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Citation
Kyriakis, John M., and Joseph Avruch. 1996. "Sounding the Alarm: Protein Kinase Cascades Activated by Stress and Inflammation." Journal of Biological Chemistry 271 (40): 24313–16. https://doi.org/10.1074/jbc.271.40.24313.

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Minireview

THE JOURNAL OF BIOLOGICAL CHEMISTRY
Vol. 271, No. 40, Issue of October 4, pp. 24313–24316, 1996
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Sounding the Alarm: Protein Kinase Cascades Activated by Stress and Inflammation*

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Eukaryotic cells respond to extracellular stimuli by recruiting signal transduction pathways, many of which employ protein Ser/Thr kinases of the ERK[1] family. The ubiquity of ERKs and their upstream activators, the MEKs, in signal transduction was first appreciated from studies of yeast (1, 2). Although a 54-kDa rat liver c-Jun kinase (SAPK-p54α1) with properties similar to the Ras-regulated MAPKs had been characterized (3–5), the physiologic roles and regulation of this and related mammalian enzymes have emerged only recently. Molecular cloning of the SAPKs and p38s, together with the paradigms derived from the "classical" MAPKs and work in lower eukaryotes has enabled rapid elucidation of the regulation and cellular functions of these newer mammalian ERK pathways. Although architecturally homologous to the Ras/MAPK pathway, the SAPK and p38 pathways are not activated primarily by mitogens but by cellular stresses and inflammatory cytokines, which stimuli result in growth arrest, apoptosis, or activation of immune and reticuloendothelial cells.

p38-mpk2/Reactivating Kinase/Upstream Activator/CSAID-binding Proteins/Mxi2: the Mammalian HOG1 Homologues

Efforts to uncover signaling mechanisms activated by inflammation and environmental stress identified mammalian homologues of the yeast-osmosensing ERK *HOG1* (6). p38 was first purified as a macrophage polypeptide that became Tyr-phosphorylated *in situ* in response to bacterial lipopolysaccharide (7). Molecular cloning revealed similarities between p38 and *HOG1* (6, 7). Lipopolysaccharide induces shock in part by causing release of TNF-α and IL-1β. Novel anti-inflammatory drugs, CSAIDs, can inhibit lipopolysaccharide-stimulated TNF-α and IL-1β production. Two major intracellular CSAID-binding proteins were identified as isoforms of p38. CSAIDs directly inhibit p38 kinase activity, pointing to a role for p38 in cytokine release (8). The p38 kinase was also identified as part of a protein kinase cascade activated by IL-1β or physiologic stress, which culminates in MAPKAP kinase-2 activation and Hsp25/Hsp27 phosphorylation; p38 phosphorylates and activates MAPKAP kinase-2 *in vitro* (9, 11). MAPKAP kinase-2 phosphorylates the heat shock protein Hsp25/Hsp27 *in vitro* at the sites phosphorylated *in situ* in response to stress (10). Although p42 MAPK can also phosphorylate and activate MAPKAP kinase-2 *in vitro*, the MAPK pathway is not activated by these stresses; conversely, activation of the MAPK pathway is not associated with activation of MAPKAP kinase-2 (9, 11).

An isoform of p38, Mxi2, was recently recovered through a "two-hybrid" screen for cDNAs encoding polypeptides that interact with Max (12), a basic helix-loop-helix polypeptide that binds the product of the immediate early gene c-*myc* and is essential for its DNA binding and *trans*-activating activity (13). Mxi2 is an mRNA splice variant of p38; the two polypeptides are identical in the first 280 amino acids but diverge thereafter such that Mxi2 lacks catalytic subdomain XI, terminating instead in a unique 17-amino acid sequence (12). Despite this difference, p38 and Mxi2 each can phosphorylate Max (12); the role of this phosphorylation is unknown.

Like other ERKs, p38 is activated by dual Tyr/Thr phosphorylation in subdomain VIII of the catalytic domain, just N-terminal to the conserved APE sequence (9, 11, 14). Like the yeast HOG1P, p38 exhibits the motif TGY, distinct from the TEY of the MAPKs and ERK5 (6, 7, 15, 16). MKK3 and MKK6, two novel MEKs related to the yeast HOG1P activator Pbs2p, specifically activate p38 (17, 18). RKK, a partially purified IL-1β- and stress-activated MEK, phosphorylates and activates p38, but not MAPKs (9, 11). The relationship of RKK to MKK3/MKK6 is unknown as are the element(s) immediately upstream of RKK/MKK3/MKK6.

The SAPKs

A 54-kDa protein kinase (SAPK-p54α1) was described in 1990 as the dominant MAP-2 kinase activated in rat liver by injection of cycloheximide (3). The p54 kinase shared with the p42/44 MAP kinases a requirement for concomitant Tyr and Thr phosphorylation for activity, as well as a requirement for a proline residue immediately C-terminal to the Ser/Thr phosphorylation site (3, 4, 19). Nevertheless, the distinctive specificity of the two MAP-2 kinases was soon evident; unlike the MAPKs, p54 was unable to phosphorylate *Xenopus* Rsk but was a much more potent c-Jun kinase (3, 5).

Molecular cloning of p54 revealed a family of protein kinases, the SAPKs or c-Jun N-terminal kinases (JNKs), encoded by at least three genes (α, β, and γ) with further diversification by alternative mRNA splicing into as many as 12 isoforms (20–22). Type 1 and 2 isoforms are identical except for the alternative expression of a 17-amino acid segment spanning subdomains IX and X of the catalytic domain. 54-kDa (p54) or 46-kDa (p46) isoforms arise from alternate mRNA splicing at the extreme C terminus, distal to the catalytic domain (20). The SAPKs all contain the motif TPY at sites of regulatory phosphorylation in subdomain VIII (20, 21).

Like p38, the SAPKs are preferentially activated by cellular stresses and inflammatory cytokines TNF-α and IL-1β (20, 21). In most cells, mitogenic stimuli acting through tyrosine kinases and Ras are poor SAPK agonists (20). Stable expression of transforming oncogenes such as *ras* and *raf-1* does give some degree of constitutive SAPK activation likely as a result of a paracrine mechanism (23). Costimulation of T cells by engagement of the T cell receptor and CD28 or by stimulation with PMA and Ca^{2+} ionophore activates MAPKs, SAPKs, and IL-2 production. Whereas MAPKs can be activated by PMA alone, SAPK activation and IL-2 production require both PMA and a Ca^{2+} signal (24). Similarly, SAPK activation and IL-2 production (but not MAPK activation) are inhibited by cyclosporin A. Based on these correlations, an important role for SAPKs in T cell activation is anticipated. Vasoactive peptides such as angiotensin II, endothelin, and thrombin, which act through seven-transmembrane receptors linked to heterotrimeric G proteins, increase the activity of SAPKs substantially more than MAPKs in hepatocytes and contractile cells, such as vascular and bronchial smooth muscle (25, 26).

Finally, the SAPKs are activated *in vivo* during reperfusion of

* This minireview will be reprinted in the 1996 Minireview Compendium, which will be available in December, 1996.

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[1] The abbreviations used are: ERK, extracellular signal-regulated protein kinase; MAPK, mitogen-activated protein kinase; SAPK, stress-activated protein kinase; CSAID, cytokine-suppressive anti-inflammatory drug; Mxi, Max interactor; HOG, hyperosmolarity glycerol; MEK, MAPK/ERK kinase; SEK, SAPK/ERK kinase; RKK, reactivating kinase kinase; MKK, MAPK kinase; MEKK, MEK kinase; MLK, mixed lineage kinase; SPRK, SH3 domain-containing, proline-rich kinase; PAK, p21-activated kinase; GCK, germinal center kinase; SPS, sporulation specific; MAPKAP, MAPK-activated protein; ATF-2, activating transcription factor-2; NF-κB, nuclear factor κB; TNF, tumor necrosis factor; IL, interleukin; PMA, phorbol 12-myristate 13-acetate; NGF, nerve growth factor. We use the more ecumenical name ERKs, rather than MAPKs, to describe all members of the eukaryotic protein kinase family composed of MAPK-related kinases, inasmuch as only a subset of the mammalian ERKs is truly "mitogen-activated."

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ischemic kidney, suggesting that SAPK activation may form part of the physiologic response to ischemic injury. A similar SAPK activation occurs in cell culture, after cyanide/2-deoxglucose-treated, ATP-depleted cells are washed free of inhibitors and incubated with glucose (27).

Regulation of the SAPKs

The preferential activation of the SAPKs by stress coupled with the (usually) poor activation of the SAPKs by mitogenic agonists suggested that the upstream regulators in the SAPK and MAPK pathways were segregated. SEK1/MKK4, a novel MEK, is a potent and specific activator of recombinant SAPKs *in vitro* that is devoid of MAPK-activating activity (17, 28). Overexpression of kinase-negative SEK1 inhibits activation of the SAPKs without inhibiting MAPK activation (28), suggesting either formation of a stable SAPK·SEK1 complex *in situ* (28) or sequestration of crucial elements immediately upstream of SEK1. SEK1 is not the only MEK upstream of the SAPKs. Extracts of 3Y1 fibroblasts exposed to hyperosmolarity contain at least four chromatographically distinguishable SAPK-activating factors, only one of which copurifies with SEK1 immunoreactivity (29).

SEK1 phosphorylates and activates p38 *in vitro* and when overexpressed *in situ* (17). The physiologic significance of this reaction is unclear. MEKK1, a potent *in situ* activator of SEK1 and SAPKs (see below), fails to activate p38 *in situ* (30). Kinase-negative SEK1 variants inhibit p38 activation in some but not all experiments. This variability probably reflects the operation of multiple upstream activators of p38, some of which do not interact with SEK1.

MEKK1 was the first mammalian homologue of the yeast MEKKs to be described (31). Although originally identified as an activator of the MAPK pathway, MEKK1 appears to function in the regulation of the SAPKs (32). Inducible expression of the MEKK1 catalytic domain at low levels results in SAPK activation, with MAPK or p38 activation remaining undetectable until MEKK1 expression far exceeds that required for maximal SAPK activation (23, 32). MEKK1 phosphorylates and activates SEK1 *in vitro* and on cotransfection *in situ* (32). Inasmuch as SEK1 can activate p38 *in vitro*, the failure of MEKK1 to recruit p38 effectively *in situ* is surprising. MEKK1 could target *in situ* SAPK kinases more selective than SEK1 or interact selectively with SEK1 bound to SAPK-specific scaffolding proteins. MEKK2 and MEKK3 have recently been described; each is about 50% identical to MEKK1 in catalytic domain sequence and 94% identical to the other (33). MEKK2 activates SAPK in slight preference to MAPK when cotransfected, whereas MEKK3 exhibits the opposite preference. Neither activates p38. MEKK2 can phosphorylate both MEK1 and SEK1 *in vitro*, whereas MEKK3 is unable to phosphorylate either substrate *in vitro* (33), suggesting that MEKK3 targets as yet unidentified MEK isoforms. Transforming growth factor-β-activated kinase-1 is a fourth, novel mammalian MEKK that is activated *in situ* by transforming growth factor-β and can phosphorylate and activate SEK1 *in vitro* (34).

Members of the "mixed lineage" kinase (MLK) subfamily are also likely physiologic activators of SEK1. The MLKs are Ser/Thr kinases whose catalytic domains contain segments most similar in sequence to tyrosine kinases. The SH3 domain-containing proline-rich kinase (SPRK) and the MLK known variously as DLK, ZPK, or MUK can activate both cotransfected SAPK and SEK1 (35–37, 76). In addition, immunoprecipitates of SPRK can phosphorylate and activate SEK1 directly *in vitro* (76). SPRK contains an N-terminal SH3 domain, followed by a kinase catalytic domain and a long C-terminal tail that encompasses several domains likely to mediate protein-protein interactions, including a tandem pair of leucine zippers, a Cdc42/Rac binding domain similar to those of the PAKs, and a proline-rich segment (36, 38).

The Regulation of SAPKs and p38 by Ras, Rac1, and Cdc42

The discovery of direct interaction between the active form of the *ras* protooncogene and the c-Raf-1 protein kinase provided the first example of a small GTPase that regulates a broad range of cellular functions by interacting with a proximal component of a protein kinase cascade (39). It has become clear that the regulation of protein kinase cascades is a general feature of the biology of each of the small GTPases in the Ras superfamily.

The Rho family GTPases Rac1 and Cdc42Hs can activate the SAPKs and p38 upon cotransfection. Little information is available concerning which receptors recruit Rac1/Cdc42Hs or how receptors stimulate GTP binding by Rac1/Cdc42Hs. Oncogenic (V12) Ras can recruit Rac to mediate mitogen-induced membrane ruffling, suggesting that Rac may serve as an effector for Ras (44). However, the most potent physiologic regulators of the SAPKs/p38 appear not to act through Ras (20, 23). Thus dominant inhibitory Rac and Cdc42 variants can partially suppress SAPK activation by TNF-α and IL-1β, whereas N17 Ras causes little or no inhibition (23, 40–43). Nevertheless, the modest SAPK activation by epidermal growth factor in COS cells is inhibited by N17 Ras more strongly than by N17 Rac. Thus Ras may contribute to SAPK/p38 activation directly in certain instances (40–42, 45).

Cdc42/Rac1-regulated Kinases: Mammalian PAKs and MLKs

The first candidate elements for coupling Rac1/Cdc42Hs to the SAPKs are the PAKs, PAK1, PAK2, β-PAK/PAK3, and γ-PAK (46–50). PAKs are 60–70-kDa proteins whose C-terminal catalytic domain is 60–70% identical to *Saccharomyces cerevisiae* Ste20p and whose N-terminal segment contains a Rac1/Cdc42 binding domain (47–50). Like Ste20p, the PAKs are activated directly upon interaction with the GTP-bound form of Rac1/Cdc42Hs *in vitro* (47–50). Inactive PAK fragments that include the Rac1/Cdc42-binding domain inhibit epidermal growth factor activation of SAPK and IL-1β activation of p38 (41, 43). Moreover, constitutively active mutants of PAK1 or -3 activate the SAPKs and p38 on cotransfection and when added to cell-free extracts of *Xenopus* oocytes (43, 51, 52). The identity of the PAK substrates that couple these kinases to the SAPK/p38 pathways is not known. Ste20p can phosphorylate the MEKK Ste11p *in vitro*, but the regulatory significance of this reaction is not established (53). Insight into the regulation of mammalian MEKKs has been slowed by the inavailability until recently of full-length cDNAs. Recently γ-PAK was shown to be activated by thrombin; thus the PAKs may mediate the potent activation of the SAPKs by ligands that signal through heterotrimeric G protein-coupled receptors, a situation analogous to the recruitment of Ste20p by the heptahelical pheromone receptor (1, 2).

The mixed lineage kinases (*e.g.* SPRK) are also candidate physiologic Rac/Cdc42 effectors in the activation of the SAPKs/p38, as some MLKs contain a Rac1/Cdc42 binding domain (38). The effect of Rac1/Cdc42 on SPRK activity, however, is not yet known and may differ from PAKs, inasmuch as SPRK and dual lineage kinase each exhibits substantial spontaneous activity during transient expression, whereas PAK overexpression *per se* is insufficient to activate SAPK/p38 (43, 51, 52).

The SPS-1 Kinase Subfamily: Germinal Center Kinase Activates SAPKs

The *S. cerevisiae SPS1* gene encodes a protein kinase required for the yeast ERK signaling pathway that regulates spore encapsulation. SPS-1p consists of an N-terminal catalytic domain approximately 40% identical to that of Ste20p and an extended C-terminal noncatalytic domain (54). Several mammalian homologues of SPS-1 are now known, including germinal center kinase (GCK) (55) and the kinase designated MST1 (for mammalian STE20-like kinase) (56). The GCK C-terminal noncatalytic domain contains three PEST sequences and a leucine-rich region. Unlike the PAKs, GCK contains no Rac/Cdc-42 binding domain.

GCK activates SAPKs and SEK1 *in situ* upon cotransfection, but unlike PAK1, GCK does not activate coexpressed p38. GCK does not activate coexpressed MAPK (57). GCK is constitutively active during transient expression and is not further activated by extracellular ligands. Interestingly, overexpression of the GCK noncatalytic C terminus alone is sufficient to partially activate the SAPKs *in situ* (58). A plausible model is that endogenous GCK is negatively regulated by a low abundance inhibitor, which interacts with the GCK C terminus; this inhibition is relieved by upstream stimuli. Overexpression of recombinant GCK or the GCK noncatalytic tail presumably sequesters the endogenous inhibitor and enables ligand-independent activation of recombinant and endogenous GCK and thus SAPK. Only TNF-α has been shown to activate reliably endogenous GCK (57). The elements that connect the

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TNF-α receptor to GCK and GCK to SEK1 are unknown, although it was recently shown that GCK interacts, in a GTP-dependent manner, with Rab8, a Ras superfamily G protein implicated in regulation of vesicular trafficking (58).

Early Signals in SAPK/p38 Activation

One of the earliest events triggered by inflammatory cytokines (TNF-α and IL-1β) and environmental stresses (UV radiation, x-rays, heat shock, H_2O_2) is the hydrolysis of membrane sphingomyelin to generate ceramide (59, 60). Addition of soluble, cell-permeant ceramide derivatives to intact cells or cell-free extracts recapitulates some of the known responses to TNF-α and IL-1β, including apoptosis, suggesting that ceramide is a second messenger for some actions of TNF-α and IL-1β (59). Ceramide, added exogenously or generated by the treatment of cells with sphingomyelinases, selectively activates the SAPKs *in situ*; moreover, dominant inhibitory mutants of SEK1 inhibit ceramide-stimulated apoptosis. Thus ceramide generated by the activation of endogenous sphingomyelinases is likely to participate in SAPK/p38 activation by TNF-α/IL-1β. A membrane-associated, ceramide-activated protein kinase has been identified that may couple TNF-α and other receptors to the p38/SAPK protein kinase cascades (61).

Some evidence points to the recruitment of specific signal transduction pathways by seemingly superficially "nonspecific" insults such as chemical, radiant, or thermal stress. Chemical mutagens and ionizing or UV radiation all cause DNA damage and can generate free radicals that alter many cell constituents. Evidence indicates, however, that DNA damage is the dominant stimulus for SAPK activation by chemical mutagens and ionizing radiation, whereas cytosolic free radicals are more significant to UV-C-induced SAPK activation (62–65). Ionizing radiation and chemically induced (cytosine arabinoside (Ara-C)) DNA damage require c-Abl and SEK1 to activate the SAPKs, whereas γ-radiation requires the ataxia telangiectasia gene product to activate the SAPKs (62–64); the relationship of these two elements in SAPK activation is unknown.

UV-C also causes DNA damage; however, UV-C activation of NF-κB occurs in enucleated cells and can be inhibited by *N*-acetylcysteine, a potent scavenger of free radicals (64, 66). Similarly, UV-C-induced SAPK activation is inhibited by low concentrations of Triton X-100 and appears to involve *N*-acetylcysteine-inhibitable activation of nonreceptor tyrosine kinases and Ras (64, 67). Activation of the SAPKs concomitant with the restoration of tissue perfusion and oxidative metabolism after ischemia (27) suggests a role for reactive oxygen intermediates. Heat-induced SAPK activation, in contrast, is not inhibited by *N*-acetylcysteine or Triton X-100 and can be initiated in cell-free extracts (67). In *S. cerevisiae*, hyperosmolarity is sensed by two independent transmembrane osmoreceptors, a histidine kinase "two-component" system that negatively regulates MEKKs in the *HOG1* pathway and an SH3 domain-containing transmembrane protein that interacts directly with the MEK Pbs2p (68, 69). Analogous mammalian osmoreceptors have not been described. Yeast also possess transmembrane receptors that are activated by misfolded proteins within the lumen of the endoplasmic reticulum and signal to the nucleus (70). Although the cytoplasmic components of these pathways are not known, tunicamycin activation of SAPKs in mammalian cells may initiate from analogous receptors (20).

Biological Functions of the SAPK and p38 Pathways

The biological functions of the SAPK and p38 pathways are only beginning to be elucidated, and few if any genetic models exist. Considerable evidence supports the view that c-Jun, Elk-1, and ATF-2 serve as physiologic substrates for the SAPKs, and in each instance, SAPK phosphorylation promotes the *trans*-activation function (20, 21, 71, 72); ATF-2 is also a substrate for p38 (17), as are Max (12) and MAPKAP kinase-2 (9, 11). This knowledge, however, does not readily define the physiologic programs initiated by the SAPKs and p38. The remainder of this discussion will focus on assessing the current information on the roles of the SAPK and p38 kinases in cell physiology. The emerging picture suggests that in most nonlymphoid cells, these two pathways function primarily to inhibit cell growth and to promote either necrotic or apoptotic cell death.

Withdrawal of NGF from differentiated PC-12 cells results in

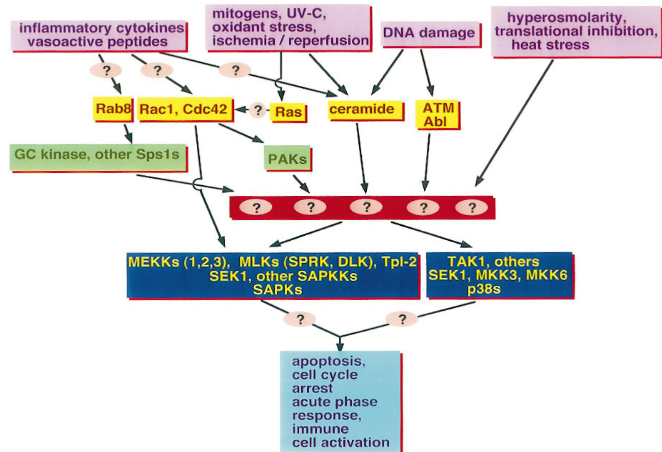

FIG. 1. **The compositions of the major known inputs into the mammalian stress-regulated ERKs (SAPKs and p38s) are shown.** *Question marks* are meant to indicate that either a critical signaling component remains to be identified or that the relationship between two signaling components has not been definitively established. These distinctions are discussed in the text.

apoptosis, coincident with the activation of the SAPKs and p38 and a decrease in MAPK activity (73). Overexpression of constitutively active MEKK1 in PC12 cells both activates the SAPKs and promotes apoptosis, even in the presence of NGF (73). Similarly, constitutively active forms of MKK3, when overexpressed with p38, can promote apoptosis in the presence of NGF (73). Reciprocally, non-phosphorylatable, dominant inhibitory mutants of c-Jun can prevent MEKK-induced apoptosis, and the expression of dominant interfering mutants of MKK3 can prevent induction of apoptosis by NGF withdrawal (73). Insofar as a constitutively active, oncogenic form of MEK1 can prevent apoptosis induced by NGF withdrawal, it is likely that the decision to initiate apoptosis in PC-12 cells depends on the balance of anti-apoptotic signals and pro-apoptotic signals (73).

TR-4 cells are a thermotolerant subline of the murine fibroblast line RIF-1. Comparative studies of the effects of heat shock and genotoxic stress on these cells have implicated the SAPKs in the regulation of stress-induced cell death (74). Although TR-4 and RIF-1 cells express identical amounts of SAPK protein, TR-4 cell SAPKs are not activated by heat shock, despite the ability of UV radiation to activate the SAPKs in both cells. Moreover, whereas heat shock and the genotoxic agent cis-platinum readily kill RIF-1 cells, these treatments are not cytocidal for TR-4 cells, which have comparable sensitivity to UV-C (74). If the thermosensitive RIF-1 cells are stably transfected with a kinase-inactive mutant of SEK1 (SEK-AL), the activation of SAPK, but not p38, by all stimuli is inhibited; the RIF-1 cells expressing SEK-AL acquire resistance to the cytocidal effects of UV-C as well as to heat shock and cis-platinum, suggesting that activation of the SAPK pathway is required for efficient induction of cell death by these stresses (74).

A different picture is observed in Swiss 3T3 cells, where overexpression of MEKK1 promotes apoptosis and activation of SAPK but not p38 (75). Dominant inhibitors of SAPK activation inhibit the activation of a Gal4-Jun reporter by MEKK but fail to suppress the MEKK induction of cell death; MEKK-induced activation of a *myc*-regulated reporter is also unaffected (75), suggesting that pro-apoptotic kinase cascades in addition to the SAPK and p38 pathways remain to uncovered.

Concluding Remarks

Fig. 1 shows the known components of the mammalian stress-regulated signaling pathways. Much remains to be clarified about the biochemical regulation and cellular role of these novel mammalian signaling pathways. Why are there two parallel pathways activated by largely overlapping stimuli? To what extent are the SAPK and p38 pathways functionally redundant or complementary? How many other stress-activated kinase cascades remain to be discovered? Given the rapid progress in this area, answers to these and many other interesting questions should be forthcoming soon.

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Acknowledgments—We thank James Woodgett, Thomas Force, Leonard Zon, John Kehrl, Dennis Templeton, Antonis Zervos, and Joseph Bonventre for valuable discussions and collaborations.

Addendum—Two recent papers have identified additional SAPK upstream activators. Salmerón *et al.* (77) demonstrated that Tpl-2, the rat homologue of the *cot* protooncogene, was able to activate MEK1 and SEK1 *in situ* and directly *in vitro*. Tpl-2 displays sequence similarities to both the MEKKs and SPS1-like kinases. Tokiwa *et al.* (78) have shown that the Ca^{2+}-regulated tyrosine kinase Pyk2 may couple UV and osmotic shock signals to the SAPKs.

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J. Biol. Chem. 1996, 271:24313-24316.
doi: 10.1074/jbc.271.40.24313

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