

# MAPKAPs

## Key References

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## Overview

Several protein kinases are activated by the MAPK family members p38 $\alpha$  (SAPK2a) and ERKs 1 and 2. The MAPKAP kinases can be subdivided into two groups; those comprising two kinase domains in a single polypeptide, and those with a single kinase domain. Both groups contain a C-terminal docking site that interacts with the activator, thereby permitting phosphorylation and activation of the MAPKAP kinases.

The two kinase domain enzymes are RSK (also called p90 Rsk), and mitogen and stress activated protein kinase (MSK). The N-terminal kinase domain of these proteins belongs to the AGC family, while the C-terminal domain is more closely related to the calmodulin dependent protein kinase family. The activation of RSK is complex and requires activation of the C-terminal kinase domain by ERK1/ERK2, which then phosphorylates a residue in the linker region between the two kinase domains. This phosphorylation event, together with the ERK1/ERK2-catalyzed phosphorylation of another site in the linker region, then activates the N-terminal domain, provided that a further site in the activation loop of the N-terminal domain has been phosphorylated by 3-phosphoinositide-dependent protein kinase-1 (PDK1). The N-terminal kinase domain then catalyzes the phosphorylation of exogenous substrates.

There are four mammalian homologs of RSK, which are activated by ERK1/ERK2. RSK is implicated in the regulation of several processes including cell survival, gene transcription and the control of meiosis. Mutations in the human RSK2 isoform is linked to Coffin-Lowry syndrome, a disease associated with mental retardation and growth defects.

As implied by its name, MSK can be activated by either ERK1/ERK2 in response to mitogens and growth factors or by p38 $\alpha$  following exposure to cellular stresses or proinflammatory cytokines. Its N-terminal kinase domain is 54% identical and its C-terminal kinase domain is 44% identical to the corresponding domains of RSK. All the phosphorylation sites in RSK are conserved in MSK, suggesting an analogous mechanism of activation. However, in contrast to RSK, PDK1 is not required for the activation of MSK, and phosphorylation of the activation loop of the N-terminal kinase domain is catalyzed by the C-terminal kinase domain of MSK. There are two isoforms of MSK in mammalian cells, termed MSK1 and MSK2. The MSKs are localized to the nucleus and their substrates include the transcription factors CREB and ATF1 and the chromatin proteins histone H3 and HMG-14. The *Drosophila* kinase JIL-1, an MSK1 homolog, has been localized to decondensed regions of chromosomes, suggesting a role in transcriptional regulation.

The MAPKAP kinases comprising a single kinase domain are members of the calmodulin dependent protein kinase family and are MAPKAP-K2, MAPKAP-K3, PRAK (also called MAPKAP-K5) and MAPK-integrating kinase (MNK). MAPKAP-K2 and MAPKAP-K3 are activated by p38 $\alpha$  *in vivo* and their physiological substrates include heat shock protein (HSP) 27 and hnRNPA0. The phosphorylation of HSP27 stimulates actin polymerization and is thought to help repair the actin microfilament network that becomes disrupted when cells are stressed, thereby aiding cell survival. MAPKAP-K2 is also involved in controlling production of the proinflammatory cytokines, tumor necrosis factor, interleukin 6 and interferon

$\gamma$ , at a post-transcriptional level. This may result from the ability of MAPKAP-K2 to regulate the stability and/or translation of the mRNAs containing AU rich regions via the phosphorylation of RNA binding proteins such as hnRNPA0. MAPKAP-K2 knockout mice show decreases in TNF and IL-6 production and increases in survival in models of endotoxic shock. PRAK is also activated *in vitro* by p38 $\alpha$ , however *in vivo* it is most likely activated by ERK3. The physiological role of PRAK is still unclear.

Two isoforms of MNK (MNK1 and MNK2) have been found in mammalian cells. Like the MSK isoforms, MNK1 can be activated by either ERK1/ERK2 or p38 $\alpha$ . However, MNK2 appears to be activated preferentially by ERK1/ERK2. One substrate of MNK1 is the eukaryotic translation initiation factor 4E (eIF4E). Phosphorylation of this protein increases its affinity for the 5' cap of the mRNA, thereby promoting translation. MNKs may also be involved in the production of TNF in the immune system.

## MAPKAPs

<b>FAMILY MEMBERS</b>	RSK	MSK	MAPKAP-K2
<b>OTHER NAMES</b>	MAPKAP-K1, p90Rsk	RSK-B	MK2
<b>MOLECULAR WEIGHT (APPROX)/ STRUCTURAL DATA</b>	83 kDa	87-90 kDa	42 kDa
<b>ISOFORMS</b>	RSK1 (MAPKAP-K1a) RSK2 (MAPKAP-K1b) RSK3 (MAPKAP-K1c) RSK4 (MAPKAP-K1d)	MSK1 MSK2	Not known
<b>SPECIES</b>	<i>C. elegans</i> , <i>Drosophila</i> , Vertebrates	Vertebrates	<i>C. elegans</i> , <i>Drosophila</i> , vertebrates
<b>DOMAIN ORGANIZATION</b>	2 kinase domains	2 kinase domains	1 kinase domain
<b>PHOSPHORYLATION SITES</b>	RSK1, Ser <sup>221</sup> , Thr <sup>369</sup> , Ser <sup>363</sup> , Ser <sup>380</sup> , Thr <sup>573</sup> , Ser <sup>749</sup> , RSK2, Ser <sup>227</sup> , Thr <sup>365</sup> , Ser <sup>369</sup> , Ser <sup>386</sup> , Thr <sup>577</sup> , (Ser <sup>736?</sup> ), RSK3, Ser <sup>218</sup> , Ser <sup>356</sup> , Ser <sup>360</sup> , Ser <sup>386</sup> , Thr <sup>570</sup> , (Ser <sup>729?</sup> ), RSK4, Ser <sup>232</sup> , Thr <sup>368</sup> , Ser <sup>372</sup> , Ser <sup>389</sup> , Thr <sup>581</sup> , (Ser <sup>742?</sup> )	MSK1, Ser <sup>212</sup> , Ser <sup>360</sup> , Ser <sup>376</sup> , Ser <sup>381</sup> , Thr <sup>581</sup> , Ser <sup>752</sup> , Ser <sup>758</sup> , MSK2, Ser <sup>196</sup> , Ser <sup>343</sup> , Ser <sup>347</sup> , Ser <sup>360</sup> , Thr <sup>568</sup>	Thr <sup>25</sup> , Thr <sup>222</sup> , Ser <sup>272</sup> , Thr <sup>334</sup> , Thr <sup>338</sup>
<b>TISSUE DISTRIBUTION</b>	Ubiquitous	Ubiquitous	Ubiquitous
<b>SUBCELLULAR LOCALIZATION</b>	Cytosolic, nuclear	Nuclear	Cytosolic, nuclear
<b>BINDING PARTNERS/ ASSOCIATED PROTEINS</b>	CBP, ERK1/2	Not known	p38
<b>UPSTREAM ACTIVATORS</b>	ERK1/2	ERK1/2, p38	p38
<b>DOWNSTREAM ACTIVATION</b>	GSK3 ( <b>G1663</b> ), BAD ( <b>B1682</b> ), LKB1, Nur77, c-fos, SRF	CREB, ATF1, histone H3, HMG-14	HSP27 ( <b>H8158</b> ), Tyrosine hydroxylase, hnRNPA0, E47
<b>ACTIVATORS</b>	Mitogens, cytokines	Mitocellular stress genes, cytokines, cellular stress	Cellular stress, cytokines
<b>INHIBITORS</b>	Ro 31 8220 ( <b>R136</b> ), H89	Ro 31 8220 ( <b>R136</b> ), H89	Not known
<b>SELECTIVE ACTIVATORS</b>	Not known	Not known	Not known
<b>PHYSIOLOGICAL FUNCTION</b>	Transcription regulation, cell survival	Transcription regulation, regulation of RNA stability	Transcription regulation
<b>DISEASE RELEVANCE</b>	Coffin-Lowry syndrome	Not known	Inflammation

## FOOTNOTES

# MAPKAPs

<b>FAMILY MEMBERS</b>	MAPKAP-K3	MAPKAP-K5	MNK
<b>OTHER NAMES</b>	3pK	PRAK	—
<b>MOLECULAR WEIGHT/ STRUCTURAL DATA</b>	42 kDa	54 kDa	46-48 kDa
<b>ISOFORMS</b>	Not known	Not known	MNK1 MNK2
<b>SPECIES</b>	Vertebrates	Vertebrates	Vertebrates
<b>DOMAIN ORGANIZATION</b>	1 kinase domain	1 kinase domain	1 kinase domain
<b>PHOSPHORYLATION SITES</b>	Thr <sup>201</sup> , Ser <sup>251</sup> , Thr <sup>313</sup> , Thr <sup>317</sup>	Thr <sup>182</sup>	MNK1 Thr <sup>197</sup> , Thr <sup>202</sup> (Ser <sup>332</sup> ?) MNK2 Thr <sup>197</sup> , Thr <sup>202</sup> (Ser <sup>332</sup> ?) Ser <sup>27</sup> , Ser <sup>384</sup> , Ser <sup>387</sup> , Ser <sup>399</sup> , Thr <sup>403</sup>
<b>TISSUE DISTRIBUTION</b>	Ubiquitous	Ubiquitous	Ubiquitous
<b>SUBCELLULAR LOCALIZATION</b>	Cytosolic, nuclear	Cytosolic, nuclear	Cytosolic
<b>BINDING PARTNERS/ ASSOCIATED PROTEINS</b>	p38 (M8057)	ERK3	Not found
<b>UPSTREAM ACTIVATORS</b>	p38 (M8057)	ERK3	ERK1/2, p38 (MNK1)
<b>DOWNSTREAM ACTIVATION</b>	HSP27 (H8158)	Not known	eIF4E
<b>ACTIVATORS</b>	Cellular stress, cytokines	Not known	Mitogens, cytokines
<b>INHIBITORS</b>	Not known	Not known	Not known
<b>SELECTIVE ACTIVATORS</b>	Not known	Not known	Not known
<b>PHYSIOLOGICAL FUNCTION</b>	Not known	Not known	Regulation of translation
<b>DISEASE RELEVANCE</b>	Not known	Not known	Not known

## Abbreviations

**BAD:** Bcl2-Associated death promoter  
**CREB:** cAMP Responsive element binding protein  
**ERK:** Extracellular signal-related kinase  
**GSK 3:** Glycogen synthase kinase-3  
**HSP 27:** Heat shock protein  
**LKB1:** Peutz-Jeghers gene  
**MAPK:** Mitogen activated protein kinase  
**MAPKAP:** MAPK-activated protein  
**MNK:** MAPK-integrating kinase  
**MSK:** Mitogen and stress activated protein kinase  
**PRAK:** p38-Regulated activated kinase  
**RSK:** Ribosomal S6 kinase  
**SAPK:** Stress activated protein kinase  
**SRF:** Serum response factor

## FOOTNOTES

\*These are well described functions for these kinases, however they may have other physiological functions in addition to these.