Review

Emerging functional cross-talk between the Keap1-Nrf2 system and mitochondria

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Nuclear factor erythroid-derived 2-related factor 2 (Nrf2) was originally identified as a positive regulator of drug detoxifying enzyme gene expression during exposure to environmental electrophiles. Currently, Nrf2 is known to regulate the expression of hundreds of cytoprotective genes to counteract endogenously or exogenously generated oxidative stress. Furthermore, when activated in human tumors by somatic mutations, Nrf2 confers growth advantages and chemoresistance by regulating genes involved in various processes such as the pentose phosphate pathway and nucleotide synthesis in addition to antioxidant proteins. Interestingly, increasing evidence shows that Nrf2 is associated with mitochondrial biogenesis during environmental stresses in certain tissues such as the heart. Furthermore, SKN-1, a functional homolog of Nrf2 in *C. elegans*, is activated by mitochondrial reactive oxygen species and extends life span by promoting mitochondrial homeostasis (i.e., mitohormesis). Similarly, Nrf2 activation was recently observed in the heart of *surfeit locus protein 1* (*Surf1*) -/- mice in which cellular respiration was decreased due to cytochrome c oxidase defects. In this review, we critically examine the relationship between Nrf2 and mitochondria and argue that the Nrf2 stress pathway intimately communicates with mitochondria to maintain cellular homeostasis during oxidative stress.

***Key Words*:** **mitochondria, Nrf2, heme oxygenase-1, p62, NRF-1**

Mitochondria are multifunctional organelles within the cell. Mitochondria generate energy by cellular respiration (i.e., normally 90% of cellular ATP) and also serve as an integrative platform for various intracellular signaling pathways such as apoptosis and the immune and inflammatory responses.[(1)] Mitochondria are also the major source of reactive oxygen species (ROS) and play an integral role in the determination of apoptosis or survival upon stress exposure.[(2)] Mitochondria possess their own genome, and human mitochondria contain 37 genes of which all of the 13 protein-coding genes encode oxidative phosphorylation machinery subunits.[(3)] However, as most mitochondrial proteins are encoded in the nuclear genome, communication between the mitochondria and nucleus is fundamental to maintain cellular homeostasis against various stresses.[(3)] Recently, a concept of mitohormesis that was increasingly dissected in many model organisms showed that the mild alteration of the mitochondrial function activates the mitochondrial retrograde signaling, leading to the prolonged mean life span.[(4)]

The Keap1-Nrf2 system was identified as a master regulator of drug detoxification and oxidative stress responses and is critical for cell survival against oxidative stress.[(5)] Therefore, a functional link between the Keap1-Nrf2 system and mitochondria is expected. Consistent with this idea, accumulating evidence suggests the existence of extensive protein interaction networks between the Keap1-Nrf2 system and the components of apoptotic signaling cascades. Furthermore, recent evidence has revealed various types of cross-talk between the Keap1-Nrf2 system and mitochondria.

The Keap1-Nrf2 System Regulates a Battery of Detoxification Enzymes and Antioxidant Proteins in Detoxification Organs

Nrf2 (nuclear factor erythroid-derived 2-related factor 2) belongs to the CNC (Cap'n'collar) transcription factor family, which is characterized by a highly conserved CNC domain and a basic region leucine-zipper (b-Zip) structure (Fig. 1A).[(5)] Nrf2 is ubiquitously expressed but is expressed at relatively higher levels in organs that interface with the environment such as the lungs and small intestine.[(6)] Nrf2 plays an important role in detoxifying environmental toxins by up-regulating a set of detoxification enzymes and antioxidant proteins (Fig. 1B).[(5)] In non-stressed cells, Nrf2 is rapidly degraded by the kelch-like ECH-associated protein 1 (Keap1)-mediated ubiquitin proteasome system (Fig. 1C and D).[(5)] Keap1 enhances Nrf2 degradation by acting as an adaptor protein for the Nrf2 and Cullin3-Rbx1 E3 ubiquitin ligase complex. Upon exposure to oxidative stress or electrophiles, Nrf2 translocates to the nucleus where it binds to antioxidant responsive elements (ARE) via heterodimerization with small Maf proteins and activates the expression of more than a hundred target genes, including drug detoxifying enzymes such as glutathione *S*-transferases or antioxidant proteins such as heme oxygenase-1 (HO-1) and thioredoxin (Fig. 1B).[(5)]

Keap1-Nrf2-centered Protein–protein Interaction Map Suggests an Important Role for the Keap1-Nrf2 System in Mitochondrial Function

Keap1 was identified in a yeast two-hybrid screen as a factor that binds to the regulatory Neh2 domain of Nrf2 (Fig. 1A).[(7)] Subsequently, we have demonstrated by yeast reverse-two-hybrid screening that the ETGE motif within the Neh2 domain of Nrf2 is essential for Nrf2-Keap1 binding.[(8)] Another weak binding motif, called the DLG motif, was identified as a motif that was further upstream of the ETGE motifs in the Neh2 domain.[(9)] The Keap1 dimer binds Nrf2 via the DLG and ETGE motifs of Nrf2, which leads to the proteasomal degradation of Nrf2 in unstressed conditions (the two-site recognition mechanism).[(5)] Oxidative stress and electrophiles cause the oxidation of cysteine residues in Keap1, leading to a conformational change in Keap1 and the inhibition of Nrf2 ubiquitination and degradation. This mechanism explains how environmental toxins are sensed by the Keap1-Nrf2 system in

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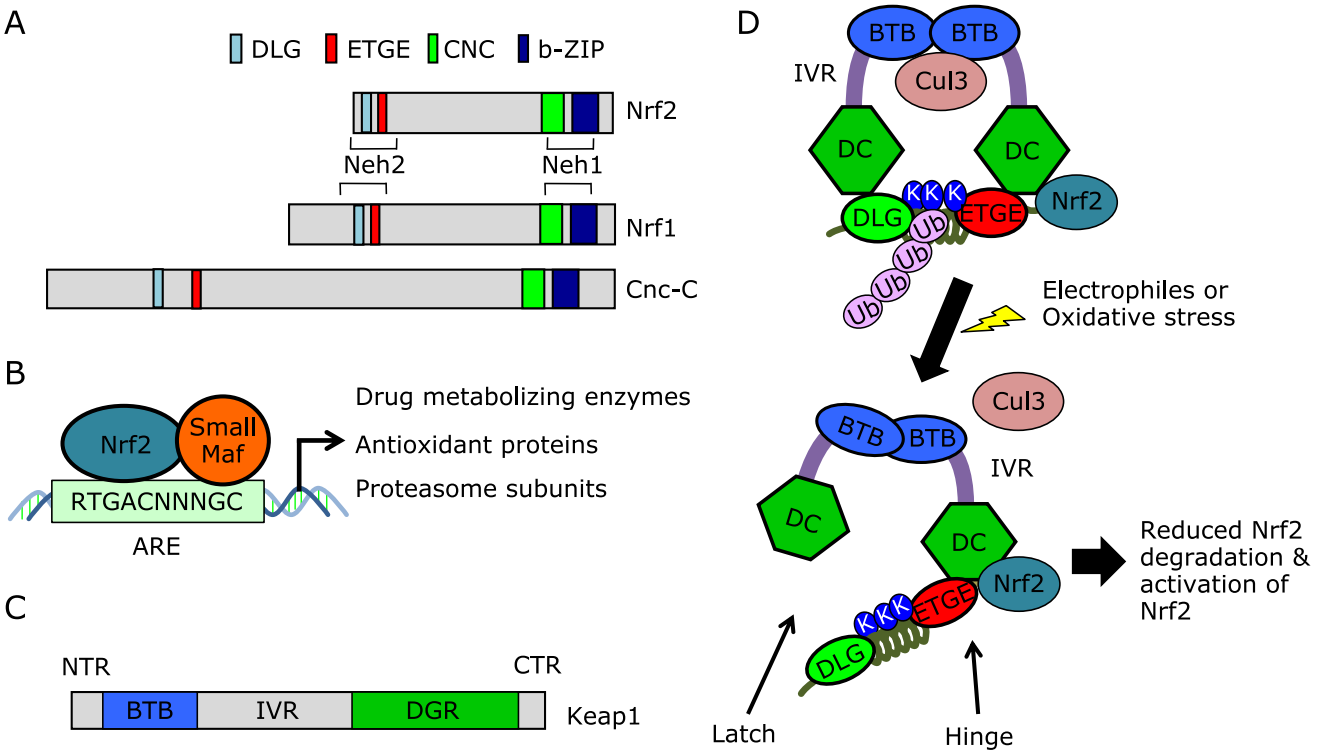

Fig. 1. Keap1-Nrf2 stress response system. (A) Schematic domain structures of Nrf2 and Nrf2-related proteins. Nrf2 possesses six evolutionarily conserved domains called Neh (Nrf2 ECH homology) 1–6 (only Neh1 and Neh2 are shown in the figure). The Neh2 domain is a regulatory domain of Nrf2 and contains ETGE and DLG motifs. Both motifs are conserved in Nrf1, which is another member of the CNC protein family, and Cnc-C, a *Drosophila* Nrf2 homolog. (B) Nrf2 heterodimerizes with small Maf proteins and binds to antioxidant-responsive elements (AREs). (C) Schematic domain structures of Keap1. Keap1 shows structural similarity to the *Drosophila* protein Kelch and has two canonical protein interaction domains, BTB (bric-a-brac, tramtrack, broad complex) and Kelch (also called double glycine-repeat, DGR). CTR, C-terminal region; IVR, intervening region; NTR, N-terminal region. (D) Schematic representation of the Nrf2-activation mechanism. Together, the DGR and CTR of Keap1 comprise a six-bladed β-propeller structure shown as DC (DGR, CTR). Keap1 homodimerizes via its BTB domain and binds to the ETGE and DLG motifs of the Nrf2 Neh2 domain. The ETGE and DLG motifs are high- and low-affinity binding sites, respectively, for Keap1. The lysine residues (K) that are ubiquitinated localize to one side of the intervening α-helix, enhancing Keap1-mediated ubiquitination. During oxidative stress, reactive cysteines in Keap1 are oxidized, leading to conformational changes in Keap1. As a result, only binding via the low-affinity site is disrupted or the Cul3 interaction with Keap1 is disrupted leading to the inhibition of Nrf2 ubiquitination. Ub; ubiquitin.

detoxification organs such as the liver and intestine. Subsequent analysis demonstrated the existence of ETGE-like motifs in several other proteins, including prothymosin-α, phosphoglycerate mutase family member 5, inhibitor of kappaB kinase β and p62, mediating their interaction with Keap1 (Fig. 2).[10–14] Furthermore, Keap1 also interacts with Bcl-2 in an ETGE-independent manner.[15] Interestingly, all these proteins are involved in the mitochondrial regulation of apoptosis or in the maintenance of mitochondrial integrity and function. This extensive protein interaction between the Keap1-Nrf2 system and the mitochondria suggests extensive cross-talk between these entities.

Roles of Nrf2 in Mitochondrial Function and Quality Control

The emerging roles of Nrf2 target genes in mitochondrial function and quality control. (a) Sqstm1/p62 (hereafter called p62) was first identified as an electrophile-inducible gene in mouse macrophages, and its expression is regulated in an Nrf2-dependent manner during oxidative stress.[16,17] p62 is a multi-functional protein that functions as a selective autophagy adaptor such as xenophagy and mitophagy.[18,19] In addition to being a target gene of Nrf2, p62 was identified as an activator of Nrf2, thus forming a positive feedback loop.[20] An STGE motif in the Keap1-interacting region of p62 has lower affinity for Keap1 compared with the Nrf2 ETGE motif.[21] However, this affinity markedly increases upon the serine phosphorylation of the p62 STGE motif by mTOR, leading to the activation of Nrf2 during selective autophagy.[22] Regarding mitochondrial function, *p62*-knockout (KO) mice show a rapid decline in mitochondrial function with age and present an accelerated aging phenotype that is accompanied by oxidative stress.[23] In addition, p62 localizes to the mitochondria and plays a protective role by enhancing the translocation of mitochondrial transcription factor A (TFAM), a critical regulator of mitochondrial transcription and mitochondrial DNA replication, to the mitochondria.[24,25]

(b) HO-1 catalyzes the conversion of heme into biliverdin, iron and carbon monoxide (CO). *HO-1* gene expression is up-regulated in response to the substrate heme as well as to various environmental stressors such as cadmium, lipopolysaccharide, nitric oxide (NO) and oxidative stress.[26] CO binds to the reduced heme of cytochrome c oxidase (COX) and inhibits cellular respiration and generates hydrogen peroxide.[27,28] Thus, CO provokes the ROS-mediated activation of nuclear respiratory factor 1 (NRF-1), which induces mitochondrial biogenesis (also discussed later).[29]

(c) NAD(P)H dehydrogenase quinone 1 (NQO1) catalyzes the two-electron reduction of quinones into hydroquinones.[30] NQO1 knockdown decreases mitochondrial membrane potential ($\Delta\Psi_m$) and increases oxidant levels in HCT116 colon carcinoma cells.[23] Furthermore, NQO1 rescues the decreased $\Delta\Psi_m$ and ROS generation induced by p62 and Nrf2 knockdown.

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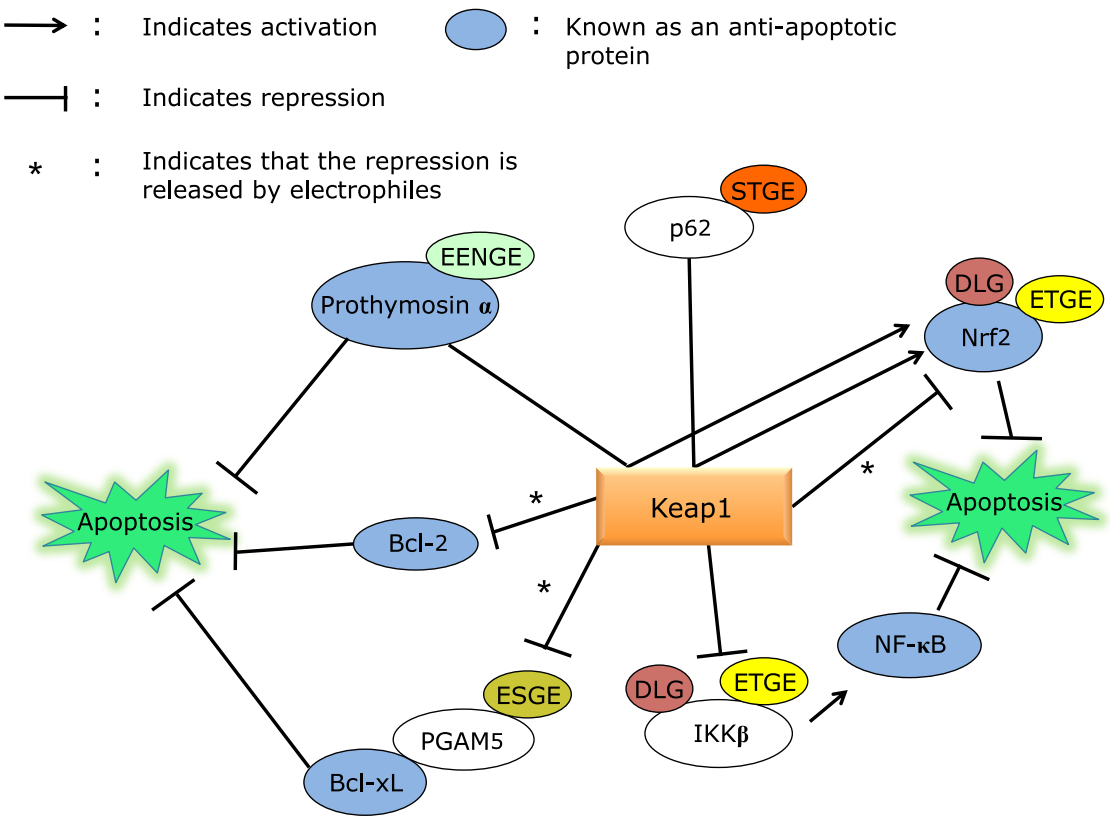

Fig. 2. Keap1 interaction with mitochondria-related proteins. Arrows in the figure indicate activation. For example, p62 and prothymosin α activate Nrf2 by competitively binding to Keap1 via their ETGE-related motifs. See text for details.

Table 1. Nrf2-mediated mitochondrial biogenesis

Signals	Indispensable factors other than Nrf2	Tissue or cells	Effect of mitochondrial biogenesis	References
HO-1 overexpression	PI3K, Akt	HL-1 mouse cardiomyocytes	Protection against doxorubicin toxicity	32
S. aureus insufflation	NA	Mouse lung (especially AT2 cells)	Anti-inflammation, cell protection	34
Exogenous CO inhalation	Akt	Mouse liver	Anti-inflammation	35
ALCAR	MEK	Rat primary hippocampal cells	Anti-apoptosis	39
NO (SNAP)	HO-1	HepG2, mouse liver	NA	40
Resveratrol	eNOS (NO), sGC (cGMP), HO-1 (CO), Akt	HepG2	NA	40

eNOS; endothelial nitric oxide synthase, sGC; soluble guanylate cyclase, SNAP; S-nitroso-*N*-acetylpenicillamine, AT2; alveolar type 2, NA; not analyzed.

Nrf2 regulates mitochondrial biogenesis and cellular respiration.

A role for Nrf2 in mitochondrial biogenesis. In mammals, mitochondrial biogenesis is regulated by several key factors, including peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α) and NRF-1, which cooperatively activate mitochondrial biogenesis.[31] Several recent findings indicate that Nrf2 is also involved in mitochondrial biogenesis (summarized in Table 1). Pioneering work by Piantadosi *et al.*[32] showed that HO-1 overexpression, which leads to CO generation, activates *NRF-1* transcription in an Nrf2-dependent manner (Fig. 3). In this cascade, CO-induced H_2O_2 leads to the activation of the PI3K-AKT pathway, activating Nrf2, which directly binds to the AREs in the *NRF-1* gene promoter.[32] Therefore, Nrf2 is indispensable for HO-1/CO-mediated mitochondrial biogenesis. AKT also phosphorylates NRF-1, which promotes NRF-1 nuclear translocation.[33] Since the work by Piantadosi *et al.*[32,33], Nrf2-mediated mitochondrial biogenesis has been demonstrated in several *in vivo* studies.[34,35,39,40] Using mitochondrial reporter mice (mt-COX8-GFP mice), Athale *et al.*[34] demonstrated that mitochondrial biogenesis was activated in the lungs (bronchial and alveolar type II epithelial cells) after *S. aureus* insufflation, which was associated with *NRF-1* and *TFAM* induction. This response was impaired in the lungs of *Nrf2* KO mice, leading to enhanced inflammation. Another study by MacGarvey *et al.*[35] demonstrated that inhaled CO activated mitochondrial biogenesis in the mouse liver and prevented lethality from *S. aureus* sepsis in an Nrf2- and AKT-dependent manner. Exposure to mild-to-moderate hypoxic conditions, including hypobaric hypoxia that mimics hypoxia at high altitudes, causes excitotoxicity and mitochondria-mediated apoptosis in hippocampal neurons, leading to cognitive impairment.[36] Acetyl-L-carnitine (ALCAR) confers neuroprotection after exposure to hypobaric hypoxia by increasing tropomyosin receptor kinase A (TrkA)-dependent Nrf2 activation in the rat

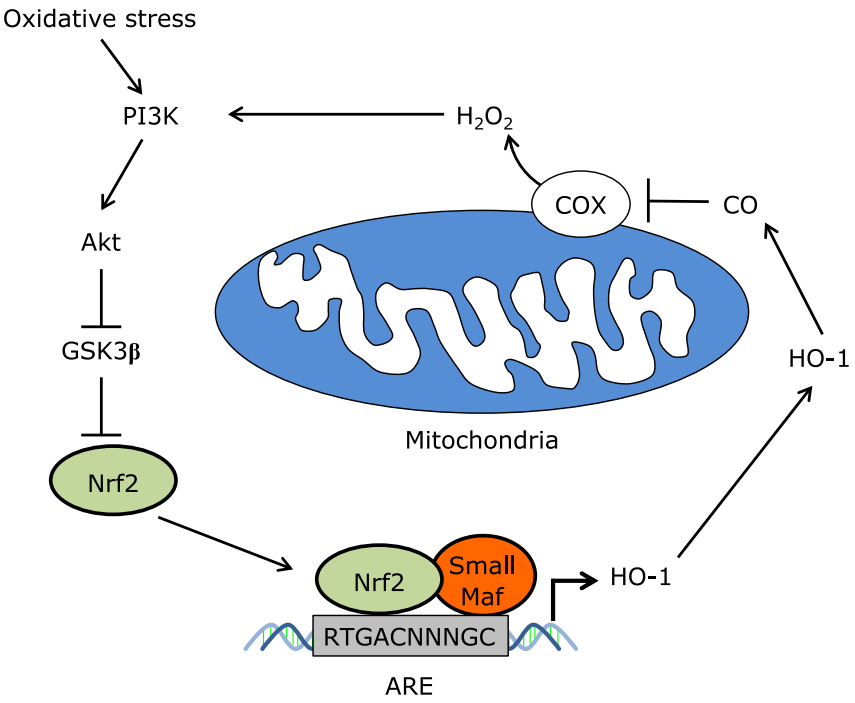

Fig. 3. Hypothetical mitochondrial retrograde signals that activate Nrf2. In specific cell types such as cardiomyocytes, HO-1-mediated CO production activates Nrf2 via the generation of H_2O_2 from the mitochondria. GSK3β is known to inhibit Nrf2 via β-TrCP-mediated degradation or Fyn-mediated nuclear export.[68,69] H_2O_2 activates the PI3K-AKT pathway and inhibits GSK3β to activate Nrf2. COX; cytochrome c oxidase, GSK3β; glycogen synthase kinase-3β.

hippocampus,[37] consistent with our previous finding that the NGF-TrkA pathway regulates Nrf2 activity in rat PC12 cells.[38] Hota *et al.*[39] demonstrated that ALCAR causes mitochondrial biogenesis by activating the Nrf2-NRF-1 cascade in an ERK1/2-dependent manner and argued that neuroprotection by ALCAR was due to intracellular calcium buffering in the mitochondria. Recently, Kim *et al.*[40] demonstrated that NO and resveratrol activate mitochondrial biogenesis in an Nrf2-dependent manner via a complex signaling cascade involving *HO-1* induction. These researchers also demonstrated that resveratrol activates mitochondrial biogenesis in the liver in an HO-1-dependent manner during an LPS sepsis model; however, Nrf2 dependence was not analyzed.[40]

A role for Nrf2 in oxidative phosphorylation. Nrf2 involvement in cellular respiration was first described by Kim *et al.*[41] who showed that Nrf2 knockdown in the human colon tumor cell lines HT29 and HCT116 cells reduces cellular O_2 consumption and cellular ATP levels, leading to the inhibition of HIF1α activation by hypoxia; however, the underlying mechanism still remains unknown. Recently, cultured neurons derived from *Nrf2* KO mice have been shown to have lower $\Delta\Psi_m$ and cytosolic ATP levels.[42] In normal healthy cells, $\Delta\Psi_m$ is maintained by cellular respiration; however, in *Nrf2* KO neurons, $\Delta\Psi_m$ is maintained by the reverse reaction of ATP synthase using ATP, which is partially compensated by increased glycolysis, indicating a respiration defect is present in the cells. Consistently, *Nrf2* KO MEFs show decreased basal O_2 consumption, and *Nrf2* KO neurons cannot increase respiration and hyperpolarize the mitochondria in response to malate/pyruvate, which increases the levels of the complex I substrate NADH or the complex II substrate methyl-succinate. Furthermore, mitochondria isolated from *Nrf2* KO brains or livers demonstrate decreased state 4 respiration in the presence of malate or succinate, a decreased respiratory control ratio (state 3/state 4; a conventional measure of coupling of oxygen consumption to phosphorylation) and a decreased ADP/O ratio (i.e., the ratio of ADP to oxygen consumed for ATP synthesis). In addition, the oxygen consumption rate induced by malate and succinate is decreased in *Nrf2* KO mitochondria as observed in the intact cells. NADH and $FADH_2$ recovery after the treatment with mitochondrial uncoupler followed by ETC inhibitor is delayed in *Nrf2* KO MEFs compared with wild-type MEFs, indicating a delay in NADH and $FADH_2$ generation. Consistently, mitochondrial NADH pool was decreased in the *Nrf2* KO MEFs compared with wild-type MEFs. The activities of respiratory chain enzymes in the brain are not different from wild-type mice; therefore, the authors argued that the availability of respiratory substrates is decreased in *Nrf2* KO mitochondria. Consistent with the above observation, $FADH_2$ generation from free fatty acids is reduced in the MEF, liver and heart mitochondria isolated form *Nrf2* KO mice.[43]

Mitochondrial Retrograde Signaling Regulates Nrf2 Activity during Oxidative Stress

A permissive signal from the mitochondria for the Nrf2-HO-1 cascade. Nrf2-dependent HO-1 expression upon oxidative stress was previously demonstrated to require a permissive signal from the mitochondria.[44] In this study, the authors demonstrated that the mitochondria-targeted thiol-reactive compound, IBTP [(4-iodobutyl)triphenylphosphonium], inhibited heme- and iodoacetamide-induced HO-1 expression without affecting mitochondrial ROS production and membrane potential, thus arguing for the existence of IBTP-sensitive permissive signals from the mitochondria downstream of ROS production. Mutations in the *PTEN-induced putative kinase 1* (*PINK1*) and *Parkin* genes cause autosomal-recessive forms of Parkinson's disease (PD).[45] The PINK1-Parkin pathway plays an important role in mitochondrial quality control by sensing mitochondrial damage and subsequently inducing mitophagy of the damaged mitochondria.[46] TNF receptor-associated protein 1 (TRAP1) is a downstream

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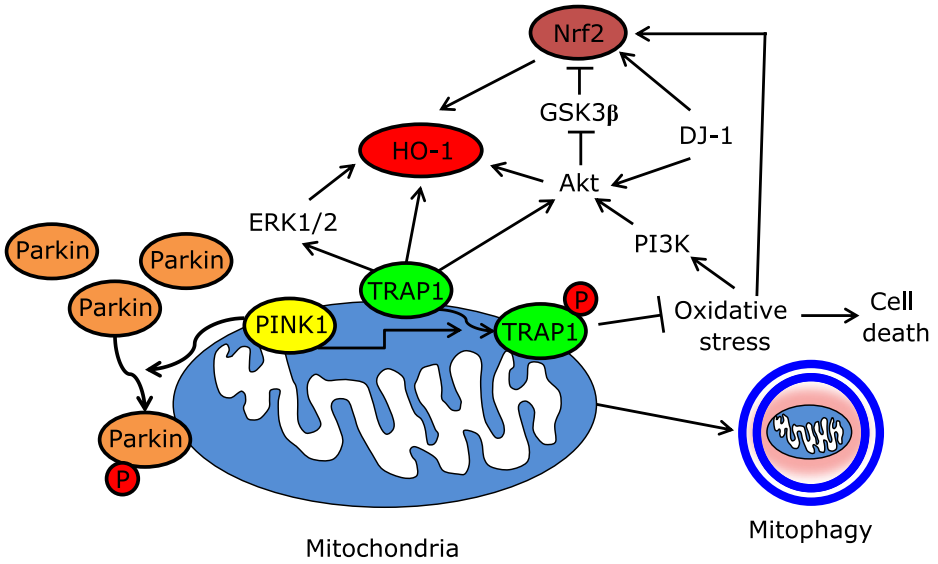

Fig. 4. Mitochondria-permissive signal for the Nrf2-HO-1 cascade. PINK1 directly phosphorylates Parkin and TRAP1, subsequently inducing the transfer of Parkin to the mitochondria and preventing mitochondrial oxidative damage. PI3K-AKT, ERK1/2 and DJ-1 signaling are indispensable for oxidative stress-induced Nrf2 activation. See text for details.

substrate of PINK1 kinase that plays a role in inhibiting oxidative stress.[47] Importantly, HO-1 induction by hydrogen peroxide is severely impaired in PINK1 kinase-dead mutant-overexpressing cells or upon TRAP1 knockdown in SH-SY5Y cells.[48] Although the role of Nrf2 in HO-1 induction was not analyzed, the results argue for the possibility that mitochondrial integrity is important for HO-1 induction by oxidative stress. In control cells, oxidative stress activates the PI3K-AKT and ERK1/2 pathways; however, these pathways are inhibited by the overexpression of the kinase-dead PINK1 mutant or by the TRAP1 knockdown. In fact, PI3K-AKT and ERK1/2 signaling is indispensable for HO-1 induction by oxidative stress in SH-SY5Y cells (Fig. 4).[48]

Loss of DJ-1 (PARK7) function has also been implicated as a familial form of PD,[49] and DJ-1 has been implicated in Nrf2 activation.[50] *DJ-1* KO mice are viable and fertile, but the dopaminergic neurons of the mice were hypersensitive to mitochondrial complex 1 inhibitor 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridne (MPTP).[51] Furthermore, embryonic cortical neurons from *DJ-1* KO mice are sensitive to oxidative stress. The oxidation of Cys106 in DJ-1 during oxidative stress is responsible for the localization of DJ-1 to the mitochondria as well as for its neuroprotective function.[52] DJ-1, such as Parkin and Pink1, is important for the quality control of mitochondria, and the loss of DJ-1 causes the mitochondrial depolarization and fragmentation.[53] Although DJ-1 does not improve the defective mitochondria phenotype caused by the PINK1 deficiency, DJ-1 protects rotenone-induced mitochondrial damage in the absence of PINK1, indicating that DJ-1 may act independently of PINK1/Parkin to control mitochondrial function.[53] DJ-1 activates AKT in dopaminergic neurons of the substantia nigra neurons in response to MPTP,[54] and DJ-1 is necessary for AKT to be recruited to the membrane in response to H_2O_2. Tanti *et al.*[55] recently showed that the WD-40 repeat protein SG2A mediates the interactions between Akt and DJ-1, and these 3 factors colocalize at the mitochondria and plasma membrane. Although Nrf2 is activated independently of DJ-1 in certain settings,[56] PINK1, Parkin and DJ-1 may act at the mitochondrial level to initiate a signaling cascade for Nrf2 activation during oxidative stress in a cell-specific manner (Fig. 4).

Nrf2 activation via electron transport inhibition. In contrast to the putative permissive role of mitochondria described above, recent studies in *C. elegans* have shown that defects in the mitochondrial ETC activate a stress response, including UPR^{mt}, mitochondrial biogenesis and the activation of the functional Nrf2 homolog SKN-1, which lead to prolonged longevity.[57] Surfeit locus protein 1 (Surf1) is a nuclear-encoded mitochondrial inner membrane protein that aids in the assembly of the COX holoenzyme. In humans, *Surf1* loss of function mutation leads to the development of Leigh's syndrome; however, the *Surf1* truncation mutation in mice prolongs the mean longevity of the mice. Interestingly, a recent study showed that a *Surf1* mutation provokes mitochondrial retrograde signaling and initiates the UPR^{mt} in skeletal muscle and Nrf2 activation in the heart.[58] Therefore, the same mutation generates different tissue-specific stress responses. Furthermore, Dassa *et al.*[59] showed that Nrf2 is activated in human fibroblasts isolated from the patients who harbor the mitochondria *ATPase6* gene mutations. In addition, Nrf2 is activated by the treatment of oligomycin, an inhibitor of ATP synthase; however, the study examined the Nrf2 activity only via immunohistochemistry and the activity of superoxide dismutase as the downstream target of Nrf2. Further studies are needed to conclude whether the inhibition of ATP synthase does indeed activate Nrf2.

The Nrf2 system is defective in several mitochondria-related diseases. Mitochondrial dysfunction plays an important role in the pathogenesis of a wide range of diseases, including neurodegenerative diseases. Mitochondrial dysfunction has been implicated as one of the etiologic factors of PD. Indeed, recent reports have demonstrated that Nrf2 activity is decreased in olfactory neurosphere-derived cells from PD patients, indicating a defect in Nrf2 activity in PD, although the involvement of mitochondria is currently unclear.[60,61] Friedreich's ataxia (FRDA) is caused by mutations in the *FXN* gene that encode the mitochondrial matrix protein frataxin, which is indispensable for iron-sulfur cluster biosynthesis in the mitochondria. Indeed, Nrf2 activation by oxidative stress is blocked in fibroblasts derived from FRDA patients or in FXN-knockdown NSC34 neurons.[62,63] The defective Nrf2 response in the fibroblasts of FRDA patients is rescued by treatment with Euk134, a catalase mimetic, indicating that chronic H_2O_2 generation is a causative factor of this response.[62] Furthermore, Nrf2 activity is suppressed in dorsal root ganglia

(DRG) neurons in the FRDA mouse model as well as in several FXN-knockdown cell line models using DRG (ND7/23 cells) and Schwann cells (T265 cells).[64] Interestingly, Sahdeo *et al.*[65] also reported that Nrf2 regulates *FXN* expression by binding to the evolutionary conserved ARE in the upstream of *FXN*. Although the precise mechanisms of Nrf2 dysfunction have yet to be determined, these results indicate that mitochondrial defects lead to Nrf2 function impairment. Therefore, the impaired Nrf2 pathway in the aforementioned diseases may be a potential target for future therapeutic drugs.

Conclusions and Perspectives

We have summarized the recent advances regarding the crosstalk between the Nrf2 system and mitochondria, specifically focusing on the interaction between Nrf2-mediated antioxidant mechanisms and the regulation of mitochondrial integrity. Consistent with the data discussed above, we propose that the coordinated induction of HO-1, p62 and NQO1 by Nrf2 activation aids in the maintenance and removal of damaged mitochondria, depending on the severity of the mitochondrial damage, and provokes the biogenesis of healthy mitochondria by inducing NRF-1 expression. However, this hypothesis remains to be tested in future studies. We described that mitochondrial abnormality both activates and represses Nrf2, and detailed mechanisms should be clarified in the future studies.

In addition to energy production and ROS production, mitochondria also play an important role in heat generation in mammals.[66] Interestingly, Nrf2 is highly expressed in thermoregulating organs such as the thyroid and brown adipose tissue in the mouse embryo and regulates the expression of uncoupling protein 3.[5,67] Therefore, we surmise that tight cooperation between Nrf2 function and the mitochondria has evolved beyond the regulation of mitochondrial quality control, which may be an interesting area to assess in future studies.

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Abbreviations

ALCAR	acetyl-L-carnitine
ARE	antioxidant responsive element
CO	carbon monoxide
$\Delta\Psi_m$	mitochondrial membrane potential
ETC	electron transport chain
HO-1	heme oxygenase-1
NQO1	NAD(P)H dehydrogenase quinone 1
NRF-1	nuclear respiratory factor 1
Nrf2	nuclear factor erythroid-derived 2-related factor 2
PD	parkinson's disease
ROS	reactive oxygen species

Conflict of Interest

No potential conflicts of interest were disclosed.

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