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Transcriptional Control of Mitochondrial Biogenesis and Its Interface with Inflammatory Processes

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Abstract

Background—Cells avoid major mitochondrial damage and energy failure during systemic inflammatory states, such as severe acute infections, by specific targeting of the inflammatory response and by inducing anti-inflammatory and anti-oxidant defenses. Recent evidence indicates that these cell defenses also include mitochondrial biogenesis and the clearance of damaged mitochondria through autophagy.

Scope of Review—This review addresses a group of transcriptional signaling mechanisms that engage mitochondrial biogenesis, including energy-sensing and redox-regulated transcription factors and co-activators, after major inflammatory events.

Major Conclusions—Stimulation of the innate immune system by activation of toll-like receptors (TLR) generates pro-inflammatory mediators, such as tumor necrosis factor-α (TNF-α) and interleukin-1β, (IL-1β), necessary for optimal host defense, but which also contribute to mitochondrial damage through oxidative stress and other mechanisms. To protect its energy supply, host cells sense mitochondrial damage and initiate mitochondrial biogenesis under the control of an inducible transcriptional program that also activates anti-oxidant and anti-inflammatory gene expression. This multifunctional network not only increases cellular resistance to metabolic failure, oxidative stress, and cell death, but promotes immune tolerance as shown in the graphical abstract.

General Significance—The post-inflammatory induction of mitochondrial biogenesis supports metabolic function and cell viability while helping to control inflammation. In clinical settings, patients recovering from severe systemic infections may develop transient immune suppression, placing them at risk for recurrent infection, but there may be therapeutic opportunities to enhance mitochondrial quality control that would improve the resolution of life-threatening host responses to such infections.

Keywords

Infection; inflammasome; innate immunity; cell metabolism; oxidative stress

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Introduction

The protection of mitochondrial function is essential not only to normal mammalian physiology, but also to the biological response to major inflammatory states, particularly when inflammation triggers significant cell stress. The innate and adaptive responses to intense, prolonged, or poorly-contained immunological stimuli produce mitochondrial damage in host cells that can impair their capacity to generate sufficient adenosine triphosphate (ATP) for homeostasis [1]. This may limit energy availability for cellular maintenance, and ultimately, compromise cell survival and organ function.

The damaging effects of inflammation on mitochondria are opposed by cellular programs that protect the quality of the cell's mitochondria by disposing of badly damaged organelles and replacing them with fresh ones [2]. This process of mitochondrial quality control involves an intricate bi-genomic program that regulates mitochondrial DNA (mtDNA) transcription and replication and mitochondrial protein synthesis. The program is tailored to specific signals from the cell to rapidly adjust mitochondrial mass, number, size, distribution, and/or phenotype [3, 4]. Such changes in mitochondrial mass and function encompass structurally distinct events within the cell, including autophagy (mitophagy), changes in cytoskeletal morphology, the mitochondrial fusion and fission cycle, and mitochondrial biogenesis [5, 6].

Since mitochondria are not generated *de novo*, the cell must rely on processes that identify and target dysfunctional mitochondria for degradation while concomitantly stimulating healthy mitochondria to proliferate and repopulate it [5]. These processes effectively segregate mitochondria into functional and non-functional sub-populations and assure uninterrupted ATP provision for essential work and for survival. The molecular regulation of this sophisticated capability is still in the discovery phase, and this concise review focuses on regulatory aspects of the transcriptional network for mitochondrial biogenesis in mammalian systems that maintain and restore mitochondrial function after inflammation-induced cell and organ damage. It is focused on broadly translatable principles, but we have identified the known exceptions and information that is restricted to lineage-specific events.

The Transcriptional Program of Mitochondrial Biogenesis

Mitochondrial biogenesis is activated by physiological and pathological stimuli including but not limited to cell division, development, exercise, thermogenesis, postnatal breathing, thyroid hormone and erythropoietin secretion, calorie restriction, oxidative stress, and inflammation [3, 4, 7–19]. Effective regulation of mitochondrial biogenesis during changing requirements for oxidative metabolism brought about by these factors provides ancillary or more efficient support for the indispensable energy-dependent functions of the cell (Figure 1). Such functions include muscle contraction, heat production, tissue growth and remodeling, and repair of cell and mitochondrial damage after exposure to stressors.

Because mitochondria are adaptive organelles, about half of the 1,000 plus mitochondrial genes are expressed in a tissue- or lineage-specific manner, suggesting much of the mitochondrial proteome is dedicated to specialized functions [20]. The regulation of mitochondrial biogenesis presents a transcriptional challenge for the cell because the control mechanisms must coordinate a large set of inducible mitochondrial genes, while simultaneously enabling tissue- and signal-specific induction of gene subsets. Most of the genes required for mitochondrial biogenesis and respiration are under the control of a nuclear network of DNA–binding transcription factors and co-regulators that allows for vigorous activation in response to diverse physiological cues, as well as tissue- or signal-specific modifications of mitochondrial function and mass. Most of the nuclear-encoded genes for mitochondrial proteins, for instance, electron transport and oxidative

phosphorylation proteins, contain conserved promoter binding motifs for nuclear respiratory factors-1 (NRF-1) and NRF-2 (also GA-binding protein or GABP). These transcription factors also activate nuclear genes that encode for proteins for mtDNA transcription and replication and mitochondrial protein importation, often operating in tandem as described in previous expert papers and reviews [4, 7, 21–23].

The identification of the peroxisome proliferator-activated receptor gamma (PPARγ) co-activator 1-α protein (PGC-1α) as a transcriptional co-activator of NRF-1, GABP, and the PPARs led to the recognition that PGC-1α integrates physiological signals with mitochondrial biogenesis and oxidative metabolism [7]. This recognition of PGC-1α also led to the identification of related co-activators (PGC-1β and the PGC-1-related co-activator, PRC) encoded by the *Ppargc1a*, *Ppargc1b*, and *Pprc1* genes [23]. Other transcription factors, such as nuclear estrogen-related receptors (ERRs) operate along the same or related pathways [24]. Many aerobic tissues also express the orphan nuclear receptor ERRα, which regulates the machinery for fatty acid β-oxidation and is a PGC-1-α partner [25]. Other transcription factors are also important in the control of respiratory function and other genes of energy metabolism including the cyclic AMP response element binding protein (CREB) and the YY1 initiator binding factor, but details of their regulation are found elsewhere [26–31].

Among the nuclear-encoded regulatory genes for mitochondrial biogenesis are the proto-oncogene protein c-Myc and the myocyte-specific enhancer factor 2A (MEF2A) [32, 33]; the former is an activator of *Ppargc1b* (PGC-1β) and the latter, controlled in part by NRF-1, is a critical regulator of the oxidative capacity of skeletal and cardiac muscle [34–36]. MEF2A also activates growth factor and stress-induced genes and positively regulates cell growth and cell survival [36].

It has been increasingly appreciated that these elaborate and interactive bi-genomic transcriptional controls serve to match the mitochondrial mass and oxidative phenotype to the needs of various tissues, to changes in physiological environment, and to the need for organelle turnover in those tissues. Since mitochondrial biogenesis is controlled mainly at the level of transcription, the expression of the large number of requisite mitochondrial genes encoded in the nucleus must be synchronized with the few genes encoded in mitochondria. This bi-genomic coordination is achieved by nuclear-encoded mitochondrial proteins, including mitochondrial transcription factor A (TFAM), TFB1M, and TFB2M that control mtDNA transcription and replication and are synthesized in response to signals for mitochondrial biogenesis [3, 4].

Calcium and Mitochondrial Biogenesis

A great deal of work on the physiological induction of mitochondrial biogenesis, for instance in exercising muscle, has focused on the role of intracellular calcium (Ca^{2+}). Calcium stimulates mitochondrial biogenesis in mammalian skeletal and cardiac muscle [37–43], but the role of Ca^{2+} in mitochondrial biogenesis in non-contractile cells, including those of the immune system is not clear [44]. In the post-inflammatory induction of mitochondrial biogenesis, calcium/calmodulin is required for the activation of two nitric oxide synthase (NOS) isoforms involved in mitochondrial biogenesis, NOS3 [16] and NOS1 [45], but NOS2, which is Ca^{2+}-independent, is also a contributor [46].

In skeletal muscle, a Ca^{2+}-sensitive PKC pathway [37] along with Ca^{2+}-dependent regulation of nuclear genes for mitochondrial biogenesis have been found [40]. The calcium/calmodulin-dependent protein kinase (CaMK) family of serine/threonine kinases is involved in PGC-1 α regulation in skeletal muscle [43]. CaMK II [47, 48] and the Ca^{2+}-activated

phosphatase calcineurin (CaN) [39] are involved in combination with other processes that regulate muscle fiber plasticity [42].

Apart from CaMK II and CaN, mitogen-activated protein kinases (MAPK), for instance p38 [49] are activated by exercise, and certain p38 isoforms, such as p38γ (MAPK12), stimulate PGC-1α activity [50]. In the heart, p38 activates the nuclear peroxisome proliferator-activated receptor alpha (PPARα) through its PGC-1α co-activator [51]. In muscle (and fat) cells, the phosphorylation of ATF-2, a cyclic AMP response element binding (CREB) protein, activates PGC-1α gene expression [49, 52]. PGC-1α gene expression is also increased by MEF-2 binding to recognition sites on the promoter [35], and MEF2A and MEF2D in skeletal muscle contribute to regulation of the GLUT4 glucose transporter [41]. MEF2 also regulates Ca^{2+}-dependent gene expression in developing cardiac muscle, which is repressed by class II histone deacetylases (HDACs). HDAC5, for instance, dissociates from MEF2 after serine phosphorylation in response to Ca^{2+}, enabling transcriptional activation of PGC-1α in the heart [35]. Moreover, the MEF2/HDAC pathway is also linked by oxidative stress to pathological cardiac hypertrophy [53].

Physiologically, CaMK and CaN are activated by certain Ca^{2+} transients, specifically by prolonged transients befitting constant muscle stimulation, which promote nuclear translocation of transcription factors [54, 55] and activation of HDACs involved in muscle plasticity [55, 56]. Finally, these calcium signals interact in indistinct ways with ROS and NO in the control of muscle fiber phenotype [50].

Inflammation and Mitochondrial Biogenesis

During inflammation, the cell faces a unique set of challenges in the need to accelerate mitochondrial turnover. The first evidence of mitochondrial damage in inflamed tissues was reported some 40 years ago after the administration of bacterial lipopolysaccharide (LPS; endotoxin) and the experimental introduction of bacterial sepsis in animals [57–59]. Over the next decade or so, many post-inflammation abnormalities were reported in mitochondria in tissues such as liver, heart, and skeletal muscle including decreases in State 3 respiration, low respiratory control ratios, low rates of ATP synthesis, and cytochrome depletion. Similar effects were noted in hemorrhagic and cardiogenic shock, but a high degree of variably made it impossible to know whether these defects were caused primarily by LPS released from circulating bacteria, by secondary microbial or endogenous ligands, or by microcirculatory disturbances leading to tissue hypoxia or ischemia [60].

It was later recognized that mitochondria are susceptible to molecular damage from the actions of pro-inflammatory cytokines, like tumor necrosis factor alpha (TNF-α) and certain interleukins generated by innate immune cells including macrophages and Kupffer cells [61]. Damaged mitochondria generate high levels of reactive oxygen species (ROS) and release calcium and intrinsic apoptosis proteins during inflammation [62–64]. Moreover, rates of inflammatory ROS and NO production can be sufficient to compromise mitochondrial structure and function at the level of the respiratory chain, either by direct chemical oxidation of proteins and lipids or by the NO-superoxide reaction, which generates the powerful oxidant peroxynitrite (ONOO-) [65].

The prospect that the host response produces important cytotoxic effects on mitochondria, themselves likely ancient endosymbiotes, was bolstered in the 1990's by the discovery of an evolutionarily-conserved system of pattern-recognition receptors (PRRs) that recognize pathogen-associated molecular patterns or PAMPs shared by classes of pathogens and identified by higher eukaryotes as "non-self" [66–68]. PAMPs can be entire molecules such as LPS or small conserved motifs within a molecule recognized by the host innate immune system as components of a class of pathogens. The first human PRRs were identified by

cloning a human homolog of the Toll protein in *Drosophila* and the demonstration that it activates innate immunity through the classical NF-kB transcription factor pathway [66].

Toll-like receptors (TLR), located for instance on macrophages and many dendritic cells, recruit specific adaptor proteins, such as MyD88 and TRIF that initiate downstream signals for the synthesis of inflammatory cytokines, chemokines, antimicrobial peptides, and type I interferon [68]. TLR4 signaling through MyD88 to NF-kB is the most potent known LPS-response pathway and leads to rapid synthesis of TNF-α and interleukin-1 beta (IL-1β) and induction of nitric oxide synthase-2 (NOS2) [67]. Over-production of these and other effectors leads to mitochondrial damage that must be mitigated and corrected in the interest of cell survival. A minimal diagram of this idea is shown in Figure 2.

A dozen TLR family members (10 in the human) are known to operate on the plasma membrane or on the endosome to initiate the innate immune response to PAMPs from bacteria, fungi, parasites, and viruses. Early-phase cytokine and chemokine production promotes pathogen elimination by activation and recruitment of myeloid immune cells, such as neutrophils, macrophages, and lymphocytes to sites of infection, resulting in phagocytosis and stimulation of adaptive immune responses like antigen presentation and antibody production [69]. Roles for TLR signaling in dendritic cells, in somatic/structural cells, and in adaptive immunity [69], as well as the discovery of non-TLR PRRs, such as C-type lectin receptors, NOD-like and RIG-I-like receptors, and endogenous TLR activators generated by tissue damage all signify that this recognition system is more elaborate and ubiquitous than originally envisioned [70].

Despite these major advances, it remained unclear why hyper-activation of the acute inflammatory response did not consistently produce measurable mitochondrial damage, energy failure, or cell death despite evidence of organ dysfunction. Here, Figure 2 is deficient because it implies that post-inflammatory stress, mitochondrial damage and ATP limitation are isolated triggers for adaptive mitochondrial biogenesis, which builds in a lag in mitochondrial recovery that would predispose the cell to energy failure and apoptosis or necrosis. Moreover, no information existed on whether variable mitochondrial function simply involved stochastic differences in the degree of damage or reflected specific molecular mechanisms linking the immune system to mitochondrial damage, metabolic need, or mitochondrial quality control [71].

Severe inflammation induces ROS and NO stress in virtually all cell and animal models, but in pathological states, ROS are pro-inflammatory and activate NF-kB and other transcription factors that regulate inflammation [72, 73]. NF-kB activation by ROS is well known, often leading to enhanced TNF-α production, which further increases ROS production, for example by inflammatory and vascular cells [74, 75]. TNF-α is also a powerful catabolic agent, especially in skeletal muscle, where it inhibits respiration, mitochondrial biogenesis, and switching to the oxidative fiber phenotype [76]. In cardiomyocytes during inflammation, the NF-kB p65 subunit also appears to bind to the PGC-1α co-activator and block its activation of gene transcription [77].

Intense inflammation up-regulates many anti-oxidant defenses, but the transcriptional activity of both PGC-1α and NRF-1 also increases [78, 79]. PGC-1α promotes gene induction for certain ROS-detoxifying enzymes like mitochondrial superoxide dismutase (SOD2) and glutathione peroxidase-1 (GPx1), and data in neuronal cells suggest that CREB plays an important role in activating the *Pargc1a* (PGC-1α) gene promoter after oxidant exposure [78]. PGC-1α can also regulate myocardial SOD2 and thioredoxin (Trx2) expression and protect the heart against myocardial oxidative stress, hypertrophy, and contractile dysfunction (in mice) after transverse aortic banding [80]. Interestingly in

macrophages, PGC-1β over-expression inhibits canonical NF-kB-dependent cytokine production, which could allay an acute inflammatory stress [81].

TNF-α is of further interest because TNF-α receptor 1 (TNF-R1) binding amplifies NF-kB activity and cytokine production, which increases oxidative stress and may lead to cell necrosis [82]. On the other hand, NF-kB is pro-survival and activates anti-oxidant enzyme genes, including SOD2 [83], and NF-kB inhibition increases TNF-mediated apoptosis in part by allowing recruitment of the FAS-associating death domain-containing protein (FADD) to a death-inducing signaling complex (DISC) that triggers caspase-8 activation [82]. The cell can avert both forms of premature death by the proteolytic shedding of TNF-R1 [84].

The TNF-R1-TNF-α ligand also causes cytosolic Ca^{2+} release and increases mitochondrial Ca^{2+} uptake [85]. The latter stimulates both respiration and mitochondrial ROS generation [86] . In lung vascular cells, when SOD2 activity is high, Complex III peroxide leak rate increases, activating the TNF-α converting enzyme (TACE or Adam17), a metalloproteinase that cleaves TNF-R1, allowing the receptor to be shed and curtailing the TNF-α mediated inflammatory response [87].

The emphasis on protecting mitochondria against damage by immune mediators has not made a clear distinction between myeloid and somatic/structural cells, but the principles of protection are probably generalizable. For instance, the macrophage, a central immune cell, relies on respiration and tends to be resistant to apoptosis [88]. Macrophage apoptosis can be induced by certain microbes, especially bacteria, a disadvantage to the host by letting the organism survive. In other cases, macrophage apoptosis may amplify the immune response to infection [89]. Lymphocyte function, for example, the cytotoxicity of NK cells, also depends on respiration [90]. T cell function, including chemotaxis and cytotoxic T cell targeting [91, 92], is supported by respiration [93–95], and evidence indicates that mitochondrial dynamics support the formation of immunological synapses (IS) involving antigen-presenting cells and T helper cells [96, 97]. Mitochondrial re-localization to the IS maintains Ca^{2+} flux across the plasma membrane involved in T helper cell activation. Lymphocyte apoptosis is rapid and frequent in severe sepsis in lymphoid tissues and intestinal mucosa [98], as well as in lung endothelial and renal tubular cells [88]. Both the intrinsic and extrinsic apoptosis pathways contribute to lymphocyte depletion in sepsis, but the importance of mitochondrial quality control in the regulation, survival, and migration of various leukocytes and the clonal expansion of lymphocytes, is only now being explored.

In skeletal muscle, exaggerated local inflammatory reactions, higher circulating levels of TNF-α and IL-6, fiber damage, and muscle wasting occur during exercise in muscle-specific PGC-1α knockout mice [99–102]. In contrast, muscle-specific PGC-1α transgenic mice show preservation of mitochondrial function and muscle integrity with aging [103]. Increased skeletal muscle PGC-1α levels prevent muscle wasting by reducing apoptosis, autophagy, and proteasome activity. This preservation of muscle structure and function also slows the decline in bone density and reduces the chronic inflammation of aging. Some evidence implicates PGC-1α as a regulator of ROS generation, and *Ppargc1a* gene over-expression can suppress intracellular and mitochondrial ROS production induced by NF-kB activity and TNF-α in smooth muscle and endothelial cells [75].

In the liver, a role for TLR signaling in *Ppargc1a* and *Ppargc1b* gene expression in early *Staphylococcal aureus* peritonitis has been shown by the rapid up-regulation of hepatocyte *Ppargc1a* and *Ppargc1b* in wild type (WT) mice, whereas both genes are concordantly deregulated in $TLR2^{-/-}$ mice (not increased) and in $TLR4^{-/-}$ mice (highly increased) while PRC is up-regulated in all three strains [104]. *Ppargc1a* and *Ppargc1b* share microRNA

binding sites for mmu-mir-202-3p, and mir-202-3p-mediated mRNA degradation has been implicated in *Ppargc1a* and *Ppargc1b* co-regulation during inflammation.

In non-sterile inflammation in animals, especially lethal poly-microbial infections (e.g. cecal ligation/puncture), long periods of intense inflammation lead to overlapping cycles of tissue damage and repair, obscuring the timing and consistency of metabolic gene expression. In models where sub-lethal LPS or heat-inactivated *E. coli* is administered, the innate immune response is accompanied by increased gene expression for mitochondrial biogenesis followed by a wave of mitochondrial proliferation throughout the tissue, e.g. in the liver and the heart [12, 105]. In both surrogate and authentic infections, observations have provided clear morphological evidence of accelerated mitochondrial turnover involving autophagy and mitochondrial biogenesis, which within days restores mitochondrial mass in the survivors while mitigating cell death [12, 106–108].

In mice, sub-lethal, but damaging LPS exposure transiently depletes hepatic mtDNA content and impairs mitochondrial transcription [12]. In response, redox-responsive mechanisms such as NRF- 1 phosphorylation and nuclear translocation directed by Akt/PKB increase the gene expression for Tfam and other proteins of the mitochondrial transcriptome. After translation and mitochondrial importation of these proteins, mtDNA copy number is restored [109]. The initial loss of mtDNA content depends on TLR4 and NF-kB activation and TNF-α and NO production leading to mtDNA depletion. Genetic ablation of TLR4 reduces, but does not eliminate this effect, and the recovery of mtDNA copy number is delayed in TLR4 null mice [110]. The cell responds to mtDNA depletion with the induction of the base excision repair glycosylase OGG1 by NRF-1 and NRF-2 binding to *OGG1* promoter elements and mitochondrial importation of active enzyme [111]. Moreover, the loss of mtDNA copy number can be abrogated by increasing SOD2 in mitochondria, by inhibiting NOS activity, or by scavenging ONOO- [112].

Innate immune system activation by TLR2 and TLR4 ligands is involved in the early up-regulation of mitochondrial biogenesis [104, 110] through several transcription factors including NF-kB [113, 114], CREB [114], nuclear factor erythroid 2-related factor 2 (Nrf2) [115], and interferon response factors (IRF-3,IRF-7) [116]. TLR4-dependent activation of NF-kB and CREB co-regulate the *NRF1* promoter with NF-kB intronic enhancement leading to NRF-1 synthesis and nuclear translocation, followed by target gene expression [114]. This also requires mitochondrial H_2O_2 production and identifies NRF-1 as an early-phase component of the host defense regulated by TLR signaling and by redox state.

Another key regulator of energy metabolism, the serine/threonine kinase AMP-activated protein kinase (AMPK) [117–123], is activated by ATP depletion and stimulates glucose and lipid catabolism and blocks energy utilizing pathways such as protein and fatty acid biosynthesis [119]. AMPK promotes mitochondrial biogenesis [117, 118, 121], NO production [124, 125], regulates autophagy [126] and opposes inflammation by interfering with NF-κB–dependent cytokine expression [127–134]. Conversely, a decrease in AMPK activity is associated with increased inflammation. The mechanism of NF-kB inhibition is not clear, but this may occur indirectly through PGC-1α, Forkhead box O (FoxO) transcription factors, and sirtuin-1 (SIRT1) [23, 122, 135, 136].

SIRT1 is an NAD-dependent deacetylase that regulates energy homeostasis in response to changing nutrient availability [122, 137–140]. As nutrients are depleted, NAD^+ increases and enhances SIRT1 activity; this deacetylates PGC-1α and increases transcription of its target genes [141]. Hepatic SIRT1 regulates lipid homeostasis by positively regulating nuclear PPARα, which cooperates in PGC-1α activation and mediates adaptation to fasting and starvation [138, 142]. Hepatocyte-specific SIRT1 deletion blocks PPARα and decreases

β-oxidation, whereas SIRT1 over-expression induces PPARα target genes. Liver-specific SIRT1$^{-/-}$ mice develop steatosis, ER stress, and hepatic inflammation. SIRT1 thus not only regulates lipid homeostasis, but is anti-inflammatory in liver and fat cells, as well as in cells of the immune system [143]. Gene expression studies in peritoneal macrophages indicate that SIRT1 silencing increases pro-inflammatory genes while SIRT1 activation inhibits LPS-stimulated inflammation, including TNF-α production [144].

The transcriptional activity of nuclear hormone receptors, particularly estrogen-related receptor ERRα, is repressed by the nuclear receptor interacting protein-1 (RIP140) [145], which also suppresses metabolic gene expression and mitochondrial biogenesis [146]. In macrophages, RIP140 co-activates certain cytokine genes, and RIP140 deficiency leads to the inhibition of the inflammatory response [147]. RIP140 interacts with the RelA subunit of NF-kB and the histone acetylase CBP (CREB-binding protein) and cooperates with CBP co-activator complex on RelA-regulated promoters. RIP140 modulation of inflammatory gene expression is thus a nice example of the cell-specific integration of control pathways for metabolism and inflammation [147].

Mitochondria and the Inflammasome

Many host danger-signals, infection and tissue damage included, lead to the assembly of inflammasomes needed for fully-developed tissue inflammation. The NLRP3 inflammasome and caspase-1 (and caspase-11 in mice) are required to generate IL-1β by the cleavage of its pro-form, and assembly of the NLRP3 inflammasome also influences metabolic pathways such as glycolysis and lipogenesis. Mitochondrial ROS production can activate the NLRP3 inflammasome, whereas removal of damaged or dysfunctional mitochondria by autophagy negatively regulates the NLRP3 inflammasome. Two lines of evidence suggest mitochondria as the main source of ROS for NLRP3 inflammasome activation and a signal-integrating organelle for inflammasome activation [148–150]. In macrophages, inflammasome activation is impaired by inactivation of the outer membrane voltage dependent anion channel, VDAC, or by depletion of mitochondrial DNA [150]. Complex I inhibitor, rotenone, and Complex III inhibitor, antimycin A, also activate the NLRP3 inflammasome [149].

To avoid destructive inflammation, the cell removes ROS-generating mitochondria by a specialized form of autophagy called mitophagy [151]. Inhibition of mitophagy leads to the retention of ROS-generating mitochondria and activation of the NLRP3 inflammasome [149, 150]. ROS-producing mitochondria removed by mitophagy must be replaced through mitochondrial biogenesis in order to avoid persistent inflammasome activation, chronic inflammation, and energy failure. In chronic conditions that display mitochondrial dysfunction, including certain neurodegenerative diseases, cancers, and cardiovascular diseases, understanding the links between inflammation, mitochondrial biogenesis, and metabolism, is important because malfunctions of any of the regulatory branches may be a root cause of disease.

Mitochondrial Biogenesis, Anti-oxidation, and Counter-inflammation

In addition to roles for innate immune activation and subsequent redox stress in up-regulating mitochondrial biogenesis, the transcriptional network coordinately up-regulates mitochondrial anti-oxidant and anti-apoptotic genes along with specific counter-inflammatory genes. Eukaryote cells balance ROS production with anti-oxidant enzyme activity to maintain redox homeostasis. Many anti-oxidant enzyme genes are regulated by the Nrf2 transcription factor through Keap1, a redox-sensitive cytosolic adaptor protein for a cullin-based ubiquitin ligase that targets Nrf2 for proteasomal degradation and prevention of Nrf2-dependent gene expression [152]. A mitochondrial Keap1-binding protein, PGAM5, a

phosphoglycerate mutase (PGM) family member has been identified that is targeted to the outer mitochondrial membrane by an N-terminal localization sequence. PGAM5 has no PGM activity, but forms a ternary complex with Keap1 and Nrf2 in which a Keap1 dimer simultaneously binds PGAM5 and Nrf2 through conserved E (S/T) GE motifs [153]. Knockdown of either Keap1 or PGAM5 activates Nrf2-dependent gene expression.

Nrf2 binds to antioxidant response elements (ARE) in the promoter regions of xenobiotic- and oxidative stress-responsive genes, including heme oxygenase-1 (HO-1; *Hmox1*) [154]. HO-1 scavenges toxic heme, generates physiological carbon monoxide (CO), and increases the cellular iron-handling defenses [155]. HO-1 induction mainly through Nrf2 protects against inflammation, oxidative stress, heavy metals, and many other stresses [152, 156]. Most electrophiles and oxidants, including the pro-oxidant effects of CO, activate Nrf2, leading to the amplification of ARE-containing genes, including *Nrf2* itself [157]. In the heart, HO-1 stimulates mitochondrial biogenesis and protects against the progressive toxic cardiomyopathy of the anthracycline chemotherapeutic drug, doxorubicin [158]. This agent disrupts mitochondrial biogenesis and causes intrinsic apoptosis, necrosis, inflammation, and myocardial fibrosis that can be prevented by low level CO administration or by over-expression of active HO-1 [158].

The role of HO-1 in the induction of mitochondrial biogenesis, e.g. in cardiac myocytes, requires CO production [159]. HO-1 activity increases endogenous CO levels and stimulates SOD2 up-regulation and mitochondrial H_2O_2 production, which activates Akt/PKB and deactivates glycogen synthase kinase-3β, permitting Nrf2 nuclear translocation and occupancy of AREs in the NRF-1 promoter [160]. This is the first clear transcriptional mechanism for the expansion of cardiac mitochondrial mass linked to inducible xenobiotic and antioxidant defenses.

HO-1 induction by inflammation, for instance by LPS, is associated not only with the induction of mitochondrial biogenesis, but with subsequent counter-inflammatory and anti-apoptotic responses mediated in part by anti-inflammatory cytokines such as IL-10 [161], and anti-apoptotic proteins such as Bcl_{XL} [162]. HO-1 promotes the expression of IL-1 receptor antagonist (IL-1Ra), and suppressor of cytokine synthesis-3 (SOCS3) [115]. Mechanistically, HO-1 acting through CO enables the Nrf2, Gabpa, and MEF2 transcription factors to bind to the *IL10* promoter and NRF-1 and MEF2 to bind to the *IL1Ra* promoter. In liver cells and in macrophages, RNA silencing of either *Nrf2* or *Hmox1* blocks IL-10 and IL-1Ra up-regulation, and post-inflammatory hepatic HO-1 induction fails in $Nrf2^{-/-}$ mice.

In short, mitochondrial ROS generate signals that lead to Nrf2 activation and HO-1 induction and result in co-induction of genes for mitochondrial biogenesis and counter-inflammation. This information together with the work above showing that PPARs, PCG-1 proteins, AMPK, and SIRT1 have anti-inflammatory effects implicates mitochondrial biogenesis in connecting the cell's anti-oxidant, anti-apoptotic, and counter-inflammatory defenses to cell metabolism into an integrated regulatory transcriptional network (Figure 3).

Mitochondrial Biogenesis and Cell Survival and Repair during Inflammation

Cell substrate metabolism is implicitly linked to survival under both homeostatic and conditions involving high energy demands, implying the existence of common regulatory processes. Nutrient and oxygen availability also determine the competency of the cell to proliferate and differentiate as well as to avoid programmed cell death in the face of imminent cytotoxic threats. The cell normally maintains a high ratio of ATP/ADP/AMP, and a rising AMP/ATP is a sensitive indicator of impending energy limitation that triggers AMPK activation, which blocks ATP-consuming pathways and switches on ATP-generating pathways [119].

AMPK blocks the mTOR pathway [163], a central growth regulator responsive to mitogens and carbon substrate [164] by phosphorylating the TSC2 (hamartin) tumor suppressor, which co-operates with TSC1 (tuberin) [163]. Signaling by mTOR is activated by the Akt/PKB survival kinase, which phosphorylates and inactivates TSC2 [165]. Akt/PKB promotes mitochondrial biogenesis through NRF-1 phosphorylation and nuclear translocation [79] and supports cell survival in part by increasing mitochondrial hexokinase (HK) activity, committing glucose to glucose-6-phosphate using ATP generated by mitochondria and thereby coupling glycolysis to oxidative phosphorylation [166]. This may be the tip of an iceberg for convergence of nutrient sensing with survival signaling.

These survival pathways also impinge on proteins involved in programmed cell death. For instance, the pro-apoptotic function of BAD, a BH3-only domain pro-apoptotic member of the Bcl-2 family is normally inactivated by phosphorylation by survival kinases resulting in cytoplasmic localization [167]. At the mitochondrion, BAD is involved in the assembly of a large protein complex that also catalyzes the first step of glycolysis through HK-4 activity (glucokinase). The absence of BAD restricts respiration in response to glucose, while glucose deprivation leads to BAD dephosphorylation and apoptosis [168]. These findings too highlight the interplay between energy metabolism and regulation of apoptosis.

It would seem self-evident that apposite regulation of mitochondrial biogenesis is pro-survival, but pathological acceleration of mitochondrial biogenesis may imply mitochondrial incompetence [169]. Although interference with mitochondrial biogenesis usually exacerbates inflammation and promotes oxidation and apoptosis, the need to support rapid mitochondrial turnover due to continual mitochondrial damage increases the likelihood of immune suppression by the production of counter-inflammatory mediators, as mentioned for IL-10 [170, 171]. Although greater than normal immune tolerance during periods of active mitochondrial biogenesis should improve the fidelity of the bi-genomic program, actual immune suppression is often encountered in patients recovering from severe sepsis [172–174]. This so-called immune paralysis puts patients at risk for recurrent and secondary infections after their initial episode of sepsis. Still, there is unexplored therapeutic potential for agents to activate mitochondrial biogenesis and allied metabolic pathways in the resolution of dangerous immunological reactions to serious infections [175].

The key events are diagrammed in Figure 4, where a scale-free time profile of mitochondrial damage and recovery is interposed between an acute inflammatory response and a long period of immune suppression. The figure sets out the usual nomenclature for the initial state of innate immune hyper-activation and the period of immune suppression following serious infections, but in practice, the situation is rarely so clear cut.

Summary and Conclusions

Activation of the innate immune response leads to rapid synthesis and release of soluble mediators that establish competency of the innate and adaptive immune systems, but a hyperactive response compromises mitochondrial function and cell metabolism both in long-lived leukocytes and in somatic cells. The over-production of effectors like TNF-α and IL-1β promotes oxidative stress, NO over-production, and calcium deregulation that injure mitochondria and initiate cycles of mitochondrial damage, cell death, and deregulation of inflammation. In response, the recovering cell induces mitochondrial biogenesis, removes damaged mitochondria by autophagy, and up-regulates anti-oxidant and counter-inflammatory defense genes. This multifaceted protective system involves a highly-integrated nuclear transcriptional network controlled by energy-sensing and inflammation- and redox-sensitive transcription factors and co-activators involved in mitochondrial biogenesis, anti-oxidant enzyme induction, cell survival, and immune tolerance as illustrated

in the graphical abstract for this paper. These mechanisms support mitochondrial function and minimize cell death and organ dysfunction until the agent of inflammation can be brought under control.

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Highlights

- The innate immune response triggers a cycle of oxidative mitochondrial damage
- The host cell activates the transcriptional program for mitochondrial biogenesis
- The program concurrently activates anti-oxidant and anti-inflammatory defense genes
- This network limits metabolic failure and apoptosis and promotes immune tolerance

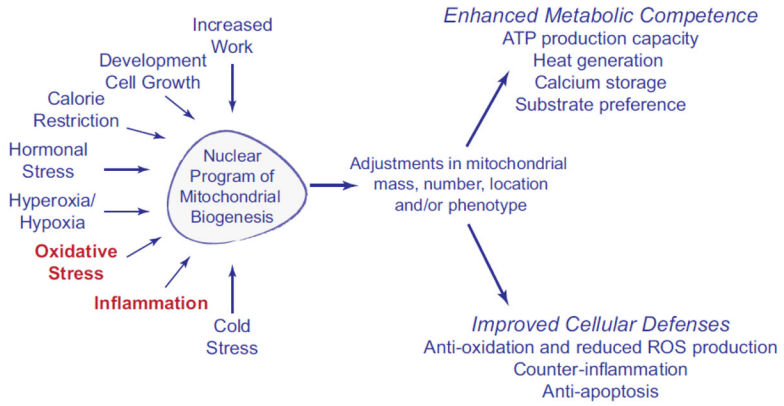


Figure 1.
The major physiological factors that are known to activate mitochondrial biogenesis and potential downstream effects on various mitochondrial functions.

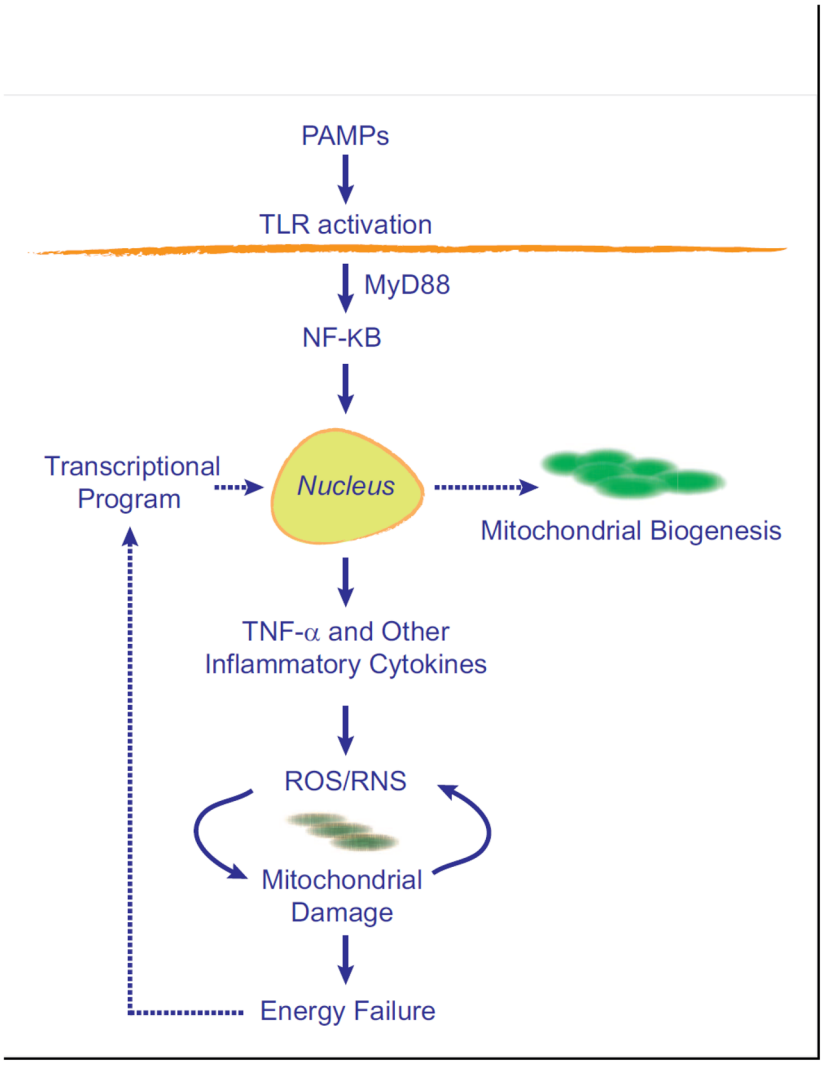


Figure 2.
A simplified concept of the induction of mitochondrial biogenesis by activation of the innate immune system. The production of pro-inflammatory cytokines creates a cycle of oxidative stress that causes mitochondrial damage and initiates retrograde signals for the transcriptional activation of mitochondrial biogenesis.

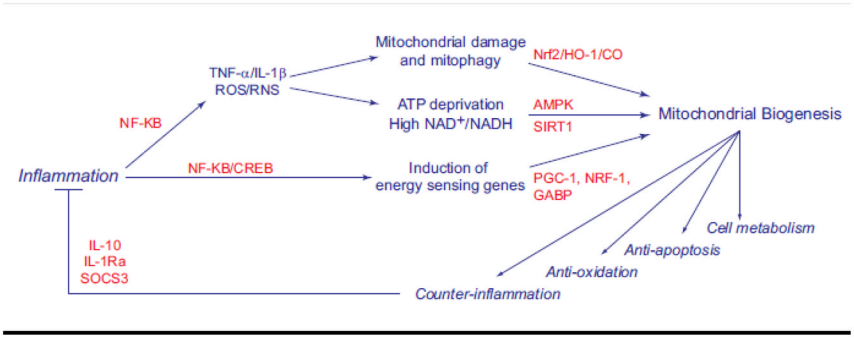


Figure 3.
Interrelationships among the innate immune response, oxidative mitochondrial damage and the induction of mitochondrial biogenesis, counter-inflammation, and the anti-oxidant defenses.

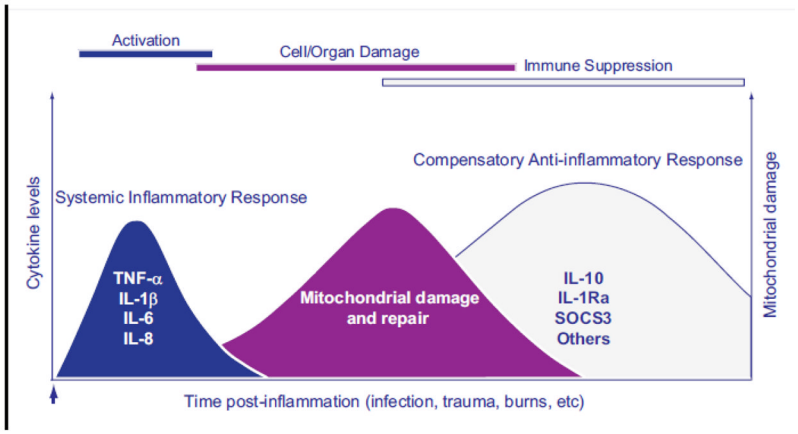
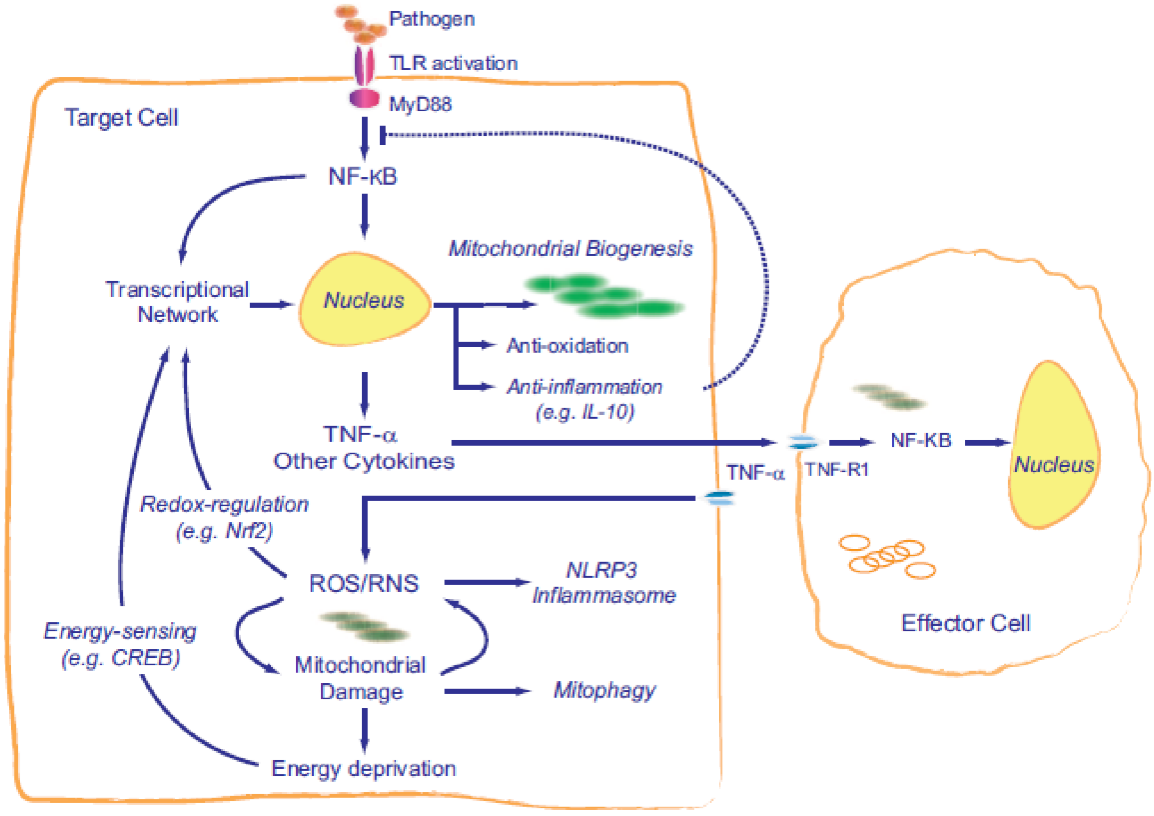


Figure 4.

A mitochondrial damage and recovery profile interposed on a hypothetical timeline between an acute inflammatory insult and a subsequent period of immune suppression. The diagram indicates the nomenclature for the systemic inflammatory response and the compensatory anti-inflammatory response used most conspicuously in bacterial sepsis to describe hyper-activation of innate immunity followed by an extended period of immune suppression. The risk of secondary or recurrent infection is increased during the period of immune suppression.



Graphical abstract.