

# MAPKs

## Key References

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## Overview

The mitogen-activated protein kinase (MAPK) family consists of both stress activated (SAPK) and mitogen-activated (MAPK) protein kinases. They form a network of signal transduction cascades that mediate cellular responses to a diverse range of stimuli, including growth factors, chemical or osmotic stress, irradiation, bacterial infection and proinflammatory cytokines. Most MAPKs are activated by dual phosphorylation on a Thr-Xaa-Tyr motif by upstream kinases, referred to as MAPK kinases or MKKs. MKKs are, in turn, activated by MKK kinases (MKKKs), over 30 of which have been described. However, the details of how they are activated or which MKKK really activates which MKK *in vivo* is still poorly understood. MAPK cascades frequently function as multi-protein complexes in which the different components are assembled on a scaffold protein and/or by specific protein-protein docking sites, thereby increasing the speed and specificity of the cascade. Nearly all MAPKs phosphorylate their substrates on serine or threonine residues that precede a proline, but their specificity *in vivo* is further enhanced by the presence of distinct docking sites that facilitate interaction with substrates.

To date, 14 different MAPK family members have been identified in mammalian cells, and homologs are found in all eukaryotic cells. The most studied cascades in mammalian cells are the classical MAPK, p38 (SAPK2) and JNK (SAPK1) cascades. The classical MAPK cascade is activated by mitogens and growth factors, and plays an important role in the control of cell growth and differentiation. However, its inappropriate activation can be a major cause of cell transformation and cancer. It comprises two closely related MAPKs,

termed extracellular signal regulated kinase 1 (ERK1) and ERK2. These kinases have many overlapping functions, but mouse knockouts have now revealed that they also have some distinct functions *in vivo*. Inhibitors which block the activation of MKK1/2 in cells, such as PD 098059, U0126 and PD 184352 and have been used extensively to investigate the functions of the classical MAPK cascade. Moreover, PD 184352 has been shown to strongly suppress the growth of human colon tumors implanted into mice. These three inhibitors were originally thought to be specific for the classical MAPK pathway, but are now known to also block the activation of MKK5, the activator of a distinct MAPK family member ERK5. ERK5 is activated by mitogens and has been suggested to be important for EGF-induced cell proliferation. Mouse knockouts have shown that ERK5 is required for embryonic development and endothelial cell survival.

The JNK cascade is activated by cellular stress, bacterial infection and proinflammatory cytokines, and results in the phosphorylation of AP1 transcription factors, such as c-Jun. There are three related isoforms of JNK each of which gives rise to several splice variants generating a total of ten different JNK variants. Mouse knockouts have shown that JNK1, 2 and 3 have distinct *in vivo* roles. The p38 cascade is activated by similar stimuli to JNK. Two of the p38 isoforms,  $\alpha$  and  $\beta$  are inhibited by a class of anti-inflammatory drugs of which SB-203580 and SB-202190 are examples. These inhibitors have been used to identify many physiological substrates and to implicate the p38 isoforms in diverse cellular processes, including cytokine production and inflammatory responses. More potent p38 inhibitors are currently in clinical trials for the treatment of arthritis. Mouse knock-

outs have shown p38 $\alpha$  is also essential for normal development. Less is known about the other p38 isoforms,  $\gamma$  and  $\delta$ . P38 $\gamma$  is highly expressed in skeletal muscle, and has been shown to bind to, and co-localize with,  $\alpha$ 1-syntrophin by virtue of the interaction of its C-terminus with the PDZ domain of  $\alpha$ 1-syntrophin. P38 $\delta$  appears to be expressed at low levels in most tissues and little is yet known about its function.

NLK (NEMO like kinase) has been extensively studied in development and can phosphorylate Tcf/Lef proteins and inhibit the DNA-binding ability of  $\beta$ -catenin/Tcf complexes, thereby blocking activation of Wnt targets.

ERK3 and ERK4 and ERK8 are more recently described MAPKs, whose functions are not yet understood. ERK8 appears to be constitutively phosphorylated on its Thr-Xaa-Tyr motif, however its substrates and activators are unknown. ERK3 is unusual in that the Thr-Xaa-Tyr phosphorylation motif is replaced by Ser-Xaa-Glu, and it appears to be rapidly turned over via the proteasome. ERK3 is also implicated in the activation of PRAK.

# MAPKs

<b>FAMILY MEMBERS</b>	MAPK ( <b>M3172</b> , <b>M9426</b> )	JNK	p38 $\alpha$ / $\beta$ ( <b>M8057</b> )
<b>OTHER NAMES</b>	p42/44 MAPK	SAPK1	SAPK2
<b>MOLECULAR WEIGHT/ STRUCTURAL DATA</b>	42 – 44 kDa	48 – 52 kDa	41 kDa
<b>ISOFORMS</b>	ERK1, ERK2 ( <b>M3172</b> , <b>M9426</b> )	JNK1, JNK2, JNK3 ( <b>C3108</b> )	p38 $\alpha$ ( <b>M8057</b> ), p38 $\beta$
<b>SPECIES</b>	Eukaryotes	<i>C. elegans</i> , <i>Drosophila</i> , vertebrates	Eukaryotes
<b>DOMAIN ORGANIZATION</b>	1 kinase domain	1 kinase domain	1 kinase domain
<b>PHOSPHORYLATION SITES</b>	ERK1: Thr <sup>202</sup> , Tyr <sup>204</sup> ERK2: Thr <sup>185</sup> , Tyr <sup>187</sup>	JNK1a: Thr <sup>183</sup> , Tyr <sup>185</sup> JNK2a: Thr <sup>183</sup> , Tyr <sup>185</sup> JNK3a: Thr <sup>221</sup> , Tyr <sup>223</sup>	Thr <sup>180</sup> , Tyr <sup>182</sup>
<b>TISSUE DISTRIBUTION</b>	Ubiquitous	Ubiquitous, SAPK1b, restricted to brain, heart and testis	Ubiquitous
<b>SUBCELLULAR LOCALIZATION</b>	Cytosolic, nuclear	Cytosolic, nuclear	Cytosolic, nuclear
<b>BINDING PARTNERS/ ASSOCIATED PROTEINS</b>	KSR, MP1, $\beta$ -arrestin	JIP ( <b>J2270</b> )	Not known
<b>UPSTREAM ACTIVATORS</b>	MKK1 ( <b>M7677</b> ), MKK2	MKK4 ( <b>M1689</b> ), MKK7 ( <b>M1814</b> )	MKK3, MKK6 ( <b>M5814</b> )
<b>DOWNSTREAM ACTIVATION</b>	MAPKAP-K1, MNK, MSK MBP ( <b>M1891</b> , <b>M2016</b> , <b>M2295</b> )	c-Jun ( <b>C5859</b> , <b>C9733</b> ), ATF2	MAPKAP-K2/3, PRAK ( <b>P0240</b> ) MNK, MSK, MBP ( <b>M1891</b> , <b>M2016</b> , <b>M2295</b> )
<b>ACTIVATORS</b>	Mitogens, cytokines	Cellular stress, cytokines some mitogens	Cellular stress, cytokines
<b>INHIBITORS</b>	PD 098059 ( <b>P215</b> )*, U0126 ( <b>U120</b> )*, PD 184352*	TAT-JBD peptide	SB-203580 ( <b>S8307</b> ), SB-202190 ( <b>S7067</b> ) BIRB8796
<b>SELECTIVE ACTIVATORS</b>	Not known	Not known	Not known
<b>PHYSIOLOGICAL FUNCTION</b>	Immune function, neuronal signaling, differentiation, cell survival	Immune function, differentiation, apoptosis	Immune function, differentiation, apoptosis
<b>DISEASE RELEVANCE</b>	Cancer	Inflammation	Inflammation

## FOOTNOTES

\* Inhibits upstream activator.

## MAPKs

<b>FAMILY MEMBERS</b>	p38 $\gamma$ / $\delta$	ERK3	ERK5
<b>OTHER NAMES</b>	SAPK3, SAPK4	—	BMK
<b>MOLECULAR WEIGHT/ STRUCTURAL DATA</b>	43 kDa	83 kDa	89 kDa
<b>ISOFORMS</b>	p38 $\gamma$ , p38 $\delta$	ERK3, ERK3 related	Not known
<b>SPECIES</b>	Vertebrates	Vertebrates	Vertebrates, possible homologs in yeast and <i>C. elegans</i>
<b>DOMAIN ORGANIZATION</b>	1 kinase domain	1 kinase domain	1 kinase domain
<b>PHOSPHORYLATION SITES</b>	p38 $\gamma$ : Thr <sup>184</sup> , Tyr <sup>186</sup> p38 $\delta$ : Thr <sup>180</sup> , Tyr <sup>18</sup>	Ser <sup>189</sup>	Thr <sup>219</sup> , Tyr <sup>221</sup>
<b>TISSUE DISTRIBUTION</b>	Low expression in most tissues, p38 $\gamma$ high levels in skeletal muscle, p38 $\delta$ highest in adrenal and pituitary	Ubiquitous	Ubiquitous
<b>SUBCELLULAR LOCALIZATION</b>	Cytosolic	Nuclear	Cytosolic, nuclear
<b>BINDING PARTNERS/ ASSOCIATED PROTEINS</b>	Not known	Not known	Not known
<b>UPSTREAM ACTIVATORS</b>	MKK6 ( <b>M5814</b> )	Not known	MKK5
<b>DOWNSTREAM ACTIVATION</b>	MBP ( <b>M1891</b> , <b>M2016</b> , <b>M2295</b> )	Not known	MBP ( <b>M1891</b> , <b>M2016</b> , <b>M2295</b> )
<b>ACTIVATORS</b>	Cellular stress	Not known	EGF ( <b>E4127</b> , <b>E9644</b> ), oxidative and osmotic stress
<b>INHIBITORS</b>	Not known	Not known	PD 098059 ( <b>P215</b> )*, U0126 ( <b>U120</b> )*, PD 184352*
<b>SELECTIVE ACTIVATORS</b>	Not known	Not known	Not known
<b>PHYSIOLOGICAL FUNCTION</b>	Not known	Not known	Required for endothelial cell survival
<b>DISEASE RELEVANCE</b>	Not known	Not known	Cancer

### FOOTNOTES

\* Inhibits upstream activator.

# MAPKs

<b>FAMILY MEMBERS</b>	ERK8/ ERK7	NLK
<b>OTHER NAMES</b>	—	—
<b>MOLECULAR WEIGHT/ STRUCTURAL DATA</b>	60 kDa	57 kDa
<b>ISOFORMS</b>	Not known	Not known
<b>SPECIES</b>	Vertebrates	<i>C. elegans</i> , <i>Drosophila</i> , vertebrates
<b>DOMAIN ORGANIZATION</b>	1 kinase domain	1 kinase domain
<b>PHOSPHORYLATION SITES</b>	Not known	Not known
<b>TISSUE DISTRIBUTION</b>	Low expression in most tissues, high levels in testis	Placenta, uterus
<b>SUBCELLULAR LOCALIZATION</b>	Cytosolic, nuclear	Nuclear
<b>BINDING PARTNERS/ ASSOCIATED PROTEINS</b>	Not known	Not known
<b>UPSTREAM ACTIVATORS</b>	Not known	HIPK2
<b>DOWNSTREAM ACTIVATION</b>	MBP (M1891, M2016, M2295)	Lef1 c-Myb
<b>ACTIVATORS</b>	Not known	wnt, TGFβ (T7039, T2815, T2926)
<b>INHIBITORS</b>	Not known	Not known
<b>SELECTIVE ACTIVATORS</b>	Not known	Not known
<b>PHYSIOLOGICAL FUNCTION</b>	Not known	Embryogenesis, mesoderm formation
<b>DISEASE RELEVANCE</b>	Not known	Not known

## Abbreviations

**ERK:** Extracellular signal-related kinase

**JNK:** c-Jun NH(2)-terminal protein kinase

**MAPKAP:** MAPK-activated protein

**MBP:** Myelin basic protein

**MNK:** MAPK-integrating kinase

**MSK:** Mitogen and stress activated protein kinase

**PD 098059:** 2-(2-Amino-3-methoxyphenyl)-4H-1-benzopyran-4-one

**PD 184352:** 2-(2-Chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluorobenzamide

**PRAK:** p38-Regulated activated kinase

**RSK:** Ribosomal S6 kinase

**SAPK:** Stress activated protein kinase

**SB-203580:** 4-(4-Fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)1H-imidazole

**SB-202190:** 4-(4-Fluorophenyl)-2-(4-hydroxyphenyl)-5-(4-pyridyl)1H-imidazole

**U0126:** 1,4-Diamino-2,3-dicyano-1,4-bis(o-aminophenylmercapto)butadien

## FOOTNOTES