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Review Article

Bidirectional regulation of NF-κB by reactive oxygen species: A role of unfolded protein response

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ABSTRACT

Nuclear factor-κB (NF-κB) is a transcription factor that plays a crucial role in coordinating innate and adaptive immunity, inflammation, and apoptotic cell death. NF-κB is activated by various inflammatory stimuli including peptide factors and infectious microbes. It is also known as a redox-sensitive transcription factor activated by reactive oxygen species (ROS). Over the past decades, various investigators focused on the role of ROS in the activation of NF-κB by cytokines and lipopolysaccharides. However, recent studies also suggested that ROS have the potential to repress NF-κB activity. Currently, it is not well addressed how ROS regulate activity of NF-κB in a bidirectional fashion. In this paper, we summarize evidence for positive and negative regulation of NF-κB by ROS, possible redox-sensitive targets for NF-κB signaling, and mechanisms underlying biphasic and bidirectional influences of ROS on NF-κB, especially focusing on a role of ROS-mediated induction of endoplasmic reticulum stress.

Contents

Abbreviations: NF-κB, nuclear factor-κB; UV, ultraviolet; IκB, inhibitor of NF-κB; IKK, IκB kinase; NEMO, NF-κB essential modulator; TNFR, tumor necrosis factor receptor; IL-1R, interleukin-1 receptor; NIK, NF-κB inducing kinase; LPS, lipopolysaccharide; PKD, protein kinase D; H/R, hypoxia/reoxygenation; SHIP-1, SH2-containing inositol 5′-phosphatase 1; PI3K, phosphatidylinositol 3-kinase; PKB, protein kinase B (Akt); PP2A, protein phosphatase 2A; HDAC, histone deacetylase; PKAc, protein kinase A catalytic subunit; TRAF, TNF receptor-associated factor; RIP1, receptor interacting protein 1; HO-1, heme oxygenase 1; ER, endoplasmic reticulum; UPR, unfolded protein response; ATF6, activating transcription factor 6; IRE1, inositol-requiring enzyme 1; PERK, PKR-like ER kinase; eIF2α, eukaryotic translation initiation factor 2α; CHOP, CCAAT/enhancer-binding protein homologous protein; S1P, site-1 protease; XBP1, X-box-binding protein 1; ERSE, ER stress response element; UPRE, UPR element; GRP78, 78-kDa glucose-regulated protein (BiP); ERAD, ER-associated degradation; C/EBPβ, CCAAT/enhancer-binding protein β; mTORC1, mammalian target of rapamycin complex 1; Nrf2, nuclear factor-E2-related factor 2; Keap-1, Kelch-like ECH-associated protein 1; DHMEQ, dehydroxymethylepoxyquinomicin

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Introduction

The transcription factor nuclear factor-κB (NF-κB) controls expression of a wide range of genes that regulate immune responses, embryogenesis and development, cell growth and proliferation, apoptosis and survival, and stress responses to a variety of noxious stimuli. The NF-κB network is critical for human health, and aberrant NF-κB activation contributes to development of various inflammatory, autoimmune and malignant disorders including rheumatoid arthritis, atherosclerosis, multiple sclerosis, inflammatory bowel diseases, and malignant tumors [1–3]. Understanding of molecular mechanisms underlying the control of NF-κB is essential for development of effective anti-inflammatory agents as well as efficient chemotherapeutic drugs.

NF-κB is activated by a wide range of external and internal stimuli including inflammatory cytokines, bacterial components, ultraviolet (UV) light, and reactive oxygen species (ROS) [4]. The Rel/NF-κB family consists five major members: p50, p52, p65 (RelA), RelB, and c-Rel. p65, RelB, and c-Rel, but not p50 and p52, contain C-terminal transactivation domains required for gene transcription. The Rel/NF-κB family of molecules forms homodimers or heterodimers and function as transcription factors [5]. In physiological conditions, NF-κB is sequestered in the cytoplasm by binding to inhibitory proteins called inhibitors of NF-κB (IκBs). When cells are stimulated, however, IκB kinase (IKK) complexes including IKKα, IKKβ, and NF-κB essential modulator (NEMO, also called IKKγ) are rapidly activated, resulting in phosphorylation and proteasome-mediated degradation of IκBs [6,7]. The resultant free NF-κB translocates into the nucleus, binds to its consensus sequence, and induces transcription of target genes. Activated NF-κB also causes production of IκBα, which enters the nucleus, captures freed NF-κB, and facilitates its export to the cytoplasm for termination of transcription [4].

There are two major signaling pathways that induce NF-κB activation [8]. The first is the canonical pathway (also called classical pathway) initiated by cytokine receptors [e.g., tumor necrosis factor receptor (TNFR) and interleukin-1 receptor (IL-1R)] and pattern recognition receptors (e.g., Toll-like receptors) [9–11]. These signals activate IKK complexes, especially IKKβ and NEMO, leading to phosphorylation and degradation of IκBα [8]. The second is the NEMO-independent, noncanonical pathway (also called alternative pathway). This pathway is triggered through lymphotoxin β receptor, B cell activating factor receptor 3, and CD40, causes activation of NF-κB inducing kinase (NIK), and induces activation of IKKα homodimers, leading to processing of p100 into p52 [12–15]. Then p52 forms heterodimer with RelB, translocates to the nucleus, and induces target genes [8].

In these signaling processes, several investigators suggested roles of ROS in the activation of NF-κB [16]. ROS are generated following exposure to cytokines and lipopolysaccharide (LPS) [17], and treatment with antioxidants blocks activation of NF-κB by these stimuli [18–20]. ROS such as superoxide anion ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), and hydroxyl radical ($OH^{\bullet}$) are generated in cells from several different sources including mitochondrial respiratory chain complexes, radical-generating xanthine/xanthine oxidase, and plasma membrane NADPH oxidase [21]. $O_2^{\bullet -}$ is the first reductant generated from oxygen molecules. $O_2^{\bullet -}$ is converted to H_2O_2 by mitochondrial superoxide dismutase (SOD), resulting in diffusion of H_2O_2 to the cytoplasm. In the presence of iron, H_2O_2 is converted to the highly reactive $OH^{\bullet}$ through the Fenton reaction. Of note, $O_2^{\bullet -}$ also acts as a reducing agent that facilitates conversion of oxidized transition metal ions to their reduced forms, leading to enhancement of the Fenton reaction. Moreover, $O_2^{\bullet -}$ rapidly reacts with nitric oxide (NO) and converted to a toxic metabolite peroxynitrite ($ONOO^-$) [22]. These ROS may cause oxidative damage of macromolecules including nucleic acids, lipids, and proteins [23,24]. ROS also function as second messengers in a number of signal transduction pathways including NF-κB signaling [25]. However, the role of ROS in NF-κB signaling is not so simple as has been proposed. In some situations, ROS trigger activation of NF-κB, whereas in other circumstances, ROS may inhibit NF-κB activity [26]. Currently, it is not well understood why and how ROS regulate NF-κB in a bidirectional fashion. In this paper, we summarize evidence for positive and negative regulation of NF-κB by ROS, possible redox-sensitive targets in NF-κB signaling, and mechanisms underlying phase- and context-dependent influences of ROS on NF-κB.

Phase-dependent regulation of NF-κB by ROS

Activation of NF-κB by ROS in the early phase

A previous review summarized roles of ROS in the activation of NF-κB [27]. A number of reports showed that ROS (or generators of ROS) have the potential to activate NF-κB in various cell types, as summarized in Table 1. However, mechanisms underlying oxidative stress-induced activation of NF-κB are different from cell type to cell type. In cancer cells, ROS-induced NF-κB activation seems to be regulated mainly by IKK complexes. Storz and colleagues reported that, in human cervical cancer cells (HeLa), H_2O_2 induced phosphorylation of protein kinase D (PKD) and consequent phosphorylation of IKKβ, leading to activation of NF-κB. They showed that the activation of PKD by ROS was mediated by both Src and Abl tyrosine kinases [28,29]. In contrast, Li et al. reported that, in human breast cancer cells (MCF7), H_2O_2 induced activation of NIK and NIK-mediated phosphorylation of IKKα, leading to activation of NF-κB via a noncanonical pathway [30]. Of note, H_2O_2 did not affect phosphorylation of IKKβ, and only the IKKα-dependent signaling was activated by H_2O_2. However, Fan et al. reported that, in HeLa cells, hypoxia/reoxygenation (H/R) induced ROS-mediated phosphorylation of IκBα at Tyr42 and consequent activation of NF-κB independently of the IKK pathway. Treatment with an inhibitor of c-Src significantly inhibited H/R-triggered phosphorylation of IκBα, suggesting involvement of c-Src in H/R-induced, ROS-mediated activation of NF-κB [31].

In leukocytes such as T lymphocytes, IκBα is a primary target for ROS to induce NF-κB signaling. Typically, inflammatory cytokines such as TNF-α and IL-1β phosphorylate IκBα on Ser32 and Ser36, leading to its proteasome-mediated degradation [7]. Using leukemic cells, Gloire et al. reported that H_2O_2 induced IKK-mediated phosphorylation of IκBα at Ser32 and Ser36 and that it was dependent on SH2-containing inositol 5′-phosphatase 1 (SHIP-1)