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Redox Regulation of Mitochondrial Biogenesis

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Abstract

Background—The cell renews, adapts, or expands its mitochondrial population during episodes of cell damage or periods of intensified energy demand by the induction of mitochondrial biogenesis. This bi-genomic program is modulated by redox-sensitive signals that respond to physiological nitric oxide (NO), carbon monoxide (CO), and mitochondrial reactive oxygen species (ROS) production.

Scope of Review: This review summarizes our current ideas about the pathways involved in the activation of mitochondrial biogenesis by the physiological gases leading to changes in the redox milieu of the cell with an emphasis on the responses to oxidative stress and inflammation.

Major Conclusions: The cell's energy supply is protected from conditions that damage mitochondria by an inducible transcriptional program of mitochondrial biogenesis that operates in large part through redox signals involving the nitric oxide synthase and the heme oxygenase-1/CO systems. These redox events stimulate the coordinated activities of several multifunctional transcription factors and co-activators also involved in the elimination of defective mitochondria and the expression of counter-inflammatory and anti-oxidant genes, such as IL10 and Sod2, as part of a unified damage-control network.

General Significance: The redox-regulated mechanisms of mitochondrial biogenesis schematically outlined in the graphical abstract link mitochondrial quality control to an enhanced capacity to support the cell's metabolic needs while improving its resistance to metabolic failure and avoidance of cell death during periods of oxidative stress.

Keywords

Carbon monoxide; cell metabolism; heme oxygenase; inflammation; mitochondria; nitric oxide; oxidative stress; reactive oxygen species

Introduction

Oxidative stress and other cellular injuries that damage mitochondria may impair the cell's capacity to generate sufficient adenosine triphosphate (ATP) for homeostasis, ultimately leading to apoptosis or necrosis [1]. The protection of mitochondrial integrity and quality is the task of cellular programs that monitor and replace dysfunctional mitochondria with organelles better suited to energy prevision under the conditions prevailing in the tissue

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microenvironment [2]. This process of mitochondrial quality control involves a bi-genomic program of nuclear- and mitochondrial-encoded gene regulation that rapidly adjust mitochondrial mass, distribution, and phenotype [3, 4]. The program requires the transcription and replication of mitochondrial DNA (mtDNA), mitochondrial protein synthesis, and distinct structural events in the cytoplasm, including mitochondrial fusion/fission, mitochondrial autophagy (mitophagy), and mitochondrial proliferation, as well as specific reorganization of the cytoskeleton.

Cells do not generate mitochondria de novo, but instead identify and dispose of defective mitochondria while stimulating healthy mitochondria to proliferate through mitochondrial biogenesis [5]. In the process, highly functional mitochondrial subpopulations are segregated from poorly functional mitochondria, which are targeted for degradation. The elucidation of this high-level capability is an area of emphasis in mitochondrial research, and this review summarizes those aspects of redox-regulation of mammalian mitochondrial biogenesis known to be involved in maintaining and restoring mitochondrial function after oxidative damage. The emphasis here is on the roles of nitric oxide and carbon monoxide, and excludes hydrogen sulfide, about which far less is known.

Mitochondrial Biogenesis

Normally, mitochondrial biogenesis is activated by changes in physiological state that require increases in the rates of ATP utilization approaching the existing capacity of the cells to produce it. Such events include, but are not limited to thermogenesis, exercise, calorie restriction, and several others listed in Table 1 [4, 6, 7]. The focus here is the activation of mitochondrial biogenesis by mitochondrial damage from oxidative stress and pathological inflammation [3, 4, 6-18]. Under such conditions, mitochondrial biogenesis indispensably supports energy-dependent cell processes, including those involved in the repair of cell and tissue damage.

Mitochondrial biogenesis is regulated mainly at the level of transcription, and numerous nuclear-encoded mitochondrial genes must be expressed in synchrony with the 13 mitochondrial-encoded genes. This coordinated bi-genomic program includes nuclear-encoded mitochondrial proteins that control mtDNA transcription and replication, and requires the induction of mitochondrial DNA polymerase (gamma), mitochondrial transcription factor A (TFAM), and TFB2M [3, 4]. These nuclear control mechanisms also lead to the induction of tissue- and signal-specific subsets of genes that serve specialized functions. Much of the mitochondrial proteome is dedicated to such lineage-specific proteins [19], and hence, the transcriptional program matches the cell's mitochondrial mass and phenotype to the physiological energy needs and the functions of each tissue.

Many nuclear-encoded genes for mitochondrial proteins, for instance, electron transport and oxidative phosphorylation proteins contain conserved binding motifs for nuclear respiratory factors-1 (NRF-1) and NRF-2 (also called GA-binding protein A or GABPA). The peroxisome proliferator-activated receptor gamma (PPARγ) co-activator 1- protein (PGC-1α) has been identified as a central transcriptional co-activator for NRF-1, GABPA, and the PPARs, and it is involved in the physiological integration of mitochondrial biogenesis with oxidative metabolism [8]. Two related co-activators (PGC-1β and the PGC-1-related co-activator, PRC) provide overlapping and reinforcing regulation of many nuclear-encoded mitochondrial genes [20]. All three family members activate genes encoding for proteins for mtDNA transcription and replication and mitochondrial protein importation [4, 8, 20-22].

The physiological induction of mitochondrial biogenesis in working tissues such as contracting skeletal and cardiac muscle involves intracellular calcium (Ca2+) signaling [23–

29]. Energy depletion is marked by the accumulation of adenosine monophosphate (AMP) an impending energy crisis activates the serine/threonine AMP-activated protein kinase (AMPK) [30–36]. AMPK interrupts ATP-consuming reactions and activates ATP-generating pathways [32]. AMPK also promotes mitochondrial biogenesis [30, 31, 34] and blocks the growth regulating mTOR pathway [37, 38] by phosphorylation of the TSC2 tumor suppressor, which co-operates with TSC1 (tuberin) [37]. Activation of mTOR signaling by Akt/PKB involves the phosphorylation and inactivation of TSC2 [39]. Akt/PKB also promotes mitochondrial biogenesis through the phosphorylation of NRF-1 and cyclic AMP response element binding protein (CREB1), thereby enabling their nuclear translocation and target gene activation[40]. This process also increases mitochondrial hexokinase (HK) activity, committing glucose to glucose-6-phosphate using ATP generated by mitochondria and coupling glycolysis to oxidative phosphorylation [41].

Energy homeostasis in the face of changes in nutrient availability is regulated in part by the NAD-dependent deacetylase, sirtuin-1 (SIRT1) [35, 42-45]. During nutrient depletion, SIRT1 increases the NAD+/NADH ratioand deacetylates PGC-1α, allowing the co-activator to facilitate target gene transcription [46]. SIRT1 positively regulates lipid homeostasis in the liver during fasting and starvation through nuclear PPAR, which cooperates in PGC-1 activation [43, 47]. A diagram of these physiological aspects of mitochondrial biogenesis is shown in Figure 1.

Other transcription factors are also involved in mitochondrial biogenesis [48]. Aerobic tissues express nuclear estrogen-related receptors (ERRs), particularly the orphan nuclear receptor ERRα, a PGC-1-partner in the expression of the genes necessary for fatty acid β-oxidation [49]. In addition to CREB1, the YY1 initiator binding factor contributes to the constitutive expression of respiratory and other genes of energy metabolism [50–55].

Other genes important for mitochondrial biogenesis include the nuclear-encoded proto-oncogene c-Myc, an activator of PGC-1, and the myocyte-specific enhancer factor 2A (MEF2A) [56, 57], a critical regulator of oxidative capacity in skeletal and cardiac muscle activated by NRF-1 [58–60]. MEF2A also activates growth factor and stress-induced genes and promotes cell growth and cell survival [60]. It is noteworthy that the p53 tumor suppressor, a well-known pro-apoptotic protein, also protects mitochondria through activation of genes encoding for respiratory and mtDNA maintenance proteins [61, 62]. In the mitochondrial matrix, p53 is bound to the hsp70 and hsp60 mitochondrial import proteins and interacts with mitochondrial DNA polymerase gamma (Pol γ) to enhance its fidelity [63]. Since the accuracy of Pol γ influences mtDNA integrity, p53 may assure mitochondrial genomic stability, and the loss of p53 indeed increases the sensitivity of mtDNA to genotoxic stress [64]. Putative p53-recognition sequences are found within mtDNA in the Complex I genes and the 12S and 16S rDNA regions [65]. The mitochondrial 16S rDNA sequence in human cancer cells appears to be p53-responsive, but it is not clear whether p53 directly binds mtDNA or indirectly affects transcription. In any case, the implication is that p53 plays integral roles in mitochondrial maintenance and ROS control.

Nitric Oxide

NO synthesis from L-arginine and O2 by the nitric oxide synthases (NOS) occurs in almost all mammalian cells [66]. Of the three recognized NOS enzyme isoforms, two, the endothelial (eNOS; NOS3) and the neuronal (nNOS; NOS1), are regulated by calcium, while the third (iNOS; NOS2) is calcium-independent and inducible by inflammation. Moreover, all three NOS isoforms can be expressed constitutively or selectively up-regulated by specific transcriptional and post-transcriptional events in a number of tissues [67].

A potent physiological vasodilator, NO also acts on mitochondria in important ways. Clearly, NOS3-dependent blood flow regulation to tissue helps supply carbon substrates to mitochondria, but NO is also released allosterically from red blood cells and thus directly regulates the O2 supply to mitochondria [68]. In the cell, nitric oxide acts on the respiratory chain by binding to subunits of Complex I and Complex IV [69]. Two chemical interactions, S-nitrosation and heme-metal binding, inhibit OXPHOS, but the inhibition of cytochrome c oxidase by the latter is especially active at low O2 concentrations [70]. Thus, for certain cells and tissues, reversible NO/cytochrome c oxidase binding is seen as an acute O2 sensing system [71]. Some mitochondria also have an associated NO synthase (mitochondrial NOS, mtNOS) probably involved in the direct regulation of respiratory function [72, 73].

The effects of NO on the regulation of the electron transport chain also lead to increased mitochondrial superoxide anion production [74, 75]. Mitochondria also consume NO, and moderate increases in NO stimulate mitochondrial biogenesis [15, 76] mainly through cGMP-dependent gene expression and activation of regulatory proteins such as peroxisome proliferator-activated receptor γ (PPARγ) co-activator 1α(PGC1-α), nuclear respiratory factor 1 (NRF-1), and mitochondrial transcription factor A (Tfam) [3, 77]. A diagram of the original pathway for mitochondrial biogenesis proposed for NOS3 is given in Figure 2.

In contractile tissues, calcium transients that activate calcineurin A and serine/threonine calcium/calmodulin-dependent protein kinases (CaMK), particularly CaMK II, can activate PGC-1α gene transcription [78]. The calcineurin A-mediated activation of PGC-1α gene transcription depends on MEF2 response elements, whereas CaMK-mediated regulation requires CREB1. In HeLa cells, mitochondrial biogenesis increases after transfection with NOS3, while inhibition of NOS abolishes the effect [15]. Furthermore, NOS3-deficient mice exhibit decreased levels of mtDNA, Complex IV and cytochrome c in brain, liver and heart tissue, indicating that loss of NOS3 is sufficient to reduce mitochondrial biogenesis even though the mice still express the other NOS isoforms [79].

Also, NOS3 expression and guanylate cyclase (GC) activation, but not NOS1 or NOS2 expression is induced in mice by calorie restriction (CR), which stimulates SIRT1 expression and mitochondrial biogenesis [17]. During CR, other mitochondrial proteins increase including NRF-1, Tfam, mitofusin 1 (Mfn1), mitofusin 2 (Mfn2), cytochrome c and cytochrome c oxidase. The NOS3 knockout mouse does not show the effect of CR on mitochondrial biogenesis and the mice have low SIRT1 levels and decreased longevity consistent with inability to generate new mitochondrial proteins [17].

Two other aspects of NO in mitochondria affect gene expression. One is the diversion of O2 to the cytoplasm, which causes the down-regulation of hypoxia-inducible factor 1 (HIF-1α) and anaerobic glycolysis, and the other is the release of mitochondrial calcium resulting in activation of the ATF6 transcription factor. In contrast, HIF-1α stabilization in tumor cells inhibits mitochondrial biogenesis through suppression of c-Myc transcriptional activity by two mechanisms. First, HIF-1α activates the Mxi1 gene, which encodes for a c-Myc transcriptional repressor, Max-interacting protein-1. Second, HIF-1α promotes proteasome-dependent degradation of c-Myc protein, which interferes with gene transcription for NRF-1 and PGC-1β [80].

Other transcription factors also contribute to NO's impact on mitochondrial quality control, particularly those responsive to redox signals, such as the NF-E2 related factor (Nfe2l2 or Nrf2) [81], which physiologically regulates anti-oxidant and cytoprotective genes [82, 83]. In endothelial cells, nitric oxide facilitates the nuclear translocation of Nrf2 by a mechanism blocked by antioxidants and by inhibitors of mitogen-activated protein kinases (MAPK)

[84]. And increases in NOS3 activation (22) and expression (23) triggered by laminar flow also induces the expression of certain Nrf2 target genes [85, 86].

One of the key transcriptional regulators activated by NO is CREB1. CREB1 is widely expressed and is involved along with NRF-1 in the growth-regulated expression of cytochrome c [21, 87]. NRF-1 regulates many nuclear-encoded genes required for the expression of the mitochondrial electron transport chain, mtDNA transcription and replication [10, 88], genes for heme biosynthesis [89, 90] and for mitochondrial protein importation and assembly [91]. NRF-1 regulates MEF2A expression in muscle, which controls muscle-specific cytochrome c oxidase subunits and other muscle-specific MEF2 target genes [60]. NRF-1 is also transcriptionally regulated by Nrf2 and NRF-1 induction by Nrf2 is followed by the induction of Tfam and mitochondrial transcription [92]. In addition, a link between NRF-1 and the LPS-induced inflammatory response is demonstrated by the identification of NF-kB-responsive elements in the NRF-1 promoter region [93]. This response is facilitated by CREB1 binding to the promoter and a functional interaction between NF-kB and CREB1 in controlling NRF-1-dependent mitochondrial biogenesis during the resolution of inflammation.

The PGC-1 co-activator genes are regulated by pathways that modulate growth, differentiation, and metabolism [4, 94] including those that converge on the CREB1-dependent induction of PGC-1α in response to nutrient deprivation, cold exposure, and exercise [29, 87, 95]. As mentioned earlier, PGC-1 activation and expression of mitochondrial fatty acid oxidation enzymes also occurs by post-translational protein modification by SIRT1, which deacetylates multiple lysine residues in PGC-1α [96]. In muscle, energy depletion triggers AMPK activation, which phosphorylates PGC-1α [36]. The subsequent mitochondrial gene expression is consistent with the idea that AMPK mediates its major effects through PGC-1α [97]. Also as indicated, SIRT1 and AMPK cooperate in promoting calcium-dependent mitochondrial biogenesis in myocytes [35].

PGC-1α is also a link between calorie restriction and mitochondrial oxidant production through SIRT3 expression. PGC-1α co-activates SIRT3 gene expression through ERRα, which binds to the proximal SIRT3 promoter [98, 99]. The SIRT3 protein is imported into mitochondria where it optimizes several key enzymatic activities of metabolic function [99]. It also opposes the effects of oxidant stress by triggering a series of reactions beginning with the activation of isocitrate dehydrogenase 2 and culminating in ROS detoxification by glutathione peroxidase [100]. It deacetylates mitochondrial superoxide dismutase (SOD2) leading to increased activity and enhanced oxidant scavenging [101, 102]. SIRT3 also deacetylates specific subunits in the respiratory complexes, and cells devoid of the SIRT3 gene show impaired energy homeostasis [103]. These SIRT3-dependent mechanisms have been implicated in mediating antioxidant effects associated with increased longevity [104].

Although mitochondrial ROS serve important redox signaling functions, excessive superoxide and H2O2 are certainly well-known disruptors of mitochondrial and cellular function. H2O2 is a potential trigger for intrinsic apoptosis, particularly in connection with the calcium-dependent mitochondrial permeability transition (MPT). For instance, one of the two mitochondrial-targeted isoforms of the gene for SHC-transforming protein 1, p66Shc, after phosphorylation at Ser36, accumulates in the intermembrane space [105]. Although initially implicated in cell growth, subsequent studies have indicated that p66Shc increases mitochondrial H2O2 production [106, 107] and predisposition to the MPT. In mice, p66Shc deletion confers resistance to oxidative damage and prolongs the lifespan [106, 107]. Genetic p66Shc−/−mice are also protected from certain diabetes complications, such as nephropathy and cardiomyopathy, while in diabetic patients, elevated p66Shc levels correlate with oxidative stress and poor glycemic control [108].

Mitochondrial biogenesis and mtDNA replication is not the sole mechanism by which nitric oxide supports bioenergetic function. Mitochondrial biogenesis is coordinated with mitochondrial division (fission),, and although the process of synchronization is incompletely understood, NO does alter intracellular mitochondrial structural networks. Mitochondria exist as a dynamic network, the nature of which is regulated by several factors, including fusion and fission and interactions with the cytoskeleton [109]. It is thought that mitochondrial fission functionally responds to O2 and metabolic fluctuations, but whether ROS promote mitochondrial fission or fission promotes mitochondrial ROS generation is not settled. However, during myogenic differentiation, NO-induced mitochondrial elongation (fusion) is a necessary for the repression of the pro-fission GTPase dynamin-related protein-1 (Drp1) [110]. Blocking these NO-mediated pathways in differentiating myoblasts negatively impacts mitochondrial function and oxidative phosphorylation. Drp1 is also a target for S-nitrosation, which promotes the toxic effects of β-amyloid in Alzheimer disease due to NO-mediated enhancement of Drp1-dependent fission and mitochondrial fragmentation [111]. A later study on the role of Drp1 in Alzheimer's disease, has suggested instead that NO promotes Drp1activation by phosphorylation rather than – SNO modification because abundant SNO-Drp1 is present in normal brains in addition to those from Parkinson's and Alzheimer's diseases [112]. In other words, the extent to which S-nitrosation, cGMP signaling or both modulate fission is still being worked out. Nonetheless, the stimulation of mitochondrial biogenesis by NO promotes matching of cell metabolism to tissue blood flow and oxygenation in relation to the physiological demand for energy.

The HO-1/CO System

The heme oxygenase enzymes (HO-1 and -2) control the degradation of heme, which if left unattended, causes oxidative stress [113]. Free heme is toxic to the cell, and both HO isoforms, in removing it, generate physiological carbon monoxide (CO), release iron, and produce biliverdin, which is promptly converted to bilirubin [114]. The inducible HO-1 gene (Hmox1) is particularly protective, safeguarding the cell against many types of stress including heat, oxidants, inflammation, heavy metals, and hypoxia [83, 115]. Although biliverdin and bilirubin have anti-oxidant properties, CO and iron are typically pro-oxidant, and CO is a relatively weak activator of GC [116]. HO-1 induction also leads to augmentation of the cell's iron-handling defenses, and most cells respond to CO by up-regulating anti-oxidant enzymes such as SOD2 [117]. Despite numerous publications demonstrating the protective effects of this enzyme and its products against a wide variety of tissue injuries, a unifying biological explanation has been elusive.

Like many other anti-oxidant enzyme genes, Hmox1 expression is also rapidly up-regulated by the Nrf2 transcription factor [118]. The Nrf2 protein, docked in the cytoplasm to Keap1, a redox-sensitive cytosolic adaptor protein, is targeted by a cullin-based ubiquitin ligase for proteasomal degradation, which normally prevents Nrf2 target gene expression [83]. In the nucleus, Nrf2 binds to antioxidant response elements (ARE) in the promoter regions of xenobiotic- and anti-oxidant genes, including Hmox1 [119]. Most electrophiles and oxidants, including the pro-oxidant actions of CO, activate Nrf2, leading to the transcription of ARE-containing genes, including Nrf2 itself [120].

A mitochondrial Keap1-binding protein, PGAM5, a phosphoglycerate mutase without PGM enzyme activity is targeted to the outer mitochondrial membrane by an N-terminal localization sequence. PGAM5 forms a ternary complex with Keap1 and Nrf2 in which Keap1 dimer simultaneously binds PGAM5 and Nrf2 through conserved E (S/T) GE motifs [121]. Loss of Keap1 or PGAM5 activates Nrf2-dependent genes.

The role of HO-1 and endogenous CO production in mitochondrial biogenesis was discovered in 2007 [122]. An increase in endogenous CO level stimulates SOD2 expression and mitochondrial H2O2 production at Complex III, which leads to activation of Akt/PKB and deactivation of glycogen synthase kinase-3 , permitting Nrf2 nuclear translocation and occupancy of AREs in the NRF-1 promoter [92]. Activation of this pathway leads to strong induction of mitochondrial biogenesis as illustrated by Figure 3.

This transcriptional mechanism also provided the first link to the expansion of mitochondrial mass with the induction of the xenobiotic and antioxidant defenses. In the mouse heart, HO-1 stimulation of mitochondrial biogenesis protects against the induction of cardiomyopathy by the anthracycline chemotherapeutic, doxorubicin [123], an agent which disrupts mitochondrial biogenesis and causes intrinsic apoptosis, necrosis, inflammation, and myocardial fibrosis. But the administration of low level CO or the expression of active HO-1 mitigates all of these effects [123].

The induction of HO-1 during inflammation not only triggers mitochondrial biogenesis, but leads to activation of counter-inflammatory genes such as IL-10 [124], and anti-apoptotic proteins such as BclXL [125]. These responses encompass the expression of the IL-1 receptor antagonist (IL-1Ra) and the suppressor of cytokine synthesis-3 (SOCS3) [126]. Mechanistically, CO release by HO-1 promotes binding of the Nrf2, GABPA, and MEF2 transcription factors to the IL10 promoter and the NRF-1 and MEF2 transcription factors to the IL1Ra promoter. In liver cells and in macrophages, Nrf2 or Hmox1 gene silencing blocks IL-10 and IL-1Ra up-regulation, and hepatic Hmox1 induction fails in response to bacterial-induced inflammation in Nrf2-/- mice.

HO-1 induction by mitochondrial ROS leads to a cycle of Nrf2 activation and further HO-1 induction, which is necessary to sustain NRF-1 and Tfam expression during mitochondrial biogenesis and for the induction of counter-inflammatory genes. The integration of this work with that mentioned above indicating that PPARs, AMPK, SIRT1, and PCG-1 family proteins produce anti-inflammatory effects implies that the program for mitochondrial biogenesis is part of an integrated transcriptional network linking cell metabolism to the cell’s anti-oxidant, anti-apoptotic, and counter-inflammatory defenses.

Oxidative Damage and Inflammation

Mitochondria are vulnerable to oxidative and nitrosative damage by the effects of proinflammatory cytokines, such as tumor necrosis factor alpha (TNF-) and interleukins generated during innate immune activation [127]. Defective mitochondria generate high ROS levels and release calcium and intrinsic apoptosis proteins during inflammation [128-130]. Excess ROS and NO production via immune effector pathways also compromises mitochondrial structure and function through direct oxidation of proteins and lipids or by peroxynitrite generation [131]. This may cause sufficient oxidative mitochondrial damage to cause cell death by apoptosis or necrosis.

During infections, higher eukaryotes recognize pathogens as “non-self” by means of evolutionarily-conserved pattern-recognition receptors (PRRs) [132-134].” The PRR detects pathogen-associated molecular patterns or PAMPs— entire molecules such as LPS or conserved motifs recognized as pathogenic. Plasma membranes or endosomes, for instance in macrophages, express toll-like receptors (TLR) that initiate the immune response to PAMPs from bacteria, fungi, parasites, and viruses. Specific adaptor proteins, MyD88 and TRIF, activate the NF-kB transcription factor and initiate signals for the synthesis of inflammatory cytokines, chemokines, antimicrobial peptides, and type I interferon [134]. TLR4 signaling through MyD88 is critical to the rapid synthesis of TNF-interleukin-1 beta (IL-1) and NOS2 in response to LPS [133].

Many cytokines and chemokines promote pathogen elimination by recruiting myeloid cells to sites of infection and stimulating phagocytosis, antigen presentation or antibody production [135]. Although NO and ROS production are characteristic of the mammalian innate immune response, these species in excess are pro-inflammatory [136, 137]. NF-kB activation by ROS in inflammatory and vascular cells enhances TNF- release, which further increases ROS production [138, 139]. TNF- is also a catabolic agent, and it inhibits respiration, mitochondrial biogenesis, and oxidative fiber phenotype in skeletal muscle [140]. In cardiomyocytes, TNF- stimulates binding of the NF-kB p65 subunit to PGC-1 , which may interfere with how one or both molecules effect downstream gene activation [141].

In addition to the up-regulation of anti-oxidant defenses, inflammation increases NRF-1 and PGC-1 expression [40, 142]. PGC-1 contributes to the induction of ROS-detoxifying enzymes, for instance SOD2 and glutathione peroxidase-1 (GPx1), and in neuronal cells after oxidant stress, CREB1 activates PGC-1 [142]. PGC-1 also promotes myocardial SOD2 and thioredoxin (Trx2) expression and protects the mouse heart against oxidative stress, hypertrophy, and contractile dysfunction [143]. PGC-1 over-expression in macrophages inhibits NF-kB-dependent cytokine production, which opposes inflammatory stress [144]. And NF-kB activates anti-oxidant enzyme genes, including SOD2 [145], while NF-kB inhibition increases TNF-mediated apoptosis in part by allowing the FAS-associating death domain-containing protein (FADD) to join a death-inducing signaling complex (DISC) that triggers caspase-8 activation [146]. The cell can avert this mode of death by shedding TNF-R1 [147].

TNF-R1 activation also increases cytosolic Ca2+ release and mitochondrial Ca2+ uptake [148], thus stimulating respiration and mitochondrial ROS production [149]. In lung vascular cells, high SOD2 activity increases the peroxide leak rate at Complex III, activating the TNF-α converting enzyme (TACE), a metalloproteinase that cleaves TNF-R1, causing receptor shedding and dampening of the TNF- response [150].

In muscle-specific PGC-1 knockout mice, high TNF- and IL-6 levels cause fiber damage and muscle wasting during exercise [151-154]. By comparison, muscle-specific PGC-1 over-expression in mice opposes aging-related declines in mitochondrial function and muscle integrity [155]. High muscle PGC-1 levels prevent muscle wasting by reducing apoptosis, autophagy, and proteasomal activity. This muscle protection also slows the decline in bone density and chronic inflammation of aging. In smooth muscle and endothelial cells, Ppargc1a over-expression suppresses mitochondrial ROS production induced by NF-kB and TNF- [139].

In the liver, TLR2/4 activation by bacterial products is accompanied by mtDNA depletion and impaired mitochondrial transcription [12] followed by a wave of mitochondrial proliferation [12, 156]. Histological observations provide evidence of accelerated mitochondrial turnover involving mitochondrial biogenesis and mitochondrial autophagy (mitophagy), which restores mitochondrial mass and mitigates cell death [12, 157-159]. TLR signaling post-inoculation with Staphylococcal aureus also leads to prompt Ppargc1a and Ppargc1b expression, but these genes are deregulated in TLR2-/- mice (fail to increase) and in TLR4-/- mice (highly increased) [160].

The initial depletion of mtDNA is related to NF-kB activation and TNF- and NO over-production. In LPS-mediated infections, TLR4 null mice show less mtDNA depletion, but restoration of mtDNA copy number is delayed [161]. The mtDNA damage induces the base excision repair glycosylase OGG1 [162] and is abrogated by increasing SOD2 levels or by limiting reactive nitrogen species production [163]. Redox- mechanisms for NRF-1

induction and including phosphorylation of the protein by Akt enable it to translocate to the nucleus and activate the genes for Tfam and other mitochondrial transcriptome proteins, allowing restoration of mtDNA copy number [164].

The TLR system also fosters the early up-regulation of mitochondrial biogenesis [160, 161] through NF-kB [93, 165], CREB1 [93], Nrf2 [126], and interferon response factors (IRF-3,IRF-7) [166]. The early-phase host defense enhances mitochondrial H2O2 production and initiation of mitochondrial biogenesis. AMPK also promotes NO production [167, 168], regulates autophagy [169] and inhibits NF-κB–dependent cytokine expression [170-177]. Conversely, low AMPK activity leads to enhanced inflammation. The NF-kB inhibition may involve PGC-1α, Forkhead box O transcription factors, and/or SIRT1 [20, 35, 178, 179]. SIRT1 is also anti-inflammatory [180] and SIRT1 deletion interferes with PPAR and -oxidation, whereas SIRT1 over-expression induces PPAR target genes. Liver-specific SIRT1−/− mice develop steatosis, ER stress, and hepatic inflammation. In peritoneal macrophages SIRT1 gene silencing stimulates the inflammatory response to LPS while SIRT1 activation inhibits it [181].

Danger signals lead to the full development of tissue inflammation through the assembly of intracellular inflammasomes. The NLRP3 inflammasome and caspase-1 (and caspase-11 in mice) generate IL-1 by cleavage of its pro-form. Mitochondria are a main source of ROS for NLRP3 activation and the NLRP3 inflammasome also influences glycolysis and lipogenesis [182-184]. In macrophages, inflammasome activation is impaired by inactivation of the outer membrane voltage dependent anion channel, VDAC, or by mtDNA depletion [184]. Complex I and Complex III inhibition also activate the NLRP3 inflammasome [183]. Dysfunctional ROS-generating mitochondria and counter-regulation the NLRP3 inflammasome occurs in part through mitochondrial autophagy or mitophagy [185]. A loss of mitophagy allows persistence of ROS-generating mitochondria and NLRP3 activation [183, 184].

Another common metabolic disorder, Type 2 diabetes, is associated with ROS production, inflammation, and alterations in mitochondrial density and function [186, 187]. Analysis of the mitochondrial transcriptome in the skeletal muscle of patients with type 2 diabetes has indicated impaired expression of OXPHOS genes [188, 189]. Hyperglycemia also increases intracellular ROS levels by several mechanisms. One that operates in neuronal tissue involves hyperpolarization of the inner mitochondrial membrane, which increases ROS leakage out of the mitochondrion [190]. In hyperglycemic, hyperlipidemic mice, muscle ROS production is associated with mitochondrial swelling and a decrease in mRNA expression for PGC1-α and its target genes. In hyperglycemia-associated oxidative stress, low molecular weight anti-oxidant administration can improve mitochondrial density and structure [191]. This implies that hyperglycemia and hyperlipidemia-induced mitochondrial dysfunction in skeletal muscle is due at least in part to increased mitochondrial ROS production and impaired redox signaling. In animal models of insulin resistance and high fat diets, AMPK activity is also down-regulated [192].

These pro-survival pathways also impinge on the regulation of apoptosis. The pro-apoptotic BAD, a BH3-only domain pro-apoptotic member of the Bcl-2 family is phosphorylated by survival kinases resulting in cytoplasmic localization and inactivation [193]. In mitochondria, BAD is part of the large protein complex that through glucokinase (HK4) catalyzes the first step of glycolysis. The loss of BAD restricts respiration in response to glucose, while glucose deprivation leads to BAD dephosphorylation and to apoptosis [194]. Although normally pro-survival, the disproportionate induction of mitochondrial biogenesis may indicate persistent mitochondrial dysfunction [195]. Interference with mitochondrial biogenesis during periods of oxidative stress exacerbates inflammation and promotes

apoptosis, but rapid mitochondrial turnover under the stimulus of continuous mitochondrial damage also increases the likelihood of immune suppression by counter-inflammatory mediator over-production [196-200].

Summary and Conclusions

Mitochondrial biogenesis can be activated by NO, CO, and mitochondrial ROS by means of retrograde signaling from damaged mitochondria to the nucleus. These redox signals give rise to nuclear transcriptional responses that lead to mitochondrial protein synthesis. The response is structured to compensate for mitochondrial dysfunction and to avoid compromise of cell metabolism, triggered for example, by oxidative stress during a hyperactive host immune response. Immune effectors elaborated by both structural and immune cells, such as TNF- and IL-1 promote oxidative stress, calcium deregulation, and NO production, which not only contributes to mitochondrial damage, but to activation of mitochondrial biogenesis. These same effectors may also interfere sufficiently with these redox signals to obfuscate such adaptive responses, ultimately leading to loss of homeostasis. There are also interactions, although not yet fully defined, among the NO, CO and calcium-mediated control mechanisms for mitochondrial biogenesis. Still, it is evident that this multifaceted transcriptional network is coordinated with the removal of damaged mitochondria and that together these processes re-establish an anti-oxidant counter-inflammatory milieu that protects against energy failure and cell death.

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Highlights

- The physiological gases NO and CO are redox regulators of mitochondrial biogenesis
- NO activates mitochondrial biogenesis mainly through cGMP and CREB1
- CO activates mitochondrial biogenesis mainly through ROS and Nrf2-dependent genes
- Adaptive mitochondrial biogenesis opposes oxidative stress and prevents energy failure

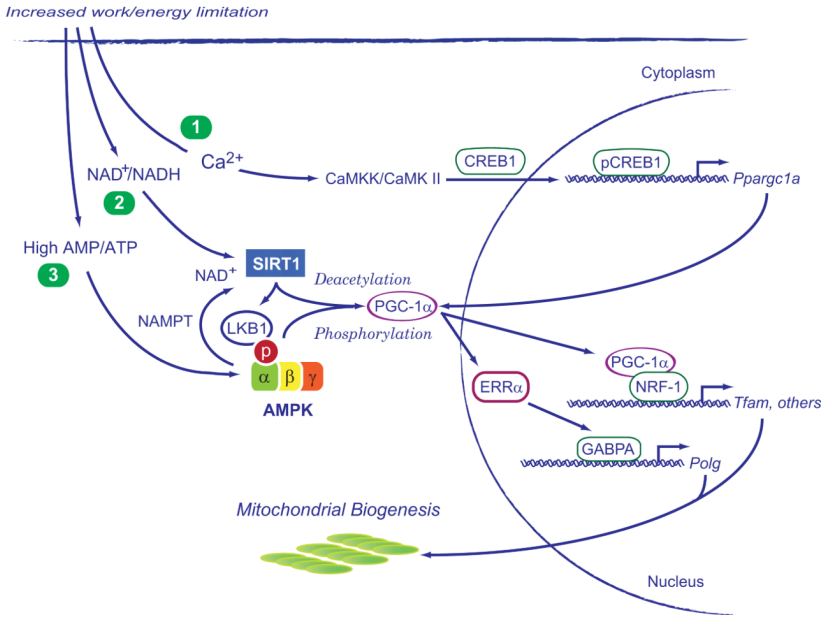

Figure 1.

Three major pathways in the activation of mitochondrial biogenesis during aerobic work and/or energy limitation. These are: 1) intracellular calcium release, particularly in contractile tissues, which activates calcium/calmodulin kinase II (CaMKII) and cAMP-responsive element binding protein 1 (CREB1); 2) the NAD+/NADH ratio, which activates sirtuin-1 (SIRT1) causing deacetylation of peroxisome proliferator-activated receptor gamma co-activator 1- PGC-1 , and 3) a high AMP/ATP ratio, which activates AMP-activated kinase (AMPK), allowing phosphorylation of PGC-1 . PGC-1 co-activates nuclear respiratory factor-1 (NRF-1) and other transcription factors involved in mitochondrial biogenesis. Other abbreviations are NAMPT, nicotinamide phosphoribosyltransferase; CaMKK, calcium/calmodulin-dependent protein kinase kinase 2; ERR , estrogen-related receptor alpha; GABPA, GA binding protein alpha; Polg, DNA-directed polymerase gamma; Tfam, mitochondrial transcription factor A.

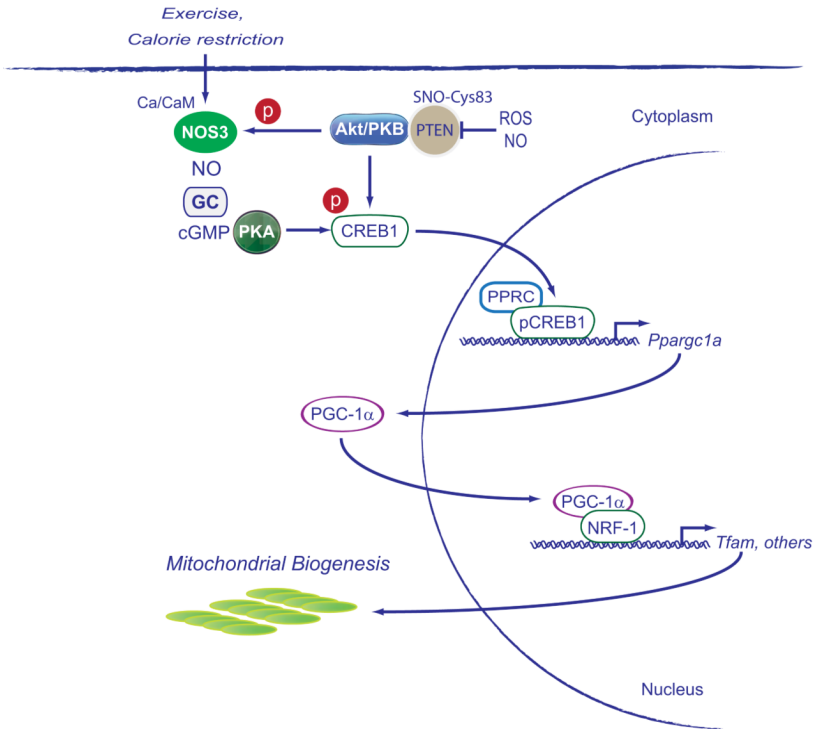

Figure 2.

The induction of mitochondrial biogenesis by nitric oxide synthase 3 (NOS3). Calcium/calmodulin (Ca/CM)-dependent NOS activates guanylate cyclase (GC) to generate cyclic GMP, which activates protein kinase A (PKA). PKA phosphorylates CREB1 at Ser 133 enabling its nuclear translocation and activation of the PGC-1 gene (Ppargc1a). PGC-1 protein is a co-activator for NRF-1 and other transcription factors for mitochondrial biogenesis. Other abbreviations are Akt, protein kinase B; PPRC, peroxisome proliferator-activated receptor gamma, co-activator-related 1, and PTEN, the phosphatase and tensin homolog. Other abbreviations are as in Figure 1.

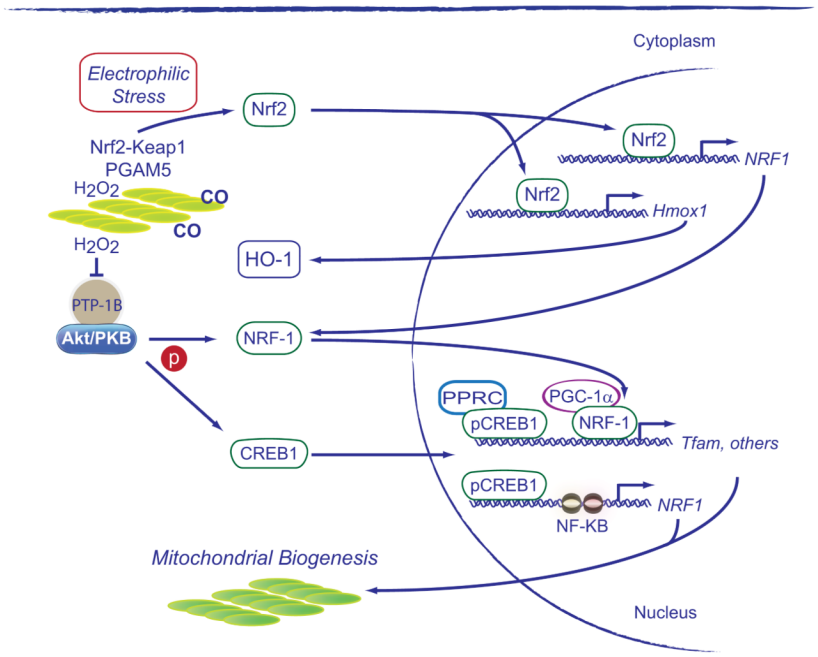

Figure 3.

The induction of mitochondrial biogenesis by the HO-1/CO system. The diagram illustrates how endogenous CO and mitochondrial H2O2 release contribute to the redox activation of Nrf2-Keap1. The oxidation of Keap1 in the vicinity of mitochondria stabilizes the protein complex and allows free cytoplasmic Nrf2 to translocate to the nucleus where it activates NRF-1 and HO-1. This creates a feed-forward cycle for the initiation and maintenance of mitochondrial biogenesis following oxidative and inflammatory stress. PTP-1B, Tyrosine-protein phosphatase non-receptor type 1 (PTPN1); PGAM5, mitochondrial serine/threonine-protein phosphatase, Other abbreviations as in Figures 1 and 2.

Table 1

Major Initiators of Mitochondrial Biogenesis

- Embryonic development
- Cell division and repair
- Changes in physiological state
  - Exercise
  - Energy limitation
  - Cold stress
  - Calorie restriction
  - Sympathetic stimulation
  - Hormones
    - Erythropoietin
    - Leptin
    - Thyroid hormone
- Mitochondrial damage/disease
  - Oxidative/nitrosative stress
  - Hypoxia/ischemia
  - Inflammation