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Review

The stress-activated protein kinase pathways

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Abstract. Part of the cellular response to toxins, physical stresses and inflammatory cytokines occurs by signalling via the stress-activated protein kinase (SAPK) and p38 reactivating kinase pathways. This results in modification of cellular gene expression. These stress-responsive kinase pathways are structurally similar, but functionally distinct, from the archetypal mitogen-activated protein kinases (MAPKs or ERKs). The ERK pathway is a hierarchical cascade originating at the cell membrane with receptors for mitogens or growth factors, which recruit, via adapter proteins and exchange factors, the small guanosine triphosphatase (GTPase) Ras (see fig. 1). Ras activates raf, a serine threonine kinase, which activates MEK (MAPK/ERK kinase). MEK, in turn, phosphorylates and activates ERK1 and ERK2, which translocate to the nucleus and transactivate transcription factors, changing gene expression to promote growth, differentiation or mitosis. By transducing signals through a cascade of kinases, several options for control are introduced for amplifying and/or modifying the output signal. The SAPK and p38 pathways are also hierarchically arranged, but less is known about the upstream components and the downstream effects of stimulation of these pathways. Among the processes modulated by stress-responsive pathways are apoptosis, transformation, development, immune activation, inflammation and adaptation to environmental changes. This review outlines the upstream componentry of these pathways that interact with a variety of agonists to modify the activity of SAPK and p38, and explores the downstream functions of this activation.

Key words. Stress-activated protein kinase (SAPK); jun N-terminal kinase (JNK); p38; mitogen activated protein kinase (MAPK); apoptosis.

The components

The stress-activated protein kinases

SAPK was isolated initially as a novel 54-kDa MAPK from the livers of rats treated with cycloheximide [1]. Subsequent amino acid determination and cloning revealed three separate genes—the α, β and γ SAPK proteins, respectively. Alternative splicing of these genes produces 8–10 isoforms (see table 1 for nomenclature) [1–5]. Several isoforms of SAPK were independently cloned and named Jun N-terminal kinases, or JNKs [2, 3].

SAPKs bind to [6] and phosphorylate the transcription factor cJun. cJun is one component of the activator protein 1 (AP-1) transcription factor complex; the others include members of the cFos and cJun families. Transactivation of cJun by the SAPKs leads to increased expression of genes with AP-1 sites in their promotors (see fig. 2). One of the primary targets of AP-1 is the cJun gene itself, so transactivation of cJun initiates a positive feedback loop. SAPKs can also phosphorylate other Jun family members if they are bound

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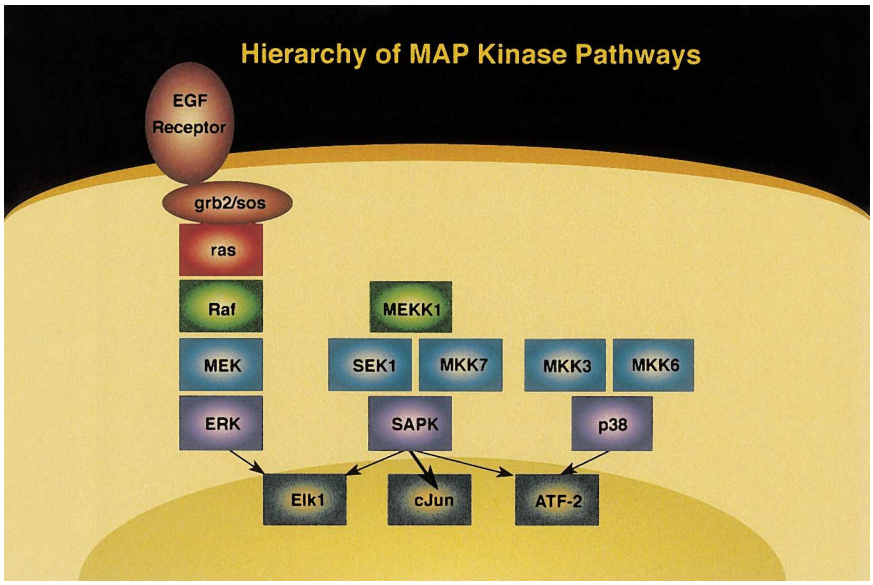

Figure 1. Signals from the cell surface are transduced through the cytoplasm by a cascade of protein kinases. In the mitogen-activated protein kinase pathway, the cascade includes Raf, MEK and ERK. Kinases structurally analogous to MEK in the SAPK pathway are SEK1 and MKK7; in the p38 pathway they are MKK3 and MKK6. SAPK and p38 are structurally similar to ERK.

to proteins with adequate docking sites [7]. Other nuclear targets include the ternary complex factors Elk-1 [8–14] and serum response factor accessory protein 1a (Sap-1a) [15]. Since these factors positively regulate the cFos promotor, their activation results in increased expression of the cFos protein, further increasing AP-1 levels. Enhanced AP-1 transcription can also be mediated by interactions of c-Jun with SMAD3 and may potentially lead to synergism with signalling by transforming growth factor β (TGFβ) family members [16]. Activating transcription factor 2 (ATF-2), which can form heterodimers with cJun and increase expression of AP-1 controlled genes, is also a SAPK target [17], as is the Ets-related transcription factor PEA3 [18]. Isoforms of SAPK bind these transcription factor targets with different affinity, perhaps leading to differential signalling based on the specific isoforms activated [5].

SAPK also phosphorylates the nuclear factor of activated T cells (NF-AT4), opposing its nuclear translocation during T cell activation [19, 20]. SAPKs translocate to the nucleus when activated, presumably to phosphorylate their nuclear targets. However, it should not be assumed that all SAPK targets are nuclear. A substantial fraction of the kinases are present in the cytoplasm even in activated cells, and it is likely that the enzymes regulate translational as well as transcriptional processes. For example, AUUUA-mediated stabilization of interleukin 3 (IL-3) RNA is influenced by SAPK [21].

The p38 family of protein kinases

A second stress-activated MAPK family was first identified in budding yeast as a kinase activated by hyperosmolarity, HOG1. There are five mammalian relatives of this enzyme termed p38α [22], p38β [23], p38γ [24], SAPK3 [25] and SAPK4 [26]. p38α and β respond to many of the same agonists that activate the structurally similar SAPKs, but under certain circumstances they are differentially regulated [27, 28]. They phosphorylate the transcription factors ATF-2, Sap-1a [12, 13, 29] and growth arrest and DNA damage transcription factor 153 (GADD153) [30] (see fig. 2), and are necessary for the induction of cJun and cFos responses to anisomycin and ultraviolet (UV) irradiation [31]. Certain isoforms

Table 1. SAPK/JNK nomenclature.

Rat	Human	Gupta et al.
p54 SAPKα1		JNK2β2
p46 SAPKα1		JNK2β1
p54 SAPKα2	JNK2	JNK2α2
p46 SAPKα2		JNK2α1
p54 SAPKβ	JNK3	JNK2α2
p46 SAPKβ		JNK3α1
p54 SAPKγ		JNK1α2
p46 SAPKγ	JNK1	JNK1α1

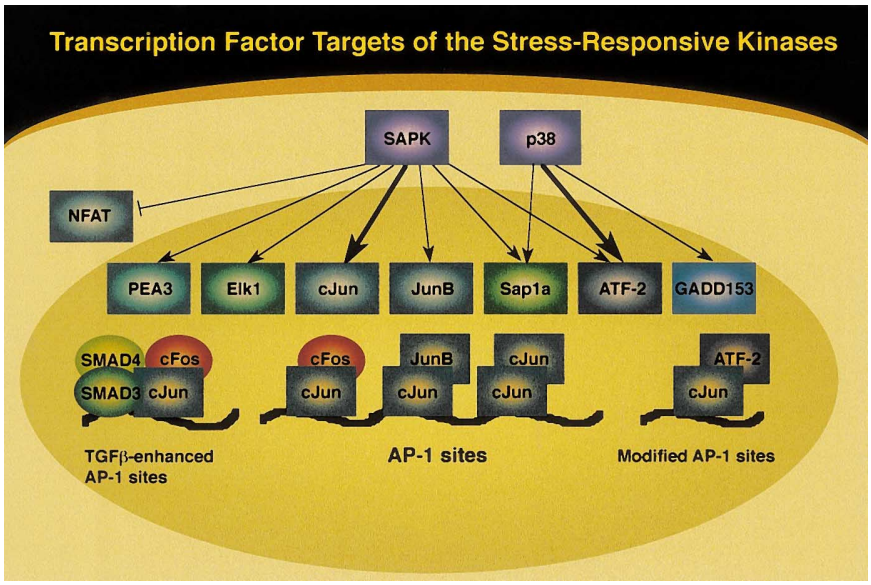

Figure 2. SAPK activation leads to phosphorylation of specific transcription factors. Homodimers, heterodimers and multimers of these transcription factors promote transcription of genes with binding sites for the AP-1 complex.

of p38 [25] also activate nontranscription factor targets such as the mitogen-activated protein kinase-activated protein kinases (MAPKAPKs -2, -3 and -5) [32, 33], and the related protein MNK1 [34]. Some of these MAPKAPKs phosphorylate and activate the small heat shock protein hsp27, which may mediate changes in the actin cytoskeleton and other downstream events [35]. New pharmacological compounds such as CSAIDs (cytokine suppressing antiinflammatory drugs) bind to the p38α and β proteins and inhibit their activity [36], and this has allowed investigation into the differential regulation of the downstream immediate early genes by the p38α/β and SAPK pathways [37].

Dual-specificity kinases

Enzymes which can phosphorylate both tyrosine and threonine residues form the next echelon in the SAPK and p38 pathways. SEK1 (SAPK and ERK kinase 1) [38] phosphorylates and activates SAPK [39]. It may also phosphorylate p38 in vitro [40]. However, SEK1 may form complexes in vivo that limit its ability to activate p38 under physiological conditions [41]. Several distinct SAPK-activating proteins have been described, based on their elution from chromatography columns [40, 42]. The generation of SEK1 doubly deficient embryonic stem cells revealed that there must be at least one additional SAPK regulator, since some agonists including UV irradiation and sorbitol could still activate SAPK in the complete absence of SEK1 [43–45]. Several groups subsequently cloned map kinase 7 (MKK7) [46–54] and have shown it to phosphorylate and activate SAPK, while having no activity towards p38. MKK7 and SEK1 are structurally quite similar (49% identity) and do not appear to display any preference for the different SAPK isoforms.

MKK3 [22] and MKK6 [55, 56] are dual-specificity kinases that target the TGY (threonine-glycine-tyrosine) activation motif within subdomain VIII of p38. MKK6 activates p38α, β and γ, while MKK3 activates α and γ [23].

The MEKKs and the MLKs

The dual-specificity kinases are themselves dependent upon phosphorylation for activity. These enzymes are phosphorylated by two families of serine/threonine kinases, the MEKKs (MAPK and ERK kinase kinases), which were initially named for their role in the ERK mitogen-activated protein kinase pathway, and the mixed lineage kinases (MLKs) (see fig. 3). MEKK1 phosphorylates and activates SEK1 and MKK7 [51, 57, 58]. Studies of the regulation of the MEKKs have been confounded by the constitutive activity of these proteins when overexpressed. However, these molecules have been reported to bind to upstream regulators (see below). In addition, recent results have demonstrated that MEKK1 is cleaved by the apoptotic machinery in the

cell, removing a regulatory domain and causing its activation [59–61]. MEKK1 may also be activated by phosphorylation [62]. MEKK -2, -3 and -4 also activate the SAPK pathway [63–67]. MEKK3 can phosphorylate and activate MKK3 in vitro, but no activation of p38 ensues when MEKK3 is expressed in vivo with or without MKK3 [66].

The MLK family currently comprises six members termed MLKs -1, -2 and -3, DLK/MUK/ZPK, LZK and MTK1. MLK-3 binds to and phosphorylates SEK1 [68, 69] and MKK6 [69], thereby activating both the SAPK and p38 pathways. MLK2 [58, 70, 71] and the related DLK [72, 73], LZK [74] and MTK1 [75] also activate SAPK with or without concomitant p38α/β activation. The MLK family is characterized by possession of several structural features, including SH3 binding domains, leucine zippers and small GTPase binding domains (see below). By binding through these domains, MLKs may integrate inputs from several upstream regulators to the SAPK and p38 pathways. MLK2 and -3 bind to components of the kinesin superfamily of motor proteins, suggesting a link between the activation of the stress-responsive kinase pathways and microtubule function [76].

Other kinases regulating the stress-responsive pathways at the level of the MEKKs and MLKs include Tpl2 (tumour progression locus 2) [77], ASK1 (apoptosis signal-regulating kinase 1) [78] and TAK1 (TGFβ-activated kinase 1) [79, 80]. Tpl-2 activates both the SAPK and MAPK protein kinase pathways via interactions with SEK1 and MEK1, thereby allowing simultaneous signalling through these two cascades [77]. Similar to MEKK1, N-terminal truncation of Tpl-2 activates this kinase [81]. TAK1 activates SEK1 and the SAPK pathway [82], perhaps integrating signals from TGFβ family members to the SAPK cascade. ASK1 activates both the SAPK and p38 pathways via SEK1 and MKK6 [78].

The Sterile 20 kinase family

The activity of the MEKK/MLK enzymes can be modulated by yet another tier of protein kinases, typified by proteins related to the Ste20 protein in yeast (which has been genetically placed upstream of the MEKK-like Ste11 enzyme). The first mammalian relative of Ste20 to be identified was germinal centre kinase (GCK) [83]. A second member of the same family, hematopoietic progenitor kinase (HPK1) stimulates the SAPK pathway by binding to and phosphorylating MLK3 [84]. HPK1 may also interact with tyrosine kinases via SH3 binding domains linked to Grb2 [85]. Nck interacting kinase (NIK) similarly may interact with adapter proteins, and it binds MEKK1 to activate SAPK [86]. Additional Sterile 20-like kinases, KHS (kinase homologous to SPS1/Ste20) [87], GLK (GCK-like kinase) [88] and GCKR (GCK-related) [89] activate SAPK, but the intermediate signalling proteins are as yet unknown. Caspases activate a protein termed Mst1 by cleaving off its C-terminal tail, and this truncated kinase activates

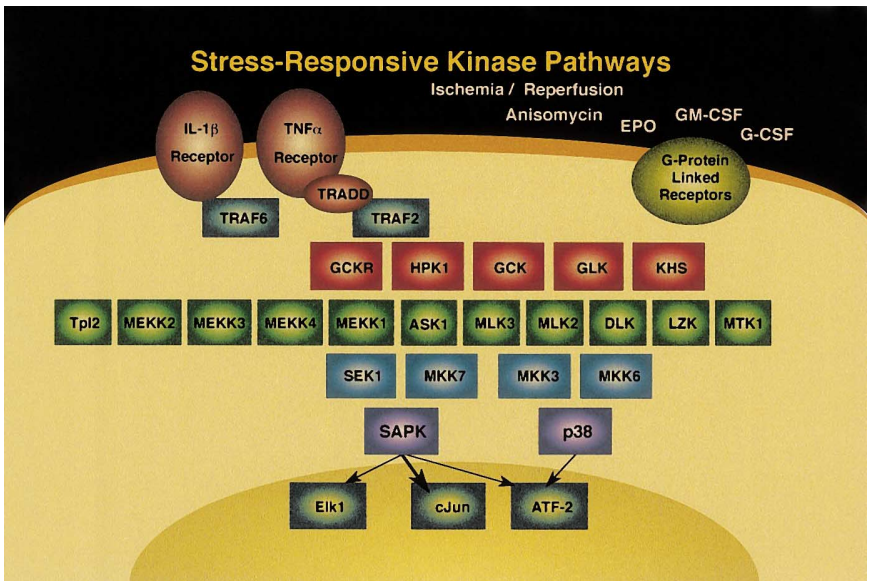

Figure 3. Increased complexity of the pathways at the MEKK/MLK (green) and sterile 20 (red) levels are shown.

MKK6, MKK7 and subsequently p38 and SAPK [90]. The p21-activated kinases (PAKs) have been proposed to transduce signals from the small GTPases Cdc42 and Rac to the SAPK and p38 pathways. Although p65Pak1 can activate SAPK in *Xenopus* oocyte extracts [91], only the constitutively active hPAK1 [92, 93] or overexpressed PAK1 [94] can activate SAPK in mammalian cells. PAK is not involved in the SAPK activation initiated by the Rho GTPase [95]. Activated PAK-3 stimulates p38 [92], and dominant-negative PAK can inhibit p38 activation by the small GTPases Rac and Cdc42 [96]. But the physiological role of PAKs in the stress-activated and p38 pathways is not yet clear.

A putative scaffold protein which has binding regions for SAPK, MKK7 and MLK family proteins, and which associates with the Ste20 HPK1, has recently been described to enhance the signalling via these kinases [97]. This JIP-1 (JNK-interacting protein 1) protein does not bind SEK1, and it would suggest that similar scaffold proteins may be responsible for aligning other signalling modules to respond perhaps to specific agonists. In this way, control of signalling may depend on the availability of scaffolds within specific cell types.

Small GTPases

Rac and Cdc42, members of the Rho family of small GTPases, activate the SAPK and p38 pathways [98–100]. They also modulate many cellular events not associated with SAPK activation, such as membrane ruffling [101, 102], filopodia formation [103], invasiveness [104] and cell cycle progression [102]. In some studies, mutants of Rac [101, 105] and Cdc42 [105] that fail to bind PAK also do not activate the SAPK pathway; however, others find that PAK binding is unnecessary for SAPK activation [102]. A specific target of Rac, POSH, contributes to SAPK activation [106].

Ras activation may lead to subsequent activation of Rac and other small GTPases, linking the ERK and SAPK pathways [99]. Ras activation also seems to be important for SAPK activation in response to some agonists, as dominant-negative Ras blocks SAPK activation by anisomycin, but not by arsenite, osmotic stress or heat shock [107], and SAPK activation by some cytokines is at least partially ras-dependent [108–110].

Exchange factors such as vav [111–114], dbl [115], C3G [116, 117], Tiam1 [118], trio [119] and FGD1 [112] that facilitate the exchange of GDP for GTP on the small GTPases also activate the SAPK and p38 pathways by activating Rac, Rho, Cdc42 [103] or other as yet uncharacterized GTPases [103, 120].

Inflammatory cytokine receptor intermediates

TNFα is one of the best-characterized agonists of the SAPK and p38 pathways. Binding of TNFα to the TNF receptor 1 leads to the recruitment of several cytoplasmic signalling molecules, including the TNF receptor-associated death domain protein (TRADD), which subsequently recruits the Fas-associated death domain protein (FADD) and leads to activation of caspases [121]. Also bound directly to the TNFα receptor II (TNFαRII), and indirectly to the TNFαRI, is the TNFα receptor-associated protein 2 (TRAF2). TRAF2, [122, 123], TRAF 5 and TRAF 6 activate the SAPK and NFκB signalling pathways via ASK1 (K. Hoeflich and J. Woodgett, personal communication) [124], and these are independent of the apoptosis-inducing FADD-mediated events [121, 125, 126]. TRAF2 may be the point of bifurcation of the signals to nuclear factor kappa B (NFκB), mediated by NIK [127, 128] and the activation of SAPK, reported to be mediated by GCKR (GCK-related), a member of the Ste20 family of kinases [89] (see above). Activation of the Fas/Apo1 receptor, a member of the TNFα receptor superfamily, leads to the activation of SAPK and the induction of apoptosis, mediated by Daxx [129], perhaps via ASK1 [130]. Another TNFα receptor superfamily member, CD27, activates the SAPK pathway via TRAF2 and TRAF5 [131].

Interleukin 1 also stimulates the SAPK and p38 pathways: IL-1 receptor-interacting kinases (IRAKs) [132] and MyD88 [133] are required for this stimulation. The human toll receptor, related to the IL-1 receptor, also signals to SAPK via MyD88 and IRAK [134].

G-protein-linked receptors

Certain agonists of the SAPK pathway signal via G-protein-associated receptors, but the intermediates in this cascade are not yet elucidated. GTPase-deficient, activated forms of Gα subunits Gαq [135], Gα12 [136–140] Gα13 [136, 138] Gα16 [135, 141] all activate the stress-activated kinases, and this activation can be inhibited by dominant-negative mutants of Ras [136, 137, 139], Rac [137, 139, 140] or Cdc42 [138]. Heterotrimeric G-protein β/γ subunits can also induce SAPK activity [142, 143].

Other agonists of the stress kinases

SAPKs were so named because they respond to noxious chemicals and physical agents. UV light stimulates SAPK, and singlet oxygen [144] or oxidative stress [145] have been proposed as mediators, as have DNA damage [146], RNA damage [147] and interactions between cell surface receptors [145, 148]. The tyrosine kinase Pyk2/CADTK/RAFTK [149], which is stimulated by changes in intracellular calcium, is also activated and may work

upstream of SAPK. In fact, several agonists of the SAPK cascade signal via changes in the intracellular concentration of calcium. Involvement of the calcium/calmodulin-dependent protein kinase IV [150] or the calcium-dependent tyrosine kinase Pyk2/CADTK/RAFTK [149, 151, 152] have been proposed.

Oxidative stress [153] and nitric oxide [154, 155] stimulate SAPK and p38 in some cell types, and intracellular reactive oxygen intermediates have been proposed as mediators of SAPK activation by cytokine receptors [156] and by sodium arsenite [157]. The activation of the cell surface Na^+/H^+ exchanger is associated with many SAPK agonists, and elevation of cytosolic pH also activates SAPK and p38 [158].

Certain chemotherapeutic agents activate the stress responsive kinases [159, 160]. Ara-C, cisplatinum, and mitomycin C have been proposed to activate the c-abl tyrosine kinase and subsequently SAPK [161, 162], but other chemotherapeutics like the alkylating agent methyl methane-sulphonate (MMS) can activate SAPK in c-abl-deficient cells [163]. Reactive intermediates may be involved in this case, as the level of intracellular glutathione contributes to the ability of MMS to activate SAPK, with decreased glutathione augmenting SAPK activity [164]. Another anticancer agent, the microtubule-disrupting drug paclitaxel (Taxol) activates SAPK via ras and the apoptosis signal regulating kinase (ASK1) [165] (see above).

Anisomycin, a protein synthesis inhibitor which inhibits peptide chain elongation, is a potent activator of SAPK. It activates SAPK at concentrations that are ineffective to block protein synthesis. Anisomycin affects specific intracellular targets, as shown by its ability to selectively desensitize SAPK responses to itself, as well as to UV light and hyperosmolar stimuli, sparing SAPK responses to cytokines and growth factors [166]. Anisomycin binds to the 28S ribosomal RNA (rRNA) and interferes with ribosomal function [167]. This 'ribotoxic stress' only occurs with ribosomes that are translationally active. Other agonists which may signal via ribotoxic stress include the tumor promotor palytoxin [168], certain antibiotics [168] and UV light [147].

Negative regulation of the SAPK and p38 pathways

As the signalling cascades are induced by a series of phosphorylation events, they are antagonized by the activation of phosphatases. Over the past 5 years several specific phosphatases have been identified that target different components. Dual-specificity phosphatases such as MAP kinase phosphatase 1 (MKP-1) terminate kinase activity of SAPK, ERK and p38 by dephosphorylating the regulatory tyrosine and threonine residues [169, 170]. Within different cell types, MKP-1 can be induced by calcium signalling [171], it can be induced by activation of the ERK pathway to inhibit SAPK and p38 signal transduction [172] or, alternatively, it can be induced by SAPK [173] or p38 [174] activation to dephosphorylate ERK. MKP-2 inactivates ERK and SAPK preferentially [169]. The related MKP-3/Pyst1 binds tightly to ERK via its N-terminal domain, and dephosphorylates ERK specifically [175]. MKP-4 is a relatively nonspecific phosphatase [176, 177], and M3/6 phosphatase dephosphorylates SAPK and p38 [178]. SH_2 domain-containing protein tyrosine phosphatase 2 (SHP-2) inactivates SAPK in response to cellular stress, but it is a positive regulator of ERK signalling [179].

SAPK is negatively regulated by protein-protein interactions which maintain it in the cytoplasm and prevent nuclear translocation and subsequent cJun activation. Overexpression of JIP-1 alone, without the upstream components MKK7, MLK3 and HPK1, can sequester SAPK in the cytoplasm, prevent its nuclear translocation and inhibit its activity [97, 180]. Binding of SAPK to the Cdk inhibitor p21/WAF1 also inhibits SAPK activity nonenzymatically [181, 182].

Retinoids and steroid hormones antagonize cJun function as their receptors compete with AP-1 for CBP, but they also inhibit the activation of the SAPK pathway by unknown mechanisms [183, 184].

Pharmacologic inhibitors of some isoforms of p38 have been described which bind to p38α and p38β [36]. These pyridinyl-imidazole compounds, known as cytokine suppressive anti-inflammatory drugs (CSAIDS), interfere with the translation of TNFα, among other effects. SAPK and the p38 family members SAPK3 and SAPK4 are not inhibited by these compounds, and this specificity lies in the binding of these drugs to certain amino acid residues in the ATP binding pocket of p38α and β [185, 186]. This differential affinity has been used to dissect the functions of p38α and β from those of SAPK; however, recent results show that much higher doses of the inhibitors can inhibit SAPK as well [187].

Functions of the stress-activated protein kinases

Apoptosis

The most quoted function of the SAPK pathway is its role in apoptosis or programmed cell death. This has been exemplified in neuronal cells, which depend on growth factors for their survival. In differentiated PC12 cells, withdrawal of nerve growth factor (NGF) results in activation of the SAPK and p38 pathways, inhibition of the ERKS and apoptosis [188]. Blockade of the SAPK pathway by expression of dominant negative cJun led to increased survival, and SAPK was therefore proposed to mediate the apoptotic events [188]. In these same cells, apoptosis can be blocked by the antioxidant N-acetylcysteine and overexpression of Bcl-2, which decrease SAPK

activity, but it can also be blocked by inhibitors of caspase function and cell cycle progression [189], interventions which do not affect SAPK activation and which suggest that caspases lie either downstream of SAPK in this programmed cell death cascade or that they are on separate pathways, simultaneously activated by growth factor withdrawal.

In sympathetic neurons in culture, expression of MEKK1 activates SAPK, increases cJun expression and phosphorylation, and induces apoptosis, all of which can be blocked by a dominant negative mutant of SEK1 termed SEK1-AL. However, SEK1-AL does not block these same events after NGF withdrawal [190], suggesting that other pathways are contributing to apoptosis physiologically. A small molecule inhibitor of neuronal apoptosis, CEP-1347, does decrease SAPK activity, but may also have more generalized effects since it does not interact with the MEKK1-SEK-SAPK cascade [191].

In vivo, after neuronal injury by ischemia and reperfusion, SAPK is active and cJun is phosphorylated for up to 5 days; Fas ligand is induced and cells undergo apoptosis [192]. However, axonal injury increases SAPK activation up to 50 days after injury, regardless of whether the cells undergo apoptosis or survive [192]. In fact, the SAPK activity is decreased only when regeneration is complete, and persists in those neurons which demonstrate chronic axonal sprouting [193].

Excitatory neurotransmitters such as glutamate, in conjunction with increased calcium, can induce apoptosis in certain neurons after prolonged excitation. JNK3 (p54 SAPKβ) knockout mice are protected from this apoptosis, suggesting that this isoform of SAPK mediates the neurotoxicity [194]. In other studies, however, inhibitors of p38 can rescue cells from glutamate-induced apoptosis [195]. In addition, insulin is neuroprotective, and in cultured fetal neurons insulin signalling specifically inhibits p38 phosphorylation and activity, suggesting p38 contributes to the cell death [196]. Taken together, these data indicate that although SAPK is activated in neurons on growth factor withdrawal or toxic injury, its activation is not always sufficient to induce apoptosis, and other pathways, including p38, may have contributing roles.

Apoptosis can be induced in susceptible cells by ligation of the Fas receptor. Fas receptor ligation induces SAPK activity, and SAPK has been proposed as the mediator of cell death, since dominant-negative components of the SAPK pathway can block apoptosis in susceptible neuroblastoma cells [197]. However, in these same cells, dominant negative ERK pathway members also block apoptosis [197], demonstrating multiple contributions to cell death.

Thymocytes are also susceptible to Fas-mediated apoptosis. Thymocytes deficient in SEK1, though, were more susceptible to Fas-induced cell death, suggesting that activation of the SAPK pathway may mediate survival signals in these cells [43]. In Jurkat T cells, SAPK activation after Fas ligation can be blocked by expressing SEK1-AL, but this does not interfere with the progression of apoptosis [198], demonstrating that SAPK activation is not necessary for apoptosis to occur. Indeed, inhibitors of caspases prevent SAPK and p38 activation [199–201], suggesting that the stress kinase pathways may be activated as a result of the apoptotic process, not as a cause.

A more direct approach to dissecting the role of SAPK in apoptosis involves induction of dominant negative FADD molecules which block Fas- and TNFα-induced apoptosis, but leave signalling to SAPK, and downstream gene transcription, intact [202]. Also, in TRAF2-deficient cells, there is a severe reduction in SAPK activity but an increased sensitivity to TNFα-induced cell death [203].

The lipid second messenger ceramide has been associated with activation of SAPK [204], and induction of apoptosis secondary to TNFα, NGF and Fas signalling [205]. Dominant negative components of the SAPK pathway [206], or the p38 inhibitor, can block Fas- and ceramide-induced apoptosis [207], suggesting a causative role for ceramide-induced SAPK in the death process. SAPK activation and ceramide signalling can be isolated from one another, though. In BAF3 cells, for example, ceramide-induced apoptosis proceeds even when SAPK is inhibited by expression of the dual-specificity phosphatase M3/6 [208]. In addition, blockade of ceramide generation after TNFα signalling does not interfere with SAPK activation [209].

A metabolite of ceramide, sphingosine-1-phosphate, activates the ERK pathway [210], and concomitant generation of sphingosine-1-phosphate [211, 212], or stimulation of the ERK pathway by agonists [213], can suppress ceramide- or TNFα-induced apoptosis. This suggests the relative balance between ERK and SAPK (and p38) signalling may determine susceptibility to apoptosis induction.

In endothelial cells, where TNFα stimulates the expression of inflammatory molecules rather than apoptosis, there is no correlation between TNFα-induced activation of SAPK, on the one hand, and ceramide production on the other [214, 215]. In addition, TNFα stimulates SAPK and p38 with bimodal kinetics, and it appears that interruption of early SAPK or p38 activation can enhance TNFα-induced apoptosis, suggesting a protective role for SAPK and p38 signals [216].

In various cell types, overexpression of components of the SAPK pathway induce apoptosis. Fibroblasts transfected with activated MEKK1 die by apoptosis [217], and T cells expressing activated Cdc42 increase SAPK and caspase activity and undergo apoptosis [218]. In both cases apoptosis induction required constitutively

activated forms of the components, and this may not reflect the in vivo situation. Moreover, these components affect multiple processes including NF-κB activation.

Heat shock-induced apoptosis is associated with SAPK activation, and expression of high levels of heat shock protein 70 inhibits SAPK [219, 220] and p38 activity [219] and reduces cell death. Constitutive expression of elevated levels of hsp70, though, while it inhibits cell death, does not affect SAPK responses to heat shock and ceramide [220]. These consitutively high hsp70 levels interfere with processing of one of the caspase proteins [220], and this may be the more relevant protective mechanism.

UV light-induced apoptosis can be blocked by the conditional expression of MKP-1 dual-specificity phosphatase, which decreases SAPK and p38 activity after UV stimulation. This treatment also decreases caspase activity, suggesting the caspases are downstream of stress-responsive kinases in this system [221].

Induction of apoptosis in response to cellular stress and chemotherapeutic agents has been linked to activation of SAPK [222]. In support of this view, expression of a dominant negative SEK1 blocks cisplatin-induced apoptosis [159], and antisense oligonucleotides to a SAPK isoform block etoposide-induced apoptosis and decrease caspase activity [223]. However, in other cell types, SAPK activation is associated with DNA repair and increased cell viability after cisplatin treatment [224]. Treatment of cells with adriamycin or vinblastine activates SAPK, but cell lines which are resistant to these drugs have higher levels of active SAPK than the susceptible lines, so SAPK activity may be in some way protective [160]. In the case of etoposide, teniposide and UV irradiation, SAPK and NFκB pathways are induced and contribute to the expression of Fas ligand, perhaps inducing apoptosis through Fas signalling [225]. Prolonged SAPK activation and Fas ligand expression are also associated with anisomycin, UV, and γ-irradiation-induced apoptosis, but interference with Fas/Fas ligand interactions only prevents apoptosis secondary to anisomycin stimulation [226], suggesting that this is not a universal mechanism. As in the case with ceramide-induced apoptosis, activation of the ERK pathway can prevent cell death secondary to drugs or oxidative stress [227, 228], implying that it is the relative balance between the outputs of the stress-responsive and ERK pathways that determines life or death.

Dexamethasone, a potent steroid, induces apoptosis in hematologic malignant cells. This cell death is independent of SAPK activation [229]. In fact, rapamycin, an immunosuppressive agent, potentiates dexamethasone-induced apoptosis by decreasing SAPK activity [230], suggesting that SAPK plays a positive role in this process.

'Anoikis' is the process of epithelial cell death after detachment from extracellular matrix interactions [231]. SAPK is activated during this process, and was initially thought to be causative for the cell death [231]. However, recent studies demonstrate that SAPK activation can be dissected from death induced by matrix detachment [232].

SAPK and p38 are stimulated by ligands and treatments which induce apoptosis in a variety of cell types. In some cases there is incontrovertable evidence that SAPK plays a role in the apoptotic process, as in the case of the JNK3 knockout mouse, where glutamate-induced hippocampal cell death is prevented [194]. In many systems, there does not seem to be a one-to-one relationship between SAPK activation and cell death, and in certain situations SAPK activity is protective. SAPK activation may induce changes in gene transcription required for response to the noxious stimuli, and while one of these responses may be apoptosis, there are clearly other functions of SAPK under these circumstances. In conclusion, although SAPK activity may be necessary for apoptosis in selected cell types using certain stimuli, and while it is often activated during the process of apoptosis, it is not sufficient to induce cell death in most systems.

Oncologic transformation

Transformation is associated with activity of the ras/Raf/MEK/ERK cascade in many systems, but a contribution of SAPK to the transformed phenotype is emerging. Recent investigations into the mechanism of ras-mediated transformation demonstrate that transfection of dominant negative SEK1 can block oncogenic ras-induced SAPK activation and ras-induced transformation, whereas transfection of wild-type SEK1 enhances ras transforming ability, all without affecting ERK [233].

The Bcr-Abl leukemia oncogene is a constitutively active tyrosine kinase which activates ras, ERK and SAPK [234]. In fibroblast and hematopoietic calls, Bcr-Abl primarily activates SAPK, and a dominant negative cJun mutant inhibits transformation [235]. Another tyrosine kinase oncogene, Tpr-Met, also activates SAPK, and dominant negative Grb-2 or Rac mutants which inhibit transformation by Tpr-Met also block SAPK activity [236].

The HER2/Neu receptor tyrosine kinase is overexpressed in over 20% of human breast tumors. HER2/Neu activates ERK and SAPK, and dominant negative mutants of components of either pathway partially inhibit downstream transcription events [237].

Epidermal growth factor (EGF) is a mitogen that can activate both the ERK and SAPK pathways. Blockade of SAPK activation inhibits EGF-stimulated cell proliferation in lung cancer cells [238]. In addition, the mu-

tant EGF receptor EGFRvIII, which is constitutively active and found in many tumors, activates SAPK, and inhibition of SAPK activity is associated with loss of the transformed phenotype [239].

The mas oncogene, a G-protein-coupled receptor, mediates transformation via Rac and strongly activates SAPK and p38 without activating ERK [240]. SAPK signalling is also stimulated by the Ret protooncogene [241], and human T lymphotrophic virus 1 (HTLV-1), which causes adult T cell leukemia, constitutively activates SAPK [242].

In Kapsosi's sarcoma, growth factors and cytokines such as vascular endothelial growth factor (VEGF), VEGF-related protein (VRP), oncostatin M, basic fibroblast growth factor, TNFα and IL-6 all activate SAPK apparently via the Pyk2/CADTK/RAFTK kinase [243]. The Kapsosi's sarcoma-associated herpes virus/human herpes virus 8 (KSHV/HHV8), which is implicated in the pathogenesis of Kaposi's sarcoma, expresses a G-protein-coupled receptor which activates SAPK and p38. This receptor mimics the growth factor signals in an agonist-independent manner, leads to cell transformation and activates angiogenesis [244]. The virus therefore subverts the normal growth factor signalling pathways involving SAPK to promote oncogenesis.

The mechanisms by which SAPK contributes to transformation may involve interactions with the cell-cycle machinery. For example, SV40 small tumor antigen contributes to SV40-induced transformation by stimulating the cyclin D1 promotor activity, and this event can be inhibited by dominant negative mutants of MEK1, ERK or SEK1, suggesting that the ERK and SAPK pathways may both contribute to transforming ability [245]. While SAPK activation may be associated with cell cycle progression, p38 activity is required in Cdc42-induced cell cycle arrest at G1/S [246], and active p38 can cause mitotic arrest in somatic cell cycles at the spindle assembly checkpoint [247].

SAPK activation, then, is associated with transformation in many oncogene and growth factor-mediated pathways, and presumably the transactivation of cJun is important for this effect. It is interesting that v-Jun, the oncogene counterpart for cellular c-Jun, which lacks the δ-domain SAPK binding region, may mediate its transforming abilities by being dissociated from SAPK signalling, and downregulating TPA response element (TRE)-induced gene expression [248, 249].

Development

While inhibition or deletion of different components of the SAPK pathway are compatible with life in a tissue culture dish, and appear to have no obvious effect on the ability of cells to grow and divide normally, the lack of SAPK components in multicellular organisms results in severe defects. In the fruit fly, mutants which lack the *Drosophila* homologues of cJun (DJUN), SAPK (DJNK) [250] and MKK7 (Hemipterous, hep) [251] die at an early stage in embryogenesis, with a failure of the dorsal epidermis to close over the amnioserosa. The agonist to which the SAPK pathway responds in normal cells at this stage in embryogenesis is unknown. This *Drosophila* SAPK pathway controls the expression of decapentplegic (dpp), a TGF family member, in the dorsalmost cells of the epithelium, instructing the ventral cells to stretch [252]. DJNK increases expression of puckered [253–257], a phosphatase which participates in a feedback loop to control DJNK activity. DJNK has nonredundant functions in phosphorylating DJun in dorsal closure; however, in the developing eye, DJun may be regulated by other MAPK pathways [258, 259]. Upstream of the *Drosophila* SAPK pathway lies Genghis Khan (GeK) [260], which is homologous to Cdc42, and possibly Dishevelled, which is also involved in the Wnt/wingless pathway [261]. Drosophila SAPK-like kinases may also be involved in the establishment of tissue polarity [262].

The SAPK pathway is also important in mammalian development. Mice deficient in SEK1 die in utero after day 12.5. These mice have a defect in hepatogenesis, which is incompatible with further development, but the specific role of the SAPK pathway in this process is not yet known [45].

The SAPK pathway is involved in the development and differentiation of the mammalian immune system. Lymphocyte development is dependent upon antigen receptor signalling. In lymphocytes deficient in SEK1, there are defects in either T cell development [43] or in maintenance of peripheral lymphocyte numbers [263].

Immune activation

The SAPK pathway plays a key role in the induction of the specific immune response to antigens mediated by T cells. T cell activation and the downstream expression of IL-2 require signalling through the T cell receptor (TCR) complex and costimulation mediated by CD28, which binds to B7-1 and B7-2 on antigen-presenting cells. SAPK is synergistically activated by simultaneous signalling through the T cell receptor and CD28, or by coadministration of phorbol myristate acetate (PMA) and calcium ionophore, which mimics TCR/CD28 signalling [264]. Activation of the SAPK pathway induces expression from the IL-2 promotor [265]. In addition to the IL-2 promotor, SAPK also regulates the IL-2 enhancer element, in conjunction with the ERK signalling pathway [266]. Stimulation of the SAPK pathway also stabilizes the messenger RNA (mRNA) for IL-2 inactivated T cells [267]. IL-2 expression is a requirement for T cell proliferation. SAPK, therefore, is stimulated by activation signals and is important in the downstream effector functions of T cells.

A role of SEK1 in this signalling cascade was demonstrated in thymocytes and T cells from RAG2/SEK1 doubly deficient mice. T cells from these mice are impaired in their proliferation and IL-2 production after CD3/CD28 costimulation, but still activate SAPK when stimulated with PMA and calcium ionophore [268]. Thymocytes, on the other hand, do not activate SAPK [268]. This suggests that SAPK activation by SEK1 is developmentally regulated. In T lymphocytes, SAPK may be activated by MKK7, and expression of dominant negative MKK7 abrogates transcription from the IL-2 promotor [269].

Upstream components of the T cell activation cascade may involve MEKK1 [265], Rac and the protein tyrosine kinase Syk [270], as well as protein kinase C θ [271]. ERK is activated by TCR signalling alone (i.e. without costimulation through CD28), and p38, while it is activated by TCR with CD28, is equally well activated by TCR ligation alone [272]. p38 does contribute to IL-2 expression, however, since a specific inhibitor of p38, SB203580, or expression of a dominant-negative MKK6 suppressed transcriptional activation of the IL-2 promotor [269].

IL-2 expression is dependent upon AP-1 and NF-AT transcription factors, and the potent immunosuppressive cyclosporine A blocks NF-AT translocation by inhibiting the phosphatase calcineurin. Cyclosporine A, however, also partially inhibits SAPK [269, 271] and p38 [269] activity, and may cause decreased IL-2 production, and therefore immunosuppression, by this mechanism.

IL-2 expression, along with IL-2 receptor expression, leads to positive feedback of T cell proliferation. ERK, SAPK and p38 are activated in T cells treated with IL-2, but blockade of p38 with SB203580 is effective in suppressing proliferation [273]. T cell responses are terminated by signals from the cell surface molecule cytotoxic T-lymphocyte antigen 4 (CTLA-4), which is induced by T cell activation to limit responses. CTLA-4 not only competes with CD28 for B7-1 and B7-2 binding [274], but also signals independently of CD28 to inhibit T cell activation [275, 276]. Ligation of CTLA-4 downregulates ERK and SAPK activity and interferes with IL-2 production and T cell proliferation [277].

T cell anergy is a state of unresponsiveness to antigens, important in the peripheral suppression of T cell function, or tolerance. T cell anergy can be induced by stimulation of the T cell receptor without costimulatory signals. SAPK and ERK activities after T cell activation stimuli are reduced in anergic T cells [278, 279], as is p38 activity [272]. Interestingly, human immunodeficiency virus (HIV) capitalizes on this phenomenon—its gp160 protein binds to CD4 on T cells, and this decreases the ability of SAPK and ERK to respond to T cell activation stimuli [280].

Other cell surface molecules stimulate T cells and contribute to their activation. CD40 ligand activates SAPK and p38 in T cells [281], and signalling via the cell adhesion molecule L-selectin activates SAPK [282]. SAPK therefore lies downstream of a number of signalling pathways involved in T cell activation, and inhibition of SAPK and p38 inhibits T cell function.

In B cells, signalling via the B cell receptor (BCR) complex (distinct from Bcr-abl) activates the ras/Raf/MEK/ERK pathway, and cross-linking BCR induces apoptosis [283, 284]. The CD40 cell surface receptor is involved in B cell proliferation, survival, memory and immunoglobulin class switching. Signalling via the CD40 receptor activates SAPK [283–285] and p38 [284]. CD40 cross-linking can rescue B cells from apoptosis secondary to BCR cross-linking, and this rescue is associated with activation of SAPK, ERK [283, 284, 286] and p38 [284]. Stress-responsive kinases, in this case, provide the survival signal and appear to be involved in proliferation. In fact, the Epstein-Barr virus latent membrane protein 1 (LMP-1) mimics CD40/CD40 ligand interactions and activates SAPK [287], but in a ligand-independent manner, leading to sustained B cell proliferation and possibly then to transformation.

In *Drosophila*, DJNK is activated by lipopolysaccharide and participates in an insect immune response [250], and homologues of p38 and its upstream kinases affect insect immunity to pathogens [288]. The roles of the stress kinases in immune function may therefore be conserved through evolution.

Inflammation

Acute inflammation is a multifaceted response to microbial invasion or loss of tissue integrity. Changes in vascular permeability, recruitment of inflammatory and immune cells and their activation, generation of reactive oxygen intermediates, and the digestion of the intercellular matrix and its repair are all aspects that require initiation, progression and resolution. The stress-activated protein kinase cascades, in conjunction with other signalling pathways such as the ERK pathway and NFκB, play prominent roles in the initiation and propagation of inflammation.

Bacterial products such as lipopolysaccharides trigger the acute inflammatory response in part by activating tissue macrophages to induce the production of inflammatory cytokines. Lipopolysaccharide (LPS)-binding protein conjugates activate the SAPK pathway via the cell surface receptor CD14 [289]. In macrophages, ERK, SAPK and p38 are all activated by LPS [290]. SAPK activation is necessary for efficient translation of TNFα mRNA stimulated by LPS [291], an effect that can be inhibited by glucocorticoids [291], contributing to their antiinflammatory effect. Translational regula-

tion of TNFα production is also inhibited by the cytokine suppressive antiinflammatory agents, CSAIDS, which specifically inhibit p38α and β [36].

Salmonella typhimurium induces a profound inflammatory response in intestinal epithelium. Secretion of bacterial proteins into the host cell cytoplasm stimulates SAPK in a Cdc42-dependent manner. In fact, one of the *Salmonella* proteins, SopE, is an exchange factor for Rac1 and Cdc42, leading to cytoskeletal rearrangement and SAPK activation [292]. Blockade of Cdc42 with a dominant negative kinase-dead mutant inhibits both SAPK activation and micropinocytosis and internalization of the bacterium, while a constitutively active Cdc42 caused cells to internalize even nonpathogenic bacteria [293]. The bacterial protein SopE, therefore, directly subverts the SAPK pathway to enhance bacterial internalization and pathogenicity. *Salmonella typhimurium* infection stimulates p38, ERK and SAPK pathways in intestinal epithelial cells, inducing the activity of NFκB and AP-1, and the production of the inflammatory cytokine IL-8. Inhibition of p38 with the specific inhibitor SB203580 prevented IL-8 production [294], demonstrating the contribution of the p38 pathway to the inflammatory response to this infection.

In a completely opposite approach, the enteropathogenic bacterium *Yersinia enterocolitica* modifies the host macrophage intracellular signalling cascades. After initial rapid activation of p38, ERK and SAPK, *Y. enterocolitica* carrying the virulence plasmid inhibits the activity of these kinases, and decreases Elk-1, ATF-2 and cJun phosphorylation [295]. The result of this inhibition is decreased TNFα release and dampening of the inflammatory response against the bacterium. A similar strategy is used by *Y. pseudotuberculosis*, where the bacterial protein YopJ encoded on the virulence plasmid downregulates p38 and SAPK and decreases TNFα production in infected macrophages [296]. Bacteria, therefore, have developed strategies to induce stress-responsive kinases when it is to their advantage, in host cell invasion, but to dampen them to inhibit the TNFα proinflammatory response.

Opsonized bacteria bound to immunoglobulin G also activate three kinase pathways via the Fcγ receptor on macrophages, and this activation leads to TNFα production [297]. Macrophages, in turn, respond to TNFα by activating SAPK (especially the p46 isoform) [298] and p38 [299], initiating a positive feedback loop. SAPK and p38 are also activated by certain chemokine receptors such as CCR5, the receptor for macrophage inflammatory protein 1b (MIP1b) [300], and may play a role in chemotaxis of macrophages.

In mast cells, aggregation of Fcε receptors for immunoglobulin E (IgE) leads to SAPK activation and subsequent cytokine expression, including expression of IL-2 [301] and TNFα [302]. Transfection of active MEKK1 into mast cells strongly stimulates SAPK and induces transcription from the TNFα promotor, which is unaffected by inhibition of ERK, p38 or NFκB [303]. The SAPK pathway, then, is important in amplifying IgE-mediated inflammatory responses.

In neutrophils, whereas ERK, SAPK and p38 are all activated in response to formyl peptides, the respiratory burst is mediated by p38 alone [304, 305]. Reactive oxygen species generated by the respiratory burst stimulate the stress-responsive kinases [306], and either arachidonic acid itself [307] or its lipoxygenase metabolites [306, 308] mediate these effects, perpetuating the inflammatory response.

Viruses activate the stress-responsive kinases in a myriad of ways. Adenovirus activates SAPK and cJun transcription via its 19K E1B protein [309], which may have implications for adenovirus-mediated gene therapy. Epstein-Barr virus LMP1 activates SAPK [310, 311], and this may contribute to the transforming potential of LMP1. Hepatitis B HBx protein activates ERK and SAPK, which may play a role in hepatitis B pathogenesis [312].

In the case of HIV, the secreted HIV Tat protein functions as a cytokine and activates SAPK [313], as well as other signal transduction systems. Since HIV requires T cells to be actively cycling in order to infect them, Tat activates ERK and SAPK in uninfected T cells, stimulating them to enter the cell cycle and making them permissive for HIV infection [314]. Tat activates SAPK, as well as other kinases, downstream of the VEGF receptor 2 (FLK1/KDR) in Kaposi's sarcoma cells, and may influence cell growth and migration [315]. In addition, the HIV1 promotor is activated by cytokines and UV, and this activation is mediated by p38 [316].

Certain parasites also activate SAPK. The intracellular parasite *Theileria parva* constitutively activates SAPK and induces the expression of both IL-2 and its receptor in infected T cells, leading to transformation [317, 318].

The stress-activated protein kinase pathways, with or without concomitant activation of ERK and other kinases, are thus stimulated by diverse categories of microbial infection. The role of these kinases appears to be augmentation of the inflammatory response by increasing the expression not only of proinflammatory cytokines, as already discussed, but also other mediators of inflammation such as nitric oxide synthase [319], matrix metalloproteinases [320–323], urokinase plasminogen activator [324, 325] and its receptor [326]. Cyclooxygenase 2 expression is also modulated by SAPK activity [327–331], linking the SAPK pathway to the generation of inflammatory prostaglandin production.

In addition to the effects on macrophages, neutrophils and mast cells, SAPK activation in endothelial cells

upregulates cell adhesion molecules such as E-selectin [332, 333], possibly leading to increased recruitment of inflammatory cells to the site of acute inflammation.

Cardiovascular responses

The potent vasoconstrictor angiotensin II stimulates SAPK in vascular smooth muscle cells [334], cardiac myocytes [335] and renal mesangial cells [336]. This SAPK activation can be inhibited by AT-1 receptor blockers [335, 336], and stimulated by constitutively active G-proteins like Gα16 [141]. In these instances, SAPK activation is dependent upon an increase in intracellular calcium [335, 337], and may be mediated by the calcium-dependent protein tyrosine kinase pyk2/CADTK/RAFTK [151]. Prolonged exposure to angiotensin II leads to vascular smooth muscle cell hypertrophy and induction of smooth muscle α-actin. Dominant negative SEK can inhibit the expression of SM α-actin induced by angiotensin II or constitutively active Gα16, suggesting a role for the SAPK pathway in mediating this adaptive effect [141].

Mechanical stresses affect vascular cells. After ballon injury to vessels in cardiac or carotid angioplasty, restenosis of the vessel wall is a major concern. Balloon injury activates SAPK and ERK [338, 339] via an AT-1 receptor-mediated process [339], and the changes in gene expression may lead to neointima formation. Shear stress also activates SAPK and ERK in endothelial cells [340, 341], and these signals may induce changes in gene expression leading to atherosclerosis.

The stress-responsive kinases have additional roles within the vasculature. VEGF stimulates p38 in endothelial cells, and this activity is required for actin reorganization and endothelial cell migration [342]. VEGF, the VEGF-related protein VRP, oncostatin and basic fibroblast growth factor all stimulate SAPK in endothelial cells [343]. Thus, stimuli implicated in angiogenesis are mediated in part by p38 and SAPK.

Phenylephrine, an agonist of α-adrenergic receptors, is a potent vasoconstrictor which induces cardiac hypertrophy. Phenylephrine activates SAPK in cardiac myocytes and induces expression of atrial natriuretic factor (ANF), one of the markers of cardiac hypertrophy [344]. To determine whether cardiac hypertrophy is mediated by the stress-responsive kinases, myocytes were transfected with MEKK1, which led to induction of ANF expression [344–346]. Infection of myocytes with MKK7 produces all three features of hypertrophy—increases in cell size, sarcomere organization and ANF expression [347]. Transfection of myocytes with MKK6 to activate p38 exclusively also induces all three markers, and phenylephrine-induced changes can be blocked by SB203580, the p38 inhibitor [348]. Independently, then, SAPK or p38 can induce features of hypertrophy, but when overexpressed together they induce cytopathic effects [347].

Mechanical strain [349, 350], pacing [351], hemodynamic load [352], osmotic stress or anisomycin [353, 354] all activate SAPK in cardiac myocytes. In isolated perfused hearts, ischemia activates p38, and reperfusion activates SAPK [346]. The stress-responsive kinases, therefore, may mediate cardiac remodelling stimulated by multiple agonists. When this response is maladaptive, p38 or SAPK may make good therapeutic targets.

Maturation and differentiation of multiple types of hematopoietic cells are mediated by cytokines and growth factors. SAPK transduces signals from granulocyte macrophage-colony stimulating factor (GM-CSF) [109, 355, 356], granulocyte-colony stimulating factor (G-CSF) [108], IL-3 [108, 355] and IL-5 [357], possibly via the common β c chain that receptors for these cytokines share. High levels of GTP-bound ras are required for SAPK stimulation by these cytokine receptors, and dominant negative ras can block this SAPK activation [109]. Ras activation alone, though, is insufficient to activate SAPK [108, 109]. Erythropoietin and thrombopoietin also signal via SAPK [358] and erythropoietin and IL-3 activate p38 [359].

In the cardiovascular system, remodelling of both the vascular smooth muscle and the heart, pathogenic processes induced by hypertension, may be modulated at least in part by activation of the stress-responsive kinases. Differentiation in the hematopoietic system also requires stress-responsive kinases to transduce cytokine signals and alter gene expression.

Hepatic functions of stress-responsive kinases

Several lines of evidence point to the SAPK pathway as an important growth regulator in the liver. It is activated in hepatocytes by hepatocyte growth factor, as well as hyperosmotic glucose and TNFα, where it stimulates DNA synthesis [360]. Another agonist of SAPK activity is thrombin, which functions as a mitogen for hepatocytes and may play a role in liver regeneration [361] Lack of SEK1 during embryonic growth leads to defects in hepatogenesis [45], but whether this effect is due to an inability to respond to hepatic growth factors is not known.

In addition to signalling for growth, stress-responsive kinases are involved in the induction of enzymes which detoxify chemicals and metabolites. p38 mediates the induction of heme-oxygenase 1, an enzyme which reduces oxidative stress injury [362]. SAPK is implicated in the induction of glutathione-S-transferase after methylcholanthrene treatment [363]. Finally, ischemia/reperfusion injury in liver stimulates SAPK [364–366], which may have important ramifications in liver transplantation.

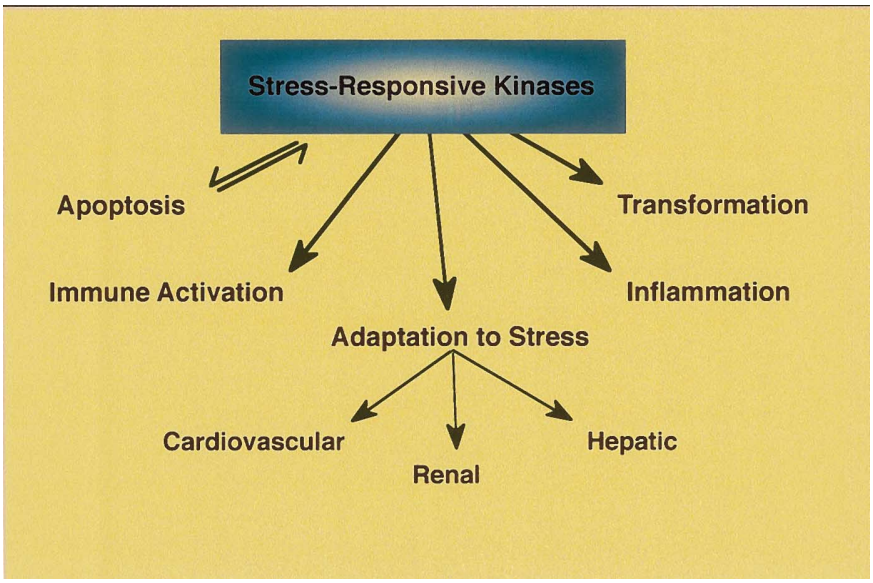

Figure 4. Downstream effects of the stress-responsive protein kinases. The stress-responsive protein kinases affect many cellular processes in various cell types. See text for details.

Renal functions of the stress responsive kinases

In the kidney medulla, tubular cells are regularly exposed to hyperosmolar stress. While osmotic stress induces apoptosis in some nonrenal cells, kidney cells respond with growth arrest and changes in expression of osmolyte transporters, to offset the osmotic stress. Exposure to hypertonic medium induces the activation of ERK, SAPK and p38, but the specific osmolyte is critical, since SAPK and p38 respond in a dose-dependent manner to increases in NaCl up to 800 mosmol/kg, but equimolar urea causes no stress-responsive kinase activation [367]. Inhibition of ERK signalling with the specific inhibitor PD098059 does not affect the cell's ability to adapt by increasing inositol uptake, suggesting SAPK or p38 might mediate transcription of organic osmolyte transporter genes [368]. Inhibition of p38 does interfere with the transcription of the osmolyte transporter betaine [369], and p38 is also responsible for the growth arrest mediated by upregulation of GADD45 and GADD 153 proteins [370]. The SAPK pathway is important in long-term hyperosmolar stress, though, since expression of a dominant negative isoform of SAPK leads to increased cell death in this circumstance [371].

Ischemia/reperfusion injury causing acute renal failure activates SAPK [372]. The antioxidant N-acetylcysteine inhibits SAPK activation, improves renal function and the histological appearance of the kidney 7 days post-ischemia, but does not reduce the extent of necrosis at day 1 [373]. These results show that SAPK activation can be dissociated from cell death, but that downstream effects of SAPK activation may be deleterious to kidney function and recovery.

Summary

The stress-responsive kinase pathways transduce signals from an incredible variety of agonists—toxic chemicals, physical agents such as irradiation, changes in the extracellular and intracellular environments, and cytokines and growth factors. They transmit signals through a complex array of intracellular proteins, many of which we do not yet know, and which can amplify or modify the signal at any point. Their responses are not digital black or white 'stress' responses, but graded adaptive responses which may include apoptosis, repair, differentiation, development, transformation, or other physiological or pathological changes in cellular behavior (see fig. 4). Clearly, this organization of intermediates allows a high degree of flexibility of response and likely accounts for the tremendous variation in ultimate responses between cell types. Perhaps the most controversial or confusing aspect is their role in apoptosis, with many examples of SAPK activation being either protective or promoting cell death. Some of this confusion likely stems from technical problems with the approaches used to assess the effects. For example, transdominantly acting mutants may have non-SAPK-

dependent effects. What appears to be the case is that the signals via this pathway modulate decisions which are perhaps ultimately determined by a combination of factors. In this model, the pathway does not have a determining role unless the other factors have been suppressed but instead pushes the cell to commit to one fate or another. This can be exemplified by considering the effects of damage. At low levels of a mutagen, the cells repair machinery must be sensitive to the incidence of the damage and initiate control. In this scenario, the pathway could be protective. However, as the damage mounts, a decision to eliminate the cell becomes important, to prevent mutagenic transformation. At this stage (i.e. chronic stress) the signal will be associated with induction of apoptosis.

Within specific tissues or cells, the stress-induced kinases are responsible for inducing genes with specialized functions. In the immune system, they promote T cell activation and B cell proliferation. Stress responsive kinases function in many cells and tissues in a proinflammatory manner by upregulating cytokines and mediators of inflammation like the respiratory burst in neutrophils, and increased cell adhesion in endothelial cells. In many tissues they induce genes which enable the cells to adapt to the specific stress—hypertrophy in vascular smooth muscle and cardiac myoctyes to cope with increased pressure; detoxifying enzymes in liver to deal with xenobiotics; inositol transporters in kidney to adapt to physiological hyperosmolar stress. Stress responsive kinases also transduce signals for differentiation in the hematopoietic system, and possibly in embryonic development. Of course it important to remember that unlike in culture dishes, these multifunctional kinases do not function in isolation in an intact tissue; often stimuli will activate the ERK pathways in conjunction with SAPK and/or p38 and other transductory systems (e.g. phosphatidylinositol 3′ kinase), and the integration of the activity from these and other signalling pathways determines the final outcome.

Clearly, there is much to be learned in understanding the physiological functions of these pathways. Many questions will likely be resolved by studies of knockout animals and from the development of specific inhibitors. The sooner the better, as considerable effort has been expended in programs to evaluate the pharmaceutical value of modulating these enzymes. Given their pleiotropic nature, any bets on the utility of such drug molecules are hedged!

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