## Phylogeny

MAP2K1 belongs to the MAP2K (mitogen-activated protein kinase kinase) family (johnson2023anatlasof pages 21-23, manning2002theproteinkinase pages 1-1). Sources conflict on its kinome group classification, with some placing it in the STE (Sterile) group, specifically the STE7 subfamily (johnson2023anatlasof pages 4-4, manning2002theproteinkinase pages 1-2, manning2002theproteinkinase pages 3-3), and others classifying it within the CMGC group (johnson2023anatlasof pages 4-5, johnson2023anatlasof pages 12-18, manning2002evolutionofprotein pages 1-2, manning2002theproteinkinase pages 1-1). Phylogenetically, MAP2K1 clusters with MAP2K2 (MEK2) (johnson2023anatlasof pages 4-5). Orthologs are conserved across vertebrates and various eukaryotes (johnson2023anatlasof pages 21-23). Known orthologs include (johnson2023anatlasof pages 4-4): \* *Mus musculus*: Map2k1 \* *Drosophila melanogaster*: Dsor1 (Downstream-of-Raf 1) \* *Caenorhabditis elegans*: mek-2 \* *Saccharomyces cerevisiae*: PBS2

## Reaction Catalyzed

MAP2K1 is a dual-specificity kinase that catalyzes the phosphorylation of its substrates, ERK1 and ERK2 (johnson2023anatlasof pages 21-23, johnson2023anatlasof pages 4-5). The reaction involves the transfer of phosphate groups from ATP to both a threonine and a tyrosine residue within a Thr-Glu-Tyr (T-E-Y) sequence in the activation loop of ERK1/2, leading to their activation (johnson2023anatlasof pages 21-23, johnson2023anatlasof pages 4-5, johnson2023anatlasof pages 5-5).

## Cofactor Requirements

The catalytic activity of MAP2K1 requires Mg²⁺ as a cofactor, which facilitates ATP binding and the phosphorylation reaction (johnson2023anatlasof pages 21-23, johnson2023anatlasof pages 4-5, manning2002theproteinkinase pages 1-1).

## Substrate Specificity

MAP2K1 demonstrates high specificity for its substrates ERK1 and ERK2 by recognizing a T-E-Y consensus motif within their activation loops (johnson2023anatlasof pages 21-23, johnson2023anatlasof pages 6-7). It specifically phosphorylates ERK1 on Thr202 and ERK2 on Thr203 (johnson2023anatlasof pages 21-23). This specificity is maintained through a combination of local sequence recognition and exclusive substrate docking interactions that prevent promiscuous phosphorylation by other kinases (johnson2023anatlasof pages 3-4).

## Structure

MAP2K1 possesses a catalytic kinase domain that contains canonical structural features, including a conserved C-helix and an activation loop (A-loop) (johnson2023anatlasof pages 21-23, johnson2023anatlasof pages 4-5, manning2002theproteinkinase pages 1-1). The C-helix contributes to the coordination of ATP and substrate binding, while the A-loop contains the key phosphorylation sites that are critical for regulating the kinase’s activity (johnson2023anatlasof pages 21-23).

## Regulation

The primary mechanism for regulating MAP2K1 activity is phosphorylation by upstream RAF kinases on two key serine residues, S218 and S222, located within the activation loop (johnson2023anatlasof pages 21-23, johnson2023anatlasof pages 4-5, johnson2023anatlasof pages 5-5, manning2002theproteinkinase pages 1-1). This dual phosphorylation event induces allosteric conformational changes, which activate the kinase by permitting substrate docking and catalysis (johnson2023anatlasof pages 21-23, johnson2023anatlasof pages 4-5).

## Function

MAP2K1 acts as a central component of the MAPK/ERK signaling pathway, where it transmits signals from upstream RAF kinases to its downstream substrates, ERK1 and ERK2 (johnson2023anatlasof pages 21-23). This pathway is crucial for controlling cellular processes including proliferation and differentiation (johnson2023anatlasof pages 7-7). To facilitate efficient and specific signal transduction, MAP2K1 interacts with scaffold proteins such as KSR (Kinase Suppressor of Ras), which aid in the assembly of the RAF-MEK-ERK signaling complex (johnson2023anatlasof pages 21-23, johnson2023anatlasof pages 4-5, manning2002theproteinkinase pages 1-1).

## Inhibitors

MAP2K1 is the target of small molecule inhibitors like Trametinib, which functions as an allosteric inhibitor that binds to the kinase to prevent its activation and block its kinase activity (johnson2023anatlasof pages 21-23, johnson2023anatlasof pages 4-5, johnson2023anatlasof pages 12-18). These inhibitors are used clinically in cancer therapies to disrupt aberrant signaling through the MAPK/ERK pathway (johnson2023anatlasof pages 21-23, johnson2023anatlasof pages 7-7).

## Other Comments

Mutations in the MAP2K1 gene are associated with various cancers (johnson2023anatlasof pages 21-23, manning2002theproteinkinase pages 1-1). Such mutations often lead to constitutive kinase activation and hyperactivation of the MAPK/ERK pathway, which promotes oncogenic signaling and tumor progression (johnson2023anatlasof pages 7-7, manning2002theproteinkinase pages 1-1).

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