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The c-Jun Kinase/Stress-activated Pathway: Regulation, Function and Role in Human Disease

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Abstract

c-Jun N-terminal kinases (JNKs), also referred to as stress-activated kinases (SAPKs), were initially characterized by their activation in response to cell stress such as UV irradiation. JNK/SAPKs have since been characterized to be involved in proliferation, apoptosis, motility, metabolism and DNA repair. Dysregulated JNK signaling is now believed to contribute to many diseases involving neurodegeneration, chronic inflammation, birth defects, cancer and ischemia/reperfusion injury. In this review, we present our current understanding of JNK regulation and their involvement in homeostasis and dysregulation in human disease.

Keywords

c-Jun N-terminal Kinase (JNK); Stress-activated Protein Kinase (SAPK); ischemia; apoptosis; metabolic regulation; obesity; neurodegeneration; chronic inflammation

Introduction

JNK/SAPKs phosphorylate c-Jun at the NH₂-terminal Ser63 and 73 residues in response to UV irradiation and other stress stimuli [1–5]. The importance of c-Jun as a member of the AP-1 transcription factors lead to an intense analysis of JNK regulation of AP-1 function. AP-1 transcription factors are heterodimers composed of Jun, Fos, Maf and ATF subunits [5]. c-Jun, ATF2 and ATF3 are substrates for phosphorylation by JNKs, which enhances AP-1 transcriptional control of specific gene expression [6].

There are three JNK genes (JNK1, JNK2, JNK3). JNK1 and JNK2 are ubiquitously expressed while JNK3 is restricted to brain, heart and testes [1,4,7,8]. Differential splicing and exon usage results in multiple isoforms of the JNK1, 2 and 3 genes [9,10]. Each JNK is expressed as a short form (46 kDa) and long form (54 kDa) [7]. The alternative forms of each JNK1, 2 and 3 appear to differ in their ability to bind and phosphorylate different substrate proteins [9,10]. The different JNK isoforms can also be differentially activated [9,10]. Targeted gene disruption of each JNK has also defined differential functions for JNK1, JNK2 and JNK3 in many different

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cell types involving gene expression, apoptosis, metabolism and other critical physiological responses [8,11–13].

JNK/SAPK Regulatory Network

As with all MAPKs, the JNKs are part of a three kinase module. The TXY motif in the activation loop of each JNK is dually phosphorylated by specific MAPK kinases (MKKs). MKK4 and MKK7 phosphorylate the threonine and tyrosine within the activation loop TXY motif (T¹⁸³ and Y¹⁸⁵ in JNK1) resulting in JNK activation. MKKs are in turn phosphorylated at specific serine or threonine residues within their activation loop (S²⁵⁷ and T²⁶⁵ for MKK4; S²⁷¹ and T²⁷⁵ for MKK7).

There are at least 20 MKKKs of which at least 14 activate the MKK4/MKK7-JNK/MAPK pathway. Several of the MKKKs capable of phosphorylating and activating either MKK4 and MKK7 in the JNK pathway are also capable of activating other MKKs including MKK1 and 2 for ERK1/2 activation, MKK3 and 6 for p38 activation, and MKK5 for ERK5 activation (Fig. 1). The twenty MKKKs outnumber the 7 MKKs and 11 MAPKs. The MKKKs are differentially regulated by protein-protein interactions and covalent modifications. Many MKKKs are activated by GTPases such as Ras (the Raf MKKKs) or Rho family GTPases (MLK3 by Cdc42, MEKK1 by RhoA) [14–16]. Ubiquitination may also regulate the activity of MKKKs; including MEKK1 auto-ubiquitination that inhibits its activity [17] or ubiquitination associated with assembly of signaling complexes such as the IL-1 receptor signaling complex for TAK1 [18]. Many of the MKKKs also are phosphorylated by MKKKs such as PAK, GCK and HPK that may be involved in controlling MKKK activity, interaction with other proteins and localization [19–21]. It is the diversity of MKKK regulation resulting from differential protein-protein interaction and covalent modifications that allow the integration of MAPK activation in the cellular response to a diverse range of stimuli. These stimuli include cytokines, growth factors, antigens, cell adhesion and cell-cell interactions, toxins, pharmacological drugs, and a range of stress stimuli including heat, cold, toxicity and shear. Of the 20 defined MKKKs it is notable that at least 14 regulate the JNK pathway, demonstrating the importance of JNK pathways in the cellular response to external stimuli.

Organization of the JNK signaling module

JNK signaling modules are organized by two different mechanisms: *i.* recognition motif between MKKK and MKK and MKK and MAPKs; and *ii.* Scaffold proteins that assemble the MKKK-MKK-MAPK module in larger protein complexes (Fig. 2&Fig. 3).

Docking interactions are achieved via conserved sequences in the MAPKs (JNK, ERK1/2, p38, ERK5) that are selective for the specific upstream MKK (MKK4 and 7 for JNKs) and substrates such as c-Jun, ATF2 and others (see Table 1 for a list of representative JNK substrates). Fig 2 depicts the interaction between the different motifs in MKKKs, MKK4/7 and JNKs. On all MAPKs, including JNKs, there is a cluster of negatively charged amino acids C-terminal to the kinase domain sequence (Fig. 2B). This site is referred to as the common docking (CD) domain and is used in the docking of MKKs, MAPK phosphatases and specific substrates and scaffold proteins [22–27]. A second conserved motif referred to as the ED (Glu-Asp) domain, also contributes to the docking interactions of MAPKs [22–26]. Docking site sequences in MKKs, substrates, MAPK phosphatases and scaffolds share a conserved motif of R/K-X4- \emptyset_A -X- \emptyset_B (where \emptyset_A and \emptyset_B are the hydrophobic residues Leu, Ile or Val) [28]. Whereas the basic residues in this docking domain (DD) bind the acidic residues of the MAPK CD domain, the hydrophobic residues reside in a docking groove that engages the \emptyset_A -X- \emptyset_B hydrophobic motif of the DD motif. These docking site interactions provide the specificity for MAPK interactions and a role in the activation of the kinase [28].

In addition to the docking interactions of MAPKs with MKKs, substrates and regulators there are specific motifs that control the interactions of MKKKs and MKKs (Figs. 2A&B) [29]. A docking site termed DVD (domain for versatile docking) is found in several MKKs including MKK4/7 for JNK regulation. The DVD site is near the extreme C-terminus of the MKK and was shown to be involved in binding MKKKs including MEKK1, MEKK4 (MTK1), ASK1, Tao2 and Tak1, all of which are able to activate the JNK pathway. The N lobe within the kinase domain of the MKKK was shown to bind to the MKK DVD site.

An additional aspect of JNK control is the organization of signaling complexes by scaffolding proteins (Fig. 3). Scaffolding proteins generally have no catalytic function themselves, but encode docking sites for binding members of the MAPK module-MKKs, MKKs and MAPKs [27]. In general, scaffolds bind additional proteins through interaction motifs such as SH2, SH3, PTB, and other domains that target MAPK signaling complexes to different locations in the cell. It is often the scaffold protein and specific MKKK that provides the selectivity and spatio-temporal dynamics of MAPK activation by different stimuli. Fig 3 lists known scaffold proteins for the JNKs. Among the different scaffolds, JIPs (JNK Interacting Proteins) bind to specific kinesins and the MLK group of MKKKs and appear to be particularly important in cytoskeletal tracking of the JNK module in cells such as neurons [27,30–32]. JNK scaffolds such as arrestins are recruited to phosphorylated G protein-coupled receptors [33], while POSH has multiple SH3 domains and is involved in JNK signaling in apoptosis in mammalian cells as well as *Drosophila* [34–36]. Crk II scaffolds JNK signaling at focal adhesions [37]. Finally, the MKKK, MEKK1, has been shown to bind both MKK4 and JNK1/2, indicating it has a scaffold-like function itself, much like PBS2 in the yeast response pathway for hyperosmotic stress [38,39].

JNK/SAPK in disease

Roles for JNK/SAPK signaling in physiology and disease stems mostly from the knowledge gained from biochemical studies and mouse models where the different JNKs or upstream regulators have been deleted by targeted homologous recombination-gene knockouts [40]. These studies have provided the rationale for targeting JNKs and their upstream regulators including specific MKKKs for therapeutic intervention with small molecule or peptide inhibitors [41–43]. The use of JNK/SAPK inhibitors has further strongly supported an important role for the JNK/SAPK pathway in several different diseases. In particular, JNK inhibitors for the prevention of cell death induced by ischemia and other stress-induced apoptotic responses has shown significant therapeutic potential [41–44]. Below the evidence for JNK/SAPK inhibitors for therapeutic benefit in human disease is presented.

JNK signaling in excitotoxicity of hippocampal neurons

One of the first demonstrations for the role of JNKs in apoptosis was made with JNK3 knockout mouse [8]. JNK3 is highly expressed in the fore- and hind- brain regions in the mouse. JNK3 is also expressed in the heart, but unlike JNK1 and JNK2, it is not required for embryonic development. Normally, treatment of mice with excitotoxic agents like kainic acid causes a marked apoptotic death of hippocampal neurons. JNK 3^{-/-} mice are resistant to glutamate-induced excitotoxicity, clearly demonstrating that JNK3 activation is a pro-apoptotic pathway in hippocampal neurons. Consistent with a role for JNK3 in excitotoxic neuronal cell death, mice expressing a mutant c-Jun having the JNK phosphorylation sites S⁶³ and S⁷³ mutated to alanines are resistant to glutamate-induced excitotoxicity. In contrast, JNK1^{-/-} and JNK2^{-/-} mice are similar to wild-type animals in their susceptibility to excitotoxic neuronal cell death [5,44].

The role of JNK3 in excitotoxicity suggested that JNK/SAPK pathways would be involved in other neuronal death responses and neurodegenerative diseases. A clear role of JNK/SAPKs

in ischemia-induced cell death has been demonstrated in mice. Borsello, et al [45,46] used two different models of cerebral artery occlusion: a transient occlusion in adult animals and a permanent occlusion in 2 week old pups. Inhibition of JNK activity in both models protected against neuronal cell death. A similar study in gerbils using a transient ischemia model showed that intracerebral administration of SB203580, a rather non-selective JNK inhibitor, reduced ischemic cell death [47].

JNK in liver ischemia/reperfusion models:

The role of JNK/SAPK pathways in ischemia-induced cell injury goes beyond that in the CNS. Ischemia/reperfusion (I/R) injury is a major clinical problem in several organs including brain, heart, kidney and liver. Hepatic injury due to I/R occur during several conditions including transplantation, liver tumor resection and circulatory shock. A recent study by Uehara, et al [48] demonstrated that JNK/SAPK activity was a major mediator of hepatic I/R injury. In this study, three ATP-competitive, reversible and highly selective JNK inhibitors (CC0209766, CC0223105, and CC-401 from Signal Pharmaceuticals, Inc.) decreased both necrosis and apoptosis of hepatocytes and sinusoidal endothelial cells. The findings are consistent with JNK inhibitors blocking hepatocyte apoptosis in culture [48].

It has also been shown that the JNK inhibitor AS601245 decreases cardiomyocyte apoptosis and infarct size in a rat cardiac I/R model in rats [49]. JNK activation in this model occurs primarily in the reperfusion phase in response to the generation of reactive oxygen species. Similarly, the JNK inhibitor SP600125 was shown to improve I/R injury in the transplantation of rat lungs [50]. In each of these models, JNK is probably mediating the release of pro-apoptotic factors from mitochondria, may directly phosphorylate pro-apoptotic Bcl family members such as Bak and Bid, and induce the expression of pro-inflammatory cytokines such as TNF α , IL-1 and IL-6.

JNK in neurodegenerative diseases

JNK3 may also prove to be a therapeutic target for neurodegenerative diseases including Parkinson's and Alzheimer's disease [44,46,51–53]. The neurotoxin 1-methyl-4-phenyl-1, 2, 4, 6-tetrahydropyridine (MPTP) induces a neuropathology with loss of dopaminergic neurons similar to that observed with Parkinson's disease in humans [54]. Mice treated MPTP have activated c-Jun, as shown by phospho-c-Jun immunostaining. A similar activation of c-Jun is seen in dopaminergic neurons from Parkinson's disease patients. JNK3^{-/-} and JNK2^{-/-}, but not JNK1^{-/-} mice are protected from MPTP dopaminergic cell death. The double knockout JNK2^{-/-}/JNK3^{-/-} mice have a greater dopaminergic cell protection than either knockout alone. An important downstream target from JNK2 and JNK3-mediated dopaminergic cell death was the expression of cyclooxygenase (COX) 2.

Alzheimer's disease is characterized by diffuse plaques primarily composed of β -amyloid peptide (A β) and neurofibrillary tangles composed of hyper-phosphorylated Tau protein [55–63]. JNK3^{-/-} are resistant to A β -induced apoptosis [55]. In this model, JNK3 activates AP-1 dependent expression of Fas-ligand [55]. There is a correlation with JNK2 and JNK3 activity with neurofibrillary pathology including JNK phosphorylation of Tau and the formation of Tau fibrils induced by JNK3 [64–70]. There is some controversy as to the exact role of c-Jun phosphorylation by JNKs versus other substrates including Nap214, a nuclear pore complex protein, in neurodegenerative models [71].

Hearing loss/deafness

JNK/SAPKs appear to play an important role in acquired deafness [72]. Exposure of hair cells in the cochlea to acoustic trauma, aminoglycoside antibiotics and cancer chemotherapy can

lead to both necrosis and apoptosis, ultimately leading to deafness. JNK inhibition using the D-JNK-1 inhibitor peptide provided otoprotective benefit in organ cultures of neonatal mouse cochlea and in adult guinea pigs exposed to acoustic trauma [73,74], suggesting JNK/SAPK inhibitors may be important therapeutic targets for the prevention of cochlear hair cell loss and deafness.

Neural tube birth defects

Concurrent loss of JNK1 and JNK2 in the JNK1^{-/-}/JNK2^{-/-} double knockout results in defective neural tube development manifested primarily as exencephaly [11,13]. The neurotube defect is not seen in either JNK1^{-/-} or JNK2^{-/-} animals indicating a compensatory function in neural tube development for the two JNK/SAPKs. Exencephaly in the JNK1/2 double knockout embryos was due to enhanced apoptosis in the forebrain and decreased apoptosis in the hindbrain [11].

Further examination of the JNK1^{-/-} and JNK2^{-/-} mice demonstrated that the anterior commissure axons are absent in JNK1 but not JNK2 knockout animals [12]. This is due to a diminished microtubule-associated protein (MAP) 1 and 2 phosphorylation, where MAP1 and MAP2 are preferential JNK1 substrates relative to JNK2 [12]. Phosphorylated MAP1 and MAP2 promote microtubule polymerization. Thus, loss of their phosphorylation causes shortening of neuronal microtubules.

JNK/SAPK signaling pathway in cancer

The most insightful evidence for a role of JNK/SAPK signaling modules in cancer has come from the identification of MKK4 as a putative tumor suppressor [75–79]. MKK4 is a MKK capable of phosphorylating both JNKs and p38 MAPKs. This distinguishes MKK4 from MKK7 which has only been shown to phosphorylate JNKs and not p38 MAPKs. Genetic inactivation of the MKK4 gene on chromosome 17p has been reported for several different tumor types including a subset of breast, biliary and pancreatic carcinomas [75,76]. In addition, in ovarian and prostatic carcinomas epigenetic loss of MKK4 expression has been shown to be correlated with metastasis [77–79]. More recently, studies with SKOV3ip.1 cells expressing kinase-inactive MKK4 showed suppression of experimental metastasis in nude mice [80]. In this study, overexpression of MKK6 (p38 pathway) but not MKK7 (JNK pathway) suppressed the SKOV3 cell growth in nude mice. The results were interpreted that the p38 pathway and not the JNK pathway, was the critical MAPK for the tumor suppressor activity of MKK4. Additional models using MKK4 and MKK6 deficient cells will be required to substantiate this interpretation.

In a mouse model, JNK1 deficiency has been shown to significantly decrease susceptibility to diethylnitrosamine-induced hepatocarcinogenesis [81]. JNK1^{-/-} but not JNK2^{-/-} mice were shown to have decreased expression of cyclin D and VEGF, diminished hepatocyte proliferation and reduced tumor neovascularization. The findings suggest that JNK1 inhibition may be useful for therapeutic intervention and chemoprevention of hepatocellular carcinoma.

Several studies suggest JNK can promote tumor cell growth and therefore, is a useful anti-tumor target [82–85]. Furthermore, JNK inhibitors block the induction of DNA repair genes in cells treated with DNA damaging drugs [86]. However, JNK signaling has also been shown to be critical for inducing apoptosis in response to chemotherapeutic drugs [87]. Thus, JNKs have opposing roles in promoting proliferation and transformation and inducing apoptosis [88]. It seems that the effectiveness of JNK inhibitors in treating human cancers may be very context dependent for the specific tumor and cell origin [88].

JNK/SAPK signaling in chronic inflammatory diseases

JNK/SAPKs appear to have a significant role in chronic inflammatory diseases involving the expression of specific proteases and cytokines [89,90]. For example, JNK signaling appears to be involved in the expression of metalloproteases, which contributes to joint destruction in rheumatoid arthritis [91]. JNKs also appear to contribute to the stimulation of TNF α expression, a major pro-inflammatory cytokine in rheumatoid arthritis. JNK inhibitors such as SP600125 and JNK1 deficiency (JNK1^{-/-} mice) suppressed metalloproteinase expression and protected mice from joint damage in rheumatoid arthritis animal models [91]. JNK2 deficiency (JNK2^{-/-}) also suppressed matrix degradation in joints, but did not significantly decrease inflammation [92].

Atherosclerosis is a second chronic inflammatory disease that appears to involve JNK/SAPK signaling [93,94]. Using the ApoE^{-/-} mouse model for atherosclerosis, it was shown that deficiency of JNK2 (ApoE^{-/-}/JNK2^{-/-}) animals developed less atherosclerosis than control ApoE^{-/-} animals. JNK1 deficiency did not reduce the level of atherosclerosis. JNK inhibitors were also able to reduce the level of atherosclerosis. The mechanism appears to be JNK2-dependent phosphorylation of the modified lipid-binding and internalizing scavenger A receptor (SR-A) that promotes uptake of lipids in macrophages contributing to foam cell formation. The findings suggest specific JNK2 inhibitors may decrease atherogenesis.

Obesity and insulin-resistant diabetes

A therapeutic benefit may be the inhibition of JNKs in metabolic regulation [95–97]. Obesity-induced insulin resistance and diabetes are now worldwide disorders and a growing health crisis. Insulin activation of its receptor stimulates the receptors tyrosine kinase activity. Insulin Receptor Substrate 1 (IRS1) is phosphorylated on tyrosines by the insulin receptor. The tyrosine phosphorylated IRS1 functions as a complex scaffolding protein recruiting numerous signaling proteins in the control of insulin signaling and metabolic regulation. The JNKs phosphorylate IRS1 at S³⁰⁷ that results in reduced insulin receptor catalyzed phosphorylation of IRS1 [98]. JNKs are activated by high fat diet and obesity, in part due to elevated levels of TNF α and IL-1 [95,97]. JNK1^{-/-} mice and JIP1^{-/-} mice have improved insulin sensitivity that correlates with reduced S³⁰⁷ phosphorylation [95,99]. JNK2^{-/-} mice are similar to wild type mice in their response to a high fat diet. JIP1, is a scaffolding protein for JNK signaling, and interestingly, a JIP1 gene mutation has been found in patients with a form of type II diabetes [100]. Consistent with these findings, a cell permeable JNK inhibitory peptide was shown to maintain insulin sensitivity in the obese mouse model [42]. These findings indicate JNK1 may be an important target in the treatment of obesity and type II diabetes.

Conclusions

JNK/SAPKs are clearly involved in ischemia-induced cell death and reperfusion injury in several different tissues and the control of insulin sensitivity in metabolic regulation. There are many other suggestions in the literature that link JNK/SAPK signaling to additional human diseases such as type I diabetes, osteosarcoma, ataxia and immune system dysfunction. JNKs probably play a role in chronic inflammation, airway hyperresponsiveness and protease-directed tissue remodeling. It is likely that selective JNK1, JNK2 and JNK3 inhibitors will be needed for specificity and lack of toxicity. It may also be useful to develop specific MKKK inhibitors to selectively block JNK activation in response to different upstream inputs [19].

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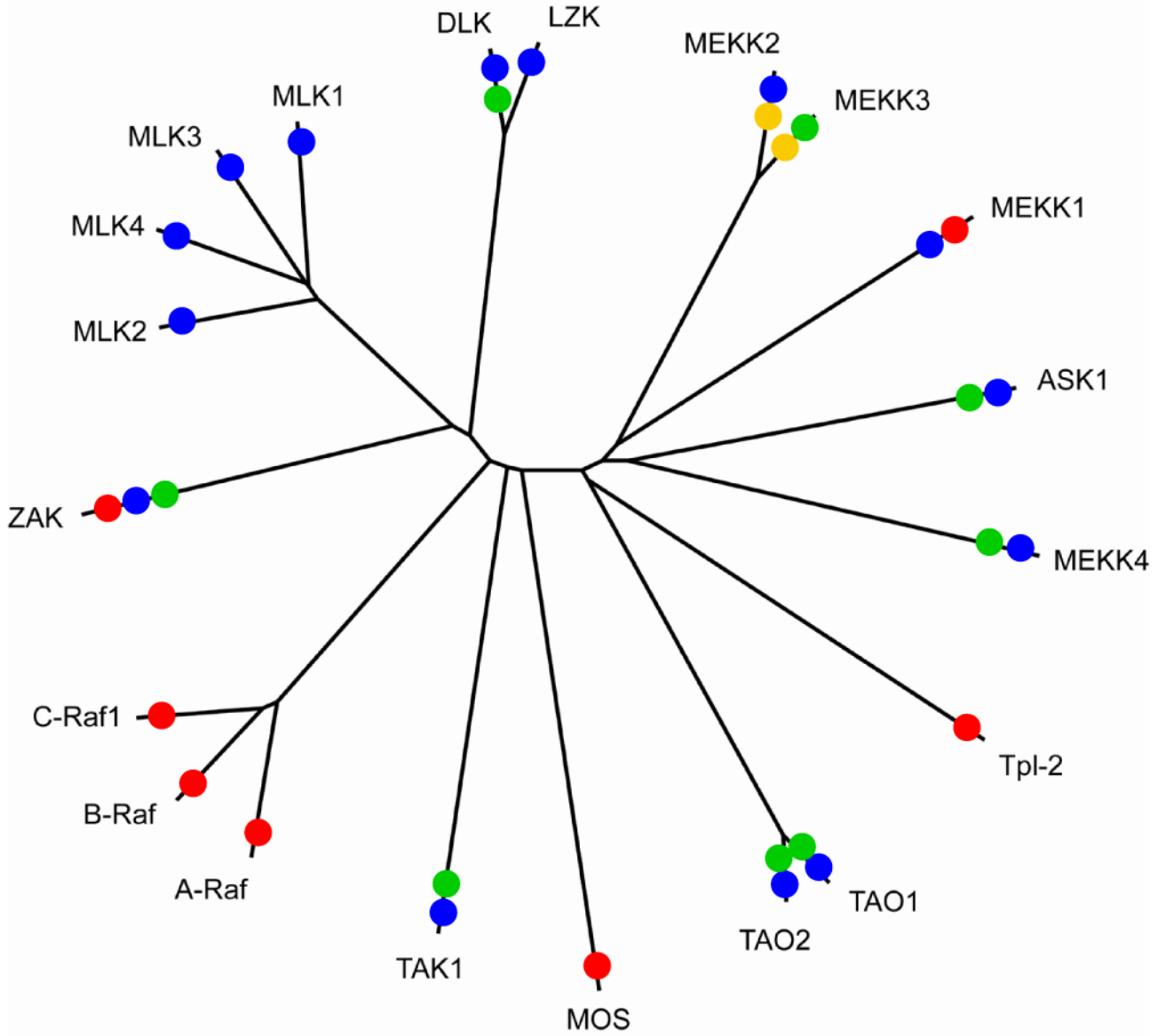
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MAPK

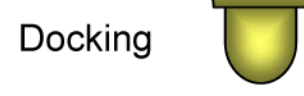
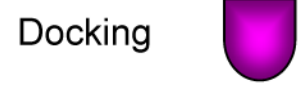
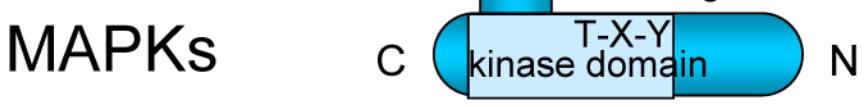
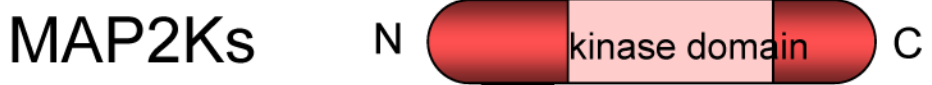
ERK 1/2 ●

JNK ●

p38 ●

ERK5 ●

Figure 1. Dendrogram showing the relationships between the kinase domains of MKKKs and their ability to activate the JNK/SAPK pathway. MKKK regulation of different MAPK pathways is accumulated from literature survey with an emphasis on MKKK knockout data when available.



	JIP-1	152	Y R PK R PTT L N L FPQVPRS	169
	JIP-2	134	S H LL R PTT L H L TTLGAQD	141
	JIP-3	201	S R KE R PT S L N V F PLADGM	218
	Consensus		R RPT T L N L F P	
			S V	
Docking Site				
	c-JUN	32	K I L K Q S M T L N LADPVGSL	49
	NFAT4	141	L E R P S R D H L L Y L PLEPSYR	158
	ATF2	25	A V H K H K H E M T L K F G P A R N	42
	ELK-1	312	Q K G R K P R D L E L P L S P S L L	329
	MKK7b1	22	R E A R R R I D L N L D I S P Q R P	39
	MKK4	34	S M Q G K R R K A L K L I N F A N P P V	51
	Consensus		R/ K -x ₃₋₄ -φxφ	
	(φ; hydrophobic residues [L,V,M,I], x; any amino acids)			
Docking Groove				
	p38alpha	105	V T H L M G A D L N N I V K C Q K L T D D H V Q F L	130
	ERK2	102	V Q D L M E T D L Y K L L K T Q H L S N D H I C Y F	127
	JNK1	107	V M E L M D A N L C Q V I Q M- E L D H E R M S Y L	131
ED site				
	p38alpha	158	V N E D C E L	164
	ERK2	155	L N T T C D L	161
	JNK1	159	V K S D C T L	165
CD domain				
	p38alpha	311	Y H D P D D E P	318
	ERK2	314	Y Y D P S D E P	321
	JNK1	324	W Y D P S E A E	331

Figure 2.

A) Organization of MKKK-MKK-MAPK interactions controlled by docking sites, docking domains (CD, ED and docking groove), DVD site and N lobe. See text for discussion. B) CD (common docking) domain (bottom) characterized by acidic residues in C-terminus of MAPK. ED site (middle) is far from CD domain in the primary sequence, the ED site and CD domain are in the same groove on the opposite side of catalytic center [25]. Crystal structures of p38 and MKK3b or MEF2A define a role of another docking groove (top) in binding to φXφ motif in docking sites [28]. Shown in red are the experimentally proved critical residues for docking site interaction.

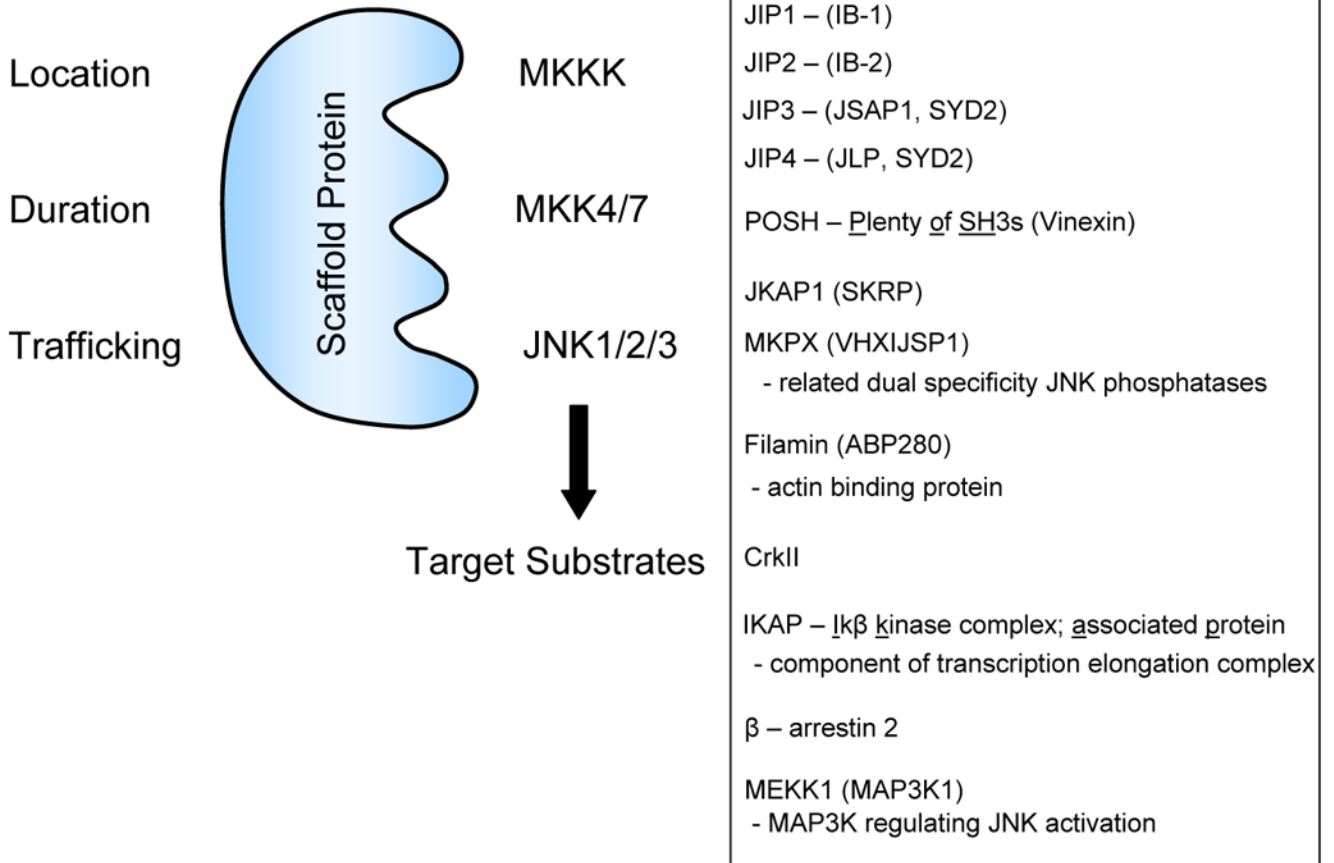


Figure 3.

Function of JNK/SAPK scaffolds in organizing the MKKK-MKK4/MKK7- JNK signaling module. Known JNK scaffold proteins are listed in the box. See text for discussion.

Table 1**SAPK/JNK Substrates**

Table 1 represents a list of known JNK substrates. The list is not comprehensive but representative.

Transcription

c-Jun
JunD
ATF2
ATF3
Elk 1
Elk-3
.p53
RXR α
RAR α
Androgen receptor
NFAT4
HSF-1
c-Myc

Nuclear Pore Complex

Nup214

Apoptosis

Smac
Bim
Bmf
Bcl-2
Bcl-XL
Mcl-1

Microtubules

Tau
MAP1
MAP2A
DCX (doublecortin)
Amyloid β Precursor Protein

Signaling

IRS-1
Paxillin
14-3-3