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Review

Nrf2-Keap1 signaling in oxidative and reductive stress

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ABSTRACT

Nrf2 and its endogenous inhibitor, Keap1, function as a ubiquitous, evolutionarily conserved intracellular defense mechanism to counteract oxidative stress. Sequestered by cytoplasmic Keap1 and targeted to proteasomal degradation in basal conditions, in case of oxidative stress Nrf2 detaches from Keap1 and translocates to the nucleus, where it heterodimerizes with one of the small Maf proteins. The heterodimers recognize the AREs, that are enhancer sequences present in the regulatory regions of Nrf2 target genes, essential for the recruitment of key factors for transcription. In the present review we briefly introduce the Nrf2-Keap1 system and describe Nrf2 functions, illustrate the Nrf2-NF-κB cross-talk, and highlight the effects of the Nrf2-Keap1 system in the physiology and pathophysiology of striated muscle tissue taking into account its role(s) in oxidative stress and reductive stress.

1. Introduction

In mammals, the NF-E2-related factor 2 (Nrf2)-Kelch-like ECH-associated protein 1 (Keap1) system, inherited from ancestors as anti-stress mechanism, is a defense system aimed to preserve cellular homeostasis. During evolution, all the living organisms had to deal with a variety of stressors and only the organisms provided with functional defense systems could survive and evolve. The system is regulated by interactions between Nrf2 and the cytosolic repressor protein Keap1. Nrf2, a member of the Cap-n-Collar family of basic leucine zipper proteins, was first described by Moi et al. [1] as an activator of β-globin gene expression, and later described as a major sensor of oxidative stress in the cell [2,3].

Domain analysis by nuclear magnetic resonance spectroscopy and high-resolution crystal structure showed that Nrf2 has seven functional domains (Neh1–7) that are involved in the regulation of its stability or its transcriptional activity (transactivation) (Fig. 1A). The N-terminal domain is responsible for the interaction at low nanomolar concentration (K_D ~5 nM) between Nrf2 and Keap1, stability of Nrf2, and ubiquitination, while the Neh5 domain regulates the cellular localization of Nrf2 [4,5]. The Neh6 domain controls Keap1-independent degradation of Nrf2 and represents a binding platform for the β-transducin repeat-containing protein. The Neh1 domain, with its basic leucine zipper motif, allows the binding of Nrf2 to the antioxidant response element (ARE) sequence. Moreover, this domain can interact with UbcM2, the E2 ubiquitin-conjugating enzyme, to regulate Nrf2 protein stability [6]. Neh1 domain, after the release from Keap1, uncovers a nuclear localization signal essential to Nrf2 nuclear translocation. The C-terminal of the Neh3 domain interacts with the transcription co-activator CHD6 (a chromo-ATPase/helicase DNA-binding protein), responsible for the transactivation of ARE-dependent genes after chromatin remodeling [4,5,7]. The Neh4 and Neh5 represent domains of transcription activation that bind to the co-activator cyclic adenosine monophosphate-responsive element-binding protein and facilitate Nrf2 transcription [7]. Neh4 and Neh5 can also interact with the nuclear cofactor RAC3/AIB1/SRC-3 and enhance Nrf2-targeted ARE gene expression [4,5,7]. Neh7 domain interacts with retinoic X receptor α thus repressing Nrf2 [8].

Keap1, the main intracellular regulator of Nrf2, is characterized by five domains (Fig. 1B), that is three broad complex-tramtrack-bric a brac (BTB), one intervening region (IVR) and two glycine repeat domains (DGR), each one being important for inhibiting Nrf2 activity. The DGR domains of the Keap1 homodimer bind with different affinity to the DLG (latch) ($Ka = 0.1 \times 10^7 M^{-1}$) and the ETGE (hinge) ($Ka = 20 \times 10^7 M^{-1}$) domains in a single Nrf2 molecule (hinge and latch hypothesis). In response to oxidants, the DLG motif in Nrf2 is released from the DGR domain in Keap1 thus blocking Nrf2 ubiquitination and degradation. The binding of Nrf2 to the DGR domain is competitively inhibited by proteins with specific motifs, such as p62 and partner and localizer of BRCA2 [6,9–12], therefore acting as a sensor of cellular stress, such as autophagy deficiency and DNA damage. The IVR domain, in addition to interacting with Cul3 protein

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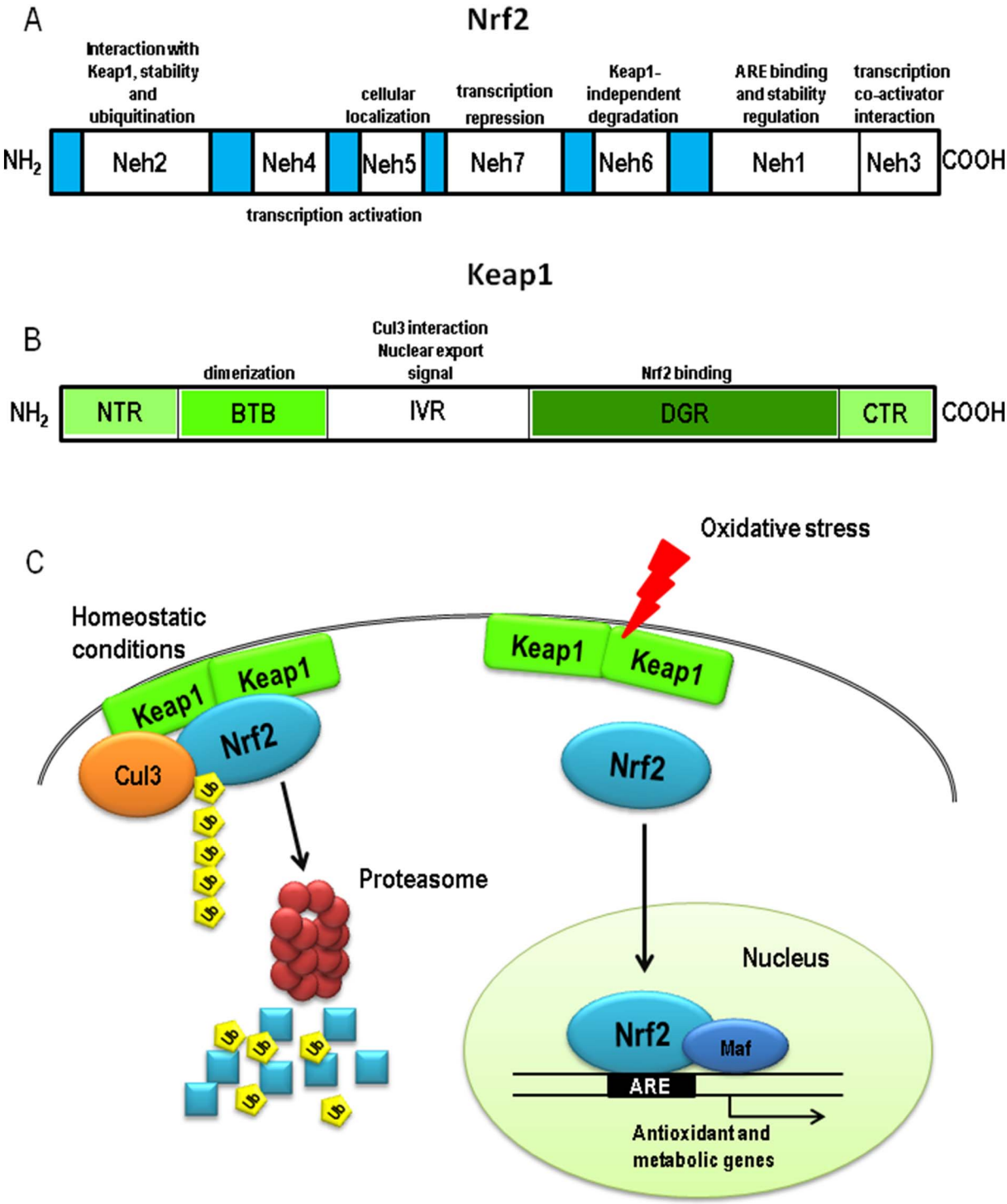

Fig. 1. (A, B) Scheme of Nrf2 (A) and Keap1 (B) primary structure. Relevant functions of Nrf2 and Keap1 domains are indicated. (C) Under homeostatic conditions Nrf2 (light blue) is kept inactive being bound to its endogenous inhibitor, Keap1 (green), associated with the F-actin cytoskeleton [14,48]. In this condition, levels of Nrf2 are principally regulated by the proteasome. Oxidative stress causes Nrf2 to detach from Keap1 and translocate to the nucleus where it heterodimerizes with Maf (blue): the Nrf2-Maf heterodimer binds to ARE (black) to induce the expression of antioxidant and metabolic genes.

which contains the E3 ligase complex together with Roc1 [13] has a consensus sequence of nuclear export signal, important for localization of Keap1 at the cytoplasm [14]. Under basal conditions, Nrf2 is sequestered by cytoplasmic Keap1 and targeted to proteasomal degradation [2,15] (Fig. 1C). Under conditions of oxidative stress, the Nrf2-Keap1 interaction is resolved in a dose-dependent manner [2] and free and newly synthesized Nrf2 translocates to the nucleus and heterodimerizes with one of the small Maf (musculoaponeurotic fibrosarcoma oncogene homolog) proteins (Fig. 1C). The heterodimers recognize the AREs, that are enhancer sequences present in the regulatory regions of Nrf2 target genes, essential for the recruitment of key factors for transcription [16]. Nrf2 affects the expression of nearly 500 genes that encode proteins acting as redox balancing factors, detoxifying enzymes, stress response proteins and metabolic enzymes [17–19].

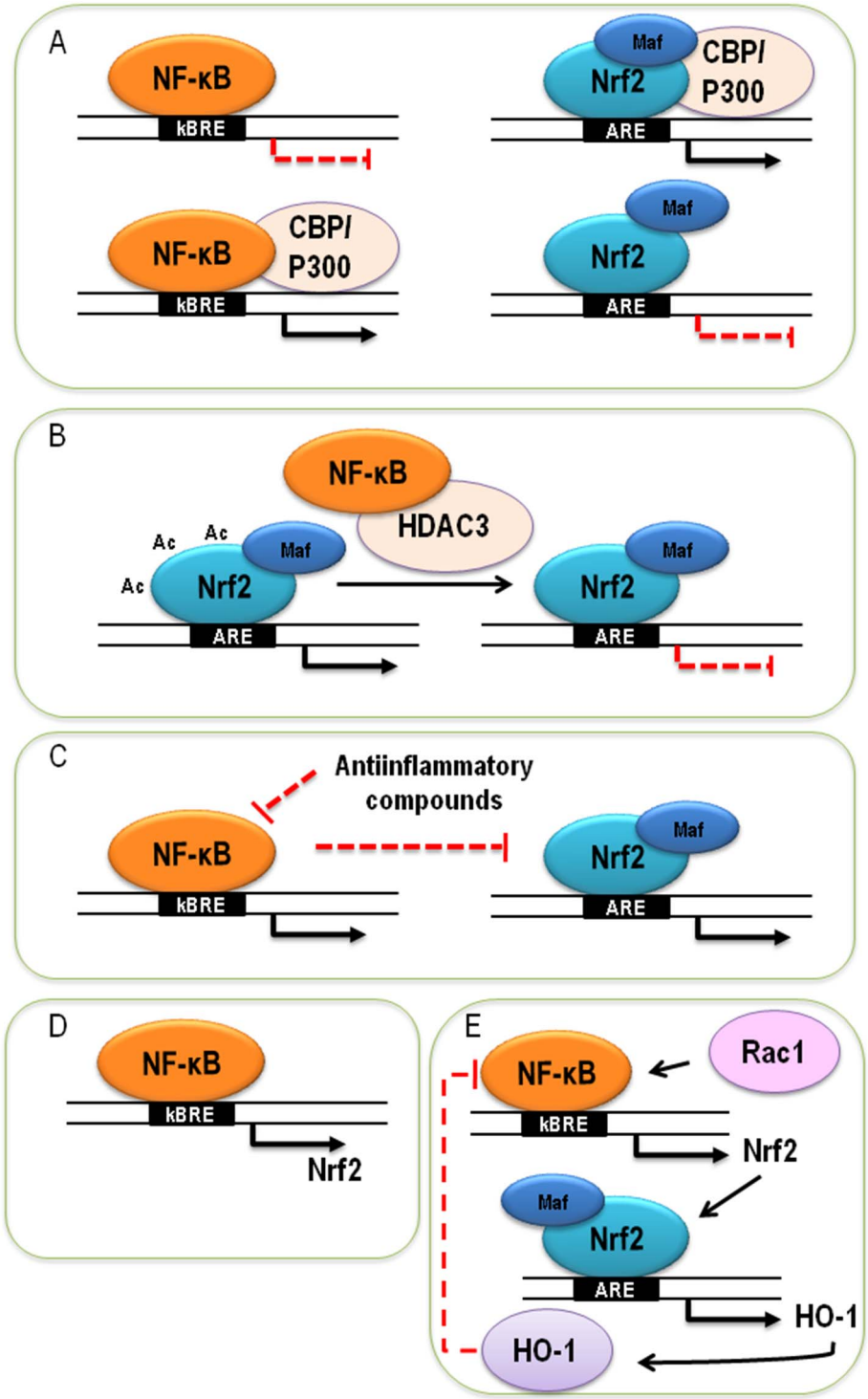

Fig. 2. Nrf2/NF-κB cross-talk. (A) Nrf2 and NF-κB compete for CBP/P300 binding in the nucleus; binding of either transcription factor to CBP/P300 is dependent on the relative amount of translocated Nrf2 and NF-κB. (B) NF-κB-recruited HDAC3 deacetylates Nrf2 inhibiting ARE-dependent gene expression. (C) Nrf2 is indirectly activated by antiinflammatory compounds that suppress NF-κB activity. (D) NF-κB binds κB responsive elements on the Nrf2 promoter region thereby inducing Nrf2 expression. (E) Rac1-activated NF-κB induces Nrf2 which upregulates HO-1 to suppress NF-κB activity.

2. Functions of Nrf2

Although Nrf2 is a homolog of nuclear factor-erythroid 2 p45 (NF-E2), its function is not related to hematopoiesis. Indeed, Nrf2-knockout mice do not show anemia, thus suggesting that Nrf2 regulates a different array of genes from NF-E2 [1,3]. Itoh and collaborators [20] were the first to report the similarity between the NF-E2 binding sequence and ARE. This regulatory sequence, usually found upstream of genes encoding phase II detoxifying enzymes, regulates the induction of these genes [21] (Fig. 1C), as shown by the fact that in Nrf2-knockout mice there is a down-regulated expression of phase II enzymes [2,20]. Phase II enzymes detoxify the intermediate metabolites generated by phase I reactions, causing a rapid excretion of toxic xenobiotics [21]. Benzo[α]pyrene is a pro-carcinogen that is detoxified by phase II reactions after forming a highly reactive intermediate after phase I metabolism. Nrf2-deficient mice are more susceptible to benzo[α]pyrene-

induced tumor formation thus suggesting that Nrf2 is essential for a complete phase II metabolism [22,23]. Other studies showed that the Nrf2 system controls phase I-related genes, as well as phase III xenobiotic transporters [24,25], thus indicating that Nrf2 is responsible for the whole process of xenobiotic metabolism. Moreover, since antioxidant genes, such as heme oxygenase 1 (HO-1), contain upstream ARE sequences, Nrf2 can be regarded as a master regulator of the oxidative stress response [26–31]. Several toxic chemical stressors produce reactive oxygen species (ROS), therefore Nrf2 plays a central role in the defense against various chemical-derived stresses [32,33] (Fig. 1C). Collectively, defending against xenobiotic metabolism and providing an efficient antioxidant system, Nrf2 can be considered as one of the main factors contributing to animal evolution in a changing environment. Endogenous signals, such as endoplasmic reticulum stress and autophagy impairment, are equally capable of activating the Nrf2 system which provides an initial cellular defense [31,34–37]. Nrf2-dependent induction of proteasome subunits [38] leads to a decrease in unfolded proteins and restores the physiological protein turnover. On the other hand, the Nrf2/Keap1 system can be epigenetically regulated by DNA methylation, histone modification, and microRNAs [39,40], which adds another layer of complexity to Nrf2 regulation and functions.

3. The Nrf2-NF-kB axis and cross-talk

The family of NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) includes seven structurally related transcription factors that regulate the expression of numerous genes. Widely expressed and inducible, NF-κB regulation depends on stimuli and cell type, thus resulting in a broad spectrum of effects. The term NF-κB usually represents a p50-p65 heterodimer, which is the major Rel/NF-κB complex in most cells [41,42]. The activation mechanisms follow several pathways that, by causing different patterns of activation in the single subunits, lead to different cellular responses [43–47]. Activation of the IκBα kinase (IKK), the resulting phosphorylation-induced proteolysis of the IκBα inhibitors followed by the nuclear translocation of the Rel A transcriptional activator which binds with high affinity to the κB elements in gene promoters characterize the canonical pathway [21,48]. This pathway regulates the temporal expression of the regulons, i.e. functionally discrete groups of genes, in an oscillatory or monophasic mode. The mode of activation is pivotal for gene selection [42]. On the other hand, the activation of NF-κB inducing kinase- and IKKα-dependent proteasomal processing of p100 into p52, which, in turn, forms a complex with Rel B and activates a distinct set of genes, characterizes the non-canonical pathway [21,42,48,49]. These pathways are activated and regulated by many upstream stimulants, such as phosphorylation by protein kinases which enhances p65 transactivation potential and degradation of inhibitory molecules. Co-activators and co-repressors, such as P300/CBP, P300/CBP-associated factor, p160 proteins (SRC-1, SRC-2 and SRC-3), SMRT, nuclear receptor co-repressor, histone deacetylase 1 (HDAC1), HDAC2 and HDAC3, can also regulate the transcriptional activity of NF-κB [46,48,50].

Nrf2 and NF-κB pathways regulate the physiological homeostasis of cellular redox status and responses to stress and inflammation. The molecular mechanisms underpinning this complex and dynamic interplay, that depend on the cell type and tissue context, are still under elucidation [51]. However, numerous studies have proposed that Nrf2 plays a critical role in counteracting NF-κB-driven inflammatory response in a variety of experimental models [21,48,52,53] (Fig. 2). At transcriptional level, Nrf2 and NF-κB competes with transcription co-activator CREB binding protein (CBP). In the presence of simultaneous nuclear increases in these two transcription factors, NF-κB(p65) antagonizes Nrf2-induced gene transcription [48] (Fig. 2A). Moreover, by recruiting HDAC3 and causing a local hypoacetylation, NF-κB reduces Nrf2 signaling [54] (Fig. 2B). Compounds that decrease the inflammatory response by suppressing NF-κB signaling, activate the Nrf2 pathway [34,47,55,56] (Fig. 2C). The connection was firstly suggested by studies reporting that Nrf2-deficient mice exhibit a neurodegenerative phenotype [57], further corroborated by the observation that the lack of Nrf2 is associated with an increase in cytokine production [58]. It is known that p65 has a dual role in regulating Nrf2 activity [59,60]. Acute myeloid leukemia cells (AML) show upregulated Nrf2 protein levels and target-gene expression in response to tumor necrosis factor-α (TNF-α). The effect is due to the presence of several κB sites in Nrf2 proximal promoter, that bind p65 and initiate Nrf2 transcription, one of the crucial player of chemoresistance of AML to the bortezomib treatment [59] (Fig. 2D). Moreover, NF-κB activation can stimulate Nrf2 activity as a protective antiinflammatory mechanism via the small GTPase Rac1 (Ras-related C3 botulinum toxin substrate 1) [60]. Indeed, once activated by LPS, Rac1 stimulates NF-κB to induce Nrf2 which upregulates HO-1 expression. In turn, HO-1 reduces the NF-κB inflammatory activity and shifts the cells to a more reducing environment, essential for terminating the NF-κB activation [29,30,60] (Fig. 2E).

4. Nrf2 in skeletal muscle

4.1. Nrf2 in physiological conditions

Skeletal muscle is a remarkably plastic tissue with the capacity to adapt by altering the type and amount of protein as a response to exercise-induced variation in cellular homeostasis [61,62]. The process of adaptation in skeletal muscle is a functional consequence of the type, intensity and frequency of stimulus and affects numerous events resulting in the activation/repression of specific signaling pathways, hence regulating gene expression and protein synthesis/degradation [61,63–65]. As a chronic response to exercise training, muscle adaptation is the outcome of acute and cumulative effects caused by the responses to single-exercise bouts [66]. Recently, it has been proposed that lysosome is the cellular organelle acting as a meeting-point of resistance- and endurance-based signals [64]. Resistance exercise triggers, via perturbation of trans-membrane structures, the activation of mTORC1 (mechanistic target of rapamycin complex 1), which, in turn, elicits cap-dependent mRNA translation thus leading to increase in cell size (Fig. 3). On the other hand, endurance-based signals activate stress-sensing pathways, i.e. CAMKII (Ca^{2+}/calmodulin-dependent protein kinase II), p38 MAPK (p38 mitogen-activated kinase), AMPK (AMP-dependent kinase), as well as SIRT1 (sirtuin 1), which post-translationally modify PGC-1 α (PPARγ-coactivator 1α) leading to an oxidative phenotype via the co-activation of nuclear- and mitochondrial-encoded genes [61,63–65,67] (Fig. 3). However, it is noteworthy that either resistance or endurance muscle exercise can cause a perturbation of cellular redox homeostasis by increasing ROS and reactive nitrogen species [64,68,69] (Fig. 3). As already mentioned, ROS are important in a plethora of cellular functions since they activate Nrf2. Oxidative stress can activate Nrf2 gene expression and transcriptional activity either in vitro (C2C12 skeletal muscle cells) or in vivo (rodent muscles) [68–74]. Data in humans are less numerous, although it has been shown that acute exercise can increase Nrf2 protein levels in peripheral blood mononuclear cells in young and older men [75]. Moreover, nuclear accumulation of Nrf2 was observed only in the young group, indicating that aging is accompanied by a reduced nuclear import of Nrf2 [66,76,77]. Therefore, Nrf2 signaling and subsequent cytoprotective response are impaired by aging and reduced Nrf2 activation can, at least partially, underpin frailty and subsequent sarcopenia, which is closely related to poor physical performance of old age [75,78–80] (Fig. 3). In young and fit males, after an acute bout of 90-min cycling exercise, Nrf2 gene expression and superoxide dismutase 2 (SOD2), its target gene, increased significantly under normoxic recovery conditions [81], whereas, under hypoxic conditions, neither Nrf2 nor SOD2 levels increased. Similarly, in middle-aged and fit women, a 30 min of moderate treadmill exercise caused an increase in Nrf2 mRNA levels, which

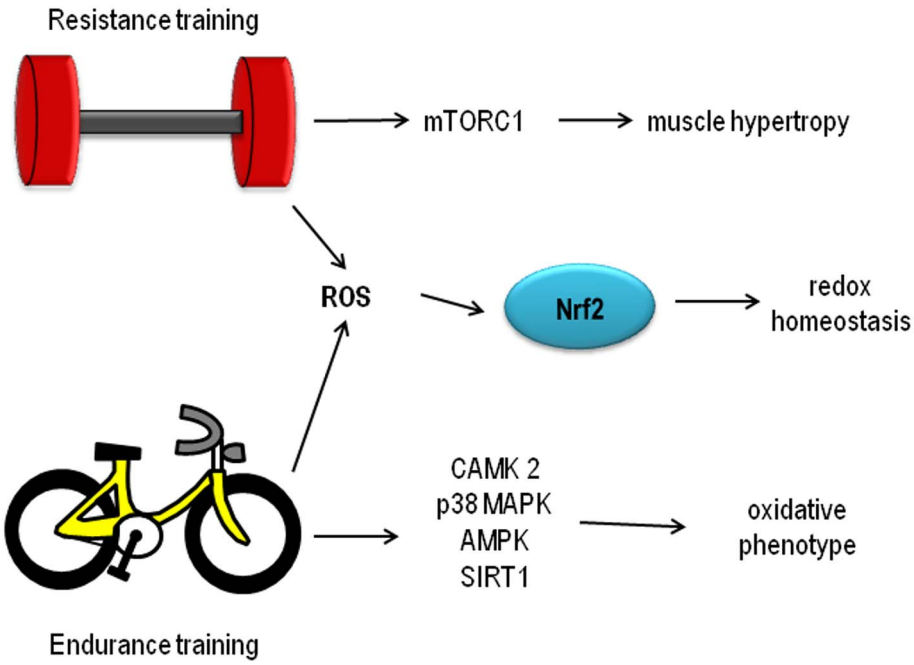

Fig. 3. Resistance and endurance training cause muscle hypertrophy and mitochondriogenesis, respectively. The resultant ROS production induces Nrf2 to regulate redox homeostasis.

did not occur in sedentary age-matched women [82]. Therefore, fitness may be one crucial factor to control the Nrf2 response in aging. Training and regular exercise also increase Nrf2 activation [62,83,84], suggesting that a regular exercise attenuates the age-related changes in Nrf2-mediated pathways and potentially restores the redox homeostasis (Fig. 3). However, compared to a late start training, a life-long training provides more marked benefits and a greater protection against age-related pathologies [62,83,84].

Studies of Nrf2 activation as response to resistance training produced less defined results, which calls for further investigation. Indeed, young animals showed no changes in Nrf2 expression, while older animals responded to the same training regimen with a decrease in Nrf2 [85]. Compared to young animals, older animals showed marked increases in baseline levels of Nrf2 expression, probably due to Nrf2 upregulation to counteract the pro-oxidant environment related to aging [26]. Thus, it is plausible that resistance exercises, by restoring the redox homeostasis, lower Nrf2 basal levels. Resistance exercise controls the maintenance of redox homeostasis in humans as well [86]. On the whole, exercise is an eligible routine to improve endogenous antioxidant defenses via Nrf2 activation. However, whether or not exogenous supplementation of antioxidants/Nrf2 activators during muscle adaptation, is beneficial is still disputed [62,87,88]. Recent work has shown that the Nrf2 activator, sulforaphane, enhances running capacity in rats by upregulation of Nrf2 signaling and downstream genes and attenuates muscle fatigue via reduction of oxidative stress caused by exhaustive exercise [89].

4.2. Nrf2 in pathological conditions

Skeletal muscle tissue is highly plastic, responding to acute noxious stimuli such as moderate trauma and vigorous physical exercise with a reparative process. Muscle regeneration relies on the activation, proliferation, migration and differentiation of satellite cells (SCs) [90], the adult stem cells of skeletal muscles located between the sarcolemma and the basal lamina [91], with the participation of other cell types such as vascular pericytes and fibro/adipogenic precursors [92–94]. Differentiated myocytes eventually fuse with damaged myofibers to repair them and form new myofibers. Contrariwise, immobilization, denervation and several chronic diseased statuses lead to a relatively rapid decrease in skeletal muscle mass known as sarcopenia [80].

Sarcopenia is a clinical condition characterized by a significant loss of skeletal muscle mass and performance, increased fatigability and risk of bone fractures [95,96]. Histologically, muscles of sarcopenic people show hypotrophic myofibers (mostly type II myofibers) and infiltration with adipose and, at later stages, fibrotic tissue, along with decreased numbers of SCs [97]. Sarcopenia may be either secondary to chronic inflammatory statuses, diabetes, hormonal alterations, vascular disturbances and immobilization [80,96], or primary, occurring in otherwise healthy, usually aged persons. The pathogenesis of sarcopenia is not completely understood. Both SCs and their progeny (i.e. the myoblasts) and myofibers can be targets of noxious stimuli leading to sarcopenia. Extrinsic, niche-related factors and intrinsic, cell-autonomous factors are proposed to concur to determine changes in SCs ultimately leading to reduced SCs' ability to maintain muscle mass [91,97–102].

Oxidative stress has long been implicated in the genesis of sarcopenia [103]. Accumulation of ROS is considered characteristic of activated aged SCs and/or proliferating aged myoblasts; possibly, ROS overproduction, due either to altered mitochondrial function or to defective ROS management, is one main cause of primary sarcopenia [103] (Fig. 4A). ROS overproduction might determine the aberrant p38 MAPK activity, deregulated p16 (INK4a) expression and JAK-STAT signaling and defective autophagy detected in aged SCs/myoblasts and suggested to be responsible for their altered proliferation and differentiation properties [99–104] (Fig. 4A). ROS overproduction, a hallmark of sarcopenic myoblasts, may also increase levels of S100B, a member of the S100 protein family [105], in myoblasts and myofibers via NF-κB activation, with resultant inhibition of myogenic differentiation [106,107] and promotion of myoblast transdifferentiation into brown adipocytes [108] via an NF-κB/Yin Yang1/miR-133 axis and NF-κB/Yin Yang1/bone morphogenetic protein-7 axis (Fig. 4B). On the other hand, denervation and/or immobilization (including a sedentary lifestyle), alterations of skeletal muscle perfusion, chronic inflammatory and/or metabolic diseases might directly affect myofiber trophism independently of the involvement of SCs/myoblasts [109,110].

However, a certain amount of ROS production is required for myogenesis. In particular, endogenous H_2O_2 generated during myoblast differentiation functions both as a signaling molecule and as a regulator of the glutathione redox state via activation of the Nrf2-glutamate-

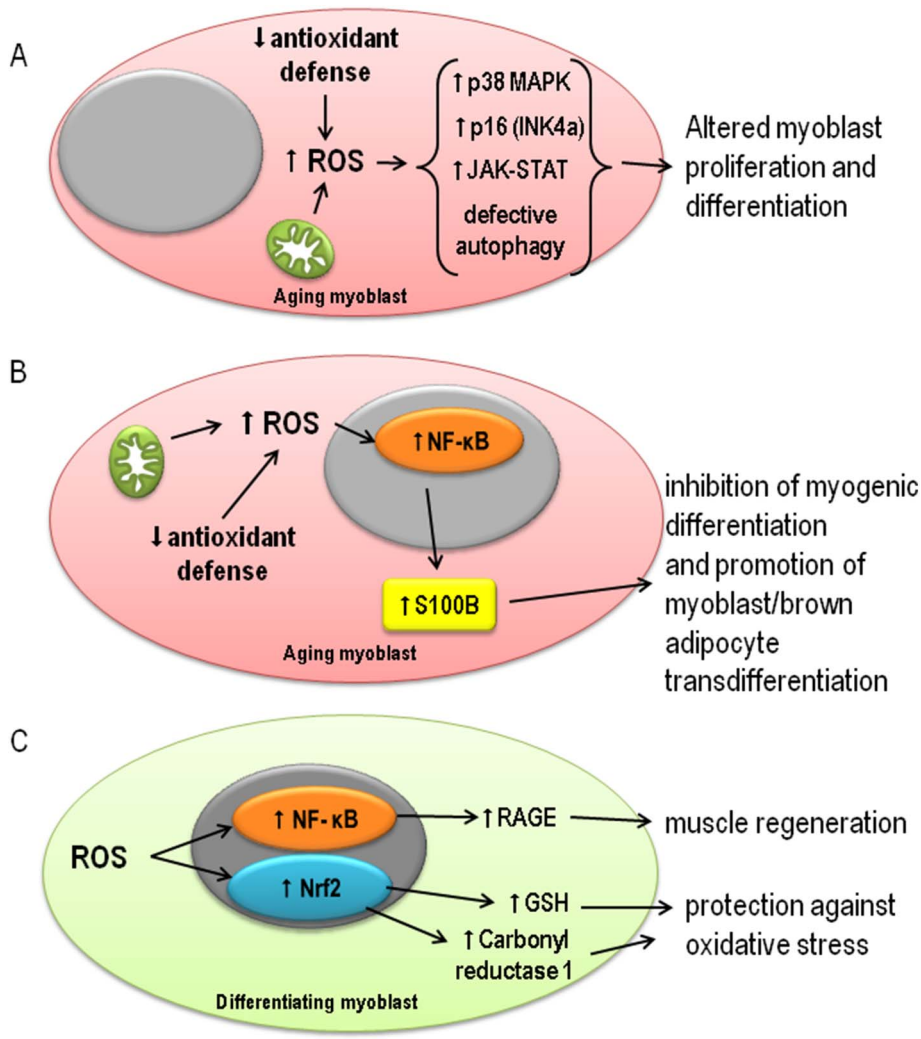

Fig. 4. NF-κB/Nrf2 cross-talk in myoblasts. (A,B) Altered mitochondrial function and/or defective antioxidant defense mechanisms in aging myoblasts lead to ROS accumulation that in turn, results in (A) altered cell proliferation and differentiation consequent to aberrant p38 MAPK activity, deregulated p16 (INK4a) expression and JAK-STAT signaling, and defective autophagy and in (B) elevated levels of S100B protein which inhibits myogenic differentiation and promotes myoblast-brown adipocyte transition. (C) However, in differentiating myoblasts moderate levels of ROS are required for induction of Nrf2 to protect against oxidative stress and for NF-κB to induce the promyogenic RAGE.

cysteine ligase/glutathione reductase-glutathione signaling pathway downstream of phosphatidylinositol 3-kinase [111]. Physical exercise generates considerable amounts of ROS that create the oxidative redox potential required for oxidizing free sulfhydryl groups of cysteine and producing the disulfide bonds used to stabilize the three-dimensional conformation of physiologically active proteins [112]. Moreover, antioxidant supplements have been shown to prevent the beneficial effects of physical exercise in humans [7], and short-term treatment with the antidiabetic drug, metformin, cancels the effect of physical exercise by enhancing insulin sensitivity consequent to attenuation of the oxidative effects of physical exercise [113,114]. Also, ROS-activated NF-κB induces in myoblasts the expression of the receptor for advanced glycation end-products (RAGE) that is required for timely muscle regeneration of acutely injured muscles, with the antioxidant, *N*-acetyl cysteine, reducing NF-κB activation and RAGE expression [115]. Moreover, Nrf2 transcriptionally upregulates carbonyl reductase 1 that plays a critical role in controlling redox balance and detoxifying lipid peroxidation during muscle differentiation and regeneration [116] (Fig. 4C). Lastly, mitochondrial ROS signaling repairs exercise-injured myofibers via RhoA-mediated F-actin assembly at injured sites [117].

As mentioned earlier, Nrf2 and its repressor, Keap1, are indispensable mediators of cellular responses to stress conditions [118]. Disruption of the Nrf2-Keap1 signaling may occur during human aging and contribute to cause sarcopenia, and inhibition of Nrf2 by caveolin-1 promotes stress-induced premature senescence via hyperactivation of ARE and inhibition of oxidative stress-induced activation of the p53/p21$^{Waf1/Cip1}$ pathway [119].

Several reports have demonstrated a beneficial role for Nrf2 in skeletal muscle regeneration following injury. Deletion of *Nrf2* in A/J mice, a model of dysferlinopathy - a muscular dystrophy due to mutations in the dysferlyn gene -, leads to significant muscle-specific functional disturbances, histopathologic alterations, and dramatically enhanced ROS levels compared to control A/J and wild-type mice [120], and genetic silencing of *Nrf2* causes defective regeneration in ischemia-induced muscle injury [121]. That oxidative stress has an important role in the pathophysiology of dysferlinopathies is an accepted notion [122]. Also, NADPH oxidase activity is elevated in muscles of *mdx* mice, an animal model of Duchenne muscular dystrophy, and stimulates stretch-induced damage in *mdx* muscles [123]. Indeed, activation of Nrf2 with therapeutic doses of its activator, sulforaphane, improves muscle performance and mitigates inflammation in muscles of *mdx* mice via Nrf2-dependent inhibition of NF-κB and resultant inhibition of the expression of the proinflammatory cytokines, TNF-α, interleukin-1β, and interleukin-6 [124] (Fig. 5A). Also, SC activation, proliferation, and differentiation require a functional Nrf2 system for timely and effective muscle regeneration following acute

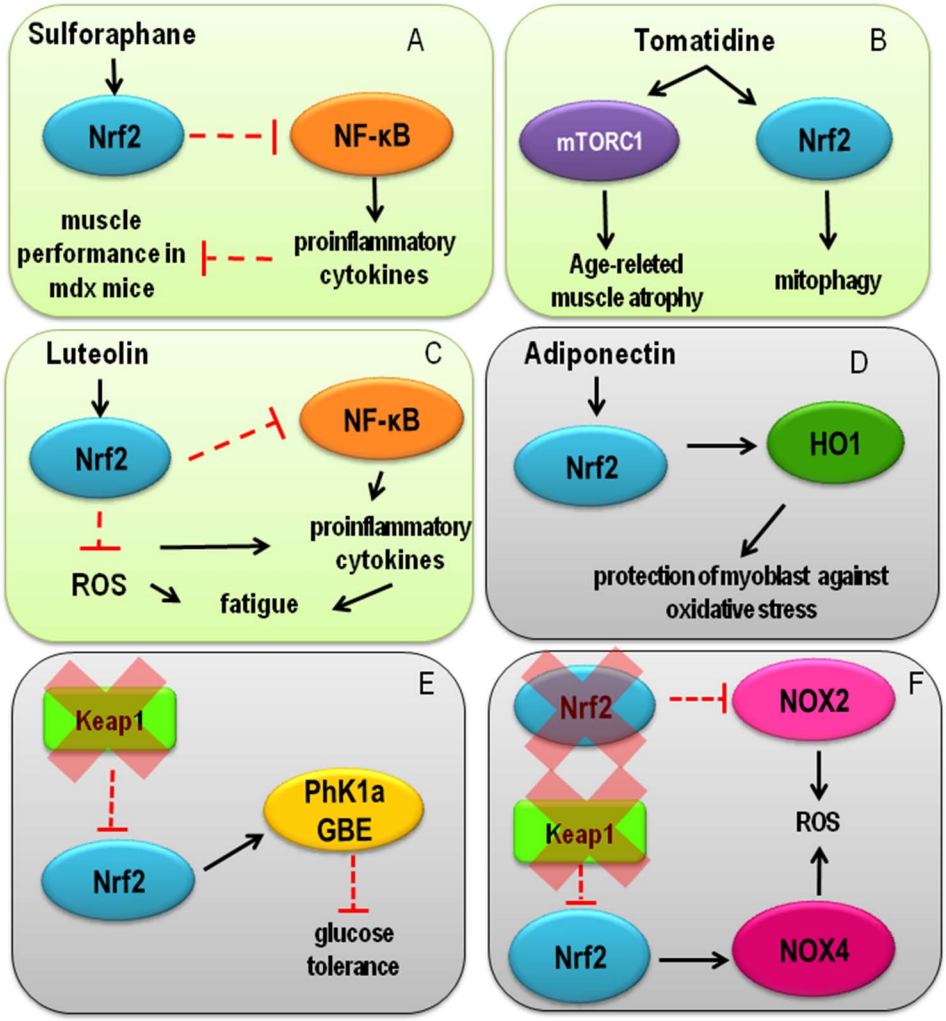

Fig. 5. Nrf2 effects in skeletal muscle. (A) Sulforaphane-activated Nrf2 improves muscle performance in *mdx* mice (an animal model of Duchenne muscular dystrophy) via inhibition of the proinflammatory NF-κB. (B) Tomatidine reduces age-related muscle atrophy via mTORC1 and stimulates mitophagy via Nrf2. (C) Luteolin reduces muscle fatigue via Nrf2-dependent inhibition of the proinflammatory NF-κB and ROS accumulation. (D) The adipokine, adiponectin, protects myoblasts against oxidative stress via Nrf2-dependent induction of HO-1. (E) Muscle-specific deletion of Keap1 leads to Nrf2-mediated improvement of glucose tolerance. (F) Deletion of either Nrf2 or Keap1 may lead to ROS overproduction suggesting that the reciprocal control of Nrf2-Keap1 and NADPH oxidases is likely to play a major role in the fine tuning of ROS levels.

injury [125]. Further, tomatidine, a natural compound abundant in unripe tomatoes that inhibits age-related skeletal muscle atrophy in mice via stimulation of mTORC1 activity [126], activates Nrf2 with resultant increased mitophagy [127] (Fig. 5B). Moreover, luteolin-6-C-neohesperidoside, a flavonoid isolated from moso bamboo leaf, exerts anti-fatigue effects by reducing forced swimming-induced oxidative stress in muscles via stimulation of the Nrf2-ARE pathway, reduced production of proinflammatory cytokine, and enhanced release of antiinflammatory cytokines [71] (Fig. 5C). Overall, physical exercise increases Nrf2 transcriptional activity [69] which is required for the maintenance of basal mitochondrial function and the normal increase in specific mitochondrial proteins in response to training, although the decrease in mitochondrial function in *Nrf2*$^{-/-}$ muscle can be rescued by exercise training, suggesting that this restorative function operates via an Nrf2-independent pathway [128]. Interestingly, adiponectin, an adipokine secreted by adipocytes [129] and endowed with antiinflammatory and protective effects against oxidative stress [130,131], protects myoblasts from oxidative stress-induced damage via activation of the Nrf2/HO-1 pathway [132] (Fig. 5D). Notably, Nrf2 activity was reported to reduce muscle glycogen content with resultant improved glucose tolerance via upregulation of the glycogen branching enzyme (GBE) and muscle-type PhKα subunit mRNAs [74] (Fig. 5E). The protective effect of stimulation of the Nrf2 antioxidant pathway has been reported in other experimental settings such as neuroinflammation [133].

However, others reported that *Nrf2*$^{-/-}$ mice show no abnormalities in skeletal muscle regeneration following acute injury, with Nrf2 inhibiting the muscle-specific transcription factors, MyoD and myogenin [134]. Also, whereas Nrf2 deficiency exacerbates denervation-induced oxidative stress, similar alterations in mitochondrial fission regulatory proteins (which were increased) and mitochondrial fusion proteins (which were decreased) and loss of skeletal muscle mass were found in denervated wild type and *Nrf2*$^{-/-}$ mice which suggests that Nrf2 does not play a role beyond regulating antioxidant gene expression [135]. While these latter results might complement results showing that exercise training is sufficient to restore mitochondrial function in *Nrf2*$^{-/-}$ muscle [128], use of a different injury model might account for discrepancies between the results obtained with the denervation model [135] and those reported in [120,121,123–127]. A more in-depth analysis of the role of Nrf2 in myogenesis is warranted.

Recent work suggests that the Nrf2-Keap1 pathway regulates cytosolic and mitochondrial ROS production; Nrf2 deficiency leads to enhanced NAPDPH oxidase 2 activity, and unrestricted Nrf2 activation as obtained by knocking down Keap1 leads to enhanced NADPH oxidase 4 activity [136] which points to an essential role of the Nrf2-Keap1 pair in redox homeostasis inasmuch as that NADPH oxidase in turn regulates Nrf2 [131,132,137,138] (Fig. 5F). Thus, the reciprocal control of Nrf2-Keap1 and NADPH oxidases is likely to play a major role in the fine tuning of ROS levels. Such reciprocal control is proposed to be altered in *mdx* muscles where excess NADPH oxidase leads to excess Src activation, which in the same time fuels NADPH oxidase activity and inhibits autophagolysosome formation with resultant cellular degeneration [139]. As the Nrf2-Keap1 pathway was not investigated in this latter study, no conclusion can be drawn about the potential role of

NADPH oxidase-mediated inactivation of the antioxidant Nrf2 as one main cause of ROS accumulation in *mdx* muscles leading to degeneration. However, the finding that pharmacological activation of Nrf2 improves performance and mitigates inflammation in muscles of *mdx* mice, as mentioned above, suggests that reduced Nrf2 expression levels and/or activity might represent an important piece of the complex mosaic of the pathophysiology of muscular dystrophy [124]. Possibly, a threshold level of ROS exists above which NADPH oxidase activity prevails over Nrf2-dependent ROS scavenging activity. Whether Nrf2 affects myogenesis and muscle trophism independently of its role in the orchestration of ROS scavenging remains an attractive possibility. Recently, Nrf2 has been shown to associate with the outer mitochondrial membrane in oxidative stress conditions and to protect mitochondria from oxidant injury, with no such protective effect occurring in *Nrf2*$^{-/-}$ mice [140].

Autophagy is a cellular process whereby the cell adapts to stressful conditions by degrading proteins, aggregates and cellular organelles for energy purposes and, hence, cell survival [139,141]. Autophagy and oxidative stress are reciprocally linked [128,142]. Besides by Keap1, levels of active Nrf2 are regulated by autophagy and p62, a ubiquitin-binding protein acting as a scaffold for several protein aggregates and triggering their degradation through the proteasome or the lysosome pathway via autophagy [143].

p62 is degraded through autophagy under normal conditions. Oxidative stress upregulates p62 with resultant sequestration of Keap1 and activation of Nrf2 and Nrf2-dependent antioxidant defense gene expression (Fig. 6A). In addition, oxidative conditions also activate NF-κB consequent to p62 upregulation and TNF receptor-associated factor 6 (TRAF6) complex formation, to turn on antioxidant-defense gene expression [144]. In autophagy-defective cells and tissues, the autophagy substrate p62 is not degraded, thus accumulating to high levels. p62 binds and sequesters Keap1 in aggregates, resulting in the constitutive activation of Nrf2 and antioxidant defense. There is relatively little information about the relationships between Nrf2 and autophagy in muscle tissue. Autophagy is required for maintenance of muscle mass [145] and inhibition of autophagy causes muscle atrophy and myopathy [146]. Indeed, muscular dystrophy shows defective autophagy, and reactivation of autophagy rescues myofiber degeneration [147,148]. Autophagy is also required for the maintenance of SC stemness and prevention of SC senescence [102]. Moreover, defective autophagy in physiologically aged SCs and in young cells with impaired autophagy induces a senescent phenotype characterized by proteostasis, mitochondrial dysfunction and redox imbalance, resulting in a decline in the function and number of SCs, however re-establishment of autophagy reverses senescence and restores regenerative functions in geriatric SCs [102]. Yet, excess autophagy is detrimental to muscle trophism even in the context of muscular dystrophy [149] (Fig. 6B).

One report on a potential link between muscle tissue, regulation of redox homeostasis and autophagy showed that in the bed rest model of human disuse, redox imbalance, impairment of antioxidant defense systems and metabolic alteration occurred early, before muscle atrophy developed, and persisted through 35 days of bed rest [150]. In this context, Nrf2 turned out to be upregulated after 24 days of bed rest and interpreted to indicate ongoing redox imbalance and the activation of a compensatory, albeit insufficient mechanism. Interestingly, levels of the atrogenes, MuRF-1 and atrogin-1, did not change [150], suggesting that disuse-induced muscle atrophy might depend on decreased protein synthesis possibly consequent to persistent redox imbalance rather than on increased protein degradation. From the side of autophagy, these authors concluded that an increased activity of macroautophagy could contribute to the progression of muscle atrophy at late stages of bed rest [150]. Later on, the same group showed that in an animal model of disuse-induced muscle atrophy, redox imbalance could be successfully treated with the antioxidant, trolox, which could not prevent activation of catabolic pathways and muscle atrophy, though [151]. Instead, in this same experimental setting, muscle-specific overexpression of PGC-1α, a master regulator of mitochondrial biogenesis [152], prevented activation of catabolic systems and disuse muscle atrophy [153]. Thus, altered mitochondriogenesis appears to be the critical pathophysiological factor in disuse muscle atrophy, quite different from muscular dystrophy in which redox imbalance appears to play a major role [124,139]. Given the critical role of inflammation in the pathophysiology of muscular dystrophy [153–156], it is possible that improvement of histopathology and muscle performance in this latter context following antioxidant-based therapy relies on reduction of the inflammatory state.

Nrf2 is also upregulated in autophagic vacuolar myopathies consequent to treatment with hydroxychloroquine or colchicine [157], which resemble histopathologically several inherited skeletal myopathies including X-linked myopathy with excessive autophagy and infantile autophagic vacuolar myopathy [158,159], disorders that are characterized by defects in lysosomal degradation that lead to secondary accumulation of autophagic vacuoles. Also, mutations in nuclear lamina proteins cause p62 accumulation, activation of the Nrf2 pathway, and reductive stress [160] (Fig. 6B). Together, these findings raise the possibility that the aberrant activation of the Nrf2 pathway observed in inherited and acquired autophagic vacuolar myopathies is maladaptive and might contribute to the pathogenesis of these diseased states by generating reductive stress. The concept is emerging that appropriate ROS production is physiologically essential to maintain the redox balance and that reductive stress is as harmful as is oxidative stress [161].

5. Nrf2 in cardiac muscle

Redox signaling is one key element involved in cardiovascular diseases. Over the past years Nrf2 and the oxidoreductase thioredoxin-1 (Trx-1) have been identified as protective factors in cardiovascular disorders [162], with Trx-1 stimulating oxidative phosphorylation and the tricarboxylic acid cycle via PGC-1α and Nrf2 in cardiomyocytes [163] and Nrf2 stimulating Trx-1 expression [162]. A similar feed-forward loop to the Trx-1/Nrf2/Trx-1 axis above involves the Nrf2-induced, HO-1, that prevents cardiomyocyte apoptosis [164] via generation of carbon monoxide (CO) which stimulates superoxide dismutase-2 upregulation and mitochondrial H_2O_2 production, which in turn activates Akt/PKB. Akt deactivates glycogen synthase kinase-3β, which permits Nrf2 nuclear translocation and occupancy of 4 AREs in the nuclear respiratory factor-1 promoter (Fig. 7). The ensuing accumulation of nuclear respiratory factor-1 protein leads to gene activation for mitochondrial biogenesis. Nrf2 also upregulates $p27^{kip1}$ to protect against angiotensin II-induced cardiac hypertrophy [165]. Moreover, Nrf2 has been reported to operate downstream of NADPH oxidase-4, an important modulator of redox signaling, that activates the Nrf2-regulated pathway to regulate glutathione redox in cardiomyocytes [166] and to protect the heart in chronic hypertension [167]. Interestingly, Nrf2 has been recently proposed to protect mitochondria against oxidative stress by interacting with the mitochondrial outer membrane with no major effects on the level of protein oxidation [140]. Although the mechanism of Nrf2 docking to mitochondria in oxidative conditions remains to be elucidated, it has been speculated that mitochondrial Nrf2/Keapk1 might serve as a sensor for ROS production from the mitochondria, with mitochondrial ROS promoting Nrf2 release from Keap1 and shuffling to the nucleus [140]. In general, Nrf2 activation in ischemia and ischemia/reperfusion injury is being considered protective towards cardiomyocytes [161,168,169].

However, as mentioned earlier, the physiological flux of ROS regulates cellular processes essential for cell survival, differentiation, proliferation, and migration. Cardiomyocytes are no exception. Indeed, there is growing evidence that redox imbalance characterized by an excess of reducing equivalents creates reductive stress, that is harmful to biological systems as much as is oxidative stress [168,169]. Indeed, some oxidative modifications to proteins can be beneficial; preventing

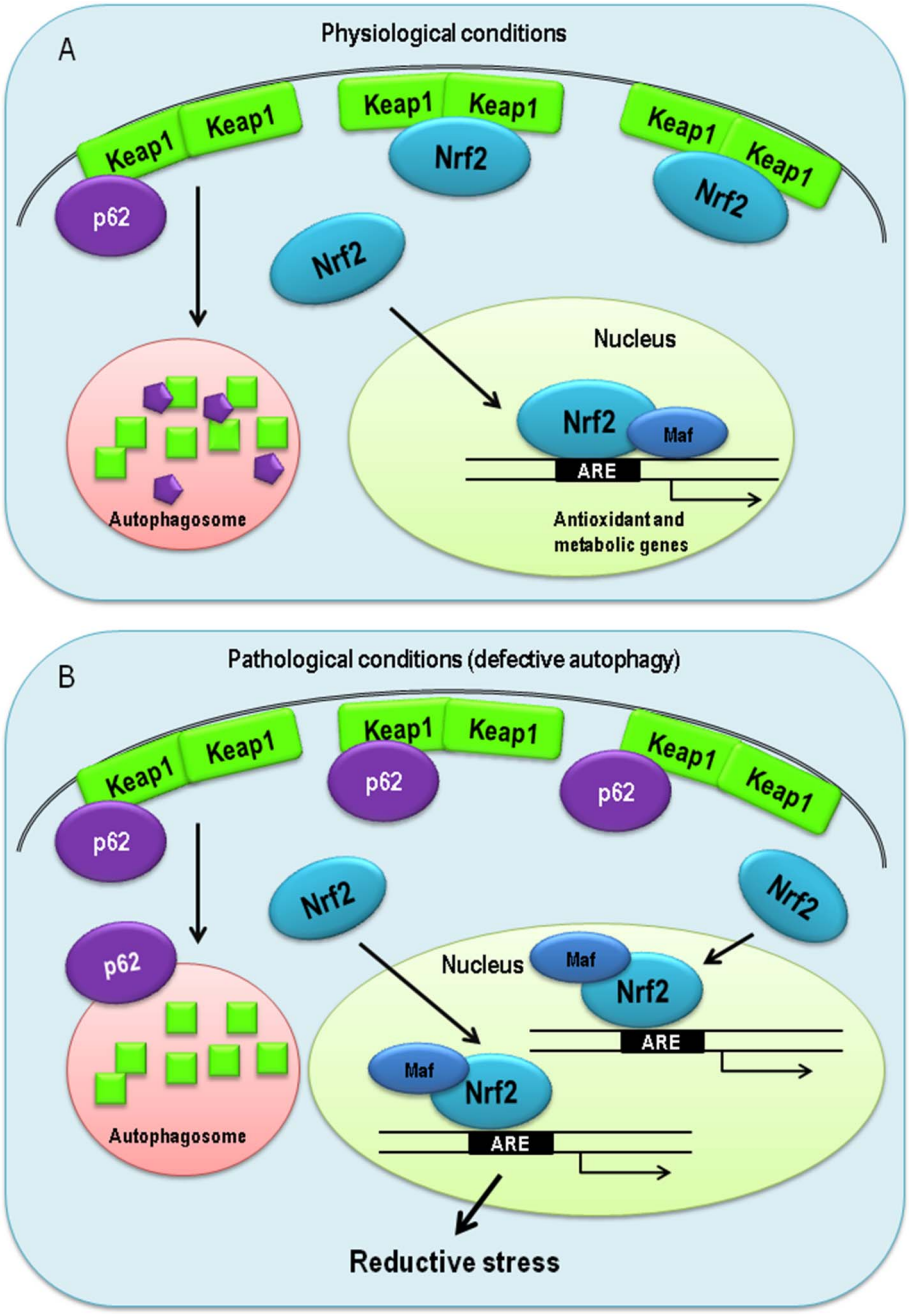

Fig. 6. Nrf2-Keap1/p62 interplay. (A) In physiological conditions levels of Keap1-p62 complexes are regulated by autophagy, which leads to the liberation of a fraction of Nrf2 and consequent Nrf2 antioxidant activity. (B) In conditions of defective autophagy accumulation of p62 results in sequestration of Keap1 with aberrant Nrf2 translocation to the nucleus causing reductive stress.

necessary cysteine oxidation may be detrimental. For example, structural disulfides are necessarily formed in the endoplasmic reticulum during protein synthesis [170], and ROS production by mitochondria or NADPH oxidase-4 have been shown to be important for receptor mediated signaling via reversible oxidation of phosphatases and consequent activation of protein kinases [171–174]. In this context, the cell compartment where ROS are produced and NADPH oxidase-4 activity appear to play a fundamental role.

6. Concluding remarks

Many aspects of the activation of the Nrf2 system in physiological and pathological settings have already been described, although the complex and finely tuned regulation of Nrf2 is still far from being fully resolved. Nrf2 as a potential target in disease prevention is well documented since its antioxidant effects lead to cell protection. By scavenging excessive ROS levels and restoring redox homeostasis, Nrf2 can prevent age-related muscle disorders and plays a crucial role in response to training exercise. On the other hand, uncontrolled Nrf2 activation can produce harmful consequences: in autophagic muscle disorders, Nrf2 is persistently activated with negative consequences on organ functions. In the presence of impaired autophagy, the accumulation of p62 causes a feed-back loop that amplifies the Nrf2 system. The chronic activation of Nrf2 in skeletal muscle results in changes in cellular redox potential, a response that contributes to muscle pathologies. Similarly, in cardiac muscle a tight control of redox is required as oxidative stress and reductive stress are equally harmful. Further work is required to elucidate the precise role(s) of Nrf2 in muscle

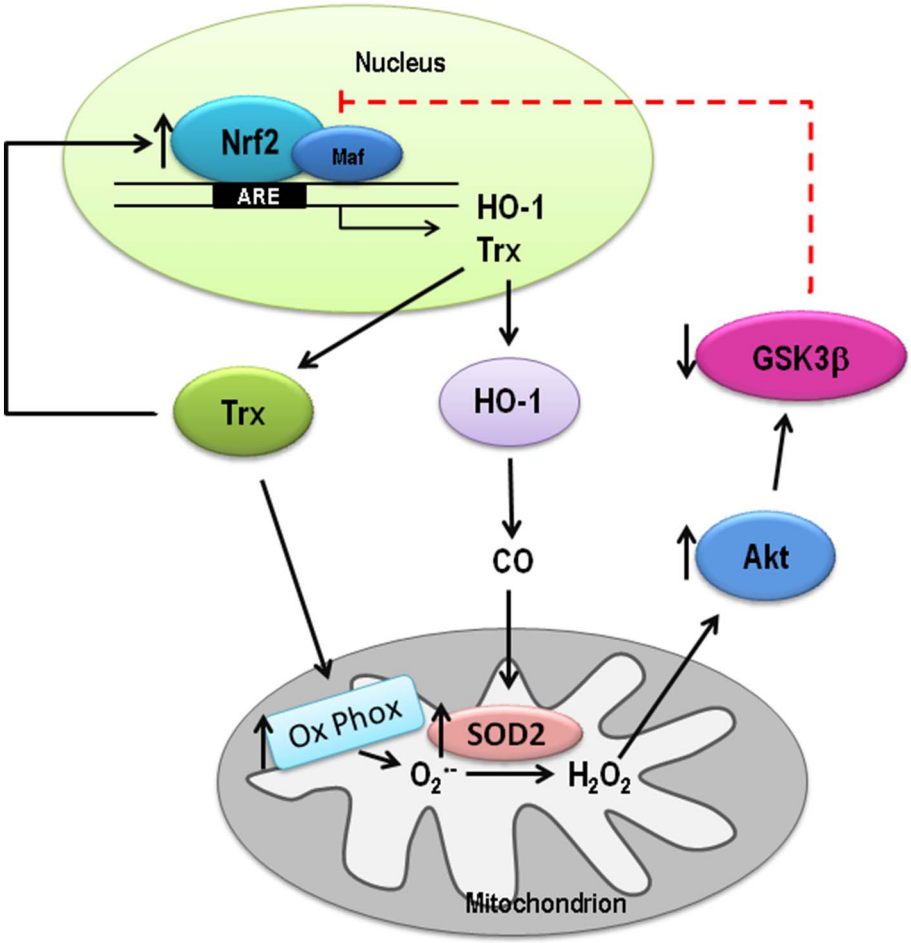

Fig. 7. Nrf2-Trx interplay in cardiac muscle. Nrf2 induces Trx-1 and HO-1. Trx-1 induces Nrf2 activation and stimulates oxidative phosphorylation resulting in increased mitochondrial superoxide anion generation. HO-1 generates carbon monoxide (CO) which stimulates superoxide dismutase-2 (SOD2) leading to mitochondrial H_2O_2 production. In turn, H_2O_2 stimulates Akt thereby inhibiting glycogen synthase kinase-3β (GSK-3β) which no longer can inhibit Nrf2 activity.

regeneration and trophism and in physiology and pathophysiology of cardiac muscle.

Transparency document

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