## Phylogeny

MAP3K1 (MEKK1) is a serine/threonine protein kinase classified within the MEKK family of mitogen-activated protein kinase kinase kinases (MAPKKKs) and the STE superfamily (hagemann2001theupsand pages 1-3, pham2013map3k1genomicalterations pages 1-3). According to the kinase motif tree from Johnson et al. 2023, MEKK1 is in the MAP3K group (johnson2023anatlasof pages 4-5). This aligns with the Manning et al. 2002 classification (charlaftis2014themekk1 pages 15-17, suddason2015aringto pages 6-8). Within its family, MEKK1 clusters closely with MEKK2 and MEKK3 (craig2008map3ksascentral pages 1-2). MAP3K1 is highly conserved, with orthologs across species including yeast and mammals (yan1994activationofstressactivated pages 1-1, craig2008map3ksascentral pages 1-2). It is a homolog of *Saccharomyces cerevisiae* kinases Ste11p and Byr2p (hagemann2001theupsand pages 1-3, suddason2015aringto pages 1-2, yan1994activationofstressactivated pages 1-1). Despite homology, MAP3K1 cannot complement the function of Ste11 in yeast (suddason2015aringto pages 1-2).

## Reaction Catalyzed

As a kinase, MAP3K1 catalyzes the ATP-dependent transfer of the gamma-phosphate from ATP to the hydroxyl group of specific serine or threonine residues on substrate proteins (charlaftis2014themekk1 pages 15-17, hagemann2001theupsand pages 5-6, craig2008map3ksascentral pages 1-2). Through its E3 ubiquitin ligase activity, it also catalyzes the transfer of ubiquitin to substrate proteins, mediating both Lys48-linked polyubiquitination for proteasomal degradation and Lys63-linked polyubiquitination for signaling regulation (charlaftis2014themekk1 pages 1-2, suddason2015aringto pages 6-8). The ubiquitination reaction requires an E1 activating enzyme and an E2 conjugating enzyme, such as UBE2N (charlaftis2014themekk1 pages 1-2).

## Cofactor Requirements

The kinase catalytic activity is ATP-dependent (yan1994activationofstressactivated pages 1-1, charlaftis2014themekk1 pages 15-17). The phosphotransferase reaction is facilitated by Mg²⁺ as a cofactor (suddason2015aringto pages 6-8).

## Substrate Specificity

MAP3K1 recognizes substrate motifs often characterized by a proline-directed context (S/T-P motifs) (charlaftis2014themekk1 pages 15-17, craig2008map3ksascentral pages 1-2). Experimental profiling places MAP3K1 in motif cluster 14, which shows selectivity for amino acid residues at positions P-3 to P+4 surrounding the phosphorylation site (johnson2023anatlasof pages 2-3). Like other MAP3Ks, it displays context-dependent selectivity, and the presence of a DFG+1 alanine residue favors threonine phosphorylation (johnson2023anatlasof pages 2-3).

## Structure

MAP3K1 is a large, multi-domain protein of ~1500 amino acids (wang2021geneticcontrolof pages 1-2). AlphaFold predictions visualize the spatial arrangement of its domains, with a central kinase domain and flanking regulatory domains (gehi2022intrinsicdisorderin pages 15-17). Its domain organization includes: - **C-terminal Kinase Domain (KD)**: Responsible for phosphorylating MAP2Ks (hagemann2001theupsand pages 3-5, wang2021geneticcontrolof pages 1-2). AlphaFold models show this domain contains a C-helix positioned for ATP interaction, a hydrophobic spine that stabilizes the active conformation, and an activation loop whose phosphorylation state modulates activity (gehi2022intrinsicdisorderin pages 15-17, wang2021geneticcontrolof pages 2-4). - **N-terminal Regulatory Region**: Contains multiple domains mediating protein-protein interactions and localization, including proline-rich sequences, a Ras-binding domain, and putative pleckstrin-homology (PH) domains (hagemann2001theupsand pages 3-5). - **RING/PHD Domain**: A RING finger domain (residues 443-492) containing a Plant Homeodomain (PHD) motif that functions as an E3 ubiquitin ligase (suddason2015aringto pages 1-2, pham2013map3k1genomicalterations pages 3-4, gehi2022intrinsicdisorderin pages 15-17, wang2021geneticcontrolof pages 1-2). - **SWIM Domain**: A zinc-chelating domain (residues 338-366) that binds c-Jun, acting as a substrate receptor for ubiquitination (pham2013map3k1genomicalterations pages 3-4, pham2013map3k1genomicalterations pages 7-8, wang2021geneticcontrolof pages 1-2). - **Additional Domains**: Includes a DEVD sequence targeted by caspase-3, an N-terminal Guanine Exchange Factor (GEF) domain interacting with RAC/RHOA, and a TOG domain that binds tubulin (wang2021geneticcontrolof pages 1-2).

## Regulation

MAP3K1 activity is controlled through multiple mechanisms including post-translational modifications, proteolytic cleavage, and protein-protein interactions. - **Phosphorylation**: Catalytic activity requires phosphorylation (hagemann2001theupsand pages 10-11). Upstream kinases include PKC isoforms and c-Abl (hagemann2001theupsand pages 10-11, pham2013map3k1genomicalterations pages 7-8). It also undergoes trans-autophosphorylation following oligomerization (pham2013map3k1genomicalterations pages 1-3). Specific autophosphorylation sites S67 and T1381 are involved in activation (charlaftis2014themekk1 pages 1-2). - **Ubiquitination**: The PHD/RING domain mediates auto-ubiquitination, which can inhibit downstream signaling to ERK1/2 and JNK pathways without leading to its own degradation (pham2013map3k1genomicalterations pages 3-4, charlaftis2014themekk1 pages 15-17). The PHD domain facilitates non-degradative, lysine-63-linked polyubiquitination crucial for signaling complex regulation (charlaftis2014themekk1 pages 15-17). - **Cleavage**: Caspase-3 cleaves MAP3K1 at a conserved DEVD site (D878 in human) upstream of the kinase domain (hagemann2001theupsand pages 6-7, pham2013map3k1genomicalterations pages 3-4, wang2021geneticcontrolof pages 1-2). This cleavage releases an active C-terminal kinase fragment that promotes apoptosis (pham2013map3k1genomicalterations pages 1-3, wang2021geneticcontrolof pages 1-2). - **Other Modifications**: Glutathionylation at C1238 inhibits kinase activity, indicating redox regulation (wang2021geneticcontrolof pages 2-4). - **Allosteric/Conformational Regulation**: An intramolecular interaction between the N-terminal regulatory domain and the C-terminal kinase domain can inhibit activity, a mechanism relieved by phosphorylation (hagemann2001theupsand pages 10-11). Binding to small G-proteins (Ras, Rac, Cdc42) also modulates its function (hagemann2001theupsand pages 8-10, pham2013map3k1genomicalterations pages 3-4).

## Function

MAP3K1 functions as both a kinase and a scaffold protein, integrating signals to regulate cell fate decisions such as apoptosis, survival, and migration (hagemann2001theupsand pages 8-10, pham2013map3k1genomicalterations pages 1-3). - **Expression Patterns**: In mice, MAP3K1 is highly expressed in the brain, glands, sensory organs (including inner ear cell types), and skin, with lower levels in the heart, liver, ovary, and testis (wang2021geneticcontrolof pages 2-4). It is also expressed in embryonic stem cells, fibroblasts, keratinocytes, cardiac myocytes, and immune cells, including B-cells and T-cells (suddason2015aringto pages 3-4, suddason2015aringto pages 4-5). - **Signaling Pathways**: MAP3K1 activates the JNK, p38, ERK, and NF-κB pathways (hagemann2001theupsand pages 6-7, suddason2015aringto pages 1-2). It is activated downstream of cytokine receptors (TNF-α, IL-1, TGF-β), growth factors (EGF), and stress stimuli (hagemann2001theupsand pages 6-7, hagemann2001theupsand pages 8-10, suddason2015aringto pages 1-2). Upstream adaptors include TRAF2, TRAF6, and TRADD (hagemann2001theupsand pages 6-7, hagemann2001theupsand pages 8-10). - **Downstream Targets & Interactors**: Kinase substrates include MAP2Ks (MKK4, MKK7, MEK1) and the IKK complex (IKKα/β) (hagemann2001theupsand pages 3-5, hagemann2001theupsand pages 6-7, suddason2015aringto pages 1-2). Ubiquitin ligase substrates include c-Jun, ERK1/2, and TAB1 (pham2013map3k1genomicalterations pages 7-8, charlaftis2014themekk1 pages 15-17). It functions as a scaffold, interacting with kinases (c-Raf, GCK, RIP), adaptors (Grb2, Axin, JSAP1), and cytoskeletal proteins (hagemann2001theupsand pages 8-10, pham2013map3k1genomicalterations pages 3-4). - **Biological Roles**: MAP3K1 regulates immune cell development, cardiac tissue protection, testis development, cell migration, and wound healing (suddason2015aringto pages 1-2). The full-length protein generally promotes cell survival and migration, whereas the caspase-cleaved fragment induces apoptosis (pham2013map3k1genomicalterations pages 1-3).

## Other Comments

Genomic alterations of *MAP3K1*, including mutations and deletions, are found in various cancers (pham2013map3k1genomicalterations pages 7-8). In uterine corpus endometrioid carcinoma, *MAP3K1* alterations are associated with a trend toward better survival (pham2013map3k1genomicalterations pages 7-8). Mutations are also frequent in luminal A breast cancer (pham2013map3k1genomicalterations pages 1-3, suddason2015aringto pages 4-5). Depending on the context, MAP3K1 can act as a metastasis suppressor (ovarian, prostate, gastric cancers) or a driver of malignancy (melanoma) (pham2013map3k1genomicalterations pages 7-8). Knockout studies in mice show that it is not absolutely essential for TNF-α-induced JNK/NF-κB activation, pointing to redundant pathways involving other MAP3Ks like MEKK2, MEKK3, or NIK (hagemann2001theupsand pages 6-7). Mice deficient in *Map3k1* show defective eyelid closure due to impaired epithelial cell migration (hagemann2001theupsand pages 3-5).

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