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Stress-Activated Protein Kinases

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MAPK kinase kinase regulation of SAPK/JNK pathways

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Abstract

SAPK/JNK members of the MAPK family are regulated by at least fourteen known MAPK kinase kinases (MKKKs). In addition to the kinase domain, each MKKK encodes different protein interaction domains and motifs to control their interaction with upstream GTPases such as Rho, Rac and Cdc42, downstream MAPK kinases, and scaffold proteins that assemble the MKKKs into signaling complexes for the control of physiological responses to a plethora of different stimuli. Several MKKKs coordinately regulate the SAPK/JNK pathway with other MAPKs including p38, ERK1/2 and ERK5. It is the diversity of MKKKs within the MAPK signaling network that provides the signaling specificity for activation of MAPKs including SAPK/JNKs and the integration with other signaling pathways within cells.

1 Introduction

SAPKs are MAPKs shown to be activated by many different stress stimuli, hence their name stress-activated protein kinases (SAPKs) (Kyriakis et al. 1994). The same kinases were shown to phosphorylate c-Jun at Ser 64 and 73 (Pulverer et al. 1991; Smeal et al. 1992; Derijard et al. 1994), hence the name Jun N-terminal kinases (JNKs). There are three SAPK/JNK genes (JNK1, JNK2, JNK3). Herein, for simplicity they are referred to as JNKs. JNK1 and JNK2 are expressed ubiquitously while JNK3 has a more limited expression primarily in brain, heart, and testis (Pulverer et al. 1991; Derijard et al. 1994; Kyriakis et al. 1994; Yang et al. 1997). Including c-Jun, several members of the AP-1 transcription factors are substrates for JNKs including JunD, ATF2, and ATF3 (Behrens et al. 1999; Shaulian and Karin 2001). Phosphorylation of AP-1 members by JNKs enhances AP-1 transcriptional control of specific gene expression. The importance of AP-1 in the transcriptional control of many different genes involved in homeostasis and the role of JNKs in regulating AP-1 activity led to an intense study of JNK regulation and it is now clear that JNKs have many substrates in addition to AP-1. The targeted gene disruption of JNK1, JNK2, and JNK3 has defined tissue-specific functions for each isoform including the control of metabolism, apoptosis, motility, proliferation, DNA repair, and the regulation of genes involved in homeostasis

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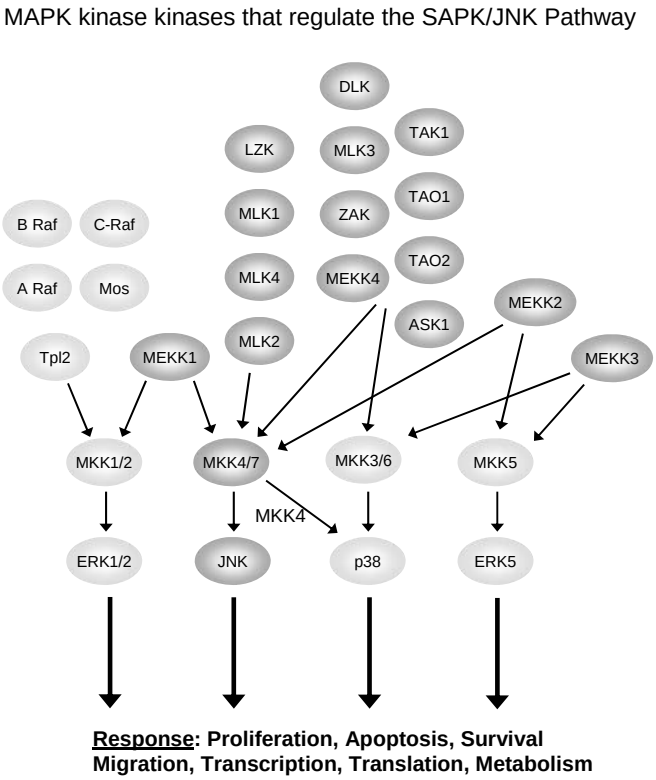

Fig. 1. MKKKs that control the MAPK pathways. There are twenty defined MKKKs known to regulate MAPK pathways. MKKKs phosphorylate and activate specific MKKs. Activated MKKs phosphorylate and activate specific MAPKs. The MKKKs and MKKs that regulate JNKs are highlighted in dark grey.

such as proteases and cytokines (Yang et al. 1997; Kuan et al. 1999; Sabapathy et al. 1999; Chang et al. 2003).

JNKs, like all MAPKs, are part of a three kinase signaling module (Fig. 1). JNKs are phosphorylated and activated by the MAPK kinases, MKK4 and MKK7. MKK4 and MKK7 are phosphorylated and activated by MAPK kinase kinases (MKKKs). Interestingly, whereas there are eleven MAPKs (JNK1/2/3, ERK1/2, p38, α/β/γ/δ, ERK5 and ERK7), there are only seven MKKs and at least twenty MKKKs. It is noteworthy that fourteen of the twenty defined MKKKs activate the MKK4/7→JNK1/2/3 pathway, demonstrating the importance of the JNK signaling pathway in the cellular response to stimuli that frequently involve potentially harmful or lethal consequences for the cell. Such stress stimuli include irradiation, toxins, drugs, osmolarity, temperature, changes in cell shape, adherence, cytoskeletal dynamics, and responses to antigens, growth factors and cytokines. Table 1 shows a partial list of substrates for JNKs that control adaptive responses of the cell to these different stimuli.

Table 1. Phosphorylation substrates for JNKs

Category	Substrate
Transcription factors	c-Jun
	JunD
	ATF2
	ATF3
	Elk-1
	Elk-3
	P53
	NFAT4
	HSF-1
	c-Myc
	Androgen receptor
	RXRα
	RARα
Signaling proteins	IRS-1
	Paxillin
	14-3-3
Microtubule-associated proteins	MAP1
	MAP2A
	Tau
	Doublecortin (DCX)
	Amyloid β precursor protein
Bcl family proteins	Bcl-2
	Bcl-xl
	Mcl-1
	Smac
	Bim
	Bmf
Nuclear core complex	Nup214

2 Organization of the MKKK-MKK4/7-JNK1/2/3 signaling module

Specificity in the organization of JNK signaling modules is controlled in part by recognition motifs for MKKK-MKK4/7 and MKK4/7-JNK1/2/3 interactions. A docking site referred to as DVD (domain for versatile docking) encoded near the C-terminus of MKK4 and 7 interacts with the N-lobe of the kinase domain of the specific MKKK (Takekawa et al. 2005), providing a docking mechanism for selective interaction of MKKKs and MKKs. Docking sites between the JNKs and MKK4 and 7 provide specificity in the interaction of the MKK and MAPK (Jacobs et al. 1999; Sharrocks et al. 2000; Fantz et al. 2001; Ho et al. 2003; Mooney and Whitmarsh 2004; Ho et al. 2006). Similar recognition motifs are present in JNK substrates such as c-Jun and ATF-2 (Sharrocks et al. 2000).

There are also several scaffolding proteins that organize specific JNK signaling modules. These scaffold proteins generally have no catalytic function, but rather

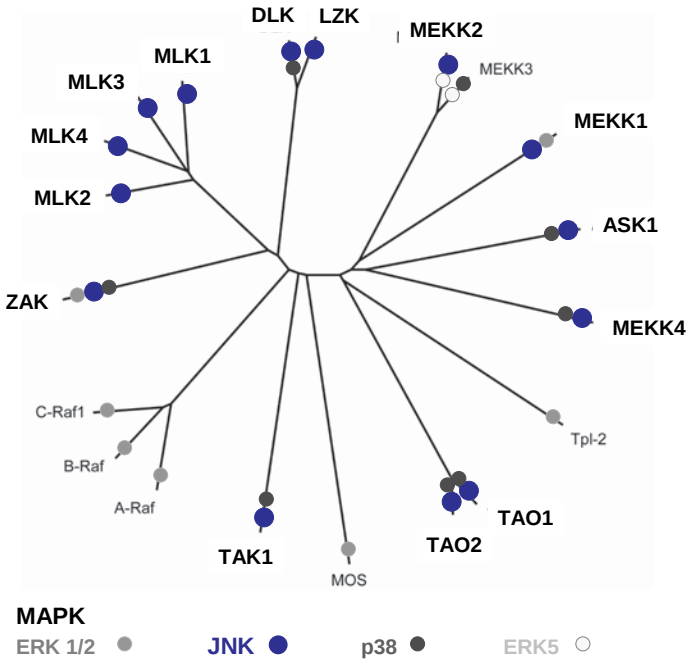

Fig. 2. Dendrogram showing the twenty MKKKs based on homology of their kinase domain primary amino acid sequences. The MAPKs activated by each MKKK are shown in the highlighted circles on the dendrogram.

have docking sites for binding specific MKKKs, MKKs, and MAPKs. Scaffold proteins that regulate the JNK signaling module include the JIP (JNK Interaction Proteins) 1-4 proteins, POSH (Plenty of SH3s), JKAP1 (SKRP), filamin, CrkII and IKAP (Morrison and Davis 2003). Scaffold proteins play an important regulatory role in controlling JNK signaling because they frequently bind specific MKKKs and localize the signaling module within the cell. Thus, scaffold proteins can regulate the spatio-temporal dynamics of JNK signaling.

3 MKKKs as signaling hubs controlling JNK activation

Figure 1 shows the MKKKs that have been defined to regulate MKK-MAPK modules. Of the twenty MKKKs, fourteen have been shown to regulate JNK activity. Six MKKKs regulate the ERK1/2 pathway while only two MKKKs are defined to regulate the ERK5 pathway. Nine MKKKs are known to regulate the p38 pathway. The restricted number of MKKKs regulating the ERK1/2 and ERK5 pathways implies a more restricted response and function for these MAPKs. For example, ERK1/2 is important in regulating cell proliferation in response to tyrosine kinases. The fact that ERK5 has a single MKK and only two defined MKKKs

shown to physiologically regulate ERK5 activity suggests a rather restricted function for this MAPK. Physiologically, ERK5 appears important in regulating vascular development and maintenance of the vasculature in adults. In contrast, the large number of MKKKs that regulate JNK and p38 indicates a role for these MAPKs in the response to diverse stress stimuli.

Figure 2 shows a dendrogram for the relationship of the different MKKKs based on sequence homology of their kinase domains. Based on the kinase homologies, the MKKKs can be divided into six groups: MEKK, MLK, Raf, Tao/Tpl2, Mos, and TAK1. Among these twenty known MKKKs, members of the MEKK, MLK, TAO, and TAK1 groups regulate JNK activation. The properties of each group of MKKKs controlling JNK activation is discussed below.

3.1 MLKs (mixed lineage kinases)

The MLK group has seven members that can be further divided into the MLKs (MLK1, 2, 3, 4), DLKs (DLK, LZK), and ZAK (Gallo and Johnson 2002). The members of the MLK subgroup each have an N-terminal Src-homology-3 (SH3) domain, kinase domain, leucine zipper region and a Cdc42/Rac interactive binding (CRIB) domain. DLKs and ZAK have kinase domains and leucine zipper regions but lack the CRIB and SH3 domains. ZAK is structurally similar to the DLKs but also encodes a sterile-alpha motif that mediates homo- or hetero-dimerization.

3.2 MEKKs (MAPK-ERK kinase kinases)

MEKK1, MEKK2, and MEKK4 have each been shown to regulate the JNK pathway in response to different stimuli. MEKK1 is a large 196 kDa protein with complex regulation. MEKK1 appears to be regulated by both Rac/Cdc42 and RhoA GTPases (Fanger et al. 1997; Gallagher et al. 2004). Furthermore, MEKK1 is the only member of the MKKK-MKK-MAPK signaling network that has a caspase 3 cleavage site. MEKK1 is also the only member of the MAPK signaling network to encode a RING domain containing E3 ubiquitin ligase function. The MEKK1 RING domain has been shown to regulate auto-ubiquitination of MEKK1 that inhibits its kinase activity as well as ubiquitinate and stimulate the degradation of ERK1 and c-Jun (Lu et al. 2002; Witowsky and Johnson 2003; Xia et al. 2007). MEKK1 is also one of only a few proteins in defined proteomes to encode a SWIM domain whose function in MEKK1 remains undefined (Makarova et al. 2002).

Whereas MEKK1 regulates both the ERK1/2 and JNK pathways, MEKK2 regulates the ERK5 and JNK pathways. MEKK2 is only one of two MKKKs, the other being MEKK3, which regulate the MEK5-ERK5 pathway (Nakamura and Johnson 2003; Uhlik et al. 2004; Nakamura et al. 2006). MEKK2 and MEKK3 encode PB1 (Phox-Bem1p) domains that selectively heterodimerize with the MEK5 PB1 domain to form a functional MEKK2 (or MEKK3)–MEK5-ERK5 ternary complex (Nakamura and Johnson 2003; Nakamura et al. 2006). The C-