: 59–69, 2006.
57. Cumming RC, Andon NL, Haynes PA, Park M, Fischer WH, and Schubert D. Protein disulfide bond formation in the cytoplasm during oxidative stress. *J Biol Chem* 279: 21749–21758, 2004.
58. Cunningham JT, Rodgers JT, Arlow DH, Vazquez F, Mootha VK, and Puigserver P. mTOR controls mitochondrial oxidative function through a YY1-PGC-1alpha transcriptional complex. *Nature* 450: 736–740, 2007.
59. Dagher A. Functional imaging in Parkinson's disease. *Semin Neurol* 21: 23–32, 2001.
60. Daiber A, Gori T, and Munzel T. Inorganic nitrate therapy improves Doxorubicin-induced cardiomyopathy a new window for an affordable cardiovascular therapy for everyone? *J Am Coll Cardiol* 57: 2190–2193, 2011.
61. Dalle-Donne I, Colombo G, Gagliano N, Colombo R, Giustarini D, Rossi R, and Milzani A. S-glutathiolation in life and death decisions of the cell. *Free Radic Res* 45: 3–15, 2011.
62. Dalle-Donne I, Milzani A, Gagliano N, Colombo R, Giustarini D, and Rossi R. Molecular mechanisms and potential clinical significance of S-glutathionylation. *Antioxid Redox Signal* 10: 445–473, 2008.
63. De Simoni S, Goemaere J, and Knoops B. Silencing of peroxiredoxin 3 and peroxiredoxin 5 reveals the role of mitochondrial peroxiredoxins in the protection of human neuroblastoma SH-SY5Y cells toward MPP+. *Neurosci Lett* 433: 219–224, 2008.
64. Dennis PB, Jaeschke A, Saitoh M, Fowler B, Kozma SC, and Thomas G. Mammalian TOR: a homeostatic ATP sensor. *Science* 294: 1102–1105, 2001.
65. Dinkova-Kostova AT, Holtzclaw WD, Cole RN, Itoh K, Wakabayashi N, Katoh Y, Yamamoto M, and Talalay P. Direct evidence that sulfhydryl groups of Keap1 are the sensors regulating induction of phase 2 enzymes that protect against carcinogens and oxidants. *Proc Natl Acad Sci U S A* 99: 11908–11913, 2002.
66. Drechsel DA and Patel M. Respiration-dependent H_2O_2 removal in brain mitochondria via the thioredoxin/peroxiredoxin system. *J Biol Chem* 285: 27850–27858, 2010.
67. Drew B and Leeuwenburgh C. Method for measuring ATP production in isolated mitochondria: ATP production in brain and liver mitochondria of Fischer-344 rats with age and caloric restriction. *Am J Physiol Regul Integr Comp Physiol* 285: R1259–R1267, 2003.
68. Drew B and Leeuwenburgh C. Ageing and subcellular distribution of mitochondria: role of mitochondrial DNA deletions and energy production. *Acta Physiol Scand* 182: 333–341, 2004.
69. Dubuisson M, Vander Stricht D, Clippe A, Etienne F, Nauser T, Kissner R, Koppenol WH, Rees JF, and Knoops B. Human peroxiredoxin 5 is a peroxynitrite reductase. *FEBS Lett* 571: 161–165, 2004.
70. Duvezin-Caubet S, Jagasia R, Wagener J, Hofmann S, Trifunovic A, Hansson A, Chomyn A, Bauer MF, Attardi G, Larsson NG, Neupert W, and Reichert AS. Proteolytic processing of OPA1 links mitochondrial dysfunction to alterations in mitochondrial morphology. *J Biol Chem* 281: 37972–37979, 2006.
71. Easlon E, Tsang F, Skinner C, Wang C, and Lin SJ. The malate-aspartate NADH shuttle components are novel metabolic longevity regulators required for calorie restric-

tion-mediated life span extension in yeast. *Genes Dev* 22: 931–944, 2008.
72. Enoksson M, Fernandes AP, Prast S, Lillig CH, Holmgren A, and Orrenius S. Overexpression of glutaredoxin 2 attenuates apoptosis by preventing cytochrome c release. *Biochem Biophys Res Commun* 327: 774–779, 2005.
73. Feigin A, Leenders KL, Moeller JR, Missimer J, Kuenig G, Spetsieris P, Antonini A, and Eidelberg D. Metabolic network abnormalities in early Huntington's disease: an [(18)F]FDG PET study. *J Nucl Med* 42: 1591–1595, 2001.
74. Finkel T and Holbrook NJ. Oxidants, oxidative stress and the biology of ageing. *Nature* 408: 239–247, 2000.
75. Finley LW and Haigis MC. The coordination of nuclear and mitochondrial communication during aging and calorie restriction. *Ageing Res Rev* 8: 173–188, 2009.
76. Foley TD, Armstrong JJ, and Kupchak BR. Identification and H_2O_2 sensitivity of the major constitutive MAPK phosphatase from rat brain. *Biochem Biophys Res Commun* 315: 568–574, 2004.
77. Frank S, Gaume B, Bergmann-Leitner ES, Leitner WW, Robert EG, Catez F, Smith CL, and Youle RJ. The role of dynamin-related protein 1, a mediator of mitochondrial fission, in apoptosis. *Dev Cell* 1: 515–525, 2001.
78. Fratelli M, Demol H, Puype M, Casagrande S, Eberini I, Salmona M, Bonetto V, Mengozzi M, Duffieux F, Miclet E, Bachi A, Vandekerckhove J, Gianazza E, and Ghezzi P. Identification by redox proteomics of glutathjionylated proteins in oxidatively stressed human T lymphocytes. *Proc Natl Acad Sci U S A* 99: 3505–3510, 2002.
79. Freeman H, Shimomura K, Horner E, Cox RD, and Ashcroft FM. Nicotinamide nucleotide transhydrogenase: a key role in insulin secretion. *Cell Metab* 3: 35–45, 2006.
80. Frenzel M, Rommelspacher H, Sugawa MD, and Dencher NA. Ageing alters the supramolecular architecture of OxPhos complexes in rat brain cortex. *Exp Gerontol* 45: 563–572, 2010.
81. Frolich L, Blum-Degen D, Bernstein HG, Engelsberger S, Humrich J, Laufer S, Muschner D, Thalheimer A, Turk A, Hoyer S, Zochling R, Boissl KW, Jellinger K, and Riederer P. Brain insulin and insulin receptors in aging and sporadic Alzheimer's disease. *J Neural Transm* 105: 423–438, 1998.
82. Garcia J, Han D, Sancheti H, Yap LP, Kaplowitz N, and Cadenas E. Regulation of mitochondrial glutathione redox status and protein glutathionylation by respiratory substrates. *J Biol Chem* 285: 39646–39654, 2010.
83. Gibson GE, Starkov A, Blass JP, Ratan RR, and Beal MF. Cause and consequence: mitochondrial dysfunction initiates and propagates neuronal dysfunction, neuronal death and behavioral abnormalities in age-associated neurodegenerative diseases. *Biochim Biophys Acta* 1802: 122–134, 2010.
84. Gomez LA, Monette JS, Chavez JD, Maier CS, and Hagen TM. Supercomplexes of the mitochondrial electron transport chain decline in the aging rat heart. *Arch Biochem Biophys* 490: 30–35, 2009.
85. Goto S, Kawakatsu M, Izumi S-i, Urata Y, Kageyama K, Ihara Y, Koji T, and Kondo T. Glutathione S-transferase p localizes in mitochondria and protects agains oxidative stress. *Free Radic Biol Med* 46: 1392–1403, 2009.
86. Greer EL, Dowlatshahi D, Banko MR, Villen J, Hoang K, Blanchard D, Gygi SP, and Brunet A. An AMPK-FOXO pathway mediates longevity induced by a novel method of dietary restriction in *C. elegans*. *Curr Biol* 17: 1646–1656, 2007.
87. Griffith OW. Biologic and pharmacologic regulation of mammalian glutathione synthesis. *Free Radic Biol Med* 27: 922–935, 1999.
88. Griffith OW and Meister A. Origin and turnover of mitochondrial glutathione. *Proc Natl Acad Sci U S A* 82: 4668–4672, 1985.
89. Grinblat L, Pacheco Bolanos LF, and Stoppani AO. Decreased rate of ketone-body oxidation and decreased activity of D-3-hydroxybutyrate dehydrogenase and succinyl-CoA:3-oxo-acid CoA-transferase in heart mitochondria of diabetic rats. *Biochem J* 240: 49–56, 1986.
90. Gwinn DM, Shackelford DB, Egan DF, Mihaylova MM, Mery A, Vasquez DS, Turk BE, and Shaw RJ. AMPK phosphorylation of raptor mediates a metabolic checkpoint. *Mol Cell* 30: 214–226, 2008.
91. Han D, Antunes F, Canali R, Rettori D, and Cadenas E. Voltage-dependent anion channels control the release of superoxide anion from mitochondria to cytosol. *J Biol Chem* 278: 5557–5563, 2003.
92. Han D, Canali R, Garcia J, Aguilera R, Gallaher TK, and Cadenas E. Sites and mechanisms of aconitase inactivation by peroxynitrite: modulation by citrate and glutathione. *Biochemistry* 44: 11986–11996, 2005.
93. Handschin C and Spiegelman BM. Peroxisome proliferator-activated receptor gamma coactivator 1 coactivators, energy homeostasis, and metabolism. *Endocr Rev* 27: 728–735, 2006.
94. Hardie DG. Sensing of energy and nutrients by AMP-activated protein kinase. *Am J Clin Nutr* 93: 891S-6, 2011.
95. Hardie DG and Pan DA. Regulation of fatty acid synthesis and oxidation by the AMP-activated protein kinase. *Biochem Soc Trans* 30: 1064–1070, 2002.
96. Hattori F, Murayama N, Noshita T, and Oikawa S. Mitochondrial peroxiredoxin-3 protects hippocampal neurons from excitotoxic injury *in vivo*. *J Neurochem* 86: 860–868, 2003.
97. Hepple RT, Baker DJ, McConkey M, Murynka T, and Norris R. Caloric restriction protects mitochondrial function with aging in skeletal and cardiac muscles. *Rejuvenation Res* 9: 219–222, 2006.
98. Hill BG and Darley-Usmar VM. S-nitrosation and thiol switching in the mitochondrion: a new paradigm for cardioprotection in ischaemic preconditioning. *Biochem J* 412: e11–e13, 2008.
99. Hill BG, Higdon AN, Dranka BP, and Darley-Usmar VM. Regulation of vascular smooth muscle cell bioenergetic function by protein glutathiolation. *Biochim Biophys Acta* 1797: 285–295, 2010.
100. Hoek JB and Rydström J. Physiological roles of nicotinamide nucleotide transhydrogenase. *Biochem J* 254: 1–10, 1988.
101. Holmgren A. Thioredoxin and glutaredoxin systems. *J Biol Chem* 264: 13963–13966, 1989.
102. Holmgren A and Aslund F. Glutaredoxin. *Methods Enzymol* 252: 283–292, 1995.
103. Holmgren A, Johansson C, Berndt C, Lonn ME, Hudemann C, and Lillig CH. Thiol redox control via thioredoxin and glutaredoxin systems. *Biochem Soc Trans* 33: 1375–1377, 2005.
104. Hsieh CC and Papaconstantinou J. The effect of aging on p38 signaling pathway activity in the mouse liver and in response to ROS generated by 3-nitropropionic acid. *Mech Ageing Dev* 123: 1423–1435, 2002.

105. Hsieh CC, Rosenblatt JI, and Papaconstantinou J. Age-associated changes in SAPK/JNK and p38 MAPK signaling in response to the generation of ROS by 3-nitropropionic acid. *Mech Ageing Dev* 124: 733–746, 2003.
106. Huang TT, Naeemuddin M, and Elchuri S, Yamaguchi M, Kozy HM, Carlson EJ, and Epstein CJ. Genetic modifiers of the phenotype of mice deficient in mitochondrial superoxide dismutase. *Hum Mol Genet* 15: 1187–1194, 2006.
107. Hurd TR, Costa NJ, Dahm CC, Beer SM, Brown SE, Filipovska A, and Murphy MP. Glutathionylation of mitochondrial proteins. *Antioxid Redox Signal* 7: 999–1010, 2005.
108. Hwang IK, Yoo KY, Kim DW, Lee CH, Choi JH, Kwon YG, Kim YM, Choi SY, and Won MH. Changes in the expression of mitochondrial peroxiredoxin and thioredoxin in neurons and glia and their protective effects in experimental cerebral ischemic damage. *Free Radic Biol Med* 48: 1242–1251, 2010.
109. Ikeyama S, Kokkonen G, Shack S, Wang XT, and Holbrook NJ. Loss in oxidative stress tolerance with aging linked to reduced extracellular signal-regulated kinase and Akt kinase activities. *FASEB J* 16: 114–116, 2002.
110. Ishihara N, Nomura M, Jofuku A, Kato H, Suzuki SO, Masuda K, Otera H, Nakanishi Y, Nonaka I, Goto Y, Taguchi N, Morinaga H, Maeda M, Takayanagi R, Yokota S, and Mihara K. Mitochondrial fission factor Drp1 is essential for embryonic development and synapse formation in mice. *Nat Cell Biol* 11: 958–966, 2009.
111. Jager S, Handschin C, St-Pierre J, and Spiegelman BM. AMP-activated protein kinase (AMPK) action in skeletal muscle via direct phosphorylation of PGC-1alpha. *Proc Natl Acad Sci U S A* 104: 12017–12022, 2007.
112. Jahani-Asl A, Cheung EC, Neuspiel M, MacLaurin JG, Fortin A, Park DS, McBride HM, and Slack RS. Mitofusin 2 protects cerebellar granule neurons against injury-induced cell death. *J Biol Chem* 282: 23788–23798, 2007.
113. Jahani-Asl A, Pilon-Larose K, Xu W, MacLaurin JG, Park DS, McBride HM, and Slack RS. The mitochondrial inner membrane GTPase, optic atrophy 1 (Opa1), restores mitochondrial morphology and promotes neuronal survival following excitotoxicity. *J Biol Chem* 286: 4772–4782, 2011.
114. Jendrach M, Mai S, Pohl S, Voth M, and Bereiter-Hahn J. Short- and long-term alterations of mitochondrial morphology, dynamics and mtDNA after transient oxidative stress. *Mitochondrion* 8: 293–304, 2008.
115. Jin MH, Lee YH, Kim JM, Sun HN, Moon EY, Shong MH, Kim SU, Lee SH, Lee TH, Yu DY, and Lee DS. Characterization of neural cell types expressing peroxiredoxins in mouse brain. *Neurosci Lett* 381: 252–257, 2005.
116. Jones DP. Redox potential of GSH/GSSG couple: assay and biological significance. *Methods Enzymol* 348: 93–112, 2002.
117. Jung KA and Kwak MK. The Nrf2 system as a potential target for the development of indirect antioxidants. *Molecules* 15: 7266–7291, 2010.
118. Kahn BB, Alquier T, Carling D, and Hardie DG. AMP-activated protein kinase: ancient energy gauge provides clues to modern understanding of metabolism. *Cell Metab* 1: 15–25, 2005.
119. Kaneto H, Kawamori D, Matsuoka TA, Kajimoto Y, and Yamasaki Y. Oxidative stress and pancreatic beta-cell dysfunction. *Am J Ther* 12: 529–533, 2005.
120. Kapogiannis D and Mattson MP. Disrupted energy metabolism and neuronal circuit dysfunction in cognitive impairment and Alzheimer's disease. *Lancet Neurol* 10: 187–198, 2011.
121. Karren MA, Coonrod EM, Anderson TK, and Shaw JM. The role of Fis1p-Mdv1p interactions in mitochondrial fission complex assembly. *J Cell Biol* 171: 291–301, 2005.
122. Karunakaran S, Saeed U, Ramakrishnan S, Koumar RC, and Ravindranath V. Constitutive expression and functional characterization of mitochondrial glutaredoxin in mouse and human brain. *Brain Res* 1185: 8–17, 2007.
123. Katic M, Kennedy AR, Leykin I, Norris A, McGettrick A, Gesta S, Russell SJ, Bluher M, Maratos-Flier E, and Kahn CR. Mitochondrial gene expression and increased oxidative metabolism: role in increased lifespan of fat-specific insulin receptor knock-out mice. *Aging Cell* 6: 827–839, 2007.
124. Kemp M, Go YM, and Jones DP. Nonequilibrium thermodynamics of thiol/disulfide redox systems: a perspective on redox systems biology. *Free Radic Biol Med* 44: 921–937, 2008.
125. Kenchappa RS and Ravindranath V. Glutaredoxin is essential for maintenance of brain mitochondrial complex I: studies with MPTP. *FASEB J* 17: 717–719, 2003.
126. Kil IS and Park JW. Regulation of mitochondrial NADP+-dependent isocitrate dehydrogenase activity by glutathionylation. *J Biol Chem* 280: 10846–10854, 2005.
127. Kim HJ, Jung KJ, Yu BP, Cho CG, and Chung HY. Influence of aging and calorie restriction on MAPKs activity in rat kidney. *Exp Gerontol* 37: 1041–1053, 2002.
128. Kim SH, Fountoulakis M, Cairns N, and Lubec G. Protein levels of human peroxiredoxin subtypes in brains of patients with Alzheimer's disease and Down syndrome. *J Neural Transm Suppl*: 223–235, 2001.
129. Kim SU, Jin MH, Kim YS, Lee SH, Cho YS, Cho KJ, Lee KS, Kim YI, Kim GW, Kim JM, Lee TH, Lee YH, Shong MH, Kim YC, Chang KT, Yu DY, and Lee DS. Peroxiredoxin II preserves cognitive function against age-linked hippocampal oxidative damage. *Neurobiol Aging* 32: 1054–1068, 2011.
130. Klatt P and Lamas S. Regulation of protein function by S-glutathiolation in response to oxidative and nitrosative stress. *Eur J Biochem* 267: 4928–4944, 2000.
131. Kobashigawa S, Suzuki K, and Yamashita S. Ionizing radiation accelerates Drp1-dependent mitochondrial fission, which involves delayed mitochondrial reactive oxygen species production in normal human fibroblast-like cells. *Biochem Biophys Res Commun* 414: 795–800, 2011.
132. Korshunov SS, Skulachev VP, and Starkov AA. High protonic potential actuates a mechanism of production of reactive oxygen species in mitochondria. *FEBS Lett* 416: 15–18, 1997.
133. Krapfenbauer K, Engidawork E, Cairns N, Fountoulakis M, and Lubec G. Aberrant expression of peroxiredoxin subtypes in neurodegenerative disorders. *Brain Res* 967: 152–160, 2003.
134. Kurth-Kraczek EJ, Hirshman MF, Goodyear LJ, and Winder WW. 5′ AMP-activated protein kinase activation causes GLUT4 translocation in skeletal muscle. *Diabetes* 48: 1667–1671, 1999.
135. Kwong LK and Sohal RS. Age-related changes in activities of mitochondrial electron transport complexes in various tissues of the mouse. *Arch Biochem Biophys* 373: 16–22, 2000.
136. LaFrance R, Brustovetsky N, Sherburne C, Delong D, and Dubinsky JM. Age-related changes in regional brain mitochondria from Fischer 344 rats. *Aging Cell* 4: 139–145, 2005.
137. Lam PY, Yin F, Hamilton RT, and Boveris A, Cadenas E. Elevated neuronal nitric oxide synthase expression during

ageing and mitochondrial energy production. *Free Radic Res* 43: 431–439, 2009.
138. Lanza IR, Befroy DE, and Kent-Braun JA. Age-related changes in ATP-producing pathways in human skeletal muscle *in vivo*. *J Appl Physiol* 99: 1736–1744, 2005.
139. Lass A, Sohal BH, Weindruch R, Forster MJ, and Sohal RS. Caloric restriction prevents age-associated accrual of oxidative damage to mouse skeletal muscle mitochondria. *Free Radic Biol Med* 25: 1089–1097, 1998.
140. Lazarov O, Mattson MP, Peterson DA, Pimplikar SW, and van Praag H. When neurogenesis encounters aging and disease. *Trends Neurosci* 33: 569–579, 2010.
141. Lebovitz RM, Zhang H, Vogel H, Cartwright J, Jr., Dionne L, Lu N, Huang S, and Matzuk MM. Neurodegeneration, myocardial injury, and perinatal death in mitochondrial superoxide dismutase-deficient mice. *Proc Natl Acad Sci U S A* 93: 9782–9787, 1996.
142. Li M, Walter R, Torres C, and Sierra F. Impaired signal transduction in mitogen activated rat splenic lymphocytes during aging. *Mech Ageing Dev* 113: 85–99, 2000.
143. Li Y, Huang T-T, Carlson EJ, Melov S, Ursell PC, Olson JL, Noble LJ, Yoshimura MP, Berger C, Chan PH, Wallace DC, and Epstein CJ. Dilated cardiomyopathy and neonatal lethality in mutant mice lacking manganese superoxide dismutase. *Nature Genetics* 11: 376–381, 1995.
144. Liesa M, Palacin M, and Zorzano A. Mitochondrial dynamics in mammalian health and disease. *Physiol Rev* 89: 799–845, 2009.
145. Lin J, Wu PH, Tarr PT, Lindenberg KS, St-Pierre J, Zhang CY, Mootha VK, Jager S, Vianna CR, Reznick RM, Cui L, Manieri M, Donovan MX, Wu Z, Cooper MP, Fan MC, Rohas LM, Zavacki AM, Cinti S, Shulman GI, Lowell BB, Krainc D, and Spiegelman BM. Defects in adaptive energy metabolism with CNS-linked hyperactivity in PGC-1alpha null mice. *Cell* 119: 121–135, 2004.
146. Lin MT and Beal MF. Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. *Nature* 443: 787–795, 2006.
147. Liot G, Bossy B, Lubitz S, Kushnareva Y, Sejbuk N, and Bossy-Wetzel E. Complex II inhibition by 3-NP causes mitochondrial fragmentation and neuronal cell death via an NMDA- and ROS-dependent pathway. *Cell Death Differ* 16: 899–909, 2009.
148. Liu Y, Guyton KZ, Gorospe M, Xu Q, Kokkonen GC, Mock YD, Roth GS, and Holbrook NJ. Age-related decline in mitogen-activated protein kinase activity in epidermal growth factor-stimulated rat hepatocytes. *J Biol Chem* 271: 3604–3607, 1996.
149. Lowell BB and Shulman GI. Mitochondrial dysfunction and type 2 diabetes. *Science* 307: 384–387, 2005.
150. Maack C and Bohm M. Targeting mitochondrial oxidative stress in heart failure throttling the afterburner. *J Am Coll Cardiol* 58: 83–86, 2011.
151. Mahadev K, Zilbering A, Zhu L, and Goldstein BJ. Insulin-stimulated hydrogen peroxide reversibly inhibits protein-tyrosine phosphatase 1b *in vivo* and enhances the early insulin action cascade. *J Biol Chem* 276: 21938–21942, 2001.
152. Marí M, Morales A, Colell A, García-Ruiz C, and Fernández-Checa JC. Mitochondrial glutathione, a key survival antioxidant. *Antioxid Redox Signal* 11: 2685–2700, 2009.
153. Marsin AS, Bouzin C, Bertrand L, and Hue L. The stimulation of glycolysis by hypoxia in activated monocytes is mediated by AMP-activated protein kinase and inducible 6-phosphofructo-2-kinase. *J Biol Chem* 277: 30778–30783, 2002.
154. Mathews CK, vn Holde KE, and Ahern KG. *Biochemistry.* San Francisco: Addison Wesley Longman, 2000.
155. Mattson MP, Gleichmann M, and Cheng A. Mitochondria in neuroplasticity and neurological disorders. *Neuron* 60: 748–766, 2008.
156. Mattson MP and Magnus T. Ageing and neuronal vulnerability. *Nat Rev Neurosci* 7: 278–294, 2006.
157. Maurer U, Charvet C, Wagman AS, Dejardin E, and Green DR. Glycogen synthase kinase-3 regulates mitochondrial outer membrane permeabilization and apoptosis by destabilization of MCL-1. *Mol Cell* 21: 749–760, 2006.
158. McElwee JJ, Schuster E, Blanc E, Piper MD, Thomas JH, Patel DS, Selman C, Wilthers DJ, Thornton JM, Partridge L, and Gems D. Evolutionary conservation of regulated longevity assurance mechanisms. *Genome Biol* 8: RI32, 2007.
159. McGee SL and Hargreaves M. AMPK and transcriptional regulation. *Front Biosci* 13: 3022–3033, 2008.
160. Mellstrom B, Savignac M, Gomez-Villafuertes R, and Naranjo JR. Ca^{2+}-operated transcriptional networks: molecular mechanisms and *in vivo* models. *Physiol Rev* 88: 421–449, 2008.
161. Melov S. Mitochondrial oxidative stress. Physiologic consequences and potential for a role in aging. *Ann N Y Acad Sci* 908: 219–225, 2000.
162. Allen EM and Mieyal JJ. Protein-thiol oxidation and cell death: regulatory role of glutaredoxins. *Antioxid Redox Signal*, 17: 1748–1763, 2012.
163. Miranda-Vizuete A, Damdimopoulos AE, and Spyrou G. The mitochondrial thioredoxin system *Antioxid Redox Signal* 2: 801–810, 2000.
164. Murphy MP. How mitochondria produce reactive oxygen species. *Biochem J* 417: 1–13, 2009.
165. Murphy MP. Mitochondrial thiols in antioxidant protection and redox signaling: distinct roles of glutathionylation and other thiol modifications. *Antioxid Redox Signal* 16: 476–495, 2012.
166. Nagy N, Malik G, Tosaki A, Ho YS, Maulik N, and Das DK. Overexpression of glutaredoxin-2 reduces myocardial cell death by preventing both apoptosis and necrosis. *J Mol Cell Cardiol* 44: 252–260, 2008.
167. Navarro A, Bández MJ, López-Cepero JM, Gómez C, Boveris AD, Cadenas E, and Boveris A. High doses of vitamin E improve mitochondrial dysfunction in rat hippocampus and frontal cortex upon aging. *Am J Physiol Regul Integr Comp Physiol* 300: R827–R834, 2011.
168. Navarro A and Boveris A. Rat brain and liver mitochondria develop oxidative stress and lose enzymatic activities on aging. *Am J Physiol Regul Integr Comp Physiol* 287: R1244–R1249, 2004.
169. Navarro A and Boveris A. Brain mitochondrial dysfunction in aging: conditions that improve survival, neurological performance and mitochondrial function. *Front Biosci* 12: 1154–1163, 2007.
170. Navarro A and Boveris A. The mitochondrial energy transduction system and the aging process. *Am J Physiol Cell Physiol* 292: C670–C686, 2007.
171. Navarro A and Boveris A. Mitochondrial nitric oxide synthase, mitochondrial brain dysfunction in aging, and mitochondria-targeted antioxidants. *Adv Drug Deliv Rev* 60: 1534–1544, 2008.
172. Navarro A, Boveris A, Bández MJ, Sanchez-Pino MJ, Gómez C, Muntané G, and Ferrer I. Human brain cortex:

mitochondrial oxidative damage and adaptive response in Parkinson's disease and in dementia with Lewy bodies. *Free Radic Biol Med* 46: 1574–1580, 2009.
173. Navarro A, López-Cepero JM, Bández MJ, Sánchez-Pino M-J, Gómez C, Cadenas E, and Boveris A. Hippocampal mitochondrial dysfunction in rat aging. *Am J Physiol Regul Integr Comp Physiol* 294: R501–R509, 2008.
174. Nemoto S, Takeda K, Yu ZX, Ferrans VJ, and Finkel T. Role for mitochondrial oxidants as regulators of cellular metabolism. *Mol Cell Biol* 20: 7311–7318, 2000.
175. Nisoli E and Carruba MO. Nitric oxide and mitochondrial biogenesis. *J Cell Sci* 119: 2855–2862, 2006.
176. Nonn L, Berggren M, and Powis G. Increased expression of mitochondrial peroxiredoxin-3 (thioredoxin peroxidase-2) protects cancer cells against hypoxia and drug-induced hydrogen peroxide-dependent apoptosis. *Mol Cancer Res* 1: 682–689, 2003.
177. Nulton-Persson AC, Starke DW, Mieyal JJ, and Szweda LI. Reversible inactivation of alpha-ketoglutarate dehydrogenase in response to alterations in the mitochondrial glutathione status. *Biochemistry* 42: 4235–4242, 2003.
178. Oakhill JS, Steel R, Chen ZP, Scott JW, Ling N, Tam S, and Kemp BE. AMPK is a direct adenylate charge-regulated protein kinase. *Science* 332: 1433–1435, 2011.
179. Oliveira-Marques V, Marinho HS, Cyrne L, and Antunes F. Role of hydrogen peroxide in NF-kB activation: from inducer to modulator. *Antioxid Redox Signal* 11: 2223–2243, 2009.
180. Pap M and Cooper GM. Role of glycogen synthase kinase-3 in the phosphatidylinositol 3-Kinase/Akt cell survival pathway. *J Biol Chem* 273: 19929–19932, 1998.
181. Parone PA, Da Cruz S, Tondera D, Mattenberger Y, James DI, Maechler P, Barja F, and Martinou JC. Preventing mitochondrial fission impairs mitochondrial function and leads to loss of mitochondrial DNA. *PLoS One* 3: e3257, 2008.
182. Patenaude A, Ven Murthy MR, and Mirault ME. Mitochondrial thioredoxin system: effects of TrxR2 overexpression on redox balance, cell growth, and apoptosis. *J Biol Chem* 279: 27302–27314, 2004.
183. Peng Y, Yang PH, Guo Y, Ng SS, Liu J, Fung PC, Tay D, Ge J, He ML, Kung HF, and Lin MC. Catalase and peroxiredoxin 5 protect Xenopus embryos against alcohol-induced ocular anomalies. *Invest Ophthalmol Vis Sci* 45: 23–29, 2004.
184. Perez VI, Lew CM, Cortez LA, Webb CR, Rodriguez M, Liu Y, Qi W, Li Y, Chaudhuri A, Van Remmen H, Richardson A, and Ikeno Y. Thioredoxin 2 haploinsufficiency in mice results in impaired mitochondrial function and increased oxidative stress. *Free Radic Biol Med* 44: 882–892, 2008.
185. Petit-Taboue MC, Landeau B, Desson JF, Desgranges B, and Baron JC. Effects of healthy aging on the regional cerebral metabolic rate of glucose assessed with statistical parametric mapping. *Neuroimage* 7: 176–184, 1998.
186. Pfanner N and Geissler A. Versatility of the mitochondrial protein import machinery. *Nat Rev Mol Cell Biol* 2: 339–349, 2001.
187. Pich S, Bach D, Briones P, Liesa M, Camps M, Testar X, Palacin M, and Zorzano A. The Charcot-Marie-Tooth type 2A gene product, Mfn2, up-regulates fuel oxidation through expression of OXPHOS system. *Hum Mol Genet* 14: 1405–1415, 2005.
188. Pinzar E, Wang T, Garrido MR, Xu W, Levy P, and Bottari SP. Angiotensin II induces tyrosine nitration and activation of ERK1/2 in vascular smooth muscle cells. *FEBS Lett* 579: 5100–5104, 2005.
189. Pletjushkina OY, Lyamzaev KG, Popova EN, Nepryakhina OK, Ivanova OY, Domnina LV, Chernyak BV, and Skulachev VP. Effect of oxidative stress on dynamics of mitochondrial reticulum. *Biochim Biophys Acta* 1757: 518–524, 2006.
190. Poderoso JJ, Carreras MC, Lisdero C, Riobo N, Schopfer F, and Boveris A. Nitric oxide inhibits electron transfer and increases superoxide radical production in rat heart mitochondria and submitochondrial particles. *Arch Biochem Biophys* 328: 85–92, 1996.
191. Poderoso JJ, Carreras MC, Schöpfer F, Lisdero C, Riobó N, Giulivi C, Boveris AD, Boveris A, and Cadenas E. The reaction of nitric oxide with ubiquinol: kinetic properties and biological significance. *Free Radic Biol Med* 26: 925–935, 1999.
192. Poderoso JJ, Lisdero C, Schopfer F, Riobo N, Carreras MC, Cadenas E, and Boveris A. The regulation of mitochondrial oxygen uptake by redox reactions involving nitric oxide and ubiquinol. *J Biol Chem* 274: 37709–37716, 1999.
193. Queiroga CS, Almeida AS, Martel C, Brenner C, Alves PM, and Vieira HL. Glutathionylation of adenine nucleotide translocase induced by carbon monoxide prevents mitochondrial membrane permeabilization and apoptosis. *J Biol Chem* 285: 17077–17088, 2010.
194. Raza H. Dual localization of glutathione S-transferase in the cytosol and mitochondria: implications in oxidative stress, toxicity, and disease. *FEBS J* 278: 4243–4521, 2011.
195. Rebrin I, Forster MJ, and Sohal RS. Effects of age and caloric intake on glutathione redox state in different brain regions of C57BL/6 and DBA/2 mice. *Brain Res* 1127: 10–18, 2007.
196. Rebrin I, Kamzalov S, and Sohal RS. Effects of age and caloric restriction on glutathione redox state in mice. *Free Radic Biol Med* 35: 626–635, 2003.
197. Rhee SG and Woo HA. Multiple functions of peroxiredoxins: peroxidases, sensors and regulators of the intracellular messenger HO, and protein chaperones. *Antioxid Redox Signal* 15: 781–794, 2011.
198. Rice ME. H(2)O(2): a dynamic neuromodulator. *Neuroscientist* 17: 389–406, 2011.
199. Rigoulet M, Yoboue ED, and Devin A. Mitochondrial ROS generation and its regulation: mechanisms involved in H(2)O(2) signaling. *Antioxid Redox Signal* 14: 459–468, 2011.
200. Riobó N, Melani M, Sanjuan N, Fiszman ML, Gravielle MC, Carreras MC, Cadenas E, and Poderoso JJ. The modulation of mitochondrial nitric oxide synthase activity in rat brain development. *J Biol Chem* 277: 42447–42455, 2002.
201. Rohrbach S, Gruenler S, Teschner M, and Holtz J. The thioredoxin system in aging muscle: key role of mitochondrial thioredoxin reductase in the protective effects of caloric restriction? *Am J Physiol Regul Integr Comp Physiol* 291: R927–R935, 2006.
202. Rydstrom J. Mitochondrial NADPH, transhydrogenase, and disease. *Biochim Biophys Acta* 1757: 721–726, 2006.
203. Saeed U, Durgadoss L, Valli RK, Joshi DC, Joshi PG, and Ravindranath V. Knockdown of cytosolic glutaredoxin 1 leads to loss of mitochondrial membrane potential: implication in neurodegenerative diseases. *PLoS One* 3: e2459, 2008.
204. Saitoh M, Nishitoh H, Fujii M, Takeda K, Tobiume K, Sawada Y, Kawabata M, Miyazono K, and Ichijo H. Mammalian thioredoxin is a direct inhibitor of apoptosis signal-regulating kinase (ASK) 1. *EMBO J* 17: 2596–2606, 1998.

205. Sastre J, Millan A, Garcia de la Asuncion J, Pla R, Juan G, Pallardo, O'Connor E, Martin JA, Droy-Lefaix MT, and Vina J. A Ginkgo biloba extract (EGb 761) prevents mitochondrial aging by protecting against oxidative stress. *Free Radic Biol Med* 24: 298–304, 1998.
206. Scarpulla RC. Transcriptional paradigms in mammalian mitochondrial biogenesis and function. *Physiol Rev* 88: 611–638, 2008.
207. Schafer FQ and Buettner GR. Redox environment of the cell as viewed through the redox state of the glutathione disulfide/glutathione couple. *Free Radic Biol Med* 30: 1191–1212, 2001.
208. Schagger H and Pfeiffer K. Supercomplexes in the respiratory chains of yeast and mammalian mitochondria. *EMBO J* 19: 1777–1783, 2000.
209. Schieke SM and Finkel T. Mitochondrial signaling, TOR, and life span. *Biol Chem* 387: 1357–1361, 2006.
210. Schuckelt R, Brigelius-Flohé R, Maiorino M, Roveri A, Reumkens J, Strassburger W, Ursini F, Wolf B, and Flohé L. Phospholipid hydroperoxide glutathione peroxidase is a selenoenzyme distinct from the classical glutathione peroxidase as evident from cDNA and amino acid sequencing. *Free Radic Res Commun* 14: 343–361, 1991.
211. Seelert H, Dani DN, Dante S, Hauss T, Krause F, Schafer E, Frenzel M, Poetsch A, Rexroth S, Schwassmann HJ, Suhai T, Vonck J, and Dencher NA. From protons to OXPHOS supercomplexes and Alzheimer's disease: structure-dynamics-function relationships of energy-transducing membranes. *Biochim Biophys Acta* 1787: 657–671, 2009.
212. Shaw RJ, Bardeesy N, Manning BD, Lopez L, Kosmatka M, DePinho RA, and Cantley LC. The LKB1 tumor suppressor negatively regulates mTOR signaling. *Cancer Cell* 6: 91–99, 2004.
213. Sheeran FL, Rydstrom J, Shakhparonov MI, Pestov NB, and Pepe S. Diminished NADPH transhydrogenase activity and mitochondrial redox regulation in human failing myocardium. *Biochim Biophys Acta* 1797: 1138–1148, 2010.
214. Simonian NA and Coyle JT. Oxidative stress in neurodegenerative diseases. *Annu Rev Pharmacol Toxicol* 36: 83–106, 1996.
215. Sohal RS, Agarwal S, Candas M, Forster M, and Lal H. Effect of age and caloric restriction on DNA oxidative damage in different tissues of C57BL/6 mice. *Mech Ageing Dev* 76: 215–224, 1994.
216. Song Z, Ghochani M, McCaffery JM, Frey TG, and Chan DC. Mitofusins and OPA1 mediate sequential steps in mitochondrial membrane fusion. *Mol Biol Cell* 20: 3525–3532, 2009.
217. St-Pierre J, Drori S, Uldry M, Silvaggi JM, Rhee J, Jager S, Handschin C, Zheng K, Lin J, Yang W, Simon DK, Bachoo R, and Spiegelman BM. Suppression of reactive oxygen species and neurodegeneration by the PGC-1 transcriptional coactivators. *Cell* 127: 397–408, 2006.
218. Steinberg GR and Kemp BE. AMPK in Health and Disease. *Physiol Rev* 89: 1025–1078, 2009.
219. Storozhevykh TP, Senilova YE, Persiyantseva NA, Pinelis VG, and Pomytkin IA. Mitochondrial respiratory chain is involved in insulin-stimulated hydrogen peroxide production and plays an integral role in insulin receptor autophosphorylation in neurons. *BMC Neurosci* 8: 84, 2007.
220. Suh JH, Shenvi SV, Dixon BM, Liu H, Jaiswal AK, Liu RM, and Hagen TM. Decline in transcriptional activity of Nrf2 causes age-related loss of glutathione synthesis, which is reversible with lipoic acid. *Proc Natl Acad Sci U S A* 101: 3381–3386, 2004.
221. Suh Y. Age-specific changes in expression, activity, and activation of the c-Jun NH(2)-terminal kinase and p38 mitogen-activated protein kinases by methyl methanesulfonate in rats. *Mech Ageing Dev* 122: 1797–1811, 2001.
222. Swerdlow RH. Treating neurodegeneration by modifying mitochondria: potential solutions to a "Complex" problem. *Antioxid Redox Signal* 10, 1591–1603, 2007.
223. Swerdlow RH. Brain aging, Alzheimer's disease, and mitochondria. *Biochim Biophys Acta* 1812: 1630–1639, 2011.
224. Szabadkai G and Duchen MR. Mitochondria: the hub of cellular Ca2+ signaling. *Physiology (Bethesda)* 23: 84–94, 2008.
225. Tang S, Le PK, Tse S, Wallace DC, and Huang T. Heterozygous mutation of Opa1 in Drosophila shortens lifespan mediated through increased reactive oxygen species production. *PLoS One* 4: e4492, 2009.
226. Taylor ER, Hurrell F, Shannon RJ, Lin TK, Hirst J, and Murphy MP. Reversible glutathionylation of complex I increases mitochondrial superoxide formation. *J Biol Chem* 278: 19603–19610, 2003.
227. Thomas JA, Poland B, and Honzatko R. Protein sulfhydryls and their role in the antioxidant function of protein S-thiolation. *Arch Biochem Biophys* 319: 1–9, 1995.
228. Turrens JF. Mitochondrial formation of reactive oxygen species. *J Physiol* 552: 335–344, 2003.
229. Turrens JF and Boveris A. Generation of superoxide anion by the NADH dehydrogenase of bovine heart mitochondria. *Biochem J* 191: 421–427, 1980.
230. Twig G, Elorza A, Molina AJ, Mohamed H, Wikstrom JD, Walzer G, Stiles L, Haigh SE, Katz S, Las G, Alroy J, Wu M, Py BF, Yuan J, Deeney JT, Corkey BE, and Shirihai OS. Fission and selective fusion govern mitochondrial segregation and elimination by autophagy. *embo J* 27: 433–446, 2008.
231. Twig G and Shirihai OS. The interplay between mitochondrial dynamics and mitophagy. *Antioxid Redox Signal* 14: 1939–1951, 2011.
232. Ursini F, Maiorino M, and Roveri A. Phospholipid hydroperoxide glutathione peroxidase (PHGPx): more than an antioxidant enzyme? *Biomed Environ Sci* 1997: 327–332, 1997.
233. Valdez LB and Boveris A. Mitochondrial nitric oxide synthase, a voltage-dependent enzyme, is responsible for nitric oxide diffusion to cytosol. *Front Biosci* 12: 1210–1219, 2007.
234. van der Heide LP, Ramakers GM, and Smidt MP. Insulin signaling in the central nervous system: learning to survive. *Prog Neurobiol* 79: 205–221, 2006.
235. Van Remmen H and Jones DP. Current thoughts on the role of mitochondria and free radicals in the biology of aging. *J Gerontol A Biol Sci Med Sci* 64: 171–174, 2009.
236. Venkatakrishnan P, Nakayasu ES, Almeida IC, and Miller RT. Absence of nitric-oxide synthase in sequentially purified rat liver mitochondria. *J Biol Chem* 284: 19843–19855, 2009.
237. Wang S, Song P, and Zou MH. AMP-activated protein kinase, stress responses and cardiovascular diseases. *Clin Sci (Lond)* 122: 555–573, 2012.
238. Wang X, Su B, Lee HG, Li X, Perry G, Smith MA, and Zhu X. Impaired balance of mitochondrial fission and fusion in Alzheimer's disease. *J Neurosci* 29: 9090–9103, 2009.
239. Wenz T, Diaz F, Spiegelman BM, and Moraes CT. Activation of the PPAR/PGC-1alpha pathway prevents a bioen-

ergetic deficit and effectively improves a mitochondrial myopathy phenotype. *Cell Metab* 8: 249–256, 2008.
240. West MB, Hill BG, Xuan YT, and Bhatnagar A. Protein glutathiolation by nitric oxide: an intracellular mechanism regulating redox protein modification. *FASEB J* 20: 1715–1717, 2006.
241. Weydt P, Pineda VV, Torrence AE, Libby RT, Satterfield TF, Lazarowski ER, Gilbert ML, Morton GJ, Bammler TK, Strand AD, Cui L, Beyer RP, Easley CN, Smith AC, Krainc D, Luquet S, Sweet IR, Schwartz MW, and La Spada AR. Thermoregulatory and metabolic defects in Huntington's disease transgenic mice implicate PGC-1alpha in Huntington's disease neurodegeneration. *Cell Metab* 4: 349–362, 2006.
242. Williamson D, Gallagher P, Harber M, Hollon C, and Trappe S. Mitogen-activated protein kinase (MAPK) pathway activation: effects of age and acute exercise on human skeletal muscle. *J Physiol* 547: 977–987, 2003.
243. Wonsey DR, Zeller KI, and Dang CV. The c-Myc target gene PRDX3 is required for mitochondrial homeostasis and neoplastic transformation. *Proc Natl Acad Sci U S A* 99: 6649–6654, 2002.
244. Wood-Allum CA, Barber SC, Kirby J, Heath P, Holden H, Mead R, Higginbottom A, Allen S, Beaujeux T, Alexson SE, Ince PG, and Shaw PJ. Impairment of mitochondrial anti-oxidant defence in SOD1-related motor neuron injury and amelioration by ebselen. *Brain* 129: 1693–1709, 2006.
245. Wu Z, Huang X, Feng Y, Handschin C, Gullicksen PS, Bare O, Labow M, Spiegelman B, and Stevenson SC. Transducer of regulated CREB-binding proteins (TORCs) induce PGC-1alpha transcription and mitochondrial biogenesis in muscle cells. *Proc Natl Acad Sci U S A* 103: 14379–14384, 2006.
246. Xiao B, Sanders MJ, Underwood E, Heath R, Mayer FV, Carmena D, Jing C, Walker PA, Eccleston JF, Haire LF, Saiu P, Howell SA, Aasland R, Martin SR, Carling D, and Gamblin SJ. Structure of mammalian AMPK and its regulation by ADP. *Nature* 472: 230–233, 2011.
247. Yankner BA, Lu T, and Loerch P. The Aging Brain. *Annu Rev Pathol*, 3: 41–66, 2008.
248. Yao J, Hamilton RT, Cadenas E, and Brinton RD. Decline in mitochondrial bioenergetics and shift to ketogenic profile in brain during reproductive senescence. *Biochim Biophys Acta* 1800: 1121–1126, 2010.
249. Yao J, Irwin RW, Zhao L, Nilsen J, Hamilton RT, and Brinton RD. Mitochondrial bioenergetic deficit precedes Alzheimer's pathology in female mouse model of Alzheimer's disease. *Proc Natl Acad Sci U S A* 106: 14670–14675, 2009.
250. Yap LP, Garcia JV, Han D, and Cadenas E. The energy-redox axis in aging and age-related neurodegeneration. *Adv Drug Deliv Rev* 61: 1283–1298, 2009.
251. Yarian CS, Toroser D, and Sohal RS. Aconitase is the main functional target of aging in the citric acid cycle of kidney mitochondria from mice. *Mech Ageing Dev* 127: 79–84, 2006.
252. Yin F, Sancheti H, and Cadenas E. Mitochondrial thiols in the regulation of cell death pathways. *Antioxid Redox Signal* 17: 1714–1727, 2012.
253. Yin F, Sancheti H, and Cadenas E. Silencing of nicotinamide nucleotide transhydrogenase impairs cellular redox homeostasis and energy metabolism in PC12 cells. *Biochim Biophys Acta* 1817: 401–409, 2012.
254. Ying W. NAD^+ and NADH in cellular functions and cell death. *Front Biosci* 11: 3129–3148, 2006.
255. Ying W. NAD^+/NADH and $NADP^+$/NADPH in cellular functions and cell death: regulation and biological consequences. *Antioxid Redox Signal* 10: 179–206, 2008.
256. Yoon Y, Krueger EW, Oswald BJ, and McNiven MA. The mitochondrial protein hFis1 regulates mitochondrial fission in mammalian cells through an interaction with the dynamin-like protein DLP1. *Mol Cell Biol* 23: 5409–5420, 2003.
257. Zhang H, Go YM, and Jones DP. Mitochondrial thioredoxin-2/peroxiredoxin-3 system functions in parallel with mitochondrial GSH system in protection against oxidative stress. *Arch Biochem Biophys* 465: 119–126, 2007.
258. Zhang Z, Wakabayashi N, Wakabayashi J, Tamura Y, Song WJ, Sereda S, Clerc P, Polster BM, Aja SM, Pletnikov MV, Kensler TW, Shirihai OS, Iijima M, Hussain MA, and Sesaki H. The dynamin-related GTPase Opa1 is required for glucose-stimulated ATP production in pancreatic beta cells. *Mol Biol Cell* 22: 2235–2245, 2011.
259. Zhen X, Uryu K, Cai G, Johnson GP, and Friedman E. Age-associated impairment in brain MAPK signal pathways and the effect of caloric restriction in Fischer 344 rats. *J Gerontol A Biol Sci Med Sci* 54: B539–B548, 1999.
260. Zheng D, MacLean PS, Pohnert SC, Knight JB, Olson AL, Winder WW, and Dohm GL. Regulation of muscle GLUT-4 transcription by AMP-activated protein kinase. *J Appl Physiol* 91: 1073–1083, 2001.
261. Zheng M, Aslund F, and Storz G. Activation of the OxyR transcription factor by reversible disulfide bond formation. *Science* 279: 1718–1721, 1998.
262. Zhong Q, Putt DA, Xu F, and Lash LH. Hepatic mitochondrial transport of glutathione: studies in isolated rat liver mitochondria and H4IIE rat hepatoma cells. *Arch Biochem Biophys* 474: 119–127, 2008.
263. Zhou Q, Lam PY, Han D, and Cadenas E. c-Jun N-terminal kinase regulates mitochondrial bioenergetics by modulating pyruvate dehydrogenase activity in primary cortical neurons. *J Neurochem* 104: 325–335, 2008.
264. Zhou Q, Lam PY, Han D, and Cadenas E. Activation of c-Jun-N-terminal kinase and decline of mitochondrial pyruvate dehydrogenase activity during brain aging. *FEBS Lett* 583: 1132–1140, 2009.
265. Zimniak P. Detoxification reactions: relevance to aging. *Ageing Res Rev* 7: 281–300, 2008.

Address correspondence to:
Prof. Enrique Cadenas
Department of Pharmacology and Pharmaceutical Sciences
School of Pharmacy
University of Southern California
Los Angeles, CA 90089

E-mail: cadenas@usc.edu

Date of first submission to ARS Central, July 2, 2012; date of acceptance, July 15, 2012.

Abbreviations Used

Akt = protein kinase B
AMPK = 5′ adenosine monophosphate-activated protein kinase
ANT = adenine nucleotide translocase
Drp1 = dynamin-related protein 1
ETC = electron transport chain
Fis1 = fission protein 1
GPx = glutathione peroxidase
GR = glutathione reductase
Grx = glutaredoxin
GSH = glutathione
GSSG = glutathione disulfide
GST = glutathione S-transferases
IDH = isocitrate dehydrogenase
IGF-1 = insulin-like growth factor-1
IIS = insulin/IGF-1 signaling
IRS = insulin receptor substrates
JNK = c-Jun N-terminal kinase
MAPK = mitogen-activated protein kinases
mtNOS = mitochondrial nitric oxide synthase
nNOS = neuronal NOS
NNT = nicotinamide nucleotide transhydrogenase
NRF = nuclear respiration factor
Nrf2 = nuclear factor erythroid 2-related factor
OPA1 = optic atrophy-1
OXPHOS = oxidative phosphorylation
PDH = pyruvate dehydrogenase
PGC-1 = peroxisome-proliferator-activated receptor γ coactivator-1
PI3K = phosphatidylinositol 3-kinase
Prx = peroxiredoxin
SCOT = succinyl-CoA:3-oxoacid Co-A transferase
SOD = superoxide dismutases
TCA = tricarboxylic acid
TFAM = mitochondrial transcription factor A
TRP = transient receptor potential
Trx = thioredoxin
TrxR = thioredoxin reductase
α-KGDH = α-ketoglutarate dehydrogenase