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Forum Review

Redox-Sensitive Kinases of the Nuclear Factor-κB Signaling Pathway

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ABSTRACT

NF-κB is an inducible transcription factor that plays a role in the expression of over one hundred genes involved in immunity, inflammation, proliferation, and in defense against apoptosis. NF-κB has been known to be redox regulated for some time and is a direct target for oxidation that can affect its ability to bind to DNA. Reactive oxygen species (ROS) have been identified as second messengers in cells, and play a role in receptor signaling and posttranslation modification of signaling molecules. These posttranslation modifications include oxidations of critical cysteines to sulfenic acids or mixed disulfides, which can affect the activity of proteins. Many kinases involved in direct or indirect activation of NF-κB are affected by oxidants and therefore, have the potential to alter NF-κB activity. This review will provide a summary of the NF-κB family, their activation and regulation, followed by a summary of cytoplasmic and nuclear kinases in this pathway whose activity is affected by oxidants. Additionally, recent investigations have revealed that the JNK signaling pathway, which is known to be redox regulated, and pro-apoptotic, is inhibited by NF-κB signaling. The crosstalk of NF-κB with other signaling pathways is therefore critical for cellular fate, notably survival or cell death under oxidative conditions, and will also be reviewed. *Antioxid. Redox Signal.* 8, 1791–1806.

NF-κB GENERAL OVERVIEW

The inducible transcription factor NF-κB was first discovered in the nuclei of B cells, bound to the Ig κ light chain enhancer, hence its name, nuclear factor-κB. Since its original discovery, NF-κB has been found in the nucleus and cytoplasm of all cell types and is known to be highly conserved among species. NF-κB plays an essential role in the innate and adaptive immune response, cell proliferation, and is a potent inhibitor of apoptosis. Mammalian NF-κB is comprised of five proteins–RelA (also known as p65), RelB, c-Rel, p100, and p105–which exist in cells as hetero- or homo- dimers. The proteins are characterized by an N terminal Rel homology domain (RHD) that is responsible for binding to DNA, and to other proteins as well as for dimerization. Two of the family members, p100 and p105, also contain a C terminus ankyrin repeat sequence that is posttranscriptionally removed to form family members p52 and p50, respectively (49).

NF-κB dimers, the most prevalent ones investigated being RelA/p50, are found in the cytoplasm of unstimulated cells bound by their RHD to inhibitors of kappa B proteins, IκBs. There are seven IκBs that bind to NF-κB dimers, masking their nuclear localization signal, NLS, and sequestering the proteins in the cytoplasm. Upon cellular stimulation IκB is phosphorylated on two critical serines and subsequently polyubiquinated by an ubiquitin ligase belonging to the SCF family and degraded by the 26S proteosome. This allows the NF-κB dimers to translocate to the nucleus and initiate transcription of cellular response genes by binding to promoter and enhancer sites containing the κB consensus sequence, GGGRNNYYCC (12). However, another consensus site for binding of a subfamily of NF-κB was recently defined and will be further discussed in the next section.

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NF-κB is known to be activated in response to diverse stimuli such as cytokines, and viral and bacterial particles, and is involved in the transcription of over 100 genes. Many of these genes are involved in the innate immune response, and are essential to alert the body to foreign antigens. Additionally, NF-κB is involved in the adaptive immune response and plays a role in T and B cell activation. The essential role of NF-κB in immunity was defined by studies using mouse models with impaired NF-κB signaling. These mice have an impaired onset of innate and adaptive immune responses and survival of T cells (39, 124). Furthermore, RelA −/− mice have an increased susceptibility to infections, a phenotype also seen in IKKβ −/− mice (13). NF-κB also plays a role in diseases such as arthritis, inflammatory bowel disease, and asthma where it is involved in initiating the inflammatory response to LPS, and ovalbumin in a model of allergic airway disease (100, 101). Since NF-κB is pro-proliferative and anti-apoptotic it also plays a role in the development of tumors and has been investigated as a target for cancer therapeutics (64, 78).

CYTOPLASMIC REGULATION OF NF-κB ACTIVATION

NF-κB controls the transcription of genes involved in a repertoire of processes, therefore, the transcription factor itself is tightly regulated. NF-κB is kept sequestered in the cytoplasm of unstimulated cells bound to IκB proteins. In response to a wide array of stimuli, IκB proteins are phosphorylated by the serine kinase: Inhibitor of kappa B kinase (IKK). Phosphorylated IκBs are ubiquitinated and degraded by the 26S proteosome, unmasking the NF-κB nuclear localization signal, allowing NF-κB to accumulate in the nucleus (Fig. 1). IKK is a complex comprised of three different proteins. Two of the IKK subunits, IKKα and IKKβ, are structurally related and contain kinase activity. The third subunit of the IKK complex is IKKγ, also known as NEMO, does not contain kinase activity but acts as a regulatory protein (111). The complex was originally isolated from mammalian cells as a 700–900 kD complex and has been shown to contain additional proteins such as Hsp90 and cdc37 (20), although the exact stoichiometric proportions of the various subunits are not fully elucidated. However, it is known that IKKα and IKKβ form heterodimers, which are necessary for kinase activity, as homodimers are rarely seen *in vivo,* and do not have optimal kinase activity (49). In addition, IKKγ is known to oligomerize at its C-terminus, which is essential for IKK activity. IKK is activated by diverse stimuli in a receptor dependent manner. The best described and predominant pathways to NF-κB are the TNFα receptor family, Toll/IL-1 receptor, and T cell receptors. All of these receptors are non-catalytic and rely on the recruitment of adaptor molecules to elicit their signal. TNFα receptor family members, such as

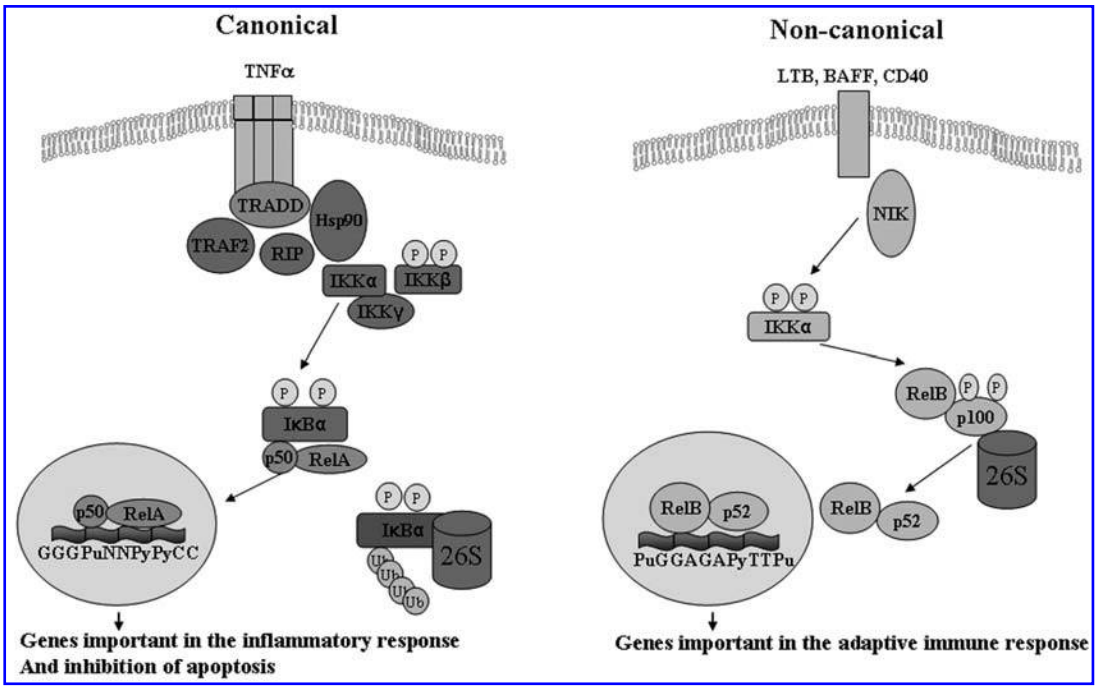

FIG. 1. Receptor-mediated activation of canonical and noncanonical NF-κB pathways. *Left panel*: Activation of the canonical NF-κB as exemplified by TNF-RI signaling. Binding of TNFα to TNF-RI leads to the recruitment and activation of the IKK complex. IKKβ phosphorylates IKBα on serines 32 and 36, resulting in the ubiquitination and degradation of IκBα. The newly exposed nuclear localization signal (NLS) of RelA/p50 heterodimers results in heterodimer accumulation in nucleus, and binding to the canonical NF-κB consensus sequence in DNA. *Right panel*: Activation of the noncanonical NF-κB pathway as exemplified by receptor signaling involved in the adaptive immune response. Binding of ligands such as LTB to their receptor leads to the activation of NIK, which directly phosphorylates IKKα. IKKα then phosphorylates p100, which is then processed into p52. p52/RelB dimers subsequently translocate to the nucleus where they bind to the alternate consensus sequence, leading to enhanced transcription of genes important for the adaptive immune response. Pu, purine; Py, pyrimidine; N, any base.

TNFα-RI activate IKK and subsequently NF-κB in response to cytokines. Toll receptors lead to IKK activation in the presence of foreign stimuli such as LPS, while T cell receptors activate IKK and NF-κB in response to specific antigens.

Two pathways of IKK-induced NF-κB have been described, termed the canonical and the noncanonical pathway (Fig. 1). In the canonical pathway, activation of IKKβ by stimuli such as the cytokine TNFα, leads to the phosphorylation of IκBα at serines 32 and 36. Knockout studies have revealed that IKKβ and IKKγ are essential for this activation pathway. IKKα is capable of phosphorylating IKBα, however, optimal NF-κB activation occurs through IKKβ, as studies have shown that in IKKβ knockout mice IKKα can not compensate for loss of kinase activity (32).

In the noncanonical pathway, NF-κB Inducing Kinase (NIK), phosphorylates IKKα (80), and in turn IKKα directly phosphorylates p100 (123), which initiates processing to p52. This leads to the formation of p52/RelB heterodimers, which translocate to the nucleus (49, 65). Activators of the noncanonical pathway include B cell activating factor (BAFF), lymphotoxin beta (LTβ), and CD40 ligand (CD40L), and this pathway is thought to be necessary for the adaptive immune response while the canonical pathway is required for the onset of the innate immune response. Through the use of chromatin immunoprecipitation (ChIP) analysis, it has been discovered that p52/RelB dimers activated through the noncanonical pathway by stimuli such as LTβ use a unique consensus site. This site, PuGGAGAPyTTPu, is located in the regulatory region of many chemokine genes involved in the adaptive immune response such as B-lymphocyte chemoattractant (BLC), and EBI-1 ligand chemokine (ELC) (12). The use of a different DNA binding consensus site by IKKα-activated RelB/p52, as compared to IKKβ-activated RelA/p50 illuminates the exquisite regulation of gene expression by the NF-κB pathway.

REGULATION OF NF-κB TRANSCRIPTIONAL ACTIVITY

In addition to the regulation of NF-κB by cytoplasmic kinases such as IKK, nuclear regulation of NF-κB family members has recently emerged as a critical component of NF-κB activation that regulates the shape, strength, and duration of the NF-κB transcriptional response (see Ref. 23 for an elegant review). NF-κB is covalently modified by direct phosphorylation and acetylation, which alter the ability of NF-κB dimers to bind to DNA, and initiate the recruitment of transcriptional co-activators. These modifications also influence the binding of NF-κB to its inhibitor IκBα (23, 49). RelA can be phosphorylated both in the cytoplasm and in the nucleus, and multiple distinct kinases specifically enhance the transactivation potential of RelA. Lipopolysaccharide (LPS) induces phosphorylation of RelA at serine 276 through the cytoplasmic action of protein kinase A (PKA_c) (155, 156), TNFα results in serine 276 phosphorylation in the nucleus through mitogen and stress-activated kinase-1 (MSK-1) (140). Additionally, TNFα leads to phosphorylation of RelA at position serine 311, through the action of protein kinase C zeta (PKCζ), which is also critical for interaction with the transcriptional cofactor, cyclic-AMP response element binding protein-binding protein (CBP), and consequently enhances NF-κB transactivation (33, 77). RelA also can be phosphorylated in the carboxyterminal transcriptional activation domain, through the actions of casein kinase-2 (CK-2) at serine 529 (10, 141), or by IKKs at serine 536 (115). Phosphorylation of RelA by IKKs demonstrates that the biological roles of IκK exceed their well-known action in phosphorylation of IκBs, and their importance in nuclear regulation is also exemplified by the phosphorylation of histone H3 by IKKα (7, 149). Other kinases that phosphorylate RelA, include 90 kd ribosomal S6 kinase-1 (RSK-1), glycogen-synthase kinase-3b (GSK-3b), AKT/phosphatidylinositiol-3-kinase (PI-3-K), and NF-κB inducing kinase (NIK), and some of their actions occur in the nucleus (122, 128, 140).

Like other transcription factors, NF-κB relies on the lysine acetylation of histones by histone acetyltransferases (HAT) to initiate DNA uncoiling and allow the accessibility for binding. Interestingly, both RelA and p50 themselves are acetylated on multiple lysine residues that regulate different functions of NF-κB, including transcriptional activation, DNA binding, IκBα assembly, and subcellular localization (21). RelA acetylation occurs on residues Lys218, Lys221, and Lys310, in response to TNFα or PMA stimulation. Lysine 310 acetylation requires prior phosphorylation of Ser276 and Ser326 (24), demonstrating a direct molecular connection between phosphorylation, acetylation, and transcriptional activity. CREB binding protein (CBP) or its homolog, p300, p300/CBP-associated factor (PCAF), or members of the p150 family have been implicated as the acetyl tranferases (21, 66, 151). Like phosphorylated RelA, acetylated RelA has a higher affinity for DNA and a decreased binding affinity for IκBα. p50 is acetylated on residues Lys 431, 440, and 441, which increases DNA binding activity and transcription by the heterodimeric NF-κB complexes (22, 23). Acetylation of RelA is reversed by histone deacetylases, HDAC1–3, resulting in loss of transcriptional activation potential, increases in association with IκBα, or enhanced nuclear export of NF-κB (22), The mammalian Sirtuin-1, SIRT-1, a member of the family of atypical class III HDACs, was recently shown to physically interact with RelA, and to inhibit transcription by deacetylating RelA at lysine 310 (151). Deacetylation increases NF-κB binding to IκBα, increasing nuclear export of NF-κB. HDACs also appear to play a crucial role in repressing NF-κB activation in unstimulated cells. HDAC1 association with p50 homodimers prevents unphosphorylated RelA from binding to its consensus site, providing a mechanism of inhibiting resident nuclear RelA-mediated transactivation in the absence of an NF-κB inducing stimulus (49, 155). While progress is made towards unraveling the chromatin remodeling processes that occur as a function of RelA posttranslational modifications, and the consequences for gene expression, a significant report has demonstrated that the intricacies whereby RelA regulates specific promoters remain unknown. This study demonstrated that the specific stimulus that mediates NF-κB activation (a cytokine compared to a cytotoxic stimulus), in fact dictates whether RelA activates or represses transcription. The authors demonstrated that while ultraviolet (UV)-C radiation or TNFα both activate NF-κB, UV-C inhibited TNFα-induced transactivation, and that RelA acted as a dominant repressor of NF-κB controlled antiapoptotic genes (19). RelA-mediated

transrepression by cytotoxic stimuli was accompanied by an increased association of RelA with co-repressors, and reduction of histone acetylation at specific promoters (19), implying that RelA became a dominant repressor at least partially by actively silencing the local chromatin environment (87). These findings raise important questions about mechanisms whereby redox changes might affect NF-κB-dependent gene expression.

CYSTEINE OXIDATION AND CELL SIGNALING

The significance of ROS as signaling molecules has been a question of considerable debate and controversy because of the difficulty in assessing the specificity of oxidation targets, or their reversibility, two critical requirements in signal transduction. However, the specificity of ROS for critical reactive thiols is being recognized, as was elegantly reviewed recently (37, 38). Oxidation of reactive protein cysteine residues by ROS can lead to the formation of cysteine sulfenic derivative (P-SOH), which is unstable and can react with another cysteine residue to form a disulfide bond. Both sulfenic acids and disulfides are readily reversed by various cellular reducing systems (8, 44), thereby restoring protein structure and function. Protein sulfenic acids can also form disulfides with small intracellular thiols such as GSH (P-SSG). This is termed *S*-glutathionylation and may be a prevalent modification due to the high abundance of GSH. Protein–glutathione mixed disulfides are reversible and can be reduced by thiols, or by enzymatic reactions involving glutaredoxins (34) (GRX, Fig. 2), or protein disulfide isomerases (44). Cysteine oxidations relevant to cell signaling in physiological settings are readily reversible; therefore, detection of these events has been difficult, if not impossible, contributing to the former lack of proper recognition of oxidants as relevant signaling moieties. Other oxidations such as protein *S*-glutathionylation can be detected by HPLC, using GSH antibodies (44), or using pre-labeled GSH (biotinylated, radiolabeled), and these avenues have been used to probe oxidations of members of the NF-κB pathway (99, 104). Many proteins in the NF-κB pathway have reactive cysteines that impact on NF-κB activation. These include p50 itself, IKKβ, and MEKKI. While cysteine residues are oxidation targets relevant to the NF-κB pathway, other amino acids particularly those containing aromatic rings, the thioester of methionine, and the protein backbone itself can also be oxidized, which may impact signaling modules, such as NF-κB activation (29). Indeed oxidation of IκBα at methionine 45 by taurine chloramine was demonstrated to inhibit TNFα-stimulated NF-κB activation (61), supporting the notion that oxidation of multiple amino acid targets may affect NF-κB signaling.

NF-κB REGULATION BY ROS

Whereas IKK is the obligatory kinase leading to IκB phosphorylation, additional kinases affect the NF-κB pathway directly and indirectly, as was discussed earlier and include MEKK-1, AKT/PI-3-K, JNK, as well as various nuclear kinases. The effect of oxidants on NF-κB directly, or on kinases

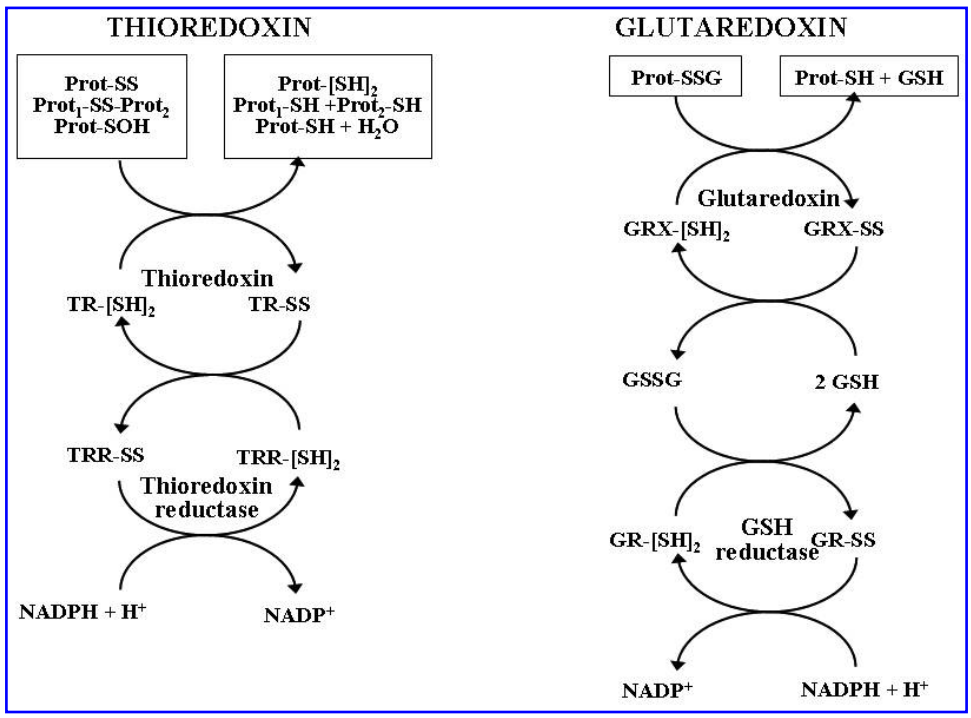

FIG. 2. Schematic representation of the reversal of protein cysteine oxidation by the Glutaredoxin (GRX) and Thioredoxin (TR) pathways. Indicated are the targets of GRX (*S*-glutathionylated cysteines) or TR (disulfides, and sulfenic acids), leading to oxidation of GRX, or TR (indicated as GRX-SS, and TR-SS). TR-SS is restored by the action of thioredoxin reductase (TRR) at the expense of NADPH, whereas reduction of GRX-SS requires GSH. Lastly, oxidized GSH (GSSG) is restored by GSH-reductase, at the expense of NADPH.

that regulate NF-κB will be the further focus of this review. While the chromatin remodeling factors that encompass histone acetyltransferases (HAT) and histone deacetylases (HDAC) are also redox regulated (3, 103, 135), with obvious relevance to NF-κB, this topic was the subject of a recent review in this Journal and will not be further considered here (2).

It has been known for well over a decade that NF-κB is a redox-sensitive transcription factor, a topic that has been reviewed extensively (36, 43, 47, 54, 58, 84, 119, 121). Work in the early 1990s established that NF-κB can be activated by H_2O_2, or ionizing radiation (120). NF-κB activation by cytokines, LPS, CD3 engagement, or phorbol ester tumor promoters, was also demonstrated to require ROS. Indeed, well-characterized activators of NF-κB, such as TNFα or IL-1β, led to enhanced ROS production, in part through activation of NADPH oxidases that contributed to NF-κB activation (14, 95, 112, 116, 130). Depletion of cellular GSH and subsequent increases in GSSG also were demonstrated to mediate IκBα phosphorylation and subsequent activation of NF-κB (85, 102). Inhibition of cytokine-induced NF-κB activation by antioxidants such as glutathione peroxidase (117), *N*-acetyl-cysteine (NAC) (5, 129), or metal chelators such as pyrrolidine dithiocarbamate (PDTC) (120), further supported the notion that NF-κB activation is mediated via a "redox" mechanism. However, the redox-dependent activation of NF-κB in early studies was contradicted by a series of subsequent investigations reporting that ROS inhibited NF-κB by interfering with its ability to bind DNA. Indeed studies from the early 1990s demonstrated that Cys 62 of the p50 subunit was sensitive to oxidation (83, 86, 134), which inhibited the ability of p50 to bind DNA. Inhibition of DNA binding of oxidized p50 was reversible by reduction with nuclear thioredoxin (83, 86). Studies evaluating the oxidative modification of p50 in response to H_2O_2, identified glutathionylation as one of the oxidations that inhibited p50 activity (99).

Collectively, these findings led to the model that oxidative activation of NF-κB occurred proximal to DNA binding. The apparent paradox of NF-κB activation by ROS, while requiring a reduced state for DNA binding, points to the some of the difficulties faced in elucidating the physiological role redox changes in the regulation of this transcription factor. The physiological role for oxidants in the activation of NF-κB was further brought into question based upon observations that redox activation was cell type specific (5, 15), and by a recent study demonstrating that NAC lowered the affinity of TNFα for its receptor, and that PDTC inhibited IκB-ubiquitin ligase activity in a cell free system where ROS production did not occur (48). The same authors also provided evidence that ROS produced by NADPH oxidases did not mediate NF-κB signaling, but lowered the magnitude of its activation (48). In support of the latter, other laboratories (including ours) suggested that upstream signaling events in the NF-κB pathway such as IKK activation by TNFα were not activated but inhibited by ROS (72, 93). Thus, the significance of redox regulation of NF-κB should be carefully considered in light of the methodologies and reagents used. Based upon the many reports in the literature, it remains nonetheless clear that ROS can impact on the NF-κB cascade. However, the outcome of NF-κB pathway modulation by oxidants is likely to be highly stimulus and cell type specific, and is unlikely to be generally applicable to diverse cells or tissues.

While NF-κB subunits themselves can be a direct target of oxidative regulation, as has been demonstrated for p50 (82, 99), upstream kinases of the NF-κB pathway are also subject to redox regulation, and may in fact determine whether NF-κB will be activated or inhibited in the presence of ROS, as will be described in the following sections. It should be noted that a detailed overview of *S*-glutathionylation of some of these protein targets was the subject of a recent review in this journal (126).

REDOX SENSITIVE CYTOPLASMIC KINASES OF THE NF-κB PATHWAY

IKK

As reviewed earlier, IKK is a large (500–700 kDa) complex consisting of IKKα and IKKβ, which are catalytic subunits, and IKKγ a regulatory subunit (153). IKK is considered the major regulatory kinase for NF-κB signaling since its activation by many cytokines, LPS, and T cell receptors leads to IκBα phosphorylation, degradation, and ensuing liberation of NF-κB. IKKα and IKKβ have two serines in their activation loops, Ser 176 and 180 and Ser 177 and 181, respectively. As mentioned earlier, identification of upstream regulatory events that control activation of IKK has been the subject of intense study. Additionally, since IKK is the most proximally known activator of the NF-κB signaling pathway, the role of redox modulation of IKK also has been investigated.

Cyclopentenone prostaglandins (cyPGs) have anti-inflammatory activities and are known NF-κB inhibitors. Cyclopentenone prostaglandins, PGA and 15dPGJ2, directly targeted and covalently modified Cys179 of IKKβ, which lead to inhibition of its kinase activity and subsequent NF-κB DNA binding in response to TNFα, IL-1β, and TPA. A cysteine to alanine mutation at residue 179 of IKKβ rendered it resistant to inhibition by cyPGs and restored kinase activity and NF-κB transactivation (109). Similar inhibition of IKK was also observed by other alkylating agents that are produced during lipid oxidation, such as 4-hydroxynonenal and acrolein (56, 137). Arsenic was also shown to inhibit TNFα-induced NF-κB gene transcription by inhibiting IKK activity and IκBα degradation in HEK293 cells (110). Inhibition of NF-κB by arsenite also occurred through oxidation of Cys179 of IKKβ in HeLa and HEK293 cells (63). Our laboratory has shown that in the presence of nitrosothiols, Cys179 of IKKβ was *S*-nitrosylated, which inhibited IKK activity and NF-κB transactivation in mouse lung epithelial cells, as well as Jurkat T cells (104).

The ability of H_2O_2 to regulate IKK activity has been investigated by multiple groups, including our own. In mouse alveolar epithelial cells, H_2O_2 alone did not lead to IKK or NF-κB activation. Furthermore, H_2O_2 inhibited the ability of TNFα to activate IKK, which was accompanied by cysteine oxidation of the IKK complex (72). Other reports have also shown that H_2O_2 inhibited TNFα-induced IKK activation (18, 92).

In contrast, H_2O_2 has been demonstrated to activate the IKK complex in human bronchial epithelial cells as well as in HeLa cells. Treatment of HeLa with H_2O_2 led to phosphorylation of Ser180 of IKKα and Ser181 of IKKβ. H_2O_2 in combination with TNFα did not inhibit IKK and actually increased the duration of TNFα-induced IKK kinase activity, and subsequent NF-κB activation (60). Furthermore, human bronchial

TABLE 1. IKKB ACTIVATION AND INHIBITION BY ROS

Study	*Cell type*	*Oxidant*	*Modification*	*Outcome*
Rossi et al. (109)	Jurkat, HeLa	Cycloprostaglandins	Oxidation of Cys179	Inhibition
Roussel and Barchowski (110)	BEAS 2B, HEK293	Arsenic	Unknown	Inhibition
Kapahi et al. (63)	HeLa, HEK293	Arsenic	Oxidation of Cys179	Inhibition
Korn et al. (72)	Mouse lung epithelial	H_2O_2	Undetermined oxidation of IKK complex	Inhibition
Jaspers et al. (55)	Human lung epithelial	H_2O_2	Unknown	Activation
Kamata et al. (60)	HeLa	H_2O_2	Phosphorylation of Ser181	Activation
Reynaert et al. (104)	Jurkat mouse lung epithelial	Nitrosothiols	S-nitrosylation of Cys179	Inhibition

epithelial cells treated with H_2O_2 also displayed increased IKK activity and IKBα phosphorylation. However, IκBα degradation and NF-κB DNA binding activity were inhibited. This opposing effect of H_2O_2 on IKK activity and NF-κB signaling was attributed to a defect in the proteosomal degradation of ubiquitinated proteins (55). Disparate effects of H_2O_2 on various component of the NF-κB pathway were also apparent in another study demonstrating that H_2O_2 was sufficient to increase NF-κB activity, which was independent of alterations in IKK activity (18).

Although the reports on IKK activation or inhibition by oxidants may seem contradictory (Table 1), it should be noted that in addition to different cell types under investigation, the concentration of oxidants employed in the aforementioned studies varied. Furthermore, oxidation and subsequent inhibition of IKK may be transient and readily reversible, thus the time of analysis can greatly impact the outcome of an oxidant on the enzymatic activity of IKK.

MEKK-1

Mitogen-activated protein kinase/ERK kinase-1 (MEKK-1) was originally characterized as a SAPK/JNK kinase kinase and was found to phosphorylate SEK/MKK4, which in turn directly phosphorylates and activates JNK (150). Since its original description, MEKK-1 has been implicated as a player in the NF-κB signaling pathway, based upon a study demonstrating that MEKK-1 directly interacts with IKKβ (91), and is a kinase for IKKβ, mediating site-specific phosphorylation (75). MEKK-1 can be activated by TNFα and IL-1β, activators of the canonical NF-κB pathway, and consequently expression of a dominant negative mutant of MEKK-1 blocks activation of NF-κB in response to cytokine stimulation (91). Receptor interacting protein (RIP)-dependent activation of IKK in response to TNFα has been shown to be dependent on MEKK-1 (67). We and others reported that that MEKK-1 increases NF-κB transactivation in lung epithelial cells, and is involved in H_2O_2 mediated activation of NF-κB in these cells, while expression of a dominant negative version of MEKK-1 decreased the ability of cytokines and oxidants to activate NF-κB mediated gene expression (53, 157). More recently, MEKK-1 has been shown to be involved in NF-κB activation and subsequent cIAP expression in transforming cells (90). Despite all of these studies, the regulation of the NF-κB pathway by MEKK-1 was brought into question by studies conducted in MEKK-1–deficient mouse embryonic stem cells that did not corroborate a role for MEKK-1 in IKK signaling (147). The lack of confirmation of the causal role of MEKK-1 in NF-κB activation in the latter report illuminates the potential concern about using strategies involving overexpression of dominant negative constructs, which were invariably used to probe the role for MEKK-1 in NF-κB activation, and point to a need of additional studies to clarify these conflicting results.

MEKK-1 is a redox sensitive kinase. MEKK-1 is glutathionylated at a critical cysteine, Cys 1238, in its ATP binding domain leading to inhibition of kinase activity (26). *S*-glutathionylation and subsequent inhibition of activity occurred after bolus addition of H_2O_2 as well as after preincubation with menadione, which generates ROS. *S*-glutathionylation was detected by MS, and the oxidation was found to be specific to ROS as the cysteine was not *S*-nitrosylated after treatment with nitrosothiols.

While the impact of MEKK-1 glutathionylation on NF-κB activation has not been formally tested, one could speculate that MEKK-1 glutathionylation may lead to temporary inhibition of NF-κB signaling under conditions of oxidative stress. This could constitute a protective mechanism to prevent survival of an oxidatively stressed cell, and allow the apoptotic pathway to prevail.

PI-3-K/Akt

Akt is a serine/threonine kinase that plays a role in cell survival (62). Akt is activated by PI-3-K through generation of 3'phosphorylated phosphoinositides, which leads to recruitment of Akt to the cell membrane where it is phosphorylated. Activation of Akt by PI-3-K was originally seen in response to growth factors but has been expanded to include CD28 and CD5 in T cells, G-coupled protein receptors, and H_2O_2 (136). Akt has been shown to be activated by NF-κB inducing cytokines, TNFα and IL-1. Additionally, PI-3-K can be activated by phorbol esters and LPS leading to Akt dependent NF-κB activation. Akt has been shown to increase NF-κB transactivation through activation of IKKβ (81), and the interaction between Akt and IKKβ was shown to be critical in mediating the NF-κB dependent antiapoptotic effects of fibro-blast growth factor-2 (138). The ability of Akt to activate NF-κB nonetheless seems to be cell type specific. More

precisely; it is considered to be dependent on the ratio of IKKα to IKKβ. Several cell lines were tested for the ability of Akt to activate NF-κB and it was determined that cells containing more IKKα than IKKβ had the greatest ability to activate NF-κB in an Akt dependent manner (46).

Akt activation in response to ROS depends on PDGF receptor or EGF receptor activation (70, 143). Additionally, ROS-dependent activation of Akt and subsequent NF-κB signaling has been shown in osteoclasts in response to RANKL, and this NF-κB activation is necessary for osteoclast survival. RANKL binds to its receptor RANK (a TNFα receptor family member) and leads to ROS production, which when inhibited by pretreatment with NAC and GSH, inhibited Akt induced NF-κB and decreases the survival of osteoclasts (8).

Akt is a serine/threonine kinase, and its own activity is regulated by phosphorylation. Akt is activated by phosphorylation at Thr308 and Ser473 and dephosphorylation of Akt by phosphatases renders the kinase inactive (6, 57). Akt also has a redox-sensitive kinase domain that can influence kinase activity. Exposure of cardiac H9C2 cells to H_2O_2 led to the formation of a disulphide between Cys297 and Cys311, causing inactivation of Akt and subsequent cell death. Overexpression of GRX prevented Akt oxidation and protected the cells from apoptosis, a phenotype that was reversible by pretreatment with cadmium, a GRX inhibitor (89). These findings demonstrate that Akt can be directly oxidized, inactivating the enzyme, and diminishing its anti-apoptotic activity in response to ROS. These observations are in contrast to the aforementioned studies that demonstrated that Akt was activated by ROS.

An upstream inhibitor of Akt, PTEN is also a redox sensitive protein. PTEN is a phosphatase that dephosphorylates lipid mediators involved in PI-3-K/AKT activation. PTEN activity is dependent on the redox state of an active site cysteine and is inhibited by H_2O_2 induced oxidation leading to formation of an intramolecular disulfide (76). Additionally, PTEN is subject to inhibition by *S*-nitrosylation (152). It appears that under low levels of ROS, where ROS exert a signaling function PTEN is inhibited, allowing Akt to exert its survival function mediated via the activation of NF-κB.

The threshold of Akt and subsequent NF-κB activation by ROS rather than inhibition has yet to be determined, and is likely to be concentration dependent: low levels of ROS may permit signaling through Akt to NF-κB, while higher levels may promote inhibition possibly through direct oxidation of Akt or other NF-κB pathway components. Analogous to earlier speculations regarding regulation of the NF-κB signaling pathway, Akt activation or inhibition by ROS and its ability to prevent apoptosis under oxidative conditions is likely to be cell type and stimulus specific.

ROS and the transactivation of NF-κB

While a large number of studies have focused on the redox regulation of cytoplasmic kinases that lead to NF-κB nuclear localization, less focus has been on the phosphorylation of NF-κB itself and the redox regulation of the kinases responsible for NF-κB subunit phosphorylation. Studies are now emerging demonstrating that kinases involved in nuclear NF-κB regulation are indeed redox regulated, extending the potential of oxidants to control NF-κB transcriptional activity (Fig. 3). Most of these studies have focused on the phosphorylation of RelA and the impact that phosphorylation has on the ability of RelA to be released from IκBα, bind to DNA and recruit essential cofactors. Therefore, the kinases that phosphorylate RelA in the cytoplasm and the nucleus aiding in the ability of NF-κB to act as an efficient transcription factor will be the focus of this section. It should be noted that this area of research is relatively new and the impact of NF-κB kinases on the structure and function of NF-κB bound promoters is only beginning to be unraveled.

PKC

The PKC family of serine/threonine kinases is ubiquitously expressed and is divided into three categories based on the cofactors required for their activation. The activation of conventional PKC members is dependent on calcium and diacylglycerol, novel members are calcium independent but activated by diacylglycerol, and the atypical family members do not re-

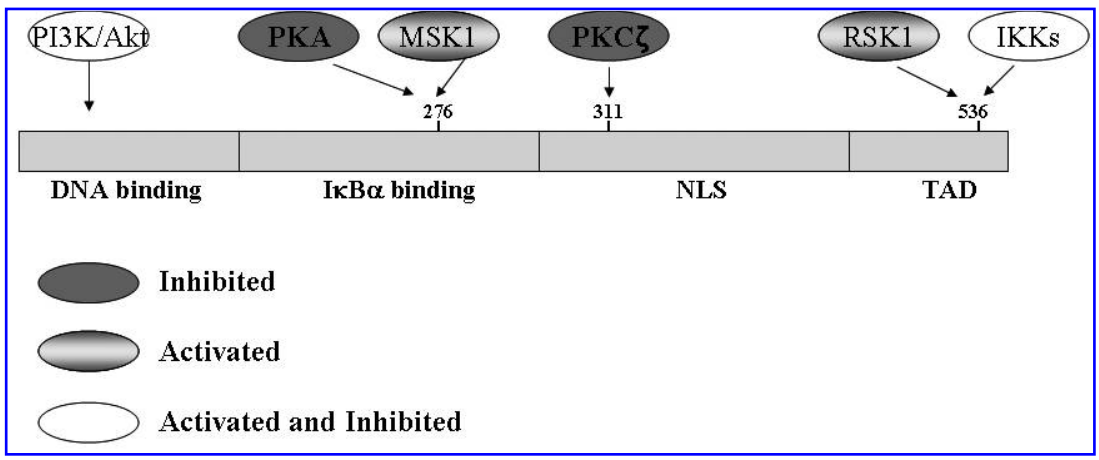

FIG. 3. Redox sensitive kinases capable of phosphorylating RelA. This diagram depicts the redox sensitive kinases known to phosphorylate RelA, leading to enhanced NF-κB transcriptional activity. Kinases in dark grey have been shown to be inhibited by ROS, kinases in light grey can be activated by ROS, and kinases depicted in white have been demonstrated to be activated and inhibited by ROS; adapted from Chen and Green (23).

quire calcium or diacylglycerol (45). PKC activation is known to occur in response to growth factors as well as stress signals.

Experiments in which the atypical family member PKCζ was overexpressed have shown that this kinase was capable of activating IKKβ and could induce NF-κB nuclear localization as well as transcriptional activity (31, 73). Through the generation of PKCζ knock out mice, PKCζ has been unequivocally characterized as an inducer of NF-κB activity. Embryonic fibroblasts from PKCζ $^{-/-}$ mice displayed decreased NF-κB reporter activity in response to TNFα and IL-1; however, IKK activation and the ability of NF-κB to translocate to the nucleus were unaltered. Furthermore, PKCζ binds to and directly phosphorylates the RHD of RelA (77). Through additional studies it was determined that PKCζ specifically phosphorylates Ser311 of RelA and that this phosphorylation is essential for association of NF-κB with the transcriptional coactivator CBP (33).

Classic PKC family members such as PKCα are targets of cysteine oxidation, including *S*-glutathionylation, as their catalytic and regulatory domains are rich in conserved cysteines (25). Indeed PKCα was shown to be *S*-glutathionylated and that this oxidative modification inhibited activity of the kinase (145). Additionally classic PKC isoforms as well as PKCζ were inactivated $ONOO^-$, which was associated with tyrosine nitration (71). PKCζ also was directly inhibited by NO gas in cultured pulmonary artery endothelial cells, which was reversible by DTT as well as Trx and Trx reductase, and attributed to S-nitrosylation. PKCζ has also been implicated in the production of ROS generation in addition to being a target, and its causal role in TNFα -induced NADPH oxidase activation has been demonstrated (40). PKCζ can phosphorylate the p47 subunit of the superoxide generating NADPH oxidase, and was demonstrated to specifically target serines 303, 304, and 315 of p47. Importantly, PKCζ translocated to the cell membrane upon stimulation with similar kinetics to p47, and its causal role of ROS production confirmed though antisense oligonucleotide and peptide antagonist strategies (28, 40). These studies illuminate a potentially critical role of PKCζ in the redox regulation of NF-κB activation, based on its ability to control oxidant production, its potential to be a target for oxidative inactivation, and its well-known role regulatory role in direct phosphorylation of RelA and subsequent transactivation. Unraveling the intricacies and interdependence of these putative regulatory events in the NF-κB pathway require many additional studies.

PKA

PKA, also known as cAMP-dependent protein kinase or protein kinase A, directly phosphorylates RelA at serine 276, which is near the NLS. In 1997 it was shown that PKA, specifically the catalytic subunit, PKAc binds to IκBα in the cytoplasm of resting cells (156). Upon cell stimulation and consequent IκBα phosphorylation and degradation, PKA is activated and phosphorylates RelA. Activation of PKA and RelA phosphorylation occurs in response to stimuli such as LPS (155, 156).

PKAc has two cysteines in its catalytic subunit at positions 199 and 343. In response to the sulfhydryl oxidant diamide, an intramolecular disulphide is formed between these cysteines, which inhibits the kinase activity of PKA (51). Cysteine 199 is reactive at physiological pH, and was demonstrated to be targeted by *S*-glutathionylation, leading to inhibition of catalytic activity (51). More recently the same investigators demonstrated that oxidation of cysteine 199 enhances its ability to be dephosphorylated at threonine 197, contributing to oxidant-induced inhibition (50).

Whether PKA is oxidized, dephosphorylated, and inactivated under physiologically relevant settings, and the subsequent impact on phosphorylation of RelA and NF-κB activity remains to be determined.

MSK-1, RSK-1, and CK-2

Mitogen and stress activated kinase-1 (MSK-1), the 90 kd ribosomal S6 kinase-1 (RSK-1), and casein kinase 2 (CK-2) are kinases that contribute to NF-κB transcriptional activity via direct nuclear phosphorylation of RelA at serines 276, 528, and 536, respectively, in response to stimuli such as TNFα, IL-1, or p53 (23, 140–142). Interestingly, at the promoter of NF-κB regulated genes such as IL-6, MSK-1 also phosphorylates histone H3, initiating chromatin remodeling, thereby contributing to enhanced transcriptional activity (140). Phosphorylation of RelA by RSK1 decreases the affinity of p65 binding to IκBα, decreasing nuclear export of NF-κB, thereby promoting the binding and action of NF-κB at promoters (11).

Direct oxidative modification of MSK-1, RSK-1, or CK-2 has not been reported. It has been suggested that in Jurkat T cells stimulated with H_2O_2, phosphorylation of the transcription factor CREB occurred in an MSK-1-dependent manner (108), although additional experiments are needed to formally test this possibility. RSK also has been shown to be activated by H_2O_2 in lymphocytes, endothelial cells, and fibroblasts, in a Ras and the Src kinase Fyn-dependent manner (1) and more recently was demonstrated to transduce redox dependent signals to leading to cardiac troponin 1 phosphorylation (52).

A link between CK-2 and the redox regulation of NF-κB was reported in a study demonstrating that NF-κB activation by oxidative stress was associated with tyrosine 42 phosphorylation of IKKβ, in contrast to IκK2-mediated phosphorylation, which occurs at serines 32 and 36 (118). The authors demonstrated that a mutant version of IκBα lacking tyrosine 42 abolished the ability of H_2O_2 to activate NF-κB. A potential role for CK-2 was suggested based upon the use of a CK-2 inhibitor that blocked NF-κB activation (118), although others have demonstrated an important role for Syk in tyrosine phosphorylation of IκBα, and subsequent NF-κB activation by H_2O_2 (131). An interesting reciprocal regulation of CK-2 and the p47 subunit of NADPH oxidase has been reported. While CK-2 was shown to bind to the NADPH oxidase subunit, p47, and that this enhanced the catalytic activity of CK-2 (69), CK-2 mediated phosphorylation of p47 appeared to mediate deactivation of the NADPH oxidase (96). Autophosphorylation of CK-2, and its subsequent ability to phosphorylate one of its substrates, c-Jun, was demonstrated to be redox dependent (88). Intriguingly, the human redox/repair protein, apurinic/apyrimidinic endonuclease (APE/Ref-1) is also a substrate for CK-2 phosphorylation that completely abolished its DNA repair activity, while not altering

its ability to act at abasic sites (148), and subsequently was demonstrated to affect redox regulation of AP-1 (41). These important findings suggest an intriguing possibility that CK-2 could also regulate effector function of NF-κB through phosphorylation of RelA.

NF-κB CROSSTALK WITH THE C-JUN-N-TERMINAL KINASE (JNK) SIGNALING PATHWAY: ROLE FOR ROS AND IMPLICATIONS FOR CELL SURVIVAL AND DEATH

In addition to the kinases already discussed that are all implicated in activation of NF-κB, NF-κB is also regulated by crosstalk with signaling modules. The best described evidence for such crosstalk reflects the balance between NF-κB and JNK, and recent evidence suggests that oxidants control the functional interplay between these two diverging pathways. Binding of TNFα to TNFα-RI leads to the coordinate activation of NF-κB and JNK. Activation of NF-κB by TNFα leads to the transcription of anti-apoptotic genes such as TRAF1, IAPs, members of the Bcl2 family, and GADD45 (16, 94). RelA knock out mice die at embryonic day 15 from liver apoptosis (9), which is rescued by also knocking out TNFα or TNFα-RI, demonstrating that signaling through this receptor in the absence of NF-κB can lead to cell death (4). Whereas NF-κB is considered anti-apoptotic, JNK is a MAPK that is well known to have pro-apoptotic activities (4, 30, 79).

NF-κB can inhibit JNK-induced cell death through the induction of the JNK inhibitor, GADD45 (94). Therefore, crosstalk between the NF-κB and JNK pathways is crucial for cell survival and death decisions. TNFα-induced activation of JNK is transient, yet when NF-κB is inhibited JNK activation by TNFα is prolonged (133), and this sustained JNK activity leads to TNFα-induced cell death (132). An additional facet of crosstalk between these two pathways reflects the inhibition of NF-κB signaling by JNK. Knockdown of *Drosophila* JNK or AP-1 increased expression of NF-κB genes in response to LPS, conversely, overexpression of JNK and AP-1 inhibited NF-κB. Relevant to the earlier review of chromatin remodeling, it has recently been determined that JNK activated AP-1 binds to NF-κB driven promoters, and recruits HDAC1, inhibiting NF-κB transcriptional activity (68).

ROS and RNS are potent activators of JNK (93, 127), and ROS have been shown to lead to the oxidative inactivation of JNK inhibitors including phosphatases and glutathione transferase (154). ROS also activate JNK by oxidizing Trx, which binds to and inhibits the MAP3K, ASK1 (113). ASK1 in turn phosphorylates MKK4/7, which are direct activators of JNK (144).

Studies conducted in mouse embryonic fibroblasts (MEFs), deficient in RelA or TRAF proteins revealed prolonged oxidant production in response to TNFα, and that ROS were responsible for JNK activation and subsequent necrotic death (114). Since TNFα-induced oxidant production and prolonged MAPK activation were not apparent in wild-type MEFs, the authors concluded that TRAF-mediated NF-κB activation functions to suppresses the TNFα-induced ROS accumulation, thereby preventing prolonged MAPK activation and necrotic cell death (114). The molecular mechanisms by which NF-κB inhibits ROS accumulation were unraveled in a subsequent study demonstrating that ferritin heavy chain, the primary iron storage factor was the essential mediator of the antioxidant and protective activities of NF-κB. Ferritin heavy chain was induced downstream of NF-κB, and was shown to prevent chronic JNK activation through the suppression of ROS accumulation, which was achieved through iron sequestration (97). The functional interplay between enhanced ROS levels, JNK activation, and cell death observed in NF-κB deficient cells was further illuminated using fibroblasts from JNK1-/+ JNK2$^{-/-}$ (JNK$^{-/-}$) deficient mice. While wild-type cells deficient in NF-κB had increased necrotic cell death and ROS generation, these outcomes were attenuated in JNK$^{-/-}$ cells (139), demonstrating a role for JNK in TNFα-dependent H_2O_2 production, and subsequent necrosis under conditions of NF-κB inhibition. A subsequent report demonstrated that under conditions of NF-κB inhibition, TNFα-induced oxidant accumulation could be suppressed by mitochondrial superoxide dismutase, and furthermore demonstrated that oxidation and inhibition of JNK-inactivating phosphatases by converting their catalytic cysteine to sulfenic acid, was critical for the prolonged activation of JNK (59). Collectively these data point to a mechanism whereby NF-κB activation suppresses ROS accumulation through the actions of the NF-κB induced genes, ferritin heavy chain and manganese superoxide dismutase, which in turn prevent the activation of JNK, or prevent its prolonged activity, and subsequent cell death (98). It should be noted that these exciting studies unraveling ROS suppression by NF-κB, and the role for JNK herein were largely conducted in cells genetically incapable of activating NF-κB, and the impact of these findings awaits careful additional analysis in NF-κB signaling competent cells. In that regard, other studies have investigated the influence of ROS on NF-κB and JNK regulation in cells with intact NF-κB pathway components. In mouse lung epithelial cells, H_2O_2 inhibited the ability of TNFα to activate IKK, while H_2O_2 alone activated JNK in a protracted manner. H_2O_2 induced JNK was attenuated in TNFα-RI −/− lung fibroblasts indicating that TNFα-RI plays a role in ROS induced JNK activity (93). Expression of a constitutively active form of IKKβ also resulted in a dampening of H_2O_2-induced JNK activity, indicating that ROS-induced JNK activation was negatively regulated by NF-κB (93). In support of these findings, the H_2O_2 generating compound L-mimosine was sufficient to inhibit TNFα-stimulated IKK, and exposure to L-mimosine alone was sufficient to stimulate JNK (92).

The complex cross regulation of NF-κB and JNK and redox sensitivity of this regulation suggests that the outcome of oxidant production is critically linked to the activation state of NF-κB and JNK in the cells, and illuminates an additional level of complexity in the redox regulation of NF-κB.

CONCLUSIONS AND FUTURE DIRECTIONS

More than a decade after its original discovery and intense investigation, it is now readily apparent that NF-κB is a

pleiotropic transcription factor that controls a wide range of biological processes ranging from cell division, inflammation and immunity, and survival. Since over 100 stimuli can promote activation of NF-κB, which in turn regulates the transcription of over 100 genes, the components of the NF-κB signaling cascade are tightly controlled. Whereas the IKK complex is obligatory in initiating the NF-κB pathway in response to many stimuli, substantial data exists in support of other kinases, described in this report, that also impinge on NF-κBs regulatory function. Many regulatory steps occur in the cytoplasm, although recent studies are shedding light on the nuclear regulation of NF-κB, and have highlighted the functional significance in direct posttranslational modification of NF-κB subunits themselves, and the subsequent impact on chromatin remodeling machinery necessary to facilitate transcription.

NF-κB was once considered a prototypic redox sensitive transcription factor. Based upon the overview of the literature provided in this article, it will be apparent that this notion has currently moved into an area of considerable controversy. This controversy is based around the lack of consistent redox responses across cell types, and subsequent lack of global applicability of redox activation of NF-κB, unlike cytokine responses. The controversy is furthermore fueled by a failure of oxidants to consistently activate the IKK complex that is required for robust NF-κB activation by most stimuli, problems associated with antioxidant compounds that have nonspecific or unexpected effects, and the concerns that when oxidants do activate NF-κB, this occurs at unphysiological concentrations in association with cell death or stress responses. These concerns are significant and warrant consideration in experimental design of future studies.

Do these concerns mean that oxidants have no physiological role within the NF-κB signaling pathway? First one should consider that the area of redox signaling *per se* reflects an area that has only recently begun to gain acceptance, based upon the technical challenges to carefully map reversible oxidations relevant to redox signaling in intact cells or tissues. Once these difficulties are overcome, investigators will be enabled to probe oxidative events relevant to the NF-κB pathway, and modulate these events, by introducing specific mutations, or by careful manipulation of the cellular redox status.

Another consideration stems from the fact that many studies regarding the redox regulation of NF-κB have been performed with transformed cell lines, or embryonic cells, which are likely to display differences in NF-κB or redox regulation, compared to primary cells or tissues that give rises to diseases. While it is unlikely that oxidative events regulate NF-κB in a manner that is globally applicable, it is not unlikely that through subtleties of reversible oxidation reactions the extent or outcome of NF-κB activation can be regulated by redox changes in a physiologically relevant setting. Based upon the discovery of enzymes that produce oxidants under these circumstances, our description of many kinases in the NF-κB pathway that have been demonstrated to be targeted by reversible oxidations, and the emerging area of redox proteomics, it is hopeful that the uncertainties about the redox regulation of NF-κB in physiologically relevant settings will indeed be unraveled.

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ABBREVIATIONS

APE/Ref-1, apurinic/apyrimidinic endonuclease; BAFF, B-cell activating factor; BLC, B lymphocyte chemoattractant; CBP, CREB binding protein; CD40L, CD40 ligand; ChIP, immunoprecipitation; CK-2, casein kinase-2; cyPGs, cyclopentane prostaglandins; ELC, EBI-1 ligand chemokine; GRX, glutaredoxin; GSK-3b, glycogen-synthase kinase-3b; HAT, histone acetyltransferases; HDAC, histone deacetylases; IKK, kappa B kinase; IκBs, kappa B proteins; JNK, *c*-Jun-N-terminal kinase; LPS, lipopolysaccharide; LTβ, lymphotoxin beta; MEKK-1, mitogen activated protein kinase/ERK kinase-1; MSK-1, mitogen and stress activated kinase-1; NIK, NF-κB inducing kinase; NEMO, IKKγ; NLS, nuclear localization signal; P-S-OOH, sulfinic acid; P-S-OOOH, sulfonic acid; P-SOH, cysteine sulfenic derivative; P-SSG, intracellular thiols such as GSH; PCAF, p300/CBP-associated factor; PDTC, pyrrolidine dithiocarbamate; PI-3-K, phosphatidylinositiol-3-kinase; PKA, cAMP-dependent protein kinase or protein kinase A; PKCζ , protein kinase C zeta; Prx, peroxiredoxins; Prx-S-OOH, overoxidized peroxiredoxin; RANK, a TNFα receptor family member; RelA, p65; RHD, rel homology domain; RNS, reactive nitrogen species; ROS, reactive oxygen species; RSK, phosphorylation of RelA; RSK-1, 90 kd ribosomal S6 kinase-1; S^-, thiolate; SH, thiols; SIRT-1, mammalian Sirtuin-1; trx, thioredoxin; UV, ultraviolet.

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