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Forum Review

Reactive Oxygen Species-Induced Activation of the MAP Kinase Signaling Pathways

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ABSTRACT

An abundance of scientific literature exists demonstrating that oxidative stress influences the MAPK signaling pathways. This review summarizes these findings for the ERK, JNK, p38, and BMK1 pathways. For each of these different MAPK signaling pathways, the following is reviewed: the proteins involved in the signaling pathways, how oxidative stress can activate cellular signaling via these pathways, the types of oxidative stress that are known to induce activation of the different pathways, and the specific cell types in which oxidants induce MAPK responses. In addition, the functional outcome of oxidative stress-induced activation of these pathways is discussed. The purpose of this review is to provide the reader with an overall understanding and appreciation of oxidative stress-induced MAPK signaling. *Antioxid. Redox Signal.* 8, 1775–1789.

INTRODUCTION

The mitogen-activated protein kinase (MAPK) signaling pathways are well known to be affected by receptor ligand interactions, as well as by different stressors placed on the cell. There are five main families of MAPK signaling pathways (180). One type of stress that induces phosphorylation and potential kinase activation within four of the five main MAPK pathways is oxidative stress (124, 159, 192). The ERK3/4 pathway has not been reported to be activated by oxidative stress and will not be considered in this review. The effect of oxidative stress results in both the activation of the MAP kinase signaling pathways (124, 159, 192), and also in the inhibition of these signaling pathways (3, 32). Which response occurs is largely dependent upon the origin of the cells and the level of oxidative stress applied. This review will focus on the work that has examined the ability of oxidative stress to induce the phosphorylation and potential activation of the MAPK signaling proteins. In a separate review that appears in this issue by Templeton *et al.*, recent evidence which indicates that oxidative stress can negatively regulate the kinase activity of several members of the MAPK family of signaling proteins by glutathionylation is discussed. The functional outcome of the effects of oxidative stress on these different MAPK pathways is determined at least in part by both the phosphorylation and glutathionylation of the components within the MAPK signaling pathways.

OXIDATIVE STRESS

Free radicals and reactive molecules containing oxygen (*i.e.*, nitric oxide and paroxynitrite) are collectively known as reactive oxygen intermediates/species and induce oxidative stress in cells. Cells can be exposed to reactive oxygen intermediates by a number of different mechanisms. Cellular respiration leads to a small level of reactive oxygen intermediate exposure for cells. This occurs because electrons are lost from the electron transport chain and combine with oxygen, resulting in the formation of superoxide anion. In aqueous solutions, superoxide anion can act as a weak oxidizing agent or as a reducing agent. Despite this weak reactivity, superoxide anions can cause biological damage, and antioxidant systems that involve the use of superoxide dismutase are upregulated

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in response to superoxide anion (193). Superoxide anion is dismutated spontaneously or by superoxide dismutase, resulting in the generation of molecular oxygen and hydrogen peroxide (52). Hydrogen peroxide is the most stable reactive oxygen species and diffuses readily in and out of cells (127). Perhaps the most biologically significant reaction is the reaction of hydrogen peroxide with Fe^{2+} to form hydroxyl radicals via the Fenton reaction (76). The hydroxyl radical is the most damaging of the reactive oxygen species. The hydroxyl radical has been shown to oxidize proteins, carbohydrates, lipids, nucleic acids, and organic acids (137). Thus, cellular respiration can result in the exposure of cells to superoxide anion, hydrogen peroxide, and hydroxyl radical.

Triggering of surface receptors on certain cells can also lead to the generation of oxygen radicals. T cell receptor triggering results in the production of hydrogen peroxide and this production has been linked to extracellular regulated kinase (ERK) phosphorylation (94). Other receptor ligand interactions can also lead to reactive oxygen intermediate production. Epidermal growth factor (EGF) receptor triggering leads to the production of reactive oxygen intermediates by epidermoid carcinoma cells (6). Hydrogen peroxide induced by the EGF receptor appears to modulate EGF receptor signaling because scavenging oxygen radicals with catalase reduces EGF-induced receptor phosphorylation (40). Angiotensin II stimulates the translation of vascular endothelial growth factor (VEGF) and this effect is also dependent on the induction of oxygen radicals (47). In some cases, the induction of oxygen radicals by these growth factor receptors may be mediated in part by RAS activity. RAS activation results in Ral1, RhoA, and Rac1 activation (172). Activation of Ral1, RhoA, or Rac1 leads to the generation of intracellular oxygen radicals (172). Members of the tumor necrosis factor (TNF) family of receptors also stimulate the production of reactive oxygen intermediates (133) and these intermediates have a critical role in activating certain signaling pathways in response to receptor ligation (108, 122, 174).

The intrinsic production of oxygen radicals can lead to the extrinsic exposure of non-ROS producing cells because hydrogen peroxide can move freely through the cellular membrane. Activated monocytes, macrophages, and neutrophils can produce high levels of superoxide anion and hydrogen peroxide via the actions of NADPH oxidase (48). Resting levels of hydrogen peroxide, the most stable ROS, differ among the various tissues in the body (67). Levels range from 35 μM in human blood plasma, to levels of 100 μM found in human urine, which appear to represent some of the highest levels reported in the body (67). In addition, UV irradiation (70), certain chemotherapeutic compounds (58, 153), exposure to heavy metals (104), environmental toxins (115), and irradiation (37, 185), as well as both ischemia and reperfusion are all well known to result in oxygen radical production (177).

Triggering of certain cellular receptors, or increases of intracellular calcium, can lead to the production of nitric oxide via the actions of nitric oxide synthase (163). Nitric oxide synthase catalyzes the formation of nitric oxide from arginine and oxygen (7, 163). Nitric oxide synthase is predominantly expressed in macrophages, endothelial-, epithelial-, and neuronal cells, and as expected, these cells can contribute to the production of the reactive nitrogen intermediate nitric oxide (7, 136, 163). Nitric oxide can form peroxynitrite in the presence of superoxide anion (136). Nitric oxide and peroxynitrite are the major forms of reactive nitrogen species found in biological systems. Like hydrogen peroxide, nitric oxide is also freely membrane permeable and can directly influence the signaling pathways of surrounding cells (4). It is well known to activate guanylate cyclase and increase cGMP production (7, 136, 163). As discussed in the forthcoming sections, nitric oxide also has a role in the activation of the MAPK pathways (158).

It would make sense that eukaryotes have devised mechanisms to protect themselves from their damaging effects because exposure to oxygen radicals is impossible to avoid. This appears to be the case. Cells have developed pathways which can scavenge oxygen radicals. For example, the glutathione and thioredoxin buffering systems and catalase can help protect cells from the deleterious effects of oxygen radicals (176). Antioxidant defense mechanisms can be upregulated by transcription induced from the antioxidant response element (ARE) promoter (26). Transcription from the ARE element is mediated in part by the transcription factor Nrf2 (26).

In addition, when cells are exposed to oxygen radicals, they also activate cellular pathways that promote cell survival or death. Reactive oxygen species are known to affect proteins, such as NF-κB, Akt, ERK, BMK1, CREB, and the EGF-receptor, in a manner which is thought to have a positive role in cell survival or proliferation (12, 16, 42, 73, 142, 160). If damage to DNA or other cellular constituents is too great to repair, organisms have evolved mechanisms to promote apoptosis. This can occur through the activation of other pathways [*i.e.*, the JNK and p38 pathways (75, 87, 181, 182)]. It has been clearly demonstrated, by a number of studies, that reactive oxygen intermediates of all types can induce cellular responses and these responses can be an adaptive/survival response or an apoptotic response depending on the duration and magnitude of exposure. It would appear that activation of MAP kinase signaling pathways by oxidative stress are pivotally involved in promoting both cellular life and death in response to reactive oxygen intermediates.

THE MAPK SIGNALING PATHWAYS

The term MAPK signaling pathways generally refers to a family of signaling cascades. The ERK proteins were the first MAP Kinases discovered and were often referred to by this moniker. The original MAPKs (ERKs) were aptly named based on the ability of the ERKs to phosphorylate microtubule associated protein and because they were activated by mitogens (mitogen activated protein kinases). With the subsequent discovery of highly related kinases, functioning in different kinase cascades, the family of proteins identified by these related activation cascades became known as the MAPK family (27). The MAPK family of signaling cascades consists of the ERK (extracellular regulated kinases), JNK (Jun N-terminal kinases) (20, 34), p38 kinase (20, 27), ERK3/4 (149), and the big mitogen-activated protein kinase 1 (BMK1, a.k.a. ERK5) pathways (84). The JNK and p38 kinase pathways are sometimes grouped together and referred to as the

stress-activated protein kinases (113). ERK, JNK, p38, and BMK1 share the similarity that they are all serine/threonine kinases that are directed by a proline residue. The pathways in which these different MAP kinases are activated also share similar homology. All four pathways operate in a cascade fashion with a MAP kinase kinase kinase (MAPKKK) phosphorylating and activating a MAP kinase kinase (MAPKK) and the MAPKK phosphorylating and activating a MAP Kinase (MAPK).

THE RAS/RAF/MEK/ERK KINASE SIGNALING CASCADE

The extracellular regulated kinases, as the name suggests, are phosphorylated following the triggering of cellular receptors (144, 170). The 42 kDa ERK2 and the 44 kDa ERK1, for which this signaling pathway is named, are activated by MEK (MAP/ERK Kinase), which resides immediately upstream of ERK1 and 2 in this signaling pathway (29–31). MEK phosphorylates ERK on critical threonine and tyrosine residues, increasing its kinase activity (22, 23, 101, 116, 130, 132, 156). The ERK proteins represent the MAPK in the prototypical MAPK cascade. There are several isoforms of MEK. The isoforms which have a role in the ERK signaling pathway are MEK1 and 2. There appear to be several pathways that can lead to the activation of MEK1 and 2. The RAF (RAF-1, A-RAF, and B-RAF) proteins are well known to be activated by RAS and in turn can active MEK1 and 2. This is the most studied pathway (RAS/RAF/MEK/ERK) that leads to the activation of the ERK kinases; however, activation of the ERK pathway can also occur in the absence of RAS activation (19). It was reported that EGF-receptor triggering resulted in ERK activation in the presence of a dominant-negative RAS in Rat1 cells. Inhibiting calcium flux alone did not prevent EGF-induced ERK activation in these cells unless this treatment was combined with the dominant-negative inhibitor of RAS. These results suggest that RAS-dependent and RAS-independent mechanisms exist for EGF-induced ERK activation. EGF receptor-induced RAS-independent ERK activation in these cells appears to be mediated by increases in intracellular calcium. This result appears to be cell specific as similar findings were not found in 3T3 fibroblasts (19). The pathways leading to ERK activation are reported to be triggered by multiple receptor tyrosine kinases (61, 146), G-protein linked receptors (56, 79, 86), PKC (19, 93, 119), and calcium (24, 49, 51, 105, 139). Negative regulation of the ERK kinases is achieved by both phosphatases and inhibition of the kinase cascade at a number of points. For example, Rap1 has been demonstrated to decrease RAS-induced RAF-1 activation, resulting in the attenuation of ERK activity (135), and phosphatase PP2 can regulate the canonical RAS/RAF/MEK/ERK pathway at multiple steps by removing activating phosphate groups (2).

Once activated, the ERKs are able to phosphorylate a number of different substrates. It is reported that ERK1/2 has over 50 known substrates and is involved in mediating a large number of responses (35, 46, 110, 167, 179). These substrates can have activities ranging from phosphotransferase and phosphatase action to the ability to bind other proteins or DNA (22, 23, 101, 116, 132, 156). ERK substrates include other kinases such as KSR, Msk1/2, and $p90^{Rsk}$, as well as transcription factors such as c-Fos, Elk-1, c-Myc, Stat1/3, and Ets. Msk1/2 and $p90^{Rsk}$ can phosphorylate the transcription factors CREB and ATF1. Depending on which ERK substrates the cell expresses a variety of responses can occur following ERK activation. The ERK pathway is depicted in Fig. 1.

Several lines of evidence suggest that the ERK pathway has an important role in modulating the survival of cells. Transfection with a constitutively active form of RAS results in the transformation of cells derived from a variety of tissues (33, 72). Expression of activated forms of the RAF kinases have also been shown to prevent cell death resulting from the removal of growth factors (10, 11, 72, 117). Not only are the kinases upstream of ERK involved in the prevention of apoptosis but also the kinases downstream of ERK in this signaling pathway. Directly downstream of ERK activation is $p90^{Rsk}$ and this kinase is reported to prevent apoptosis via multiple mechanisms including the phosphorylation of CREB (14) and of BAD on serine residue 112 (109, 161).

OXIDATIVE STRESS AND THE ERK SIGNALING PATHWAY

Oxidative stress is well known to induce the activation of ERK. Oxidative stress-induced ERK activation is reported in cardiomyocytes (183), hepatocytes (28), T lymphocytes (62), astrocytes (165), fibroblasts (89), smooth muscle- (12), epithelial- (17), breast- (Franklin *et al*. unpublished results), pleural- (78), and endothelial-cells (171). Nitric oxide treatment of Jurkat T lymphocytes results in activation of the ERK pathway, as does treatment with reactive nitrogen releasing compounds such as SNP (98). Peroxynitrite has been show to increase ERK activation in epithelial cells (143). Clearly, the ability of reactive oxygen species to induce increases in the ERK kinase signaling pathway is pleiotropic and induced by a range of different reactive oxygen intermediates and in a variety of cell types.

The activating actions of oxidative stress on ERK do not appear to be direct but instead seem to be upstream of ERK. U0126 and PD98059 are MEK1 and 2 inhibitors and both of these inhibitors block oxidative stress-induced ERK activation (100, 103). In some cases, reactive oxygen intermediates can act directly on receptors which are known to induce the ERK signaling pathway (92). Triggering of the EGF receptor results in the activation of RAS and the subsequent activation of the RAF/MEK/ERK module. It has also been demonstrated that oxygen radicals lead to increased phosphorylation of the EGF receptor in the absence of EGF and results in the activation of a number of downstream signaling pathways important in proliferative responses or increases in cell viability (55, 60, 74, 194). In addition, reactive oxygen intermediates also induce the activation of the PDGF receptor which can also stimulate RAS and the subsequent activation of ERK (92).

Receptor activation is not the only mechanism by which oxygen radicals can activate the ERK signaling pathway in cells. Reactive oxygen intermediates are known to result in the activation of certain Src kinases (88, 102). Src kinases are reported to have a role in RAS activation and they could

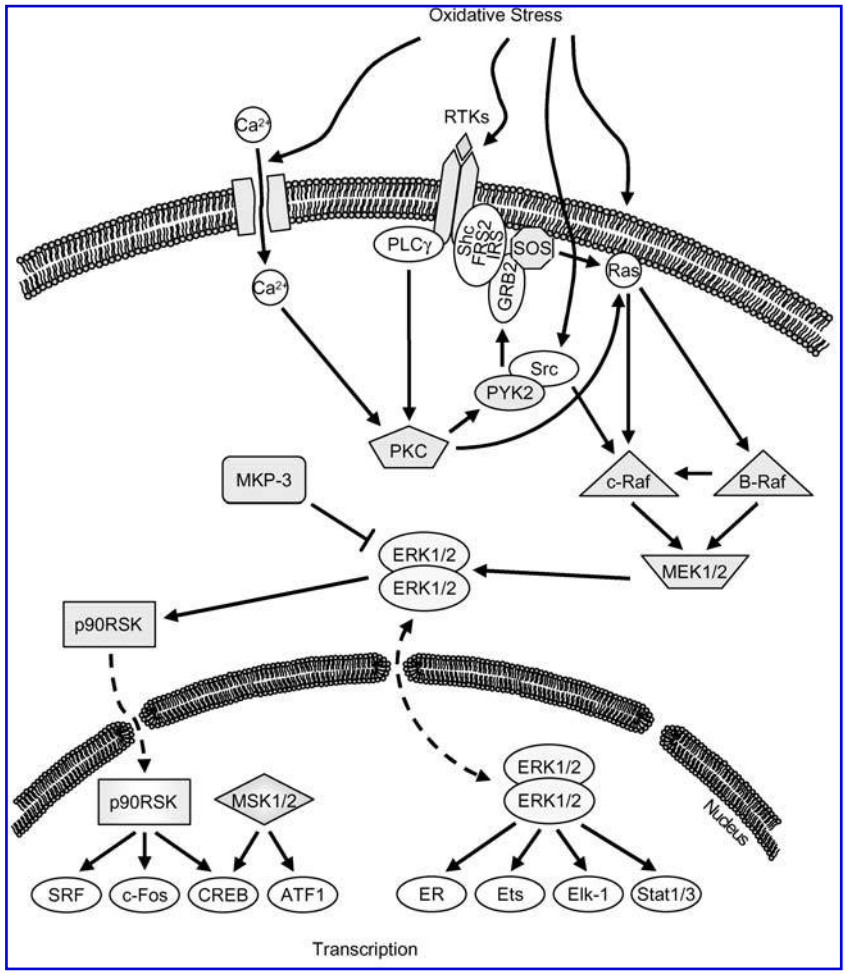

FIG. 1. The ERK1/2 kinase signaling pathway. The major components of the Erk1/2 signaling pathway are shown along with the transcription factors that this pathway is known to regulate. Oxidative stress activates calcium channels, receptor tyrosine kinases, RAS, and Src.

potentially mediate oxidative stress-induced ERK activation via this activity (66, 148). Nitric oxide causes the nitrosylation of a reactive cysteine residue in RAS and leads to increases in RAS activity, and is a potential mechanism by which nitric oxide induces ERK activation (99). Thus, reactive oxygen intermediates are not required to act via growth factor receptor stimulation but also appear to mediate activation of RAS independently of reactive oxygen intermediate-induced receptor activation. Inhibition of phosphatase activity results in the activation of the ERK signaling pathways (102), and the hydroxyl radical inhibits protein phosphatases (134, 178). Thus, inhibition of certain protein phosphatases suggests an additional mechanism by which the hydroxyl radical can induce ERK activation in the absence of growth factor receptors.

Hydrogen peroxide treatment can induce a calcium flux in a number of cell types (71, 147). How this occurs is not completely known. In some cells, treatment with hydrogen peroxide induces phospholipase C (PLC)-gamma phosphorylation (8). This phosphorylation results in PLC activation and the subsequent generation of inositol trisphophate (IP3) and diacylglycerol (DAG). IP3 induces the release of calcium from intracellular stores. Increases in intracellular calcium can mediate activation of a number of signaling pathways including the ERK pathway (5). Increases in calcium are reported to induce ERK activation via the CaM-kinases (44, 50, 59, 145) or pyk2 (41, 105).

RAS expression is not an absolute requirement for reactive oxygen intermediate activation of the ERK signaling pathway either. Reactive oxygen intermediates will induce the activation of the ERK signaling pathway in RAS-negative cells (196). Src can phosphorylate and activate PLC-gamma (175). This induces the generation of DAG and increases in intracellular calcium which results in the activation of several forms of protein kinase C (PKC). Although PKC can lead to RAS activation, it also directly activates RAF (18). It is thought that in cardiomyocytes RAS-independent oxidant-induced ERK kinase activation occurs via PKC-induced activation of RAF (196). It should be noted, that in some cell types, RAS is essential for hydrogen peroxide-induced ERK activation (65) but in others it is clearly not required.

The ERK signaling pathway can play an adaptive role in protecting cells from oxidative stress (128). In a nonmalignant murine alveolar epithelial cell line, bloScking MEK activation using the MEK inhibitor U0126 prevents hypoxia-induced Nrf2 upregulation (128). Although activation of the ERK pathway has been shown in many cases to have a role in cell survival, there is increasing evidence that it can also have a role in apoptosis induction (100, 103). Lee *et al*. reported that inhibition of ERK activation, using a MEK inhibitor, protected human glioma cells and renal epithelial cells from hydrogen peroxide-induced cell death (100, 103), indicating

that in some cases the ERK signaling pathway can promote cell death.

THE JNK SIGNALING PATHWAY

The JNK pathway involves a kinase cascade similar to the ERK pathway with a MAPKKK activating a MAPKK, and the MAPKK subsequently activating Jun-N-terminal kinase (JNK). The JNK pathway is also sometimes referred to as the stress activated protein kinase pathway (SAPK). MKK4 and MKK7 (MAPKKs) are dual specificity kinases which phosphorylate JNK on critical threonine and tyrosine residues and result in JNK activation (36). The activation of MKK4 and 7 can occur by a number of different pathways. MEKK1, 2, 3, and 4, MLK, and apoptosis signal-regulating kinase 1 (ASK1) have all been shown to activate MKK (57, 64, 75, 114). MEKK4 is the only MEKK that is specific for the JNK pathway, as MEKK1–3 have roles in the ERK and JNK pathways (57). The JNK pathway is known to be activated by ligation of a variety of receptors. In particular, the tumor necrosis factor (TNF) and FAS receptors are well known to activate the JNK signaling pathway (83, 157). Activation of this pathway by the TNF family of receptor is thought to occur via ASK1- or cdc42-induced activation of MLK (114, 157). It should be noted that certain growth factor receptors, via the activation of RAS, will also activate JNK signaling in addition to the ERK signaling pathway (189). RAS activation results in Rac activation, and Rac can induce the activation of JNK via MLK (162). Recently, it was reported that Ral can also induce JNK activation (45).

The JNK pathway can be activated by a variety of cellular stressors (39, 53, 68, 96, 97), exposure of cells to ultraviolet light (118), heavy metals (104), irradiation (38), chemotherapeutic drugs (191), and reactive oxygen intermediates (28, 123). Downstream targets of the JNKs include Jun, ATF-2, Elk2, and Nrf2 (13, 126). Although at one time it was thought that activation of the JNKs opposed ERK signaling, this is no longer accepted. The JNK pathway is depicted in Figure 2.

OXIDATIVE STRESS AND ACTIVATION OF THE JNK SIGNALING PATHWAY

Reactive oxygen intermediates induce the activation of MEKK1 (77) and ASK1 (169). ASK1 is directly modulated by the redox state of the cell by thioredoxin binding. In the absence of any oxidative stress, reduced thioredoxin (141, 150) binds to the N-terminal of ASK1. This binding prevents ASK1 activation. Upon an oxidative stress, thioredoxin becomes oxidized and disassociates from ASK1, allowing ASK1 to oligomerize, autophosphorylate, and become activated (112). Reactive nitrogen containing species can have multiple effects

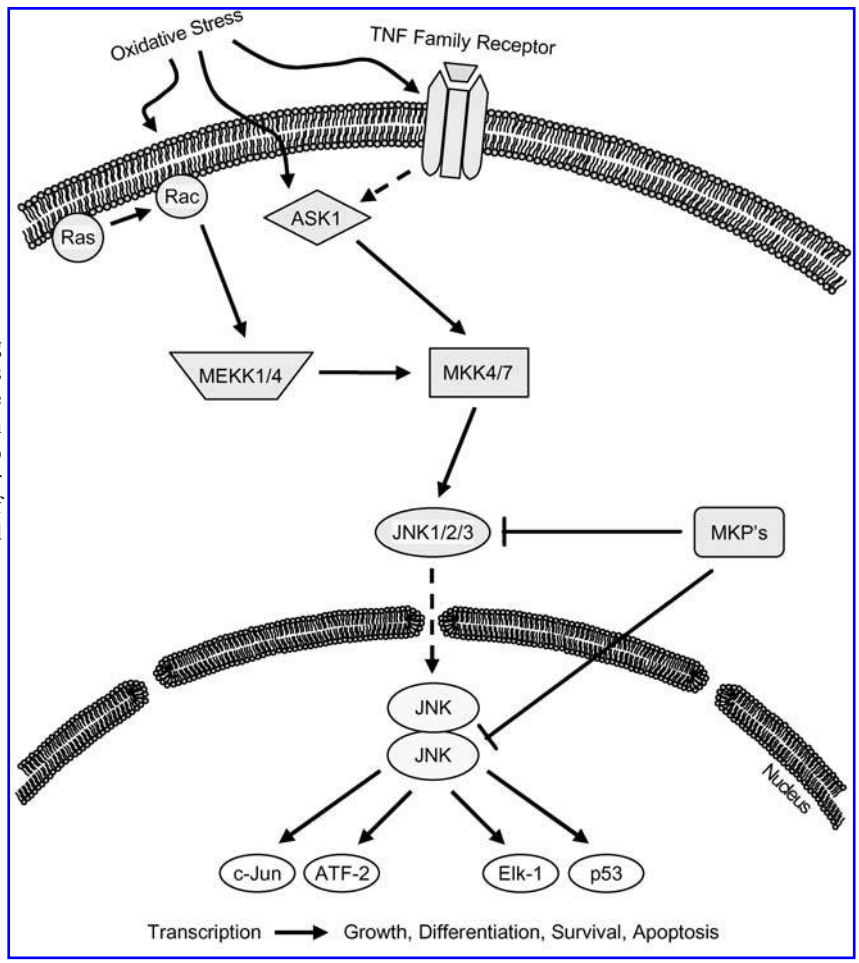

FIG. 2. The JNK kinase signaling pathway. The major components of the JNK signaling pathway are shown along with the transcription factors that this pathway is known to regulate. Oxidative stress directly or indirectly affects the TNF family of receptors, ASK1, MEKK1–4, and MLK.

on ASK1 activation. First, reactive nitrogen species are able to nitrosylate thioredoxin and prevent thioredoxin binding to ASK1 (187). This mechanism favors the activation of ASK1. However, reactive nitrogen species can also directly nitrosylate ASK1, inhibiting ASK1 kinase activity (129).

UV light has been shown to increase the production of oxygen radicals by cells (70). UV light will also induce the activation of TNF signaling in the absence of a ligand (150) similar to the way that certain oxygen radicals (82) and UV light can induce EGF receptor activation (140). Activation of the TNF receptor is well established to lead to JNK signaling (96, 107). JNK activation mediated by TNF receptor signaling is also thought to be mediated in part by oxygen radicals because superoxide anion- and lipid peroxide-scavengers inhibit JNK activation (152). These results suggest that oxygen radicals can work both upstream and downstream of the TNF receptor to promote JNK activation. In support of this idea, TNF-induced substrate phosphorylation is increased in antioxidant-downregulated cells (155).

Peptide inhibitors of JNK are extremely effective in inhibiting cell death in response to ischemia (15). Deletion of ASK1 protects cells from oxidant-induced cell death but not death receptor-induced apoptosis (114). The ability of RAS to activate both RAF and MEKK1–4 may help explain why in some cases transfection with RAS can also lead to or augment apoptosis (54, 168, 173), and indicates an additional mechanism by which reactive oxygen intermediates may promote JNK activation.

The JNK pathway also has some anti-apoptotic properties in certain cell types. Hydrogen peroxide is capable of inducing apoptosis in cardiomyocytes. Sensitivity of cardiomyocytes to hydrogen peroxide was increased in MEKK1-negative cells, suggesting an anti-apoptotic role (120). JNK can upregulate transcription via ARE promoters via the phosphorylation Nrf2 (126), and this response has the capacity to protect cells from oxidant-induced cell death.

The kinetics of JNK activation has been proposed to play a role in determining whether JNK promotes or inhibits apoptosis. Sustained activation of JNK has been proposed to have a role in promoting apoptosis (113). Kamata *et al*. found that a dual specificity phosphatase, responsible for JNK dephosphorylation, was inhibited by oxygen radicals, leading to sustained JNK activation (81). This may potentiate the apoptotic response. It will be important to determine the reactive oxidant sensitivity of the factors that lead to the activation of the JNK signaling pathway to the sensitivity of the phosphatase. It is possible that low levels of reactive oxygen intermediates leave phosphatase activity intact, resulting in a transient activation of JNK and an inhibition of apoptosis. Higher levels of reactive oxygen intermediates may activate the pathway but also inactivate the phosphatases resulting in prolonged activation of JNK activity.

THE P38 SIGNALING PATHWAY

p38 MAPK is phosphorylated and activated by either MKK3 or MKK6. Similar to the MAPKKs in the JNK and ERK pathways, MKK3 and MKK6 phosphorylate the MAPK component, in this case p38, on both a tyrosine and threonine residue. MKK3 and MKK6 are directly downstream of a kinase known as MLK3 in this pathway. MLK3 is activated by the small G-proteins Rac1 and cdc42 (162). Both growth factor receptors and members of the TNF family of receptors are known to activate this pathway. The TNF family of receptors activate the p38 pathway via the activation of cdc42 (95), whereas growth factor receptors have been proposed to active this pathway via the sequential activation of RAS and Rac1 (63, 151). Thus, many of the initial proteins and activation events in the JNK pathway are also involved in the activation of the p38 pathway. ASK1 is also able to induce the activation of the p38 pathway. This activation is thought to occur via ASK1 phosphorylation of MKK3 and 6 (75). In some cases growth factor removal can result in the activation of the p38 pathway (9).

Targets of p38 kinase activity include multiple transcription factors such as MEF2 (184), ATF-2 (106), Elk-1 (188), and indirectly CREB (138, 154). The p38 pathway is the only MAPK pathway that does not induce an antioxidant response via the phosphorylation of Nrf2. In fact, signaling via the p38 pathway may actually inhibit Nrf2 phosphorylation by other MAPK pathways (126, 190). This finding may explain the ability of this pathway to strongly promote apoptosis (182). The ability of RAS to activate Rho, and subsequently the p38 signaling pathway, may be the reason that transfection with RAS can lead to or augment apoptosis in some cases (54, 168, 173).

Removal of IL-3 from cultures of the cytokine-dependent TF-1 hematopoietic cell line results in the induction of apoptosis, and activation of the JNK and p38 pathways (9). The p38 pathway under these conditions appeared to be important for the induction of apoptosis because inhibitors of p38 prevented IL-3-deprived TF-1 cells from undergoing apoptosis. To determine if the balance between the ERK and p38 signaling pathways determines the fate of the cell, Birkenkamp *et al.* incubated cells with IL-1 (9). IL-1 will induce the activation of the ERK, JNK, and p38 signaling pathways, whereas IL-3 removal only induced JNK and p38 expression. They found that IL-1, unlike cytokine withdrawal, did not induce apoptosis in these cells. These investigators then demonstrated that inhibition of the ERK signaling pathway with PD98059 allowed IL-1 to induce apoptosis in these cells. These data suggest that although the activation of the p38 pathway may be required for growth factor withdrawal-induced apoptosis, in the presence of high enough levels of ERK activation, p38 activation may not be sufficient in itself for apoptosis to occur. These data also demonstrate that the effects of the ERK signaling pathway can overcome the pro-apoptotic effects of the p38 signaling pathways, at least in certain experimental conditions (Fig. 3).

ACTIVATION OF THE P38 PATHWAY BY OXIDATIVE STRESS

Singlet oxygen (25, 91, 195), hydrogen peroxide (65), nitric oxide (98, 99), and peroxynitrite (143) all activate the p38

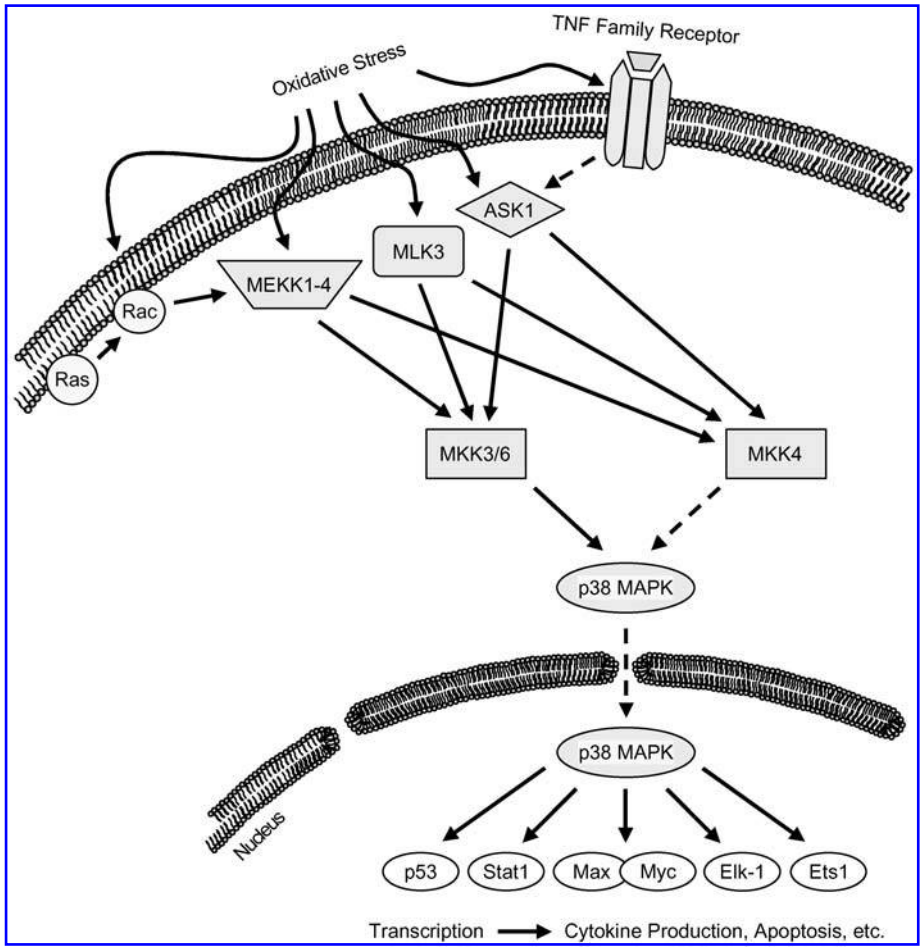

FIG. 3. The p38 kinase signaling pathway. The major components of the p38 signaling pathway are shown, along with the transcription factors that this pathway is known to regulate. Oxidative stress directly or indirectly affects ASK1 and MEKK1–4.

MAPK pathway. The p38 MAPK pathway is known to be activated in a number of different cell types in response to reactive oxygen intermediates. These cell types include: Jurkat, 3T3, HeLa, fibroblasts, and endothelial cells (90). The mechanism by which this occurs is likely very similar to the mechanisms by which JNK activation occurs, as many of the same signals activate both pathways concurrently and in many of the same cell types.

RAS activation and subsequent signaling via Rho can also activate this pathway as does ligation of the TNF receptor (75, 121, 162). Thus, the ability of oxygen radicals to induce receptor signaling by the TNF receptor in the absence of any receptor ligand binding could also have a potential role in activating the p38 pathway. The ability of nitric oxide to increase RAS activity indicates a potential mechanism by which reactive nitrogen intermediates can induce signaling via the p38 pathway (98). Similar to the JNK pathway, ASK1 has a role in oxidant-induced activation of the p38 pathway (112, 114) and is yet another mechanism by which oxygen radicals may induce p38 activation. Deletion of ASK1 protects against hydrogen peroxide-induced apoptosis in fibroblasts and also prevents prolonged p38 activation, suggesting an apoptotic role for p38 in response to oxidative stress (164). These data also suggest that the kinetics of p38 activation may also be important in determining the fate of the cell.

THE BIG MITOGEN-ACTIVATED PROTEIN KINASE 1 (BMK1) PATHWAY

The BMK signaling pathway represents the most recently discovered MAPK signaling pathway, and there is less known about this pathway than the others. BMK1, also known as ERK5, is activated by cellular stress (80), certain G-coupled protein receptors (111), and growth factor receptors, such as the NGF (80) and EGF receptors (80, 85). BMK1 is proposed to have a role in proliferation (85), differentiation (21), and cell survival (21). BMK1 has not been associated with the induction of apoptosis. Similar to the ERK, JNK, and p38 pathways, BMK is phosphorylated on threonine and tyrosine residues by a dual specificity kinase. Phosphorylation of BMK1 on these residues is performed by MEK5 which in turn is phosphorylated by MEKK2 and 3. The BMK1 pathway is

depicted in Figure 4. Downstream targets of BMK1 include Mef2C (125, 160), c-Myc (43), $p90^{Rsk}$ (131), and possibly Nrf2 (126).

ACTIVATION OF THE BMK SIGNALING PATHWAY BY OXIDATIVE STRESS

Hydrogen peroxide is able to stimulate BMK1 activation in human skin fibroblasts, human vascular smooth muscle cells, and human umbilical vein endothelial cells (1). In PC12 cells, hydrogen peroxide-induced BMK activation requires the activation of a Src kinase (160). In fibroblasts, superoxide anion generated by phenazine methosulfate treatment is not sufficient to induce BMK1 phosphorylation (69), nor is nitric oxide reported to activate BMK1 in endothelial cells (186). However, superoxide anion may play a role in BMK1 activation, as superoxide scavengers prevented Angiotensin II- and endothelin-1-induced BMK1 phosphorylation (166).

Redox activation of BMK1 exhibits an anti-apoptotic effect (160). U0126 and PD98059 are also reported to inhibit the activity of MEK5, the MAPKK involved in BMK1 activation (21, 80). Suzuki *et al.* found that these inhibitors decreased PC12 cell viability in response to hydrogen peroxide treatment. This decrease in cell viability occurred when the ERK protein was completely downregulated using siRNA, suggesting that the effects of U0126 and PD98059 were mediated in part via BMK1 pathway (160). They also indicate that much of the earlier data generated on the role of ERK in the prevention of hydrogen peroxide-induced cell death using these two compounds may have to be examined with care.

CONCLUSIONS

It has become clear that reactive oxygen intermediates are signaling molecules that can activate a variety of receptors and signaling pathways with kinase activity. In particular, all types of reactive oxygen intermediates are capable of activating four major MAPK signaling pathways. These pathways can mediate the activation of a wide variety of transcription factors and cellular responses. Reactive oxygen intermediates can induce apoptosis and proliferation depending on cell type and the concentration of the oxygen radicals. It will be important in the future to understand how the MAPK pathways influence these two responses and why in some cases either proliferation or apoptosis occurs. The kinetics of activation of the MAPK pathways appear to have a role in the outcome. It will also be important to understand how the MAPK pathways are regulated in other ways by oxidative stress, either through glutathionylation or via the activation/inactivation of other signaling pathways which can interact with the MAPK pathways. Once key components in these responses are identified, potential targets to treat a large number of pathologies mediated by reactive oxygen intermediates will be better understood.

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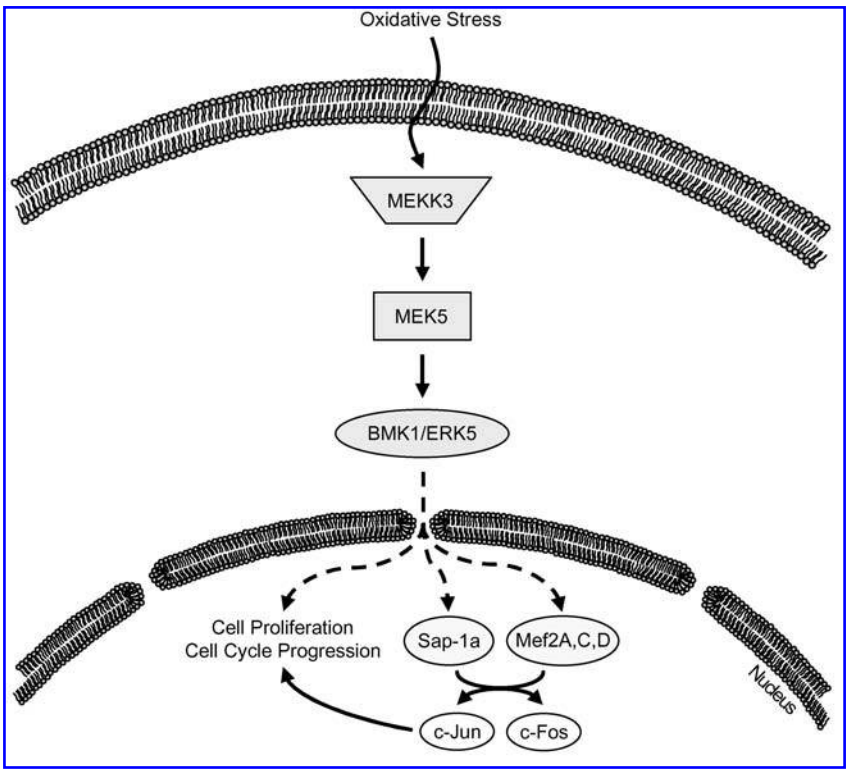

FIG. 4 The BMK1 kinase signaling pathway. The major components of the JNK signaling pathway are shown along, with the transcription factors that this pathway is known to regulate. Oxidative stress indirectly affects MEKK3 activity.

ABBREVIATIONS

ARE, antioxidant response element; ASK1, apoptosis signal-regulating kinase 1; DAG, diacylglycerol; EGF, epidermal growth factor; IP3, inositol trisphosphate; PKC, protein kinase C; PLC, phospholipase C; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

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