

MAPKKKs

Key References

- Chadee, D.N. and Kyriakis, J.M., MLK3 is required for mitogen activation of B-Raf, ERK and cell proliferation., *Nat. Cell. Biol.*, **6**, 770-776 (2004).
- Chen, Z and Cobb, M.H., Regulation of stress-responsive mitogen-activated protein kinase pathways by TAO2., *J. Biol. Chem.*, **276**, 16070-16075 (2001).
- Gallo, K.A. and Johnson, G.L., Mixed-lineage kinase control of JNK and p38 MAPK pathways., *Nat. Rev. Mol. Cell. Biol.*, **3**, 663-672 (2002).
- Hagemann, C. and Blank, J.L., The ups and downs of MEK kinase interactions., *Cell. Signal.*, **13**, 863-875 (2001).
- Kyriakis, J.M. and Avruch, J., Mammalian mitogen-activated protein kinase signal transduction pathways activated by stress and inflammation., *Physiol. Rev.*, **81**, 807-869 (2001).
- Lu, Z., et al., The PHD domain of MEKK1 acts as an E3 ubiquitin ligase and mediates ubiquitination and degradation of ERK1/2., *Mol. Cell.*, **9**, 945-956 (2002).
- Morrison, D.K. and Davis, R.J., Regulation of MAP kinase signaling modules by scaffold proteins in mammals., *Annu. Rev. Cell. Dev. Biol.*, **19**, 91-118.
- O'Neill, E. and Kolch, W., Conferring specificity on the ubiquitous Raf/Mek signaling pathway., *Br. J. Cancer*, **90**, 283-288 (2004).
- Takeda, K., et al., Roles of MAPKKK ASK1 in stress-induced cell death., *Cell. Struct. Funct.*, **28**, 23-29 (2003).
- Tunquist, B.J. and Maller, J.L., Under arrest: cytostatic factor (CSF)-mediated metaphase arrest in vertebrate eggs., *Genes. Dev.*, **17**, 683-710 (2003).
- Wang, C., et al., TAK1 is a ubiquitin-dependent kinase of MKK and IKK., *Nature*, **412**, 346-351 (2001).
- Wellbrock, C., et al., The Raf proteins take centre stage., *Nat. Rev. Mol. Cell. Biol.*, **5**, 875-885 (2004).

Overview

Mitogen-activated protein kinase (MAPK) signaling pathways mediate cellular responses to many stimuli including growth factors, hormones, cytokines and environmental stresses. MAPK pathways can be divided into those that predominantly respond to mitogens and those that predominantly respond to stress. The extra cellular signal regulated kinase (ERK1 and ERK2) pathways are activated by mitogens and play an important role in controlling cell growth and differentiation. The stress-activated MAPK pathways include the c-Jun N-terminal kinase (JNK) and p38 pathways that are implicated in apoptosis and the immune response. The ERK5 MAPK pathway responds to both growth signals and certain stresses. All MAPK pathways feature a three-kinase cascade whereby MAPKs are activated by phosphorylation by a MAPK kinase (MKK or MEK) and MKKs are activated by serine/threonine phosphorylation by MAPK kinase kinases (MAPKKK or MAP3K).

The MAP3K group consists of a large diverse group of protein kinases with overlapping specificities for MKKs. They include members of the RAF, MEKK (MEK kinase), MLK (mixed lineage kinase), and TAO (thousand and one amino acid) families and the protein kinases MOS, ASK1 (apoptosis signal-regulating kinase-1), TAK1 (TGF β -activated kinase-1) and TPL2 (tumor progression locus-2). The activities of MAP3Ks can be regulated by a number of mechanisms including phosphorylation, interaction with small GTPases, proteolysis, and binding to regulatory or scaffold proteins.

The RAF family are components of ERK signaling pathways and phosphorylate the highly related MEK1 and MEK2. RAF proteins are activated by their recruitment to Ras GTPase at membranes and by phos-

phorylation at regulatory sites. Mutations in RAF, particularly B-RAF, are associated with human cancers. A second MAP3K that is specific for the ERK pathway is MOS which is primarily expressed in germline cells and is implicated in oocyte maturation. The TPL2 MAP3K activates the ERK pathway and plays an important role in the innate immune response.

The MEKK and MLK families of MAP3Ks and the less well characterized TAO family are components of stress-activated MAPK pathways. The MEKK and MLK families can be activated by Rho-family GTPases and STE20-like protein kinases. MEKK1 can also be activated by proteolysis following apoptotic stimuli. Caspases cleave MEKK1 to release the catalytically active C-terminus that is highly pro-apoptotic. While predominantly involved in stress-signaling some members of these families can function as regulators of ERK pathways. For example MEKK2 and MEKK3 are components of the ERK5 cascade, MEKK1 can function as a ubiquitin ligase and cause degradation of ERK1/2, and MLK3 has recently been suggested to be required for B-RAF signaling to ERK1/2.

Additional MAP3Ks that are components of JNK and p38 signaling pathways include ASK1 and TAK1. These MAP3Ks have distinct mechanisms of activation. ASK1 mediates apoptosis induced by oxidative stress and is activated by dissociation from a redox-sensitive inhibitory protein, thioredoxin. TAK1 is activated by TGF β and cytokines via a mechanism dependent on the ubiquitination of an associated protein, TRAF6.

In addition to their central roles in MAPK signaling some MAP3Ks are components

of other signaling pathways. For example C-RAF, MEKKs and TAK1 can activate the NF- κ B signaling pathway independently of MAPKs. Also, a MAP3K related kinase NIK (NF- κ B inducing kinase) is a component of NF- κ B signalling pathways but has no reported role in MAPK signalling.

The large body of literature on MAPK pathways suggests that there is a high level of promiscuity at the level of MAP3Ks. However it is becoming clear from gene-deletion studies in mice and lower eukaryotes that individual MAP3Ks have distinct cellular roles. One important regulatory mechanism for achieving specificity is by scaffold proteins linking particular MAP3Ks to particular MAPK modules in response to a stimulus.

MAPKKKs

| FAMILY MEMBERS | RAF | MOS | MEKK |
|--|---|--|--|
| OTHER NAMES | Proto-oncogene serine-threonine protein kinase | Proto-oncogene serine-threonine protein kinase | Mitogen-activated protein kinase kinase kinase; MAP3K |
| MOLECULAR WEIGHT/ STRUCTURAL DATA | 67 – 85 kDa | 39 kDa | 69 – 182 kDa |
| ISOFORMS | A-RAF B-RAF C-RAF (RAF1) | Not known | MEKK1 (MAP3K1) (M6939) MEKK2 (MAP3K2) MEKK3 (MAP3K3) MEKK4 (MTK1, MAP3K4) |
| SPECIES | Vertebrate, fly, worm | Vertebrate, fly | Vertebrate, fly, worm, yeast |
| DOMAIN ORGANIZATION | Ser/Thr-protein kinase domain, Cys-rich domain, Ubiquitin-like domain, Ras-binding domain | Ser/Thr-protein kinase domain | Ser/Thr-protein kinase domain, Ring-ZF domain, Ras-binding domain, (MEKK1, (M6939), PH-domain (MEKK1, MEKK4), CRIB (MEKK4) |
| PHOSPHORYLATION SITES | Ser ²¹⁴ , Ser ²⁹⁹ , Tyr ³⁰² , Thr ⁴⁵² , Thr ⁴⁵⁵ , Ser ⁵⁸² (A-RAF). Ser ³⁶⁴ , Ser ⁴⁴⁵ , Thr ⁵⁹⁸ , Ser ⁶⁰¹ , Ser ⁷²⁸ (B-RAF). Ser ⁴³ , Ser ²³³ , Ser ²⁵⁹ , Ser ³³⁸ , Tyr ³⁴¹ , Thr ⁴⁹¹ , Ser ⁴⁹⁴ , Ser ⁶²¹ (C-RAF) | Ser ³ | Thr ¹³⁸³ , Thr ¹³⁹⁵ (MEKK1) Thr ⁵²³ (MEKK2) Thr ⁵³⁰ (MEKK3) Thr ¹⁵⁰⁴ (MEKK4) |
| TISSUE DISTRIBUTION | Ubiquitous | Germ cells | Ubiquitous |
| SUBCELLULAR LOCALIZATION | Cytosol | Cytosol | Cytosol |
| BINDING PARTNERS/ ASSOCIATED PROTEINS | KSR1, 2, RKIP, CNK, BAG1 SUR8, Paxillin, 14-3-3 | Not known | LAD (L3151), OSM (O1637 , O9635), JLP, Mip1 (M6167 , M6292 , M6542 , M6417) GADD45, JSAP1, TRAFs, 14-3-3, JNKBP1 |
| UPSTREAM ACTIVATORS | RAS (R9894), RAP1 (R2152), PAK | CDC2-cyclin B (C0484) | RAS, RAC1, HPK1, CDC42, GCK, RIP (T1569) |
| DOWNSTREAM ACTIVATION | MEK1 (M8568), MEK2 | MEK1, 2; Myt1, MyoD | MEK1 (M8568), MEK2; MKK3, MKK4 (M1689), MKK5, MKK6 (M5814), MKK7 (M1814); IKK |
| ACTIVATORS | Growth factors | Progesterone (P9776 , P3972), growth factors | Stress, cytokines, growth factors |
| INHIBITORS | BAY-43-9006 | Not known | Not known |
| SELECTIVE ACTIVATORS | Not known | Not known | Not known |
| PHYSIOLOGICAL FUNCTION | Cell growth | Oocyte maturation | Stress responses, development |
| DISEASE RELEVANCE | Cancer (B-RAF) | Not known | Not known |

FOOTNOTES

MAPKKs

| | | | |
|--|---|--|--|
| FAMILY MEMBERS | MLK | TAO (323179) | ASK |
| OTHER NAMES | Mitogen lineage kinase | PSK, JIK, KFC | — |
| MOLECULAR WEIGHT/ STRUCTURAL DATA | 91 – 122 kDa | 105 – 138 kDa | 112 – 155 kDa |
| ISOFORMS | MLK1 (MAP3K9) MLK2 (MST, MAP3K10) MLK3 (SPRK, PTK1, MAP3K11) MLK4 MLK7 (ZAK, MRK, MLTK) DLK (MUK, ZPK, MAP3K12) LZK (MAP3K13) | TAO1 (PSK2, KFC-B, MARRK) TAO2 (PSK1, KFC-C) TAO3 (JIK, KFC-A) | ASK1 (MAPKKK5, MAP3K5) ASK2 (MAPKKK6, MAP3K6) |
| SPECIES | Vertebrate, fly, worm | Vertebrate, fly, worm | Vertebrate, fly, worm |
| DOMAIN ORGANIZATION | Ser/Thr-protein kinase domain, Leucine-zippers domain, SH3 domain, CRIB domain (MLK1-4), SAM domain (MLK7) | Ser/Thr-protein kinase domain | Ser/Thr-protein kinase domain |
| PHOSPHORYLATION SITES | Thr ²⁷⁷ , Ser ²⁸¹ + 11 C-terminal sites (MLK3) | Not known | Ser ⁸³ , Thr ⁸³⁸ (ASK1) |
| TISSUE DISTRIBUTION | Ubiquitous | Ubiquitous | Ubiquitous |
| SUBCELLULAR LOCALIZATION | Cytosol | Cytosol | Cytosol |
| BINDING PARTNERS/ ASSOCIATED PROTEINS | JIP1 (J2270), JIP2, JIP3, MBIP, POSH, 14-3-3 | Tubulin | β-Arrestin-2, TRAF2, CDC25A, Thioredoxin (T0910 , T3658), AIP1, SKRP1, Daxx, Nef, 14-3-3, JIP3 |
| UPSTREAM ACTIVATORS | RAC1, CDC42, HPK1, PAK | Not known | CaMKII, IRE1 |
| DOWNSTREAM ACTIVATION | MKK3, MKK4 (M1689), MKK6 (M5814), MKK7 (M1814) | MKK3, MKK4 (M1689), MKK6 (M5814), MKK7 (M1814) | MKK3, MKK4 (M1689), MKK6 (M5814), MKK7 (M1814) |
| ACTIVATORS | Stress, cytokines, growth factors | Carbachol, osmotic stress | Stress, calcium |
| INHIBITORS | CEP-1347 | Not known | Not known |
| SELECTIVE ACTIVATORS | Not known | Not known | Not known |
| PHYSIOLOGICAL FUNCTION | Stress responses, development neuronal apoptosis | Stress responses | Stress responses, neuronal apoptosis heart function |
| DISEASE RELEVANCE | Not known | Not known | Not known |

FOOTNOTES

MAPKKs

| | | |
|--|---|---|
| FAMILY MEMBERS | TAK1 | TPL-2 |
| OTHER NAMES | MAP3K7 | COT, MAP3K8 |
| MOLECULAR WEIGHT/ STRUCTURAL DATA | 67 kDa | 58 kDa |
| ISOFORMS | Not known | Not known |
| SPECIES | Vertebrate, fly, worm | Vertebrate |
| DOMAIN ORGANIZATION | Ser/Thr-protein kinase | Ser/Thr-protein kinase |
| PHOSPHORYLATION SITES | Thr ¹⁸⁷ , Ser ¹⁹² | Thr ²⁹⁰ , Ser ⁴⁰⁰ |
| TISSUE DISTRIBUTION | Ubiquitous | Ubiquitous |
| SUBCELLULAR LOCALIZATION | Cytosol | Cytosol |
| BINDING PARTNERS/ ASSOCIATED PROTEINS | TAB1, 2, 3; SMAD3, TRAF6, SEF, RKIP | NF-κB1/p105, AKT (A8729 , A9729 , A9104), KSR2, ABIN-2, TRAF2 |
| UPSTREAM ACTIVATORS | K63-polyubiquitination | Not known |
| DOWNSTREAM ACTIVATION | MKK3, MKK4 (M1689), MKK6 (M5814), IKK, HIPK2 | MEK1 (M8568), MEK2; MKK4 (M1689), MKK5, MKK6 (M5814), NIK |
| ACTIVATORS | Stress, cytokines, Wnt, TGF-β | Cytokines, LPS (L2630) |
| INHIBITORS | Not known | Not known |
| SELECTIVE ACTIVATORS | Not known | Not known |
| PHYSIOLOGICAL FUNCTION | Stress responses | Inflammation response |
| DISEASE RELEVANCE | Not known | T-cell lymphoma |

FOOTNOTES