ANTIOXIDANTS & REDOX SIGNALING
Volume 7, Numbers 3 & 4, 2005
© Mary Ann Liebert, Inc.

Forum Review

Redox Regulation of NF-κB Activation: Distinct Redox Regulation Between the Cytoplasm and the Nucleus

YASUAKI KABE, KOZUE ANDO, SATOSHI HIRAO,
MAKOTO YOSHIDA, and HIROSHI HANDA

ABSTRACT

Reduction/oxidation (redox) regulation mediates numerous cellular responses and contributes to several physiological diseases. The transcription factor nuclear factor κB (NF-κB) is known to be a redox-sensitive factor. NF-κB plays a central role in immune responses and inflammation, through regulation of the gene expression of a large number of cytokines and other immune response genes. NF-κB is trapped in the cytoplasm in stimulated cells and translocates into the nucleus in response to several stimuli, including oxidative stress. Reactive oxygen species enhance the signal transduction pathways for NF-κB activation in the cytoplasm and translocation into the nucleus. In contrast, the DNA binding activity of oxidized NF-κB is significantly diminished, and that activity is restored by reducing enzymes, such as thioredoxin or redox factor 1. This review describes the signal transduction pathways for NF-κB activation and redox regulation of NF-kB activation in the cytoplasm and nucleus. *Antioxid. Redox Signal.* 7, 395–403.

INTRODUCTION

MOLECULAR OXYGEN is important for aerobic organisms using an electron acceptor in respiration. Although respiration is essential for generating energy in living organisms, it is harmful as well, due to formation of reactive oxygen species (ROS). ROS include the superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radical ($OH^\bullet$), which are generated from incomplete reduction of dioxygen primarily through mainly mitochondrial oxidative metabolism. ROS, which cause oxidative stress, can easily react with biological macromolecules, resulting in lipid peroxidation, strand breaks in nucleic acids, and oxidation of proteins. In contrast, it is known that several types of intracellular antioxidant molecules, such as glutathione (GSH), catalase, superoxide dismutase (SOD), and thioredoxin (TRX), protect cells from oxidative damage. For instance, ROS are reduced by GSH, in which the thiol residue is changed from GSH to GSSG. Regulation of intracellular reduction/oxidation processes is referred to as "redox" regulation.

In mammalian cells, the presence of ROS not only results in cell damage, but also triggers activation of protein kinase pathways, which regulate gene expression and control cell proliferation. In particular, it has been shown that ROS production modulates the immune response and is a critical regulator of cellular function. Activation of the transcription factor nuclear factor-κB (NF-κB) is known to be regulated by ROS (for review, see 33). NF-κB is a ubiquitous transcription factor that plays a crucial role in the regulation of numerous genes involved in immune response to pathogens and in cellular defense mechanisms. ROS can modulate NF-κB activation both positively and negatively. Studies of ROS regulation of NF-κB activation will provide new insight into understanding immune function and developing therapeutic agents for inflammatory diseases. Under basal conditions, NF-κB is localized in the cytoplasm in an inactive form; in response to stimuli, NF-κB is allowed to translocate into the nucleus where it activates target genes. This review will summarize recent advances in our understanding of the redox regulation of NF-κB activation, as well as the redox regulation of NF-

Graduate School of Bioscience and Biotechnology, Tokyo Institute of Technology, Yokohama, Japan.

κB DNA binding activity in the nucleus by redox factor 1 (Ref-1).

NF-κB STRUCTURE AND PRINCIPAL FEATURES

NF-κB was originally identified as a transcriptional activator regulating κ immunoglobulin gene expression (78). NF-κB transcriptional activity was induced in response to several stimuli, including tumor necrosis factor-α (TNFα), interleukin-1 (IL-1), lipopolysaccharide (LPS), H_2O_2, and T-cell receptor induction, and so on. Typically, NF-κB induces gene expression of a large number of immune molecules, including cytokines (IL-2, IL-6, IL-8, interferon-γ, TNFα), growth factors (granulocyte, monocyte, and granulocyte-monocyte colony-stimulating factors), immune receptors (T-cell receptor, MHC class I, IL-2 receptors, Fas), adhesion molecules (E-selectin, ICAM-1), and inducible nitric oxide (NO) synthase, among others (for review, see 5). Furthermore, NF-κB plays an important role in both apoptosis and cellular proliferation (for review, see 65). The NF-κB p65 subunit-deficient mouse exhibits embryonic lethality due to massive degeneration of the liver by programmed cell death or apoptosis of cells (8). The p65-deficient cells show an enhanced sensitivity to TNF-induced cell death (89). NF-κB induces several antiapoptotic molecules, including A20, inhibitor of apoptosis proteins c-IAP1 and c-IAP2, TNF receptor (TNFR)-associated factor 1 (TRAF1), TRAF2, Bcl-2, and Bcl-X (for review, see 65). In some cases, aberrant expression of NF-κB is attributed to oncogenesis and resistance of tumor chemotherapy (for review, see 68).

NF-κB is a member of the Rel family proteins, which include p50/p105, p52/p100, p65 (RelA), RelB, and c-Rel. These proteins form homodimers or heterodimers with other Rel family proteins (for review, see 90). As illustrated in Fig. 1, each NF-κB/Rel family protein has a conserved domain as the Rel homology domain in the amino-terminal region of ~300 amino acids. The Rel homology domain consists of a DNA binding domain, a dimerization domain, and a nuclear localization signal. Within the DNA binding domain, the Cys62 residue of the p50 subunit is critical for ROS-regulated DNA binding (49, 52). The carboxy-terminal domains of the Rel family proteins are divided into two classes. p50/p105 and p52/p100 subunits have the ankyrin repeats motif in the carboxy-terminal region. This region is removed from p105 or p100 by proteolysis, generating the mature NF-κB subunits p50 or p52, respectively (10, 19). The precursor subunit as p105 or p100 plays the inhibitory role for NF-κB activation (70). In contrast, p65, RelB, and c-Rel have transactivation domains in their carboxy-terminal domains, and protein kinase A phosphorylation of Ser276 of the p65 subunit has been shown to enhance its transcriptional activity (100). Although Rel family proteins can form homodimers with each other (except RelB), the most prevalent form is a heterodimer of p50 and p65, which binds with high affinity to the DNA consensus sequence 5′-GGGPuNNPyPyCC-3′ and exhibits transactivation (4, 88).

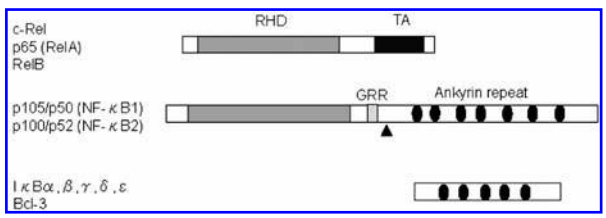

FIG. 1. The representative structures of NF-κB/Rel family proteins and IκBs. Rel family proteins have a conserved domain, the Rel homology domain (RHD). p65, RelB, and c-Rel have a transactivation domain (TA) in the carboxy-terminal region. The central region of p105/p50 and p100/p52 includes a protease cleavage site (marked by triangle) and a glycine-rich region (GRR), which is a protease recognition sequence. The carboxy-terminal region of p50 and p52 has an ankyrin repeat domain, which shares homology with IκB family proteins.

NF-κB is maintained in the cytoplasm through its interaction with the inhibitor of NF-κB (IκB) in unstimulated cells. Several members of the IκB family proteins have been identified, including IκBα, β, γ, δ, ϵ, and Bcl-3. Each IκB family protein has ankyrin repeats, which share homology with the carboxy-terminal region of the NF-κB precursors p105 and p100 (for review, see 90). Crystal structure analysis of the NF-κB/IκB complex clearly shows that interaction of NF-κB with IκB induces a conformational change in the NF-κB subunit that masks the nuclear localization signal region of NF-κB (29, 32). The NF-κB/IκB interaction is disrupted by modification of IκB phosphorylation sites in response to stimulation. Phosphorylation of IκB results in its ubiquitination and degradation and, consequently, NF-κB is activated and translocates from the cytoplasm to the nucleus. Activated NF-κB induces expression of numerous target genes, including the IκBα and β genes (41, 86). It is thought that newly synthesized IκB helps terminate NF-κB activation by resequestering NF-κB.

REGULATION OF SERINE PHOSPHORYLATION OF IκB

In unstimulated cells, NF-κB subunits are trapped in the cytoplasm by their interaction with IκB. In response to various stimuli, IκB undergoes phosphorylation on serine/threonine residues, ubiquitination, and subsequent proteolytic degradation, thereby releasing NF-κB to translocate into the nucleus and activate gene expression. The signal transduction pathway mediating IκB serine phosphorylation upon TNFα stimulation has been well elucidated (for review, see 6). As shown in Fig. 2, TNFα binds TNFR2 and recruits TRAF2 to TNFR2 (72). Activated TRAF2 leads to activation of NF-κB-inducing kinase (NIK), and also mitogen-activated protein (MAP) kinases (7, 50, 66). NIK interacts with IκB kinase (IKK) (69). IKK was originally identified as a multiprotein kinase complex, which includes the IKKα and IKKβ kinases that specifically phosphorylate Ser32 and Ser36, respectively, of IκBα (42, 69). The serine-phosphorylated IκB is ubiquitinated and degraded. Additionally, NF-κB activation by IL-1 or LPS stimulation also activates the IKK pathway and phos-

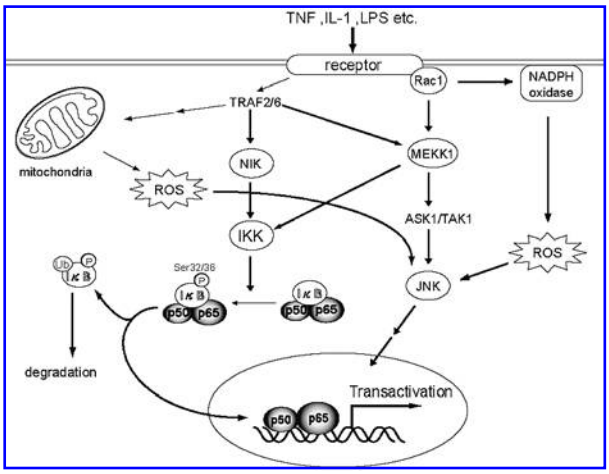

FIG. 2. Redox regulation of NF-κB activation via serine phosphorylation of IκB. TNF or other stimuli induce the phosphorylation of IκB Ser32/Ser36 through parallel pathways: TRAF2/6–NIK or TRAF2/6–MEKK1. Phosphorylated IκB undergoes proteosomal degradation allowing NF-κB to translocate into the nucleus. MEKK1-mediated JNK activation results in further activation of NF-κB. ROS generated by stimulation of mitochondria or NADPH oxidase synergistically induce NF-κB activation.

phorylates the serine residues of IκB (57, 97). It has been reported that the cellular reductant *N*-acetylcysteine (NAC) represses TNF-induced NF-κB activation (63). NAC also inhibits phosphorylation of NIK, IKKα, and IKKβ in TNF-stimulated cells. Recently, Hayakawa *et al.* showed that the inhibition NF-κB activation by NAC and pyrrolidinedithiocarbamate (PDTC) is independent of antioxidative function upon TNF stimulation (22). They showed that NAC directly bound to TNFR1 and inhibited TNF-mediated signaling. Furthermore, PDTC inhibits ubiquitin ligase activity toward phosphorylation of IκBα, independent of ROS. In contrast, H_2O_2 increases and prolongs the activity of TNFα-activated IKKα in HeLa cells, but it has been known that H_2O_2-induced NF-κB activation is highly cell type-dependent (36). Thus, NF-κB activation does not seem to be a universal response to oxidative stress.

The tyrosine kinases Src and Abl are activated in response to oxidative stress and target cell death signals to mitochondria (40). Recently, Storz and Toker showed that protein kinase D (PKD) was required for oxidative stress-induced NF-κB activation by inducing tyrosine phosphorylation of IKK in HeLa cells (83). PKD activation in response to H_2O_2 stimulation is mediated by Src and Abl, via phosphorylation of Tyr463 in the PKD pleckstrin homology domain. Furthermore, oxidative stress-activated Src induced the activation of not only the Abl-PKD pathway, but also the protein kinase Cδ (PKCδ) pathway (84). PKCδ, in turn, phosphorylates Ser738/742 of PKD, independently of Abl-mediated phosphorylation. PKD activation requires the coordinated signaling of both the Src-Abl and Src-PKCδ pathways. As mentioned later, oxidative stress, such as H_2O_2 production, also induces phosphorylation of IκB, via activation of protein tyrosine kinases (PTKs). It is still unclear which of these diverse pathways of IκB phosphorylation at serine or tyrosine residues results from oxidative stress.

REDOX REGULATION OF NF-κB ACTIVATION VIA THE MAP KINASE PATHWAY

TNF, IL-1, or LPS stimulation induces not only activation of the IKK pathway, but also activation of the MAP kinase pathways mediated by c-Jun amino-terminal kinases (JNK) and p38, which are activated by TRAF2 upon TNF stimulation (82). It has been reported that TNF-activated TRAF2 interacts with several MAP kinase kinase kinases (MAP3Ks or MEKKs), thereby activating JNK or p38 (for review, see 44). MEKK1 interacts with the RING finger domain of activated TRAF2 or TRAF6 (7). The MAP3Ks, transforming growth factor-β-activated kinase 1 (TAK1) and apoptosis signal-regulating kinase 1 (ASK1), have been also implicated in TRAF-dependent signaling pathways. IL-1 stimulation activates TAK1 through TRAF6 (60), whereas TNF stimulation activates ASK1 via TRAF2 (62). JNK coordinately activates IKK and induces phosphorylation of IκB serine residues in response to TNF (42). Furthermore, MEKK1 directly activates IKKα and β within the IKK complex (42, 43). NIK can also directly activate IKKα and β (see below), but it remains unclear whether NIK and JNK pathways are independent or overlapping mechanisms of NF-κB activation. Activated JNK mediates many cellular functions, including apoptosis, cellular proliferation, tumorigenesis, and embryonic morphogenesis (for review, see 14). Activated JNK mediates serine phosphorylation of c-Jun (67), and phosphorylated c-Jun recruits its transcriptional coactivator CBP/p300 to from an active transcription factor (3). JNK also interacts with the NF-κB subunit c-Rel and induces NF-κB transactivation, but JNK does not directly phosphorylate NF-κB subunits (54). The mechanism of NF-κB activation by JNK is still unclear.

It is known that under TNF or IL-1 induction, intracellular ROS levels rise and ROS production up-regulates the JNK-mediated NF-κB activation (47). The small GTP binding protein Rac1, which belongs to the Ras superfamily of proteins, mediates signaling downstream of the IL-1 or LPS (CD14) receptors (64, 91). Rac proteins regulate NF-κB activity by activating JNK (13, 56). JNK activation by Rac is mediated by MEKK1, which phosphorylates JNK (16, 45, 74). The Rac proteins are also involved in the assembly of the neutrophil plasma membrane-associated NADPH oxidase system and regulate NADP oxidase-mediated ROS production (1, 37). Sulciner *et al.* showed that the constitutively active mutant of Rac1, V12rac1, induced NF-κB activity through a redox-dependent pathway in HeLa cells (85). Expression of V12rac1 increased intracellular ROS, and treatment with the antioxidants PDTC or NAC decreased NF-κB activation by V12rac1. Rac-induced ROS production is also required for NF-κB activation upon IL-1 or LPS stimulation (11, 75). In contrast, TNF stimulation of mitochondrial ROS production, which also induces NF-kB activity, depends on TRAF2 (12). Furthermore, TNF induces Mn-SOD expression in mitochondria and enhances intracellular ROS levels, independently of Rac-

mediated ROS production by IL-1 or LPS stimulation (71). Thus, ROS production is closely correlated with NF-κB activation via the IKK pathway, but a full understanding of the molecular mechanisms of ROS-mediated NF-κB activation will require further studies.

REDOX REGULATION VIA TYROSINE PHOSPHORYLATION OF IκB

In addition to activation of NF-κB via serine phosphorylation of IκB, IκBα is also regulated by phosphorylation at Tyr42 (80), as illustrated in Fig. 3. Exposure of cells to hypoxia or H_2O_2 stimulates IκBα tyrosine phosphorylation and NF-κB activation (38, 77). Interestingly, the tyrosine phosphatase inhibitor pervanadate induces IκBα tyrosine phosphorylation and activates NF-κB without proteolytic degradation of IκBα (31). Engagement of receptor-associated PTKs stimulates the ras/raf1/MAP kinases pathway (for review, see 35). Lck, a member of the Src family PTKs, is activated by oxidative stress, such as diamide or H_2O_2 (59, 99). In T-lymphocytes, induction of IκBα tyrosine phosphorylation and NF-κB activation in response to treatment with pervanadate or hypoxia/reoxygenation (H/R) is dependent on Lck (31, 46). Analysis of Lck-deficient JCaM1 cells demonstrated that Lck is required for ceramide-induced NF-κB activation, but not TNFα-mediated induction of NF-κB activity (51). Livolsi *et al.* showed that loss of Lck in Jurkat cells suppressed the phosphorylation of Tyr42 of IκBα (46). Furthermore, H/R exposure activates Lck and results in IκBα tyrosine phosphorylation (48).

Similarly, it is known that Src is required for NF-κB activation by UV irradiation or TNFα stimulation (2, 17). Fan *et al.* showed that under H/R or pervanadate stimulation, the phosphorylation of IκBα Tyr42 is significantly decreased in the presence of the Src inhibitor protein phosphatase 2 or in Src-deficient T-lymphocytes (20). Furthermore, overexpression of the ROS scavengers catalase or glutathione peroxidase-1, but not Mn-SOD or Cu,Zn-SOD, reduced Src kinase activity, IκBα Tyr42 phosphorylation, and NF-κB activation in response to pervanadate stimulation. These results suggested that ROS may regulate the signaling pathways mediating IκBα tyrosine phosphorylation. In contrast, Krejsa *et al.* showed that the activation of NF-κB by pervanadate was independent of redox regulation (39). Treatment with antioxidants, such as PDTC or NAC, diminished both intracellular oxidation and pervanadate-induced tyrosine phosphorylation. However, antioxidants did not block the DNA binding activity of NF-κB, induced by the pervanadate compounds, sodium oxodiperoxo(1,10-phenanthroline)vanadate [pV(phen)] or bis(maltolato)-oxovanadium(IV) (BMOV) in Jurkat cells. However, ROS regulation of IκBα phosphorylation may differ, depending on the cell type or stimulation conditions, and the molecular mechanism of pervanadate-induced NF-κB activation is unclear

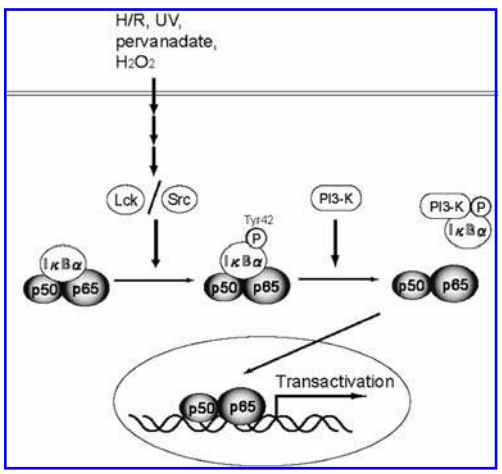

FIG. 3. Redox regulation of NF-κB activation via tyrosine phosphorylation of IκB. Oxidative stress or other stimuli induce the activation of tyrosine kinases, Lck or Src, and result in the phosphorylation of IκB Tyr42. NF-κB is released from phosphorylated IκB and translocates into the nucleus. Phosphorylated IκB interacts with PI3-K.

As mentioned above, tyrosine phosphorylation of IκBα does not lead to proteolytic degradation of IκBα. Beraud *et al.* showed that the p85 subunit of phosphatidylinositol 3-kinase (PI3-K) was an interactor of tyrosine-phosphorylated IκBα using a phosphor-peptide of the Tyr42 region of IκBα (9). Furthermore, the PI3-K inhibitor wortmannin repressed the activation of NF-κB, but did not affect tyrosine phosphorylation of IκBα in response to pervanadate induction. Sizemore *et al.* showed that treatment with the PI3-K inhibitor LY294,002 did not affect NF-κB nuclear translocation or DNA binding activity upon IL-1 stimulation, but decreased the phosphorylation of p65/RelA and repressed p65/RelA mediated transactivation (81). Furthermore, Akt, which is the PI3-K-activated protein kinase, also induces p65/RelA activation. The exact mechanism mediating the interaction between PI3-K and Tyr42-phosphorylated IκBα is unclear, but this interaction may mediate PI3-K/Akt-dependent p65/RelA transcription.

REDOX REGULATION OF NF-κB DNA BINDING ACTIVITY IN THE NUCLEUS

In the cytoplasm, oxidative stress or ROS can directly or synergistically mediate an up-regulation of NF-κB activation. In contrast, it is known that oxidation of NF-κB decreases its DNA binding activity in the nucleus (87). Under oxidative conditions, Cys62 of the p50 subunit is critical to DNA binding activity *in vitro* (51). Furthermore, NO also inhibits the NF-κB DNA binding activity, through nitrosylation of the p50 Cys62 (52). Activation of NF-κB induces a large amount of NO production, by up-regulating the expression of inducible NO synthase (96). It is thought that NO production serves as a negative regulator of NF-κB activation in the nucleus.

TRX is a ubiquitously expressed small protein, which can reduce oxidized proteins, including activator protein-1

(AP-1) (76). TRX can also reduce the oxidized p50 subunit and restore DNA binding activity of NF-κB. Initially, TRX was thought to be an inhibitor of NF-κB activation, because overexpression of TRX inhibits IκB degradation upon TNF stimulation and suppresses NF-κB transactivation (55). Furthermore, TRX directly inhibits ASK1 activation, which mediates JNK activation (see below) (73). Hirota *et al.* showed that TRX was mainly localized in the cytoplasm, but under phorbol 12-myristate 13-acetate (PMA) or TNFα stimulation, TRX translocated into the nucleus and enhanced the DNA binding activity of NF-κB (24, 25). Thus, TRX has opposing actions: up-regulating NF-κB activation in the nucleus, while down-regulating NF-kB activation in the cytoplasm. Glutaredoxin (GRX) and nucleoredoxin (NRX), well-known intracellular oxidoreducing enzymes, can regulate activation of NF-κB, as well as other transcription factors, such as AP-1 and CREB (26). However, whereas TRX translocates from the cytoplasm to the nucleus upon stimulation, GRX and NRX are constitutively located in the cytoplasm or nucleus, respectively, independent of stimulation. The exact mechanism by which these reducing enzymes modulate NF-κB activity is still unclear, but TRX, GRX, and NRX may play either distinct or overlapping roles in redox regulation of NF-κB activation.

The quinone derivative E3330, which has a therapeutic effect on endotoxin-induced hepatitis in mice, inhibits LPS-induced TNFα production and selectively suppresses NF-κB-mediated gene expression (23, 58). In PMA-stimulated cells, E3330 does not suppress IκB degradation or translocation of NF-κB, but significantly reduces the NF-κB DNA binding activity. Ref-1 has been identified as an E3330 binding protein using latex affinity beads (79). Ref-1 is a nuclear protein that was first identified as an apurinic/apyrimidinic endonuclease (APE), and participates in base exicision repair in response to genotoxic stress (for review, see 21). Ref-1 mediates the redox regulation of several transcription factors, including AP-1, CREB/ATF, p53, and hypoxia-inducible factor-1α (18, 34, 94). The oxidatively repressed DNA binding activity of NF-κB is repaired by Ref-1, and E3330 blocks this rescue through its interaction with Ref-1 (79). However, the APE domain of Ref-1 is located in the carboxy-terminal region, whereas Ref-1 modulation of the redox activation of AP-1 requires a cysteine residue in the amino-terminal region (92, 95). Maleimide labeling of the oxidized NF-κB p50 subunit clearly showed that Ref-1 selectively reduced the oxidized Cys62 of p50 (61). Furthermore, from *in vivo* analysis, Cys62 is oxidized in the cytoplasm, but following PMA stimulation, p50 is in the reduced form in the nucleus. E3330 selectively inhibits the reduction of p50 Cys62. This study strongly suggests that Ref-1-mediated p50 reduction is a prerequisite for NF-κB activation in the nucleus. Ref-1 can interact directly with targeted transcription factors and with TRX (24). In cells subjected to ionizing radiation, Ref-1 interacts with TRX in the nucleus and both Ref-1 and TRX are required for DNA binding activity of AP-1 (93). Thus, Ref-1 and TRX may synergistically contribute to redox regulation of transcription factors in the nucleus (as illustrated in Fig. 4).

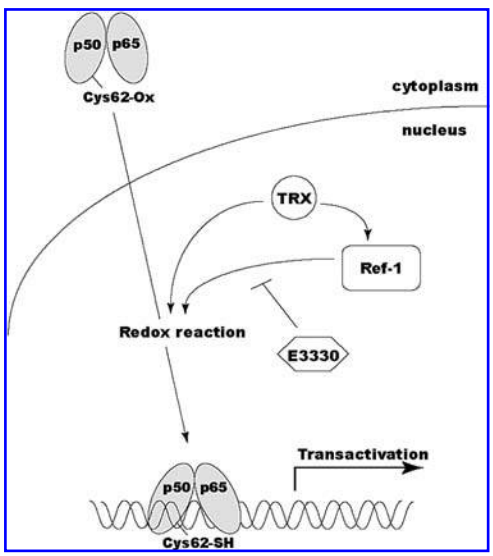

FIG. 4. Redox regulation of NF-κB activation in the nucleus. Upon stimulation, NF-κB, with an oxidized p50 subunit Cys62, translocates into the nucleus. TRX and Ref-1 directly or synergistically reduce the oxidized cysteine and enhance the DNA binding activity of NF-κB. The antiinflammatory agent E3330 selectively inhibits Ref-1-mediated NF-κB reduction.

CONCLUSION

NF-κB translocates from the cytoplasm to the nucleus and activates gene expression in response to a number of stimuli. Interestingly, ROS production exerts opposing effects on NF-κB, inducing activation in the cytoplasm, but causing inactivation in the nucleus. In this review, several of the signal transduction pathways of NF-κB activation in the cytoplasm and redox regulation of DNA binding activity in the nucleus have been described. The pathways leading to NF-κB activation can be classified roughly into two groups, depending on the type of stimulation: those that result in serine phosphorylation, and those that result in tyrosine phosphorylation of IκB (Figs. 2 and 3). But these two pathways are not strictly divided. For instance, in some cases, oxidative stress induces serine phosphorylation of IκB. However, further study is needed to understand how phosphorylation pathways are selected in response to various stimuli, because the signal transduction pathways are complicated, and the two different pathways may interact with each other. ROS production, as well as oxidative stimulation, can mediate NF-κB activation in the cytoplasm, either independently of, or synergistically with, phosphorylation pathways. In contrast, the DNA binding activity of oxidized NF-κB is significantly suppressed, and enzymes such as TRX or Ref-1 act to reduce NF-κB and restore DNA binding activity of the protein in the nucleus (Fig. 4). The molecular mechanism of ROS-mediated NF-κB regulation is largely unknown. NF-κB activation is responsible for numerous cellular responses, such as inflammation, oncogenesis, and aging. Studies addressing the molecular basis of

redox regulation of NF-κB will provide an understanding of pathogenic diseases and will aid in developing selective agents for NF-κB-mediated disorders.

ABBREVIATIONS

AP-1, activator protein-1; APE, apurinic/apyrimidinic endonuclease; ASK1, apoptosis signal-regulating kinase 1; GRX, glutaredoxin; GSH, glutathione; H_2O_2, hydrogen peroxide; H/R, hypoxia/reoxygenation; IκB, inhibitor of NF-κB; IKK, IκB kinase; IL, interleukin; JNK, c-Jun amino-terminal kinase; LPS, lipopolysaccharide; MAP, mitogen-activated protein; MAP3K and MEKK, MAP kinase kinase kinase; NAC, *N*-acetylcysteine; NF-κB, nuclear factor-κB; NIK, NF-κB-inducing kinase; NO, nitric oxide; NRX, nucleoredoxin; PDTC, pyrrolidinedithiocarbamate; PI3-K, phosphatidylinositol 3-kinase; PKC, protein kinase C; PKD, protein kinase D; PMA, phorbol 12-myristate 13-acetate; PTK, protein tyrosine kinase; Ref-1, redox factor 1; ROS, reactive oxygen species; SOD, superoxide dismutase; TAK1, transforming growth factor-β-activated kinase 1; TNF, tumor necrosis factor; TNFR, TNF receptor; TRAF, TNFR-associated factor; TRX, thioredoxin.

ACKNOWLEDGMENTS

This work was supported in part by a Grant for Research and Development Projects in Cooperation with Academic Institutions from the New Energy and Industrial Technology Development Organization to H.H. This work was also supported by a Grant of the 21st Century COE Program, Ministry of Education, Culture, Sports, Science and Technology.

REFERENCES

1. Abo A, Pick E, Hall A, Totty N, Teahan CG, and Segal AW. Activation of the NADPH oxidase involves the small GTP-binding protein p21rac1. *Nature* 353: 668–670, 1991.
2. Abu-Amer Y, Ross FP, McHugh KP, Livolsi A, Peyron JF, and Teitelbaum SL. Tumor necrosis factor-alpha activation of nuclear transcription factor-kappaB in marrow macrophages is mediated by c-Src tyrosine phosphorylation of Ikappa Balpha. *J Biol Chem* 273: 29417–29423, 1998.
3. Arias J, Alberts AS, Brindle P, Claret FX, Smeal T, Karin M, Feramisco J, and Montminy M. Activation of cAMP and mitogen responsive genes relies on a common nuclear factor. *Nature* 370: 226–229, 1994.
4. Baeuerle PA and Baltimore D. Activation of DNA-binding activity in an apparently cytoplasmic precursor of the NF-kappa B transcription factor. *Cell* 53: 211–217, 1988.
5. Baeuerle PA and Henkel T. Function and activation of NF-kappa B in the immune system. *Annu Rev Immunol* 12: 141–179, 1994.
6. Baud V and Karin M. Signal transduction by tumor necrosis factor and its relatives. *Trends Cell Biol* 11: 372–377, 2001.
7. Baud V, Liu ZG, Bennett B, Suzuki N, Xia Y, and Karin M. Signaling by proinflammatory cytokines: oligomerization of TRAF2 and TRAF6 is sufficient for JNK and IKK activation and target gene induction via an amino-terminal effector domain. *Genes Dev* 13: 1297–1308, 1999.
8. Beg AA, Sha WC, Bronson RT, Ghosh S, and Baltimore D. Embryonic lethality and liver degeneration in mice lacking the RelA component of NF-kappa B. *Nature* 376: 167–170, 1995.
9. Beraud C, Henzel WJ, and Baeuerle PA. Involvement of regulatory and catalytic subunits of phosphoinositide 3-kinase in NF-kappaB activation. *Proc Natl Acad Sci U S A* 96: 429–434, 1999.
10. Blank V, Kourilsky P, and Israel A. Cytoplasmic retention, DNA binding and processing of the NF-kappa B p50 precursor are controlled by a small region in its C-terminus. *EMBO J* 10: 4159–4167, 1991.
11. Bonizzi G, Piette J, Schoonbroodt S, Greimers R, Havard L, Merville MP, and Bours V. Reactive oxygen intermediate-dependent NF-kappaB activation by interleukin-1beta requires 5-lipoxygenase or NADPH oxidase activity. *Mol Cell Biol* 19: 1950–1960, 1999.
12. Chandel NS, Schumacker PT, and Arch RH. Reactive oxygen species are downstream products of TRAF-mediated signal transduction. *J Biol Chem* 276: 42728–42736, 2001.
13. Coso OA, Chiariello M, Yu JC, Teramoto H, Crespo P, Xu N, Miki T, and Gutkind JS. The small GTP-binding proteins Rac1 and Cdc42 regulate the activity of the JNK/SAPK signaling pathway. *Cell* 81: 1137–1146, 1995.
14. Davis RJ. Signal transduction by the JNK group of MAP kinases. *Cell* 103: 239–252, 2000.
15. de Martin R, Vanhove B, Cheng Q, Hofer E, Csizmadia V, Winkler H, and Bach FH. Cytokine-inducible expression in endothelial cells of an I kappa B alpha-like gene is regulated by NF kappa B. *EMBO J* 12: 2773–2779, 1993.
16. Derijard B, Raingeaud J, Barrett T, Wu IH, Han J, Ulevitch RJ, and Davis RJ. Independent human MAP-kinase signal transduction pathways defined by MEK and MKK isoforms. *Science* 267: 682–685, 1995.
17. Devary Y, Rosette C, DiDonato JA, and Karin M. NF-kappa B activation by ultraviolet light not dependent on a nuclear signal. *Science* 261: 1442–1445, 1993.
18. Ema M, Hirota K, Mimura J, Abe H, Yodoi J, Sogawa K, Poellinger L, and Fujii-Kuriyama Y. Molecular mechanisms of transcription activation by HLF and HIF1alpha in response to hypoxia: their stabilization and redox signal-induced interaction with CBP/p300. *EMBO J* 18: 1905–1914, 1999.
19. Fan CM and Maniatis T. Generation of p50 subunit of NF-kappa B by processing of p105 through an ATP-dependent pathway. *Nature* 354: 395–398, 1991.
20. Fan C, Li Q, Ross D, and Engelhardt JF. Tyrosine phosphorylation of I kappa B alpha activates NF kappa B through a redox-regulated and c-Src-dependent mecha-

nism following hypoxia/reoxygenation. *J Biol Chem* 278: 2072–2080, 2003.
21. Fritz G, Grosch S, Tomicic M, and Kaina B. APE/Ref-1 and the mammalian response to genotoxic stress. *Toxicology* 193: 67–78, 2003.
22. Hayakawa M, Miyashita H, Sakamoto I, Kitagawa M, Tanaka H, Yasuda H, Karin M, and Kikugawa K. Evidence that reactive oxygen species do not mediate NF-kappaB activation. *EMBO J* 22: 3356–3366, 2003.
23. Hiramoto M, Shimizu N, Sugimoto K, Tang J, Kawakami Y, Ito M, Aizawa S, Tanaka H, Makino I, and Handa H. Nuclear targeted suppression of NF-kappa B activity by the novel quinone derivative E3330. *J Immunol* 160: 810–819, 1998.
24. Hirota K, Matsui M, Iwata S, Nishiyama A, Mori K, and Yodoi J. AP-1 transcriptional activity is regulated by a direct association between thioredoxin and Ref-1. *Proc Natl Acad Sci U S A* 94: 3633–3638, 1997.
25. Hirota K, Murata M, Sachi Y, Nakamura H, Takeuchi J, Mori K, and Yodoi J. Distinct roles of thioredoxin in the cytoplasm and in the nucleus. A two-step mechanism of redox regulation of transcription factor NF-kappaB. *J Biol Chem* 274: 27891–27897, 1999.
26. Hirota K, Matsui M, Murata M, Takashima Y, Cheng FS, Itoh T, Fukuda K, and Yodoi J. Nucleoredoxin, glutaredoxin, and thioredoxin differentially regulate NF-kappaB, AP-1, and CREB activation in HEK293 cells. *Biochem Biophys Res Commun* 274: 177–182, 2000.
27. Howe CJ, LaHair MM, Maxwell JA, Lee JT, Robinson PJ, Rodriguez-Mora O, McCubrey JA, and Franklin RA. Participation of the calcium/calmodulin-dependent kinases in hydrogen peroxide-induced Ikappa B phosphorylation in human T lymphocytes. *J Biol Chem* 277: 30469–30476, 2002.
28. Hu Y, Jin X, and Snow ET. Effect of arsenic on transcription factor AP-1 and NF-kappaB DNA binding activity and related gene expression. *Toxicol Lett* 133: 33–45, 2002.
29. Huxford T, Huang DB, Malek S, and Ghosh G. The crystal structure of the IkappaBalpha/NF-kappaB complex reveals mechanisms of NF-kappaB inactivation. *Cell* 95: 759–770, 1998.
30. Imbert V, Peyron JF, Farahi Far D, Mari B, Auberger P, and Rossi B. Induction of tyrosine phosphorylation and T-cell activation by vanadate peroxide, an inhibitor of protein tyrosine phosphatases. *Biochem J* 297 (Pt 1): 163–173, 1994.
31. Imbert V, Rupec RA, Livolsi A, Pahl HL, Traenckner EB, Mueller-Dieckmann C, Farahifar D, Rossi B, Auberger P, Baeuerle PA, and Peyron JF. Tyrosine phosphorylation of I kappa B-alpha activates NF-kappa B without proteolytic degradation of I kappa B-alpha. *Cell* 86: 787–798, 1996.
32. Jacobs MD and Harrison SC. Structure of an IkappaB-alpha/NF-kappaB complex. *Cell* 95: 749–758, 1998.
33. Janssen-Heininger YM, Poynter ME, and Baeuerle PA. Recent advances towards understanding redox mechanisms in the activation of nuclear factor kappaB. *Free Radic Biol Med* 28: 1317–1327, 2000.
34. Jayaraman L, Murthy KG, Zhu C, Curran T, Xanthoudakis S, and Prives C. Identification of redox/repair protein Ref-1 as a potent activator of p53. *Genes Dev* 11: 558–570, 1997.
35. Johnson GL and Vaillancourt RR. Sequential protein kinase reactions controlling cell growth and differentiation. *Curr Opin Cell Biol* 6: 230–238, 1994.
36. Kamata H, Manabe T, Oka S, Kamata K, and Hirata H. Hydrogen peroxide activates IkappaB kinases through phosphorylation of serine residues in the activation loops. *FEBS Lett* 519: 231–237, 2002.
37. Knaus UG, Heyworth PG, Evans T, Curnutte JT, and Bokoch GM. Regulation of phagocyte oxygen radical production by the GTP-binding protein Rac 2. *Science* 254: 1512–1515, 1991.
38. Koong AC, Chen EY, and Giaccia AJ. Hypoxia causes the activation of nuclear factor kappa B through the phosphorylation of I kappa B alpha on tyrosine residues. *Cancer Res* 54: 1425–1430, 1994.
39. Krejsa CM, Nadler SG, Esselstyn JM, Kavanagh TJ, Ledbetter JA, and Schieven GL. Role of oxidative stress in the action of vanadium phosphotyrosine phosphatase inhibitors. Redox independent activation of NF-kappaB. *J Biol Chem* 272: 11541–11549, 1997.
40. Kumar S, Bharti A, Mishra NC, Raina D, Kharbanda S, Saxena S, and Kufe D. Targeting of the c-Abl tyrosine kinase to mitochondria in the necrotic cell death response to oxidative stress. *J Biol Chem* 276: 17281–17285, 2001.
41. Le Bail O, Schmidt-Ullrich R, and Israel A. Promoter analysis of the gene encoding the I kappa B-alpha/MAD3 inhibitor of NF-kappa B: positive regulation by members of the rel/NF-kappa B family. *EMBO J* 12: 5043–5049, 1993.
42. Lee FS, Hagler J, Chen ZJ, and Maniatis T. Activation of the IkappaB alpha kinase complex by MEKK1, a kinase of the JNK pathway. *Cell* 88: 213–222, 1997.
43. Lee FS, Peters RT, Dang LC, and Maniatis T. MEKK1 activates both IkappaB kinase alpha and IkappaB kinase beta. *Proc Natl Acad Sci U S A* 95: 9319–9324, 1998.
44. Lin A. Activation of the JNK signaling pathway: breaking the brake on apoptosis. *Bioessays* 25: 17–24, 2003.
45. Lin A, Minden A, Martinetto H, Claret FX, Lange-Carter C, Mercurio F, Johnson GL, and Karin M. Identification of a dual specificity kinase that activates the Jun kinases and p38-Mpk2. *Science* 268: 286–290, 1995.
46. Livolsi A, Busuttil V, Imbert V, Abraham RT, and Peyron JF. Tyrosine phosphorylation-dependent activation of NF-kappa B. Requirement for p56 LCK and ZAP-70 protein tyrosine kinases. *Eur J Biochem* 268: 1508–1515, 2001.
47. Lo YY, Wong JM, and Cruz TF. Reactive oxygen species mediate cytokine activation of c-Jun NH_2-terminal kinases. *J Biol Chem* 271: 15703–15707, 1996.
48. Mahabeleshwar GH and Kundu GC. Tyrosine kinase p56lck regulates cell motility and nuclear factor kappaB-mediated secretion of urokinase type plasminogen activator through tyrosine phosphorylation of IkappaB-alpha following hypoxia/reoxygenation. *J Biol Chem* 278: 52598–52612, 2003.

49. Mahon TM and O'Neill LA. Studies into the effect of the tyrosine kinase inhibitor herbimycin A on NF-kappa B activation in T lymphocytes. Evidence for covalent modification of the p50 subunit. *J Biol Chem* 270: 28557–28564, 1995.
50. Malinin NL, Boldin MP, Kovalenko AV, and Wallach D. MAP3K-related kinase involved in NF-kappaB induction by TNF, CD95 and IL-1. *Nature* 385: 540–544, 1997.
51. Manna SK, Sah NK, and Aggarwal BB. Protein tyrosine kinase p56lck is required for ceramide-induced but not tumor necrosis factor-induced activation of NF-kappa B, AP-1, JNK, and apoptosis. *J Biol Chem* 275: 13297–13306, 2000.
52. Matthews JR, Wakasugi N, Virelizier JL, Yodoi J, and Hay RT. Thioredoxin regulates the DNA binding activity of NF-kappa B by reduction of a disulphide bond involving cysteine 62. *Nucleic Acids Res* 20: 3821–3830, 1992.
53. Matthews JR, Botting CH, Panico M, Morris HR, and Hay RT. Inhibition of NF-kappaB DNA binding by nitric oxide. *Nucleic Acids Res* 24: 2236–2242, 1996.
54. Meyer CF, Wang X, Chang C, Templeton D, and Tan TH. Interaction between c-Rel and the mitogen-activated protein kinase kinase kinase 1 signaling cascade in mediating kappaB enhancer activation. *J Biol Chem* 271: 8971–8976, 1996.
55. Meyer M, Schreck R, and Baeuerle PA. H_2O_2 and antioxidants have opposite effects on activation of NF-kappa B and AP-1 in intact cells: AP-1 as secondary antioxidant-responsive factor. *EMBO J* 12: 2005–2015, 1993.
56. Minden A, Lin A, Claret FX, Abo A, and Karin M. Selective activation of the JNK signaling cascade and c-Jun transcriptional activity by the small GTPases Rac and Cdc42Hs. *Cell* 81: 1147–1157, 1995.
57. Muzio M, Ni J, Feng P, and Dixit VM. IRAK (Pelle) family member IRAK-2 and MyD88 as proximal mediators of IL-1 signaling. *Science* 278: 1612–1615, 1997.
58. Nagakawa J, Hishinuma I, Hirota K, Miyamoto K, Yamanaka T, Yamatsu I, and Katayama K. Protective effects of E3330, a novel quinone derivative, on galactosamine/tumor necrosis factor-alpha-induced hepatitis in mice. *Eur J Pharmacol* 229: 63–67, 1992.
59. Nakamura K, Hori T, Sato N, Sugie K, Kawakami T, and Yodoi J. Redox regulation of a src family protein tyrosine kinase p56lck in T cells. *Oncogene* 8: 3133–3139, 1993.
60. Ninomiya-Tsuji J, Kishimoto K, Hiyama A, Inoue J, Cao Z, and Matsumoto K. The kinase TAK1 can activate the NIK-I kappaB as well as the MAP kinase cascade in the IL-1 signalling pathway. *Nature* 398: 252–256, 1999.
61. Nishi T, Shimizu N, Hiramoto M, Sato I, Yamaguchi Y, Hasegawa M, Aizawa S, Tanaka H, Kataoka K, Watanabe H, and Handa H. Spatial redox regulation of a critical cysteine residue of NF-kappa B in vivo. *J Biol Chem* 277: 44548–44556, 2002.
62. Nishitoh H, Saitoh M, Mochida Y, Takeda K, Nakano H, Rothe M, Miyazono K, and Ichijo H. ASK1 is essential for JNK/SAPK activation by TRAF2. *Mol Cell* 2: 389–395, 1998.
63. Oka S, Kamata H, Kamata K, Yagisawa H, and Hirata H. *N*-Acetylcysteine suppresses TNF-induced NF-kappaB activation through inhibition of IkappaB kinases. *FEBS Lett* 472: 196–202, 2000.
64. O'Neill LA, Bird TA, Gearing AJ, and Saklatvala J. Interleukin-1 signal transduction. Increased GTP binding and hydrolysis in membranes of a murine thymoma line (EL4). *J Biol Chem* 265: 3146–3152, 1990.
65. Perkins ND. The Rel/NF-kappa B family: friend and foe. *Trends Biochem Sci* 25: 434–440, 2000.
66. Pomerantz JL and Baltimore D. NF-kappaB activation by a signaling complex containing TRAF2, TANK and TBK1, a novel IKK-related kinase. *EMBO J* 18: 6694–6704, 1999.
67. Pulverer BJ, Kyriakis JM, Avruch J, Nikolakaki E, and Woodgett JR. Phosphorylation of c-jun mediated by MAP kinases. *Nature* 353: 670–674, 1991.
68. Rayet B and Gelinas C. Aberrant rel/nfkb genes and activity in human cancer. *Oncogene* 18: 6938–6947, 1999.
69. Regnier CH, Song HY, Gao X, Goeddel DV, Cao Z, and Rothe M. Identification and characterization of an IkappaB kinase. *Cell* 90: 373–383, 1997.
70. Rice NR, MacKichan ML, and Israel A. The precursor of NF-kappa B p50 has I kappa B-like functions. *Cell* 71: 243–253, 1992.
71. Rogers RJ, Monnier JM, and Nick HS. Tumor necrosis factor-alpha selectively induces MnSOD expression via mitochondria-to-nucleus signaling, whereas interleukin-1beta utilizes an alternative pathway. *J Biol Chem* 276: 20419–20427, 2001.
72. Rothe M, Wong SC, Henzel WJ, and Goeddel DV. A novel family of putative signal transducers associated with the cytoplasmic domain of the 75 kDa tumor necrosis factor receptor. *Cell* 78: 681–692, 1994.
73. Saitoh M, Nishitoh H, Fujii M, Takeda K, Tobiume K, Sawada Y, Kawabata M, Miyazon o K, and Ichijo H. Mammalian thioredoxin is a direct inhibitor of apoptosis signal-regulating kinase (ASK) 1. *EMBO J* 17: 2596–2606, 1998.
74. Sanchez I, Hughes RT, Mayer BJ, Yee K, Woodgett JR, Avruch J, Kyriakis JM, and Zon LI. Role of SAPK/ERK kinase-1 in the stress-activated pathway regulating transcription factor c-Jun. *Nature* 372: 794–798, 1994.
75. Sanlioglu S, Williams CM, Samavati L, Butler NS, Wang G, McCray PB Jr, Ritchie TC, Hunninghake GW, Zandi E, and Engelhardt JF. Lipopolysaccharide induces Rac1-dependent reactive oxygen species formation and coordinates tumor necrosis factor-alpha secretion through IKK regulation of NF-kappa B. *J Biol Chem* 276: 30188–30198, 2001.
76. Schenk H, Klein M, Erdbrugger W, Droge W, and Schulze-Osthoff K. Distinct effects of thioredoxin and antioxidants on the activation of transcription factors NF-kappa B and AP-1. *Proc Natl Acad Sci U S A* 91: 1672–1676, 1994.
77. Schieven GL, Kirihara JM, Myers DE, Ledbetter JA, and Uckun FM. Reactive oxygen intermediates activate NF-kappa B in a tyrosine kinase-dependent mechanism and in combination with vanadate activate the p56lck and p59fyn tyrosine kinases in human lymphocytes. *Blood* 82: 1212–1220, 1993.

78. Sen R and Baltimore D. Multiple nuclear factors interact with the immunoglobulin enhancer sequences. *Cell* 46: 705–716, 1986.
79. Shimizu N, Sugimoto K, Tang J, Nishi T, Sato I, Hiramoto M, Aizawa S, Hatakeyama M, Ohba R, Hatori H, Yoshikawa T, Suzuki F, Oomori A, Tanaka H, Kawaguchi H, Watanabe H, and Handa H. High-performance affinity beads for identifying drug receptors. *Nat Biotechnol* 18: 877–881, 2000.
80. Singh S, Darnay BG, and Aggarwal BB. Site-specific tyrosine phosphorylation of IkappaBalpha negatively regulates its inducible phosphorylation and degradation. *J Biol Chem* 271: 31049–31054, 1996.
81. Sizemore N, Leung S, and Stark GR. Activation of phosphatidylinositol 3-kinase in response to interleukin-1 leads to phosphorylation and activation of the NF-kappaB p65/RelA subunit. *Mol Cell Biol* 19: 4798–4805, 1999.
82. Song HY, Regnier CH, Kirschning CJ, Goeddel DV, and Rothe M. Tumor necrosis factor (TNF)-mediated kinase cascades: bifurcation of nuclear factor-kappaB and c-jun N-terminal kinase (JNK/SAPK) pathways at TNF receptor-associated factor 2. *Proc Natl Acad Sci U S A* 94: 9792–9796, 1997.
83. Storz P and Toker A. Protein kinase D mediates a stress-induced NF-kappaB activation and survival pathway. *EMBO J* 22: 109–120, 2003.
84. Storz P, Doppler H, and Toker A. Protein kinase Cdelta selectively regulates protein kinase D-dependent activation of NF-kappaB in oxidative stress signaling. *Mol Cell Biol* 24: 2614–2626, 2004.
85. Sulciner DJ, Irani K, Yu ZX, Ferrans VJ, Goldschmidt-Clermont P, and Finkel T. rac1 regulates a cytokine-stimulated, redox-dependent pathway necessary for NF-kappaB activation. *Mol Cell Biol* 16: 7115– 7121, 1996.
86. Suyang H, Phillips R, Douglas I, and Ghosh S. Role of unphosphorylated, newly synthesized I kappa B beta in persistent activation of NF-kappa B. *Mol Cell Biol* 16: 5444–5449, 1996.
87. Toledano MB and Leonard WJ. Modulation of transcription factor NF-kappa B binding activity by oxidation–reduction in vitro. *Proc Natl Acad Sci U S A* 88: 4328–4332, 1991.
88. Urban MB, Schreck R, and Baeuerle PA. NF-kappa B contacts DNA by a heterodimer of the p50 and p65 subunit. *EMBO J* 10: 1817–1825, 1991.
89. Van Antwerp DJ, Martin SJ, Kafri T, Green DR, and Verma IM. Suppression of TNF-alpha-induced apoptosis by NF-kappaB. *Science* 274: 787–789, 1996.
90. Verma IM, Stevenson JK, Schwarz EM, Van Antwerp D, and Miyamoto S. Rel/NF-kappa B/I kappa B family: intimate tales of association and dissociation. *Genes Dev* 9: 2723–2735, 1995.
91. Voncken JW, van Schaick H, Kaartinen V, Deemer K, Coates T, Landing B, Pattengale P, Dorseuil O, Bokoch GM, Groffen J, *et al.* Increased neutrophil respiratory burst in bcr-null mutants. *Cell* 80: 719–728, 1995.
92. Walker LJ, Robson CN, Black E, Gillespie D, and Hickson ID. Identification of residues in the human DNA repair enzyme HAP1 (Ref-1) that are essential for redox regulation of Jun DNA binding. *Mol Cell Bio* 13: 5370–5376, 1993.
93. Wei SJ, Botero A, Hirota K, Bradbury CM, Markovina S, Laszlo A, Spitz DR, Goswami PC, Yodoi J, and Gius D. Thioredoxin nuclear translocation and interaction with redox factor-1 activates the activator protein-1 transcription factor in response to ionizing radiation. *Cancer Res* 60: 6688–6695, 2000.
94. Xanthoudakis S and Curran T. Identification and characterization of Ref-1, a nuclear protein that facilitates AP-1 DNA-binding activity. *EMBO J* 11: 653–665, 1992.
95. Xanthoudakis S, Miao GG, and Curran T. The redox and DNA-repair activities of Ref-1 are encoded by nonoverlapping domains. *Proc Natl Acad Sci U S A* 91: 23–27, 1994.
96. Xie QW, Kashiwabara Y, and Nathan C. Role of transcription factor NF-kappa B/Rel in induction of nitric oxide synthase. *J Biol Chem* 269: 4705–4708, 1994.
97. Yamaoka S, Courtois G, Bessia C, Whiteside ST, Weil R, Agou F, Kirk HE, Kay RJ, and Israel A. Complementation cloning of NEMO, a component of the IkappaB kinase complex essential for NF-kappaB activation. *Cell* 93: 1231–1240, 1998.
98. Ye J, Ding M, Zhang X, Rojanasakul Y, Nedospasov S, Vallyathan V, Castranova V, and Shi X. Induction of TNFalpha in macrophages by vanadate is dependent on activation of transcription factor NF-kappaB and free radical reactions. *Mol Cell Biochem* 198: 193–200, 1999.
99. Yurchak LK, Hardwick JS, Amrein K, Pierno K, and Sefton BM. Stimulation of phosphorylation of Tyr394 by hydrogen peroxide reactivates biologically inactive, non-membrane-bound forms of Lck. *J Biol Chem* 271: 12549–12554, 1996.
100. Zhong H, SuYang H, Erdjument-Bromage H, Tempst P, and Ghosh S. The transcriptional activity of NF-kappaB is regulated by the IkappaB-associated PKAc subunit through a cyclic AMP-independent mechanism. *Cell* 89: 413–424, 1997.

Address reprint requests to:
Hiroshi Handa, Ph.D.
Graduate School of Bioscience and Biotechnology
Tokyo Institute of Technology
4259 Nagatsuta-cho
Midori-ku
Yokohama 226-8501, Japan

E-mail: hhanda@bio.titech.ac.jp

Received for publication May 8, 2004; accepted October 9, 2004.

This article has been cited by:

1. Fernanda S. Manoel-Caetano, Danilo J. Xavier, Adriane F. Evangelista, Paula Takahashi, Cristhianna V. Collares, Denis Puthier, Maria C. Foss-Freitas, Milton C. Foss, Eduardo A. Donadi, Geraldo A. Passos, Elza T. Sakamoto-Hojo. 2012. Gene expression profiles displayed by peripheral blood mononuclear cells from patients with type 2 diabetes mellitus focusing on biological processes implicated on the pathogenesis of the disease. *Gene* . [CrossRef]
2. Gregory Baptista, Anne-Marie Dupuy, Audrey Jaussent, Richard Durant, Emilie Ventura, Pauline Sauguet, Marie-Christine Picot, Claude Jeandel, Jean Paul Cristol. 2012. Low-grade chronic inflammation and superoxide anion production by NADPH oxidase are the main determinants of physical frailty in older adults. *Free Radical Research* **46**:9, 1108-1114. [CrossRef]
3. Akiyo Koshiyama, Tomoko Ichibangase, Kazuhiro Imai. 2012. Comprehensive fluorogenic derivatization-liquid chromatography/tandem mass spectrometry proteomic analysis of colorectal cancer cell to identify biomarker candidate. *Biomedical Chromatography* n/a-n/a. [CrossRef]
4. Anna Pastore, Fiorella Piemonte. 2012. S-Glutathionylation signaling in cell biology: Progress and prospects. *European Journal of Pharmaceutical Sciences* **46**:5, 279-292. [CrossRef]
5. Aaron K. Holley, Sanjit Kumar Dhar, Daret K. St. Clair. 2012. Curbing cancer's sweet tooth: Is there a role for MnSOD in regulation of the Warburg effect?. *Mitochondrion* . [CrossRef]
6. Xue Shao, Zhengtao Hu, Chunyan Hu, Qian Bu, Guangyan Yan, Pengchi Deng, Lei Lv, Dan Wu, Yi Deng, Jinxuan Zhao, Ruiming Zhu, Yan Li, Hongyu Li, Youzhi Xu, Hanshuo Yang, Yinglan Zhao, Xiaobo Cen. 2012. Taurine protects methamphetamine-induced developmental angiogenesis defect through antioxidant mechanism. *Toxicology and Applied Pharmacology* **260**:3, 260-270. [CrossRef]
7. Cristina Lanni, Marco Racchi, Maurizio Memo, Stefano Govoni, Daniela Uberti. 2012. p53 at the crossroads between cancer and neurodegeneration. *Free Radical Biology and Medicine* **52**:9, 1727-1733. [CrossRef]
8. Jessica Wing-Man Ho, Philip Wing-Lok Ho, Hui-Fang Liu, Danny Hon-Fai So, Koon-Ho Chan, Zero Ho-Man Tse, Michelle Hiu-Wai Kung, David Boyer Ramsden, Shu-Leong Ho. 2012. UCP4 is a target effector of the NF-#B c-Rel prosurvival pathway against oxidative stress. *Free Radical Biology and Medicine* . [CrossRef]
9. Melba C. Jaramillo, Margaret M. Briehl, James D. Crapo, Ines Batinic-Haberle, Margaret E. Tome. 2012. Manganese Porphyrin, MnTE-2-PyP5+, Acts as a Pro-Oxidant to Potentiate Glucocorticoid-Induced Apoptosis in Lymphoma Cells. *Free Radical Biology and Medicine* **52**:8, 1272-1284. [CrossRef]
10. Jin-A. Kim, Hyeon-Soo Park, Sang-Rim Kang, Kwang-Il Park, Do-Hoon Lee, ArulKumar Nagappan, Sung-Chul Shin, Won-Sup Lee, Eun-Hee Kim, Gon-Sup Kim. 2012. Suppressive Effect of Flavonoids from Korean Citrus aurantium L. on the Expression of Inflammatory Mediators in L6 Skeletal Muscle Cells. *Phytotherapy Research* n/a-n/a. [CrossRef]
11. Ali A Sovari, Adhir Shroff, Abraham G Kocheril. 2012. Postinfarct cardiac remodeling and the substrate for sudden cardiac death: role of oxidative stress and myocardial fibrosis. *Expert Review of Cardiovascular Therapy* **10**:3, 267-270. [CrossRef]
12. Hyeran Won , Sangbin Lim , Miran Jang , Yeonghwan Kim , Md Abdur Rashid , K.R. Jyothi , Amarjargal Dashdorj , Insug Kang , Joohun Ha , Sung Soo Kim . 2012. Peroxiredoxin-2 Upregulated by NF-#B Attenuates Oxidative Stress During the Differentiation of Muscle-Derived C2C12 Cells. *Antioxidants & Redox Signaling* **16**:3, 245-261. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links] [Supplemental material]
13. Lei Li, John C. Wataha, Casey Cate, Hai Zhang, Dennis DiJulio, Whasun O. Chung. 2012. Ni(II) alters the NF#B signaling pathway in monocytic cells. *Journal of Biomedical Materials Research Part B: Applied Biomaterials* n/a-n/a. [CrossRef]
14. Byung-Koo Yoon, Young-Hee Kang, Won-Jong Oh, Kyungwon Park, Dong-Yun Lee, DooSeok Choi, Duk-Kyung Kim, YoungJoo Lee, Mee-Ra Rhyu. 2012. Impact of Lysophosphatidylcholine on the Plasminogen Activator System in Cultured Vascular Smooth Muscle Cells. *Journal of Korean Medical Science* **27**:7, 803. [CrossRef]
15. Yuxing Zhang , Yanzhi Du , Weidong Le , Kankan Wang , Nelly Kieffer , Ji Zhang . 2011. Redox Control of the Survival of Healthy and Diseased Cells. *Antioxidants & Redox Signaling* **15**:11, 2867-2908. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]
16. Benjamin P.C. Chen, Mengxia Li, Aroumougame Asaithamby. 2011. New Insights into the Roles of ATM and DNA-PKcs in the Cellular Response to Oxidative Stress. *Cancer Letters* . [CrossRef]
17. Rakesh Kumar Tandon , Pramod Kumar Garg . 2011. Oxidative Stress in Chronic Pancreatitis: Pathophysiological Relevance and Management. *Antioxidants & Redox Signaling* **15**:10, 2757-2766. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]

18. G. Gong, C. Méplan, H. Gautrey, J. Hall, J. E. Hesketh. 2011. Differential effects of selenium and knock-down of glutathione peroxidases on TNF# and flagellin inflammatory responses in gut epithelial cells. *Genes & Nutrition* . [CrossRef]
19. Javier Escobar, Javier Pereda, Gerardo López-Rodas, Juan Sastre. 2011. Redox signaling and histone acetylation in acute pancreatitis. *Free Radical Biology and Medicine* . [CrossRef]
20. Regina Brigelius-Flohé , Leopold Flohé . 2011. Basic Principles and Emerging Concepts in the Redox Control of Transcription Factors. *Antioxidants & Redox Signaling* **15**:8, 2335-2381. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]
21. Shubhra Dutta, Anindya Roy Chowdhury, SK Srivastava, Ilora Ghosh, Kasturi Datta. 2011. Evidence for Serpentine as a novel antioxidant by a redox sensitive HABP1 overexpressing cell line by inhibiting its nuclear translocation of NF-#B. *Free Radical Research* 1-10. [CrossRef]
22. Magdalena L. Circu, Tak Yee Aw. 2011. Redox biology of the intestine. *Free Radical Research* 1-22. [CrossRef]
23. Jamie L. Barger, Tsuyoshi Kayo, Thomas D. Pugh, James A. Vann, Ronan Power, Karl Dawson, Richard Weindruch, Tomas A. Prolla. 2011. Gene expression profiling reveals differential effects of sodium selenite, selenomethionine, and yeast-derived selenium in the mouse. *Genes & Nutrition* . [CrossRef]
24. Hongwei Yao, Irfan RahmanEnvironment and the Role of Inflammation in Chronic Pulmonary Diseases **20115234**, . [CrossRef]
25. J. Vidya Sarma, Peter A. WardOxidants and Redox Signaling in Acute Lung Injury . [CrossRef]
26. Hongmei Liu, Congcong Zhang, Kaixun Huang. 2011. Lanthanum chloride suppresses oxysterol-induced ECV-304 cell apoptosis via inhibition of intracellular Ca2+ concentration elevation, oxidative stress, and activation of ERK and NF-#B signaling pathways. *JBIC Journal of Biological Inorganic Chemistry* **16**:5, 671-681. [CrossRef]
27. Imad Al Ghouleh, Nicholas K.H. Khoo, Ulla G. Knaus, Kathy K. Griendling, Rhian M. Touyz, Victor J. Thannickal, Aaron Barchowsky, William M. Nauseef, Eric E. Kelley, Phillip M. Bauer, Victor Darley-Usmar, Sruti Shiva, Eugenia Cifuentes-Pagano, Bruce A. Freeman, Mark T. Gladwin, Patrick J. Pagano. 2011. Oxidases and peroxidases in cardiovascular and lung disease: New concepts in reactive oxygen species signaling. *Free Radical Biology and Medicine* . [CrossRef]
28. D. Liu, H. He, G. L. Li, J. Chen, D. Yin, Z. P. Liao, L. Tang, Q. R. Huang, Z. F. Lai, M. He. 2011. Mechanisms of chloride in cardiomyocyte anoxia-reoxygenation injury: the involvement of oxidative stress and NF-kappaB activation. *Molecular and Cellular Biochemistry* . [CrossRef]
29. Ming Che Tsai, Wei Ju Chen, Ming Shi Tsai, Cheng Hsin Ching, Jih Ing Chuang. 2011. Melatonin attenuates brain contusion-induced oxidative insult, inactivation of signal transducers and activators of transcription 1, and upregulation of suppressor of cytokine signaling-3 in rats. *Journal of Pineal Research* no-no. [CrossRef]
30. Lee S. Gloyne, Gary D. Grant, Anthony V. Perkins, Katie L. Powell, Catherine M. McDermott, Peter V. Johnson, Gregory J. Anderson, Milton Kiefel, Shailendra Anoopkumar-Dukie. 2011. Pyocyanin-induced toxicity in A549 respiratory cells is causally linked to oxidative stress. *Toxicology in Vitro* . [CrossRef]
31. Ying Qu, Jinhua Wang, Partha S. Ray, Hua Guo, Jian Huang, Miyung Shin-Sim, Bolanle A. Bukoye, Bingya Liu, Adrian V. Lee, Xin Lin, Peng Huang, John W. Martens, Armando E. Giuliano, Ning Zhang, Ning-Hui Cheng, Xiaojiang Cui. 2011. Thioredoxin-like 2 regulates human cancer cell growth and metastasis via redox homeostasis and NF-#B signaling. *Journal of Clinical Investigation* **121**:1, 212-225. [CrossRef]
32. Gloria Lopez-Castejón, Alberto Baroja-Mazo, Pablo Pelegrín. 2011. Novel macrophage polarization model: from gene expression to identification of new anti-inflammatory molecules. *Cellular and Molecular Life Sciences* **68**:18, 3095. [CrossRef]
33. Michael J Morgan, Zheng-gang Liu. 2011. Crosstalk of reactive oxygen species and NF-#B signaling. *Cell Research* **21**:1, 103-115. [CrossRef]
34. Takayuki Maruyama, Takaaki Tomofuji, Yasumasa Endo, Koichiro Irie, Tetsuji Azuma, Daisuke Ekuni, Naofumi Tamaki, Tatsuo Yamamoto, Manabu Morita. 2011. Supplementation of green tea catechins in dentifrices suppresses gingival oxidative stress and periodontal inflammation. *Archives of Oral Biology* **56**:1, 48-53. [CrossRef]
35. Joseph Shlomai . 2010. Redox Control of Protein–DNA Interactions: From Molecular Mechanisms to Significance in Signal Transduction, Gene Expression, and DNA Replication. *Antioxidants & Redox Signaling* **13**:9, 1429-1476. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]
36. Nina Queisser, Gholamreza Fazeli, Nicole Schupp. 2010. Superoxide anion and hydrogen peroxide-induced signaling and damage in angiotensin II and aldosterone action. *Biological Chemistry* **391**:11, 1265-1279. [CrossRef]

37. Xu Chao, Jiang Zao, Gu Xiao-Yi, Meng Li-Jun, Shi Tao. 2010. Blocking of PI3K/AKT induces apoptosis by its effect on NF-#B activity in gastric carcinoma cell line SGC7901. *Biomedicine & Pharmacotherapy* **64**:9, 600-604. [CrossRef]

38. Li Xiao, Hisae Aoshima, Yasukazu Saitoh, Nobuhiko Miwa. 2010. Fullerene-polyvinylpyrrolidone clathrate localizes in the cytoplasm to prevent Ultraviolet-A ray-induced DNA-fragmentation and activation of the transcriptional factor NF-kappaB. *Journal of Cellular Biochemistry* **111**:4, 955-966. [CrossRef]

39. Kaïs H. Al-Gubory, Paul A. Fowler, Catherine Garrel. 2010. The roles of cellular reactive oxygen species, oxidative stress and antioxidants in pregnancy outcomes. *The International Journal of Biochemistry & Cell Biology* **42**:10, 1634-1650. [CrossRef]

40. Li Gan. 2010. Therapeutic potential and challenges of targeting sirtuins in neurodegenerative diseases. *Frontiers in Biology* **5**:4, 324-330. [CrossRef]

41. Aaron K. Holley, Yong Xu, Daret K. St. Clair, William H. St. Clair. 2010. RelB regulates manganese superoxide dismutase gene and resistance to ionizing radiation of prostate cancer cells. *Annals of the New York Academy of Sciences* **1201**:1, 129-136. [CrossRef]

42. Marco Romagnoli, Mari-Carmen Gomez-Cabrera, Maria-Giulia Perrelli, Fiorella Biasi, Federico V. Pallardó, Juan Sastre, Giuseppe Poli, Jose Viña. 2010. Xanthine oxidase-induced oxidative stress causes activation of NF-#B and inflammation in the liver of type I diabetic rats. *Free Radical Biology and Medicine* **49**:2, 171-177. [CrossRef]

43. Antero Salminen, Kai Kaarniranta. 2010. Genetics vs. entropy: Longevity factors suppress the NF-#B-driven entropic aging process. *Ageing Research Reviews* **9**:3, 298-314. [CrossRef]

44. Inflammation and Innate Immune Response 181-238. [CrossRef]

45. E. B. Menshikova, V. O. Tkachev, N. K. Zenkov. 2010. Redox-dependent signaling system Nrf2/ARE in inflammation. *Molecular Biology* **44**:3, 343-357. [CrossRef]

46. A. Raquel Esteves, Jane Lu, Mariana Rodova, Isaac Onyango, E Lezi, Richard Dubinsky, Kelly E. Lyons, Rajesh Pahwa, Jeffrey M. Burns, Sandra M. Cardoso, Russell H. Swerdlow. 2010. Mitochondrial respiration and respiration-associated proteins in cell lines created through Parkinson's subject mitochondrial transfer. *Journal of Neurochemistry* **113**:3, 674-682. [CrossRef]

47. Marco Tafani, Andrea Russo, Maura Di Vito, Patrizio Sale, Laura Pellegrini, Luana Schito, Stefano Gentileschi, Roberto Bracaglia, Ferdinando Marandino, Enrico Garaci, Matteo A Russo. 2010. Up-regulation of pro-inflammatory genes as adaptation to hypoxia in MCF-7 cells and in human mammary invasive carcinoma microenvironment. *Cancer Science* **101**:4, 1014-1023. [CrossRef]

48. Shylet Chengedza, Doris Mangiaracina Benbrook. 2010. NF-#B is involved in SHetA2 circumvention of TNF-# resistance, but not induction of intrinsic apoptosis. *Anti-Cancer Drugs* **21**:3, 297-305. [CrossRef]

49. F. L. van de Veerdonk, S. P. Smeekens, L. A. B. Joosten, B. J. Kullberg, C. A. Dinarello, J. W. M. van der Meer, M. G. Netea. 2010. Reactive oxygen species-independent activation of the IL-1 inflammasome in cells from patients with chronic granulomatous disease. *Proceedings of the National Academy of Sciences* **107**:7, 3030-3033. [CrossRef]

50. Luis A. Videla. 2010. Hormetic responses of thyroid hormone calorigenesis in the liver: Association with oxidative stress. *IUBMB Life* n/a-n/a. [CrossRef]

51. R.E. Singer , K. Moss , J.D. Beck , S. Offenbacher . 2009. Association of Systemic Oxidative Stress with Suppressed Serum IgG to Commensal Oral Biofilm and Modulation by Periodontal Infection. *Antioxidants & Redox Signaling* **11**:12, 2973-2983. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]

52. Aidan Ryan, Madeline Murphy, Catherine Godson, Fionnuala B. Hickey. 2009. Diabetes mellitus and apoptosis: inflammatory cells. *Apoptosis* **14**:12, 1435-1450. [CrossRef]

53. Dan Liu, Do-Hee Kim, Jong-Min Park, Hye-Kyung Na, Young-Joon Surh. 2009. Piceatannol Inhibits Phorbol Ester-Induced NF-# B Activation and COX-2 Expression in Cultured Human Mammary Epithelial Cells. *Nutrition and Cancer* **61**:6, 855-863. [CrossRef]

54. Woojin Jeong, Yuyeon Jung, Hojin Kim, Sun Joo Park, Sue Goo Rhee. 2009. Thioredoxin-related protein 14, a new member of the thioredoxin family with disulfide reductase activity: Implication in the redox regulation of TNF-# signaling. *Free Radical Biology and Medicine* **47**:9, 1294-1303. [CrossRef]

55. M. E. Letelier, M. FaÃºndez, J. Jara-Sandoval, A. Molina-BerrÃos, J. CortÃ©s-Troncoso, P. Aracena-Parks, R. MarÃn-CatalÃ¡n. 2009. Mechanisms underlying the inhibition of the cytochrome P450 system by copper ions. *Journal of Applied Toxicology* **29**:8, 695-702. [CrossRef]

56. Kai Chen , Siobhan E. Craige , John F. Keaney , Jr. . 2009. Downstream Targets and Intracellular Compartmentalization in Nox Signaling. *Antioxidants & Redox Signaling* **11**:10, 2467-2480. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]
57. Melissa A. Chambers, Jennifer S. Moylan, Michael B. Reid. 2009. Physical inactivity and muscle weakness in the critically ill. *Critical Care Medicine* **37**, S337-S346. [CrossRef]
58. Geoffrey Gloire , Jacques Piette . 2009. Redox Regulation of Nuclear Post-Translational Modifications During NF-#B Activation. *Antioxidants & Redox Signaling* **11**:9, 2209-2222. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]
59. Barrie J. Carter , Pervin Anklesaria , Stephanie Choi , John F. Engelhardt . 2009. Redox Modifier Genes and Pathways in Amyotrophic Lateral Sclerosis. *Antioxidants & Redox Signaling* **11**:7, 1569-1586. [Abstract] [Full Text PDF] [Full Text PDF with Links]
60. Allison J. Stewart, Amanda Pettigrew, Anna M. Cochran, James K. Belknap. 2009. Indices of inflammation in the lung and liver in the early stages of the black walnut extract model of equine laminitis. *Veterinary Immunology and Immunopathology* **129**:3-4, 254-260. [CrossRef]
61. Alberto Bindoli, Maria Pia Rigobello, Guido Scutari, Chiara Gabbiani, Angela Casini, Luigi Messori. 2009. Thioredoxin reductase: A target for gold compounds acting as potential anticancer drugs. *Coordination Chemistry Reviews* **253**:11-12, 1692-1707. [CrossRef]
62. Jae–Min Yuk , Chul–Su Yang , Dong–Min Shin , Kwang–Kyu Kim , Sang Ki Lee , Yun Jeong Song , Hye–Mi Lee , Chung–Hyun Cho , Byeong Hwa Jeon , Eun–Kyeong Jo . 2009. A Dual Regulatory Role of Apurinic/Apyrimidinic Endonuclease 1/Redox Factor-1 in HMGB1-Induced Inflammatory Responses. *Antioxidants & Redox Signaling* **11**:3, 575-588. [Abstract] [Full Text PDF] [Full Text PDF with Links]
63. Heon-Yeong Joo, Kye-Taek Lim. 2009. Glycoprotein isolated from Cudrania tricuspidata Bureau inhibits iNO and COX-2 expression through modulation of NF-#B in LPS-stimulated RAW 264.7cells. *Environmental Toxicology and Pharmacology* **27**:2, 247-252. [CrossRef]
64. Maria Sehlstedt, Grethe Neumann Andersen, Kenneth Nilsson, Anders Blomberg, Lucia Mincheva-Nilsson, Anders Waldenström, Solbritt Rantapää-Dahlqvist, Thomas Sandström. 2009. Suppressed signal transduction in the bronchial epithelium of patients with systemic sclerosis. *Respiratory Medicine* **103**:2, 301-308. [CrossRef]
65. Aaron K Holley, Daret K St Clair. 2009. Watching the watcher: regulation of p53 by mitochondria. *Future Oncology* **5**:1, 117-130. [CrossRef]
66. Po Sing Leung , Yuk Cheung Chan . 2009. Role of Oxidative Stress in Pancreatic Inflammation. *Antioxidants & Redox Signaling* **11**:1, 135-166. [Abstract] [Full Text PDF] [Full Text PDF with Links]
67. Anouk Waeytens, Martine De Vos, Debby Laukens. 2009. Evidence for a Potential Role of Metallothioneins in Inflammatory Bowel Diseases. *Mediators of Inflammation* **2009**, 1-9. [CrossRef]
68. Ji Ae Lee, Ha Yong Song, Sung Mi Ju, Su Jin Lee, Hyung-Joo Kwon, Won Sik Eum, Sang Ho Jang, Soo Young Choi, Jinseu Park. 2009. Differential regulation of inducible nitric oxide synthase and cyclooxygenase-2 expression by superoxide dismutase in lipopolysaccharide stimulated RAW 264.7 cells. *Experimental and Molecular Medicine* **41**:9, 629. [CrossRef]
69. P. J. McMILLAN, E. M. PATZEWITZ, S. E. YOUNG, G. D. WESTROP, G. H. COOMBS, L. ENGMAN, S. MÜLLER. 2009. Differential inhibition of high and low Mr thioredoxin reductases of parasites by organotelluriums supports the concept that low Mr thioredoxin reductases are good drug targets. *Parasitology* **136**:01, 27. [CrossRef]
70. Ali A. Sovari, Norishige Morita, Hrayr S. Karagueuzian. 2008. Apocynin: a potent NADPH oxidase inhibitor for the management of atrial fibrillation. *Redox Report* **13**:6, 242-245. [CrossRef]
71. Arjun Saha, Sung-Jo Kim, Zhongjian Zhang, Yi-Ching Lee, Chinmoy Sarkar, Pei-Chih Tsai, Anil B. Mukherjee. 2008. RAGE signaling contributes to neuroinflammation in infantile neuronal ceroid lipofuscinosis. *FEBS Letters* **582**:27, 3823-3831. [CrossRef]
72. Kazuhiro Imai, Tomoko Ichibangase, Ryoichi Saitoh, Yutaka Hoshikawa. 2008. A proteomics study on human breast cancer cell lines by fluorogenic derivatization-liquid chromatography/tandem mass spectrometry. *Biomedical Chromatography* **22**:11, 1304-1314. [CrossRef]
73. Y. Sun. 2008. Myocardial repair/remodelling following infarction: roles of local factors. *Cardiovascular Research* **81**:3, 482-490. [CrossRef]
74. Alberto Bindoli , Jon M. Fukuto , Henry Jay Forman . 2008. Thiol Chemistry in Peroxidase Catalysis and Redox Signaling. *Antioxidants & Redox Signaling* **10**:9, 1549-1564. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]

75. Jae-Min Yuk, Chul-Su Yang, Dong-Min Shin, Kwang-Kyu Kim, Sang Ki Lee, Yun Jeong Song, Hye-Mi Lee, Chung-Hyun Cho, Byeong Hwa Jeon, Eun-Kyeong Jo. 2008. A Dual Regulatory Role of Apurinic/apyrimidinic Endonuclease 1/Redox Factor-1 in HMGB1-induced Inflammatory Responses. *Antioxidants & Redox Signaling* **0**:ja, 080820082827668. [CrossRef]

76. Dunyaporn Trachootham , Weiqin Lu , Marcia A. Ogasawara , Nilsa Rivera-Del Valle , Peng Huang . 2008. Redox Regulation of Cell Survival. *Antioxidants & Redox Signaling* **10**:8, 1343-1374. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]

77. Fulvio Lauretani , Richard D. Semba , Stefania Bandinelli , Margaret Dayhoff-Brannigan , Fabrizio Lauretani , Anna Maria Corsi , Jack M. Guralnik , Luigi Ferrucci . 2008. Carotenoids as Protection Against Disability in Older Persons. *Rejuvenation Research* **11**:3, 557-563. [Abstract] [Full Text PDF] [Full Text PDF with Links]

78. Myung-Jeom Ryu, Vadim Anikin, Seok-Ho Hong, Hyesung Jeon, Yeon Gyu Yu, Myeong-Hee Yu, Sergey Chernysh, Cheolju Lee. 2008. Activation of NF-#B by alloferon through down-regulation of antioxidant proteins and I#B#. *Molecular and Cellular Biochemistry* **313**:1-2, 91-102. [CrossRef]

79. Cheng-Xiong Xu, Hua Jin, Youn-Sun Chung, Ji-Young Shin, Min-Ah Woo, Kee-Ho Lee, Grace N. Palmos, Byeong-Dae Choi, Myung-Haing Cho. 2008. Chondroitin sulfate extracted from the Styela clava tunic suppresses TNF-#-induced expression of inflammatory factors, VCAM-1 and iNOS by blocking Akt/NF-#B signal in JB6 cells. *Cancer Letters* **264**:1, 93-100. [CrossRef]

80. Li Gan, Lennart Mucke. 2008. Paths of Convergence: Sirtuins in Aging and Neurodegeneration. *Neuron* **58**:1, 10-14. [CrossRef]

81. Sadatomo Tasaka , Fumimasa Amaya , Satoru Hashimoto , Akitoshi Ishizaka . 2008. Roles of Oxidants and Redox Signaling in the Pathogenesis of Acute Respiratory Distress Syndrome. *Antioxidants & Redox Signaling* **10**:4, 739-754. [Abstract] [Full Text PDF] [Full Text PDF with Links]

82. Kirubakaran Shanmugam, Lina Holmquist, Megan Steele, Grant Stuchbury, Katrin Berbaum, Oliver Schulz, Obdulio Benavente García, Julián Castillo, Jim Burnell, Vernon Garcia Rivas, Geoff Dobson, Gerald Münch. 2008. Plant-derived polyphenols attenuate lipopolysaccharide-induced nitric oxide and tumour necrosis factor production in murine microglia and macrophages. *Molecular Nutrition & Food Research* **52**:4, 427-438. [CrossRef]

83. Antero Salminen, Jari Huuskonen, Johanna Ojala, Anu Kauppinen, Kai Kaarniranta, Tiina Suuronen. 2008. Activation of innate immunity system during aging: NF-kB signaling is the molecular culprit of inflamm-aging. *Ageing Research Reviews* **7**:2, 83-105. [CrossRef]

84. M. Dayhoff-Brannigan, L. Ferrucci, K. Sun, L. P. Fried, J. Walston, R. Varadhan, J. M. Guralnik, R. D. Semba. 2008. Oxidative Protein Damage Is Associated With Elevated Serum Interleukin-6 Levels Among Older Moderately to Severely Disabled Women Living in the Community. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences* **63**:2, 179-183. [CrossRef]

85. Alois Kozubík, Alena Vaculová, Karel Sou#ek, Jan Vondrá#ek, Jaroslav Turánek, Ji#ina Hofmanová. 2008. Novel Anticancer Platinum(IV) Complexes with Adamantylamine: Their Efficiency and Innovative Chemotherapy Strategies Modifying Lipid Metabolism. *Metal-Based Drugs* **2008**, 1-15. [CrossRef]

86. Jacky Jacquot, Olivier Tabary, Philippe Le Rouzic, Annick Clement. 2008. Airway epithelial cell inflammatory signalling in cystic fibrosis. *The International Journal of Biochemistry & Cell Biology* **40**:9, 1703-1715. [CrossRef]

87. John F. Moxnes, Olav Albert christophersen. 2008. The Spanish flu as a worst case scenario?. *Microbial Ecology in Health and Disease* **20**:1, 1-26. [CrossRef]

88. Cheng Li , Parastu Hossieny , Ben J. Wu , Abdelqader Qawasmeh , Konstanze Beck , Roland Stocker . 2007. Pharmacologic Induction of Heme Oxygenase-1. *Antioxidants & Redox Signaling* **9**:12, 2227-2240. [Abstract] [Full Text PDF] [Full Text PDF with Links]

89. Richard D. Semba, Luigi Ferrucci, Kai Sun, Jeremy Walston, Ravi Varadhan, Jack M. Guralnik, Linda P. Fried. 2007. Oxidative Stress and Severe Walking Disability among Older Women. *The American Journal of Medicine* **120**:12, 1084-1089. [CrossRef]

90. Jorge H. Limón-Pacheco, Norma A. Hernández, María L. Fanjul-Moles, María E. Gonsebatt. 2007. Glutathione depletion activates mitogen-activated protein kinase (MAPK) pathways that display organ-specific responses and brain protection in mice. *Free Radical Biology and Medicine* **43**:9, 1335-1347. [CrossRef]

91. Richard D. Semba, Luigi Ferrucci, Kai Sun, Jeremy Walston, Ravi Varadhan, Jack M. Guralnik, Linda P. Fried. 2007. Oxidative Stress Is Associated with Greater Mortality in Older Women Living in the Community. *Journal of the American Geriatrics Society* **55**:9, 1421-1425. [CrossRef]

92. Yao Sun. 2007. Oxidative Stress and Cardiac Repair/Remodeling Following Infarction. *The American Journal of the Medical Sciences* **334**:3, 197-205. [CrossRef]
93. C YUN, J YANG, S KANG, Y YANG, J CHO, C SON, S HAN. 2007. NF-#B signaling pathway, not IFN-#/STAT1, is responsible for the selenium suppression of LPS-induced nitric oxide production. *International Immunopharmacology* **7**:9, 1192-1198. [CrossRef]
94. S CHOI, J HWANG, H KO, J PARK, S KIM. 2007. Nobiletin from citrus fruit peel inhibits the DNA-binding activity of NF-#B and ROS production in LPS-activated RAW 264.7 cells. *Journal of Ethnopharmacology* **113**:1, 149-155. [CrossRef]
95. Ahmed M. Elsharkawy, Derek A. Mann. 2007. Nuclear factor-#B and the hepatic inflammation-fibrosis-cancer axis. *Hepatology* **46**:2, 590-597. [CrossRef]
96. Jason M. Hansen, Siobhan Moriarty-Craige, Dean P. Jones. 2007. Nuclear and cytoplasmic peroxiredoxin-1 differentially regulate NF-#B activities. *Free Radical Biology and Medicine* **43**:2, 282-288. [CrossRef]
97. Yusuke Shibata, Noriaki Kume, Hidenori Arai, Kazutaka Hayashida, Atsuko Inui-Hayashida, Manabu Minami, Eri Mukai, Masako Toyohara, Akiko Harauma, Toshinori Murayama, Toru Kita, Saburo Hara, Kaeko Kamei, Masayuki Yokode. 2007. Mulberry leaf aqueous fractions inhibit TNF-#-induced nuclear factor #B (NF-#B) activation and lectin-like oxidized LDL receptor-1 (LOX-1) expression in vascular endothelial cells. *Atherosclerosis* **193**:1, 20-27. [CrossRef]
98. Christian Schwarzer, Beate Illek, Jung H. Suh, S. James Remington, Horst Fischer, Terry E. Machen. 2007. Organelle redox of CF and CFTR-corrected airway epithelia. *Free Radical Biology and Medicine* **43**:2, 300-316. [CrossRef]
99. Stephen J. Polyak, Chihiro Morishima, Margaret C. Shuhart, Chia C. Wang, Yanze Liu, David Y.–W. Lee. 2007. Inhibition of T-Cell Inflammatory Cytokines, Hepatocyte NF-#B Signaling, and HCV Infection by Standardized Silymarin. *Gastroenterology* **132**:5, 1925-1936. [CrossRef]
100. Mikael G. V. Hanson, Volkan Özenci, Mattias C. V. Carlsten, Bengt L. Glimelius, Jan-Erik A. Frödin, Giuseppe Masucci, Karl-Johan Malmberg, Rolf V. R. Kiessling. 2007. A short-term dietary supplementation with high doses of vitamin E increases NK cell cytolytic activity in advanced colorectal cancer patients. *Cancer Immunology, Immunotherapy* **56**:7, 973-984. [CrossRef]
101. Dr. Nikolai V. Gorbunov , Dipak K. Das , Shyamal K. Goswami , Narasimman Gurusamy , James L. Atkins . 2007. Spatial Coordination of Cell-Adhesion Molecules and Redox Cycling of Iron in the Microvascular Inflammatory Response to Pulmonary Injury. *Antioxidants & Redox Signaling* **9**:4, 483-495. [Abstract] [Full Text PDF] [Full Text PDF with Links]
102. Lena LAVIE, Alona VISHNEVSKY, Peretz LAVIE. 2007. Oxidative stress and systemic inflammation in patients with sleep apnea: Role of obesity. *Sleep and Biological Rhythms* **5**:2, 100-110. [CrossRef]
103. Jennifer S. Moylan, Michael B. Reid. 2007. Oxidative stress, chronic disease, and muscle wasting. *Muscle & Nerve* **35**:4, 411-429. [CrossRef]
104. Johan Bylund, Kelly L. MacDonald, Kelly L. Brown, Piotr Mydel, L. Vincent Collins, Robert E. W. Hancock, David P. Speert. 2007. Enhanced inflammatory responses of chronic granulomatous disease leukocytes involve ROS-independent activation of NF-#B. *European Journal of Immunology* **37**:4, 1087-1096. [CrossRef]
105. Karnati R. Roy, Kalle M. Arunasree, Amit Dhoot, Rachamallu Aparna, Gorla Venkateswara Reddy, Shireen Vali, Pallu Reddanna. 2007. C-Phycocyanin inhibits 2-acetylaminofluorene-induced expression of MDR1 in mouse macrophage cells: ROS mediated pathway determined via combination of experimental and In silico analysis. *Archives of Biochemistry and Biophysics* **459**:2, 169-177. [CrossRef]
106. Kenneth T. Kishida , Dr. Eric Klann . 2007. Sources and Targets of Reactive Oxygen Species in Synaptic Plasticity and Memory. *Antioxidants & Redox Signaling* **9**:2, 233-244. [Abstract] [Full Text PDF] [Full Text PDF with Links]
107. Richard D. Semba, Fulvio Lauretani, Luigi Ferrucci. 2007. Carotenoids as protection against sarcopenia in older adults. *Archives of Biochemistry and Biophysics* **458**:2, 141-145. [CrossRef]
108. Andrzej Mazur, Jeanette A.M. Maier, Edmond Rock, Elyett Gueux, Wojciech Nowacki, Yves Rayssiguier. 2007. Magnesium and the inflammatory response: Potential physiopathological implications. *Archives of Biochemistry and Biophysics* **458**:1, 48-56. [CrossRef]
109. Christopher Horst Lillig , Arne Holmgren . 2007. Thioredoxin and Related Molecules–From Biology to Health and Disease. *Antioxidants & Redox Signaling* **9**:1, 25-47. [Abstract] [Full Text PDF] [Full Text PDF with Links]
110. Antonysunil Adaikalakoteswari, Mohan Rema, Viswanathan Mohan, Muthuswamy Balasubramanyam. 2007. Oxidative DNA damage and augmentation of poly(ADP-ribose) polymerase/nuclear factor-kappa B signaling in patients with Type 2 diabetes and microangiopathy. *The International Journal of Biochemistry & Cell Biology* **39**:9, 1673-1684. [CrossRef]

111. Zhihao Wu, Brian Rogers, Shu Kachi, Sean F. Hackett, Anna Sick, Peter A. Campochiaro. 2006. Reduction of p66Shc suppresses oxidative damage in retinal pigmented epithelial cells and retina. *Journal of Cellular Physiology* **209**:3, 996-1005. [CrossRef]
112. Kenneth T. Kishida, Eric Klann. 2006. Sources and Targets of Reactive Oxygen Species in Synaptic Plasticity and Memory. *Antioxidants & Redox Signaling*, ahead of print061121054212009. [CrossRef]
113. Pamela Maher . 2006. Redox Control of Neural Function: Background, Mechanisms, and Significance. *Antioxidants & Redox Signaling* **8**:11-12, 1941-1970. [Abstract] [Full Text PDF] [Full Text PDF with Links]
114. Jill B. Lewis, Regina L. Messer, Veronica V. McCloud, Petra E. Lockwood, Stephen D. Hsu, John C. Wataha. 2006. Ni(II) activates the Nrf2 signaling pathway in human monocytic cells. *Biomaterials* **27**:31, 5348-5356. [CrossRef]
115. J BEAUDEUX, J PEYNET, D BONNEFONTROUSSELOT, P THEROND, J DELATTRE, A LEGRAND. 2006. Sources cellulaires des espèces réactives de l'oxygène et de l'azoteImplication dans la transcription et la régulation des gènes. *Annales Pharmaceutiques Françaises* **64**:6, 373-381. [CrossRef]
116. C Bubici, S Papa, K Dean, G Franzoso. 2006. Mutual cross-talk between reactive oxygen species and nuclear factor-kappa B: molecular basis and biological significance. *Oncogene* **25**:51, 6731-6748. [CrossRef]
117. Richard A. Franklin , Oswaldo G. Rodriguez–Mora , Michelle M. LaHair , James A. McCubrey . 2006. Activation of the Calcium/Calmodulin-Dependent Protein Kinases as a Consequence of Oxidative Stress. *Antioxidants & Redox Signaling* **8**:9-10, 1807-1817. [Abstract] [Full Text PDF] [Full Text PDF with Links]
118. Eric A. Schwartz, Peter D. Reaven. 2006. Molecular and Signaling Mechanisms of Atherosclerosis in Insulin Resistance. *Endocrinology and Metabolism Clinics of North America* **35**:3, 525-549. [CrossRef]
119. Fariba Alidoost, Marjan Gharagozloo, Bahram Bagherpour, Abbas Jafarian, Seyed Ebrahim Sajjadi, Hamid Hourfar, Behjat Moayedi. 2006. Effects of silymarin on the proliferation and glutathione levels of peripheral blood mononuclear cells from #-thalassemia major patients. *International Immunopharmacology* **6**:8, 1305-1310. [CrossRef]
120. Joshua Wayne, Jennifer Sielski, Ahmed Rizvi, Ketleine Georges, Dorothy Hutter. 2006. ERK regulation upon contact inhibition in fibroblasts. *Molecular and Cellular Biochemistry* **286**:1-2, 181-189. [CrossRef]
121. Andrey Kropotov, Vladimir Serikov, Jung Suh, Alexandra Smirnova, Vladimir Bashkirov, Boris Zhivotovsky, Nikolai Tomilin. 2006. Constitutive expression of the human peroxiredoxin V gene contributes to protection of the genome from oxidative DNA lesions and to suppression of transcription of noncoding DNA. *FEBS Journal* **273**:12, 2607-2617. [CrossRef]
122. E CHOI, H JANG, J KIM, H KIM, H KANG, Y PAEK, H LEE, S LEE, W OH, I KANG. 2006. Enhancement of cytokine-mediated NF-#B activation by phosphatidylinositol 3-kinase inhibitors in monocytic cells. *International Immunopharmacology* **6**:6, 908-915. [CrossRef]
123. PINGHUA LI, SHRINIVASRAO P. MANE, ALLAN A. SIOSON, CECILIA VASQUEZ ROBINET, LENWOOD S. HEATH, HANS J. BOHNERT, RUTH. GRENE. 2006. Effects of chronic ozone exposure on gene expression in Arabidopsis thaliana ecotypes and in Thellungiella halophila. *Plant, Cell and Environment* **29**:5, 854-868. [CrossRef]
124. Dr. Irfan Rahman , Se-Ran Yang , Saibal K. Biswas . 2006. Current Concepts of Redox Signaling in the Lungs. *Antioxidants & Redox Signaling* **8**:3-4, 681-689. [Abstract] [Full Text PDF] [Full Text PDF with Links]
125. Hae Young Chung , Bokyung Sung , Kyung Jin Jung , Yani Zou , Byung Pal Yu . 2006. The Molecular Inflammatory Process in Aging. *Antioxidants & Redox Signaling* **8**:3-4, 572-581. [Abstract] [Full Text PDF] [Full Text PDF with Links]
126. Joseph P. Sanderson, Dean J. Naisbitt, B. Kevin Park. 2006. Role of bioactivation in drug-induced hypersensitivity reactions. *The AAPS Journal* **8**:1, E55-E64. [CrossRef]
127. Dimitris Tousoulis, Charalambos Antoniades, Christodoulos Stefanadis. 2006. Nitric oxide in coronary artery disease: effects of antioxidants. *European Journal of Clinical Pharmacology* **62**:S1, 101-107. [CrossRef]
128. HEATHER I. DIEPERINK, TIMOTHY S. BLACKWELL, LAWRENCE S. PRINCE. 2006. Hyperoxia and Apoptosis in Developing Mouse Lung Mesenchyme. *Pediatric Research* **59**:2, 185-190. [CrossRef]
129. P ATHERFOLD, J JANKOWSKI. 2006. Molecular biology of Barrett's cancer. *Best Practice & Research Clinical Gastroenterology* **20**:5, 813-827. [CrossRef]
130. M. Tien Kuo, Niramol Savaraj. 2006. Roles of reactive oxygen species in hepatocarcinogenesis and drug resistance gene expression in liver cancers. *Molecular Carcinogenesis* . [CrossRef]
131. Eric B. Staros. 2006. Innate Immune Molecular Connections Between Atherosclerosis and Statins. *American Journal of Clinical Pathology* **125**:1, 8. [CrossRef]
132. Kumuda C. Das . 2005. Thioredoxin and Its Role in Premature Newborn Biology. *Antioxidants & Redox Signaling* **7**:11-12, 1740-1743. [Abstract] [Full Text PDF] [Full Text PDF with Links]

133. Anne Burke-Gaffney, Matthew E.J. Callister, Hajime Nakamura. 2005. Thioredoxin: friend or foe in human disease?. *Trends in Pharmacological Sciences* **26**:8, 398-404. [CrossRef]

134. Kiyoshi Nose . 2005. Redox Control of Protein Trafficking. *Antioxidants & Redox Signaling* **7**:3-4, 303-307. [Citation] [Full Text PDF] [Full Text PDF with Links]

135. Oswaldo Rodriguez-Mora, Michelle M LaHair, Christopher J Howe, James A McCubrey, Richard A Franklin. 2005. Calcium/calmodulin-dependent protein kinases as potential targets in cancer therapy. *Expert Opinion on Therapeutic Targets* **9**:4, 791. [CrossRef]

136. Ken Itoh, Masayuki Yamamoto. 2005. Regulatory Role of the COX-2 Pathway in the Nrf2-Mediated Anti-Inflammatory Response. *Journal of Clinical Biochemistry and Nutrition* **37**:1, 9-18. [CrossRef]