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NF- κ B in Oxidative Stress

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Abstract

The transcription factor nuclear factor- κ B (NF- κ B) modulates gene expression in diverse cellular processes such as innate immune response, embryogenesis and organ development, cell proliferation and apoptosis, and stress responses to a variety of noxious stimuli. When cellular production of reactive oxygen species (ROS) overwhelms its antioxidant capacity, it leads to a state of oxidative stress, which in turn contributes to the pathogenesis of several human diseases. Different models of oxidative stress have been studied to elucidate the effects of oxidant stress on NF- κ B related activities. ROS can both activate and repress NF- κ B signaling in a phase and context dependent manner. The NF- κ B pathway can have both anti- and pro-oxidant roles in the setting of oxidative stress. In this review, we focus on role of oxidative stress on different mediators of the NF- κ B pathway, and the role of NF- κ B activation in the modulation of oxidative stress. A greater understanding of the complex interplay between the NF- κ B signaling and oxidative stress may lead to the development of therapeutic strategies for the treatment of a myriad of human diseases for which oxidative stress has an etiologic role.

The NF- κ B pathway

Initially identified as a DNA binding protein in activated B cells [1], the transcription factor nuclear factor- κ B (NF- κ B) modulates gene expression in diverse cellular processes such as innate immune response, embryogenesis and organ development, cell proliferation and apoptosis, and stress responses to a variety of noxious stimuli [2]. The NF- κ B (nuclear factor kappa-light-chain-enhancer of activated B cells) transcription factor consists of homo- and heterodimers of five distinct proteins, the REL subfamily proteins (p65/RELA, RELB, and c-REL) and the NF- κ B subfamily proteins (p50, and p52, and its precursors p105 and p100, respectively). The canonical (also known as the classical pathway) and the non-canonical (or the alternative pathway) are the two main signaling pathways described that lead to the activation of NF- κ B target genes. p50, the product of p105, is involved in the canonical pathway usually in conjunction with RelA (or c-Rel), and is activated by cytokine

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receptors (IL-1R, TNFR) or pattern recognition receptors like the toll like receptors. The non-canonical pathway involves p52 (product of p100) and RelB and is triggered by lymphotoxin β receptor, B cell activating factor receptor 3, and CD40 [3] [2].

NF- κ B is normally localized in the cytoplasm as a heterodimer; the p50/p65 (RelA) being the most abundant form. The Rel homology domain (RHD) in these proteins is responsible for dimerization, recognition and binding to DNA as well as interaction with the inhibitory κ B (I κ B) proteins. The I κ B families of proteins possess typical ankyrin repeats that bind to the RHD of NF- κ B/REL proteins, and interfere with their function. The I- κ B proteins mask the DNA binding domain of NF- κ B/REL proteins and keep them sequestered in the cytoplasm. I- κ B proteins also possess nuclear export signals and remove NF- κ B proteins from the nucleus, and thereby keep the pathway in check. Inflammatory signals (eg: tumor necrosis factor alpha or lipopolysaccharide) induce phosphorylation of I- κ B proteins by upstream kinases (IKK), which lead to the ubiquitination and degradation of I- κ B. IKK β and NEMO are involved in the canonical pathway, while NIK and IKK- α participate in the non-canonical pathway. Active NF- κ B then translocates into the nucleus and activates the target genes [4]. Negative feedback loops comprising of I- κ B- α and ϵ and the deubiquitinase A20 function upstream of IKK to regulate activity [5]. Different members of the I- κ B family may have varied downstream effects depending on the type of stimulus. I- κ B α functions more rapidly and is primarily involved in determining NF- κ B signaling in response to cytokines. I- κ B- δ on the other hand has a longer half-life and is not subject to canonical IKK mediated degradation. This allows I- κ B- δ to accumulate and limit NF- κ B activation upon exposure to pathogen mediated TLR mediated signals. [6] NF- κ B thus oscillates, changing between an inactive form outside of the nucleus and an active form inside [7]. Environmental stimuli can modulate these oscillations, which can affect downstream gene expression that also cycles and resets.

Effect of increased oxidative stress on the NF- κ B pathway

When cellular production of ROS overwhelms the antioxidant capacity, this leads to a state of oxidative stress, which in turn contributes to the pathogenesis of several human diseases. The ROS molecules can mediate cellular toxicity by reacting with proteins (especially cysteine residues), lipids (lipid peroxidation), and nucleic acids (DNA damage and strand breaks). Different models of oxidative stress have been studied to elucidate the effects of oxidant stress on the NF- κ B signaling pathway. The prototypical activators of the NF- κ B pathway are comprised of tumor necrosis factor α (TNF- α), lipopolysaccharide (LPS), and interleukin 1 (IL-1) [8]. The role of ROS in NF- κ B activation by inflammatory cytokines and LPS has been the focus of several studies, and has revealed different mechanisms for different stimuli [9].

One of the molecules generated during conditions of oxidative stress generated by inflammatory signals is hydrogen peroxide (H₂O₂). In one of the early reports, in human T cells, NF- κ B was activated by micromolar concentrations of hydrogen peroxide and this activation was blocked by treatment of the cells with the anti-oxidant N-acetyl cysteine (NAC) [11]. However, it is now recognized that H₂O₂ may in fact not act as a direct inducer but more of a modulator of the NF- κ B pathway [10].

Redox regulation of NFκB

Endogenous redox regulating molecules like thioredoxin also play a role in NF-κB regulation in a model of oxidative stress involving UV irradiation. In the cytoplasm, thioredoxin has been shown to block the degradation of I-κB, while in the nucleus, it enhances NF-κB activity by increasing its ability to bind DNA [13]. Other cellular proteins like LC8 (8-kDa dynein light chain) can also play a role in the redox regulation of NF-κB pathway. LC8 is a component of the dynein motor complex but also binds to and modulates the biological functions of many proteins. It binds to I-κBα in a redox-dependent manner and thereby prevents its phosphorylation by IKK. Exposure to TNF-α and the resulting ROS production oxidized LC8 and resulted in its dissociation from I-κBα leading to NF-κB activation [14]. *In vitro*, modulation of the redox state of NF-κB (with alkylating or oxidizing agents) decreases DNA binding by modification of the free sulfhydryl groups. This could represent a post-translational control mechanism for this pathway under conditions of oxidative stress [15].

NF-κB heterodimers may be directly modified under conditions of increased oxidative stress. A cysteine residue (Cys-62) in the RHD domain of the p50 subunit is prone to oxidation, which decreases the DNA binding [16]. Interestingly, this domain exhibits spatial redox regulation, wherein it is oxidized in the cytoplasm but reduced in the nucleus. This reduction of NF-κB is mediated by the protein Ref-1 in the nucleus, which restores the DNA binding capacity [17]. Phosphorylation of Ser-276 on RelA has been shown to be ROS dependent [18], which is required for transcriptional expression of some NF-κB target genes. In this context, N-acetyl cysteine induces phosphorylation at Ser-536 and increases DNA binding by activating phosphatidylinositol-3 kinase (PI3K) [19]. Wu *et al* showed that exposure to sustained oxidative stress may lead to inactivation of the proteasome and subsequently inhibit NF-κB activation by impeding the degradation of I-κB [20]. Thus, the early phase of oxidative stress is associated with activation of the NF-κB pathway but sustained oxidative stress decreases activity.

ROS mediated oxidation of upstream kinases can also influence the NF-κB pathway. Korn *et al* showed that H₂O₂ markedly decreased the ability of TNF to induce IKK activity, resulting in the prevention of I-κB degradation and NF-κB activation. Direct addition of H₂O₂ to immunoprecipitated IKK complex inhibited enzyme activity and was associated with oxidation of cysteine residues [21]. Similar inhibition of IKK was noted with arsenite [22] and nitric oxide [23] both of which targeted the cysteine 179 residue IKK-β. In contrast, NIK (involved in the non-canonical pathway) was activated by H₂O₂ following IL-1β treatment leading to subsequent NIK-mediated phosphorylation of IKK-α and increased NF-κB activity [24].

The NF-κB pathway can also be induced via activation of the serine/threonine kinase Akt [25]. Kim *et al* showed that H₂O₂ modulates IKK-dependent NF-κB activation by promoting the redox-sensitive activation of the PI3K/Pten/Akt and NIK/IKK pathways. [26] These findings are summarized in Figure 1.

Interplay between Nrf2 and NF- κ B pathways

Complex molecular mechanisms (transcriptional and post-transcriptional) link Nrf2 and NF- κ B under conditions of oxidative stress in a cell-type dependent manner. Abrogation of Nrf2 increases NF- κ B activity leading to increased cytokine production, whereas NF- κ B modulates Nrf2 transcription and activity. Nrf2 knockout cells show more pronounced NF- κ B activity and enhanced IKK- β function [27] [28]. Heme oxygenase-1 also plays a role in Nrf2 mediated inhibition of NF- κ B by decreasing NF- κ B-mediated transcription of adhesion molecules in endothelial cells [29]. On the other hand, NF- κ B inhibits Nrf2 by competing for the transcriptional co-activator CBP (CREB-binding protein)-p300 complex [30]. In human acute myeloid leukemia cells, abnormal NF- κ B-driven constitutive expression of Nrf2 was reported. Lee et al showed that KEAP1 functions as an IKK β E3 ubiquitin ligase and can prevent NF- κ B pathway activation. The same protein also promotes NRF2 degradation through the 26S ubiquitin proteasome pathway [31]. Thus, NF- κ B can have divergent roles on Nrf2 expression and activity and vice-versa [32].

Anti- and pro-oxidant role of NF- κ B pathway in oxidative stress

NF- κ B may play a protective role under conditions of oxidative stress by suppressing ROS accumulation. Inhibition of NF- κ B activation results in an increase in TNF α -induced ROS production, lipid peroxidation and protein oxidation [33]. Modulation of autophagy may be another NF- κ B mediated protective mechanism. In retinal pigment epithelial cells under H₂O₂ induced oxidative stress, NF κ B p65 phosphorylation at Ser-536 was found to be critical for p62 upregulation, which promotes autophagy. A decrease in autophagy rendered the cells more susceptible to oxidative damage [34]. ROS have been shown to cause prolonged activation of the JNK pathway [35] by causing oxidation and inhibition of JNK-inactivating phosphatases via mechanisms entailing conversion of the catalytic cysteine to sulfenic acid. Decreases in NF- κ B-mediated inhibition of JNK activation contributes to TNF- α -induced apoptosis [36]. Thus, the anti-apoptotic function of NF- κ B maybe mediated by its downregulation of the JNK pathway, with ROS as the bridging molecules. [37] Wu et al showed that inhibition of NF- κ B activation during recovery from transient oxidative stress significantly reduced the cell viability thus showing that NF- κ B activation was important for cell recovery [20].

NF- κ B has also been shown to have many anti-oxidant targets. One of the well-known targets is manganese superoxide dismutase (MnSOD) [38]. In TNF- α treated Ewing's sarcoma cells, NF- κ B activation increased both thioredoxin and MnSOD levels [33]. Pham et al identified ferritin heavy chain as a pivotal mediator of antioxidant activity of NF- κ B following exposure to TNF- α . Ferritin heavy chain protects the cell from oxidative damage by preventing iron-mediated generation of highly reactive hydroxyl radicals from H₂O₂. [39]. Other reported anti-oxidant targets induced by NF- κ B include Glutathione S-transferase pi, Metallothionein-3, NAD(P)H dehydrogenase [quinone]1, heme oxygenase-1 and glutathione peroxidase-1 [37]. Alternatively, the NF- κ B pathway can also have a pro-oxidant role by induction of genes such as NADPH oxidase NOX2 subunit gp91phox [40]. These findings are summarized in Figure 2.

Role of the unfolded protein response (UPR) and ER Stress on NF- κ B pathway in oxidative stress

Activation of the unfolded protein response (UPR) on exposure to oxidative stress is an adaptive mechanism to preserve cell function and survival. Persistent oxidative stress and protein misfolding can lead to cellular apoptosis [41]. Oxidative stress can induce ER stress by causing inhibition of Ca^{2+} ATPase in the ER, accumulation of abnormal proteins modified by oxidation or decrease the function of key proteins (chaperones and foldases) involved in the UPR [12]. Similar to oxidative stress, ER stress also activates the NF- κ B pathway in the early phase and leads to its suppression in the late phase. In the early phase, phosphorylation of eIF2 α by PERK leads to translational suppression of I- κ B [42], IRE1–TRAF2 complexes recruit IKK, leading to phosphorylation and degradation of I- κ B [43] and activation of the ATF6 pathway leads to phosphorylation of Akt and consequent activation of NF- κ B [44]. In the late phase, down-regulation of TRAF2, up-regulation of A20, induction of C/EBP β , and/or dephosphorylation of Akt leads to suppression of the NF- κ B pathway [12].

Role of on NF- κ B pathway in hyperoxic lung injury

Exposure to hyperoxia produces increased oxidative stress in all organs but particularly in the lungs, and leads to hyperoxic lung injury in adult mice and alveolar and vascular developmental arrest in neonatal mice [45]. These conditions simulate ARDS (acute respiratory distress syndrome) and BPD (bronchopulmonary dysplasia) seen in human patients. Neonatal lungs preferentially activate the NF- κ B pathway upon exposure to hyperoxia compared to adult lungs, suggesting a maturational difference [46]. Murine alveolar epithelial cells exposed to hyperoxia show activation of the NF- κ B pathway and is associated with a decrease in I- κ B α expression [47]. Conversely, sustained activation of NF- κ B has been shown to attenuate hyperoxia-induced mortality in adults and improve survival and preserve lung development in neonatal mice [48]. This sustained induction of the NF- κ B pathway decreases apoptosis and protects the neonatal lung and human pulmonary epithelial cells from acute hyperoxic injury [46,49]. Furthermore, NF- κ B activation preserves alveolarization by inhibiting the anti-angiogenic cytokine; macrophage inflammatory protein 2, in neonatal mice exposed to LPS [50]. Sex-specific differences in activation of the NF- κ B pathway under hyperoxic conditions have been reported in neonates both *in vivo* and *in vitro* with female lungs and endothelial cells showing greater activation compared to similarly exposed males [51, 52][52].

Summary and concluding remarks

Modulation of the NF- κ B pathway by oxidative stress is cell type and context specific. Over the past few decades, considerable progress has been made in understanding the mechanisms underlying the redox regulation of the NF- κ B pathway. Further studies in this important area will help us understand how interactions between NF- κ B pathway and oxidative stress are integrated into other cellular signaling pathways. A greater understanding of the complex interplay between the NF- κ B pathway and oxidative stress may lead to the development of therapeutic strategies for the treatment of human disease.

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Highlights

1. Modulation of the NF- κ B pathway by oxidative stress is cell type and context specific.
2. Reactive oxygen species have bidirectional effects on NF- κ B signaling, causing either activation or suppression depending on the duration and context of exposure.
3. Activation of NF- κ B pathway can have both anti- and pro-oxidant effects

Figure 1. Effect of increased oxidative stress on NF- κ B pathway

Oxidative stress can both activate and inhibit the NF- κ B pathway by targeting the upstream kinases (IKK, NIK and Akt), facilitating or inhibiting the degradation of I- κ B or modulation the nuclear translocation and DNA binding of the transcription factor by modifying the NF- κ B heterodimers. (RHD: Rel homology domain)

Figure 2. Anti- and pro-oxidant role of NF-κB pathway in oxidative stress

The NF-κB pathway may play a protective role in the setting of oxidative stress by various mechanisms as shown. Activation of the pathway may also cause induction of pro-oxidant genes such as NADPH oxidase NOX2 subunit gp91phox.