## Phylogeny

MAP3K10 belongs to the mixed-lineage kinase (MLK) sub-family within the STE group of MAP3Ks in the human kinome (Gallo & Johnson, 2002). It clusters with the paralogues MAP3K9/MLK1, MAP3K11/MLK3 and MAP3K21/MLK4; neighbouring branches include MAP3K12/DLK and MAP3K13/LZK (Modi & Dunbrack, 2019). Orthologues are conserved from vertebrates to invertebrates (e.g., Drosophila Slipper, C. elegans MLK), consistent with an evolutionarily preserved JNK-activating module (Gallo & Johnson, 2002).

## Reaction Catalyzed

ATP + protein-Ser/Thr → ADP + protein-Ser/Thr-P (Hirai et al., 1997).

## Cofactor Requirements

No divalent-cation requirement has been demonstrated (Sapkota, 2013).

## Substrate Specificity

Peptide-library profiling places MAP3K10 in a MAP3K-specific cluster that disfavors acidic residues at −2/−3, prefers a hydrophobic residue or Gln at +1, and shows a modest bias toward Thr as the phospho-acceptor (Johnson et al., 2023). Verified protein substrates include the MAP2Ks MKK4 (SEK1) and MKK7, which are phosphorylated by MAP3K10 on their activation-loop Thr/Tyr sites (Hirai et al., 1997).

## Structure

The protein comprises an N-terminal SH3 domain, the catalytic kinase core, a central leucine-zipper (LZ), and a C-terminal CRIB motif followed by a proline-rich tail (Gallo & Johnson, 2002). Crystal structures of the isolated SH3 domain (PDB: 5K28, 5K26, 6AQB) reveal two distinct peptide-binding pockets (Kokoszka et al., 2018). LZ-mediated homodimerisation brings the activation segments of each protomer into proximity, enabling trans-autophosphorylation (Gallo & Johnson, 2002). No full-length or isolated kinase-domain structure has yet been reported; structural features are inferred from the conserved bilobal kinase fold shared across MLKs (Gallo & Johnson, 2002).

## Regulation

• LZ-driven dimerisation followed by activation-loop autophosphorylation is essential for activity (Gallo & Johnson, 2002).  
• HPK1 further phosphorylates the activation loop, increasing catalytic output (Gallo & Johnson, 2002).  
• JNK phosphorylates C-terminal Ser/Thr residues, providing negative feedback on activity and stability (Gallo & Johnson, 2002).  
• GTP-bound Rac1 or Cdc42 binds the CRIB motif, relieving SH3-mediated autoinhibition and recruiting MAP3K10 to membranes; prenylation facilitates this membrane association (Gallo & Johnson, 2002).  
• Wild-type huntingtin sequesters the kinase; release from polyglutamine-expanded huntingtin promotes activation (Gallo & Johnson, 2002).

## Function

MAP3K10 is highly expressed in brain, skeletal muscle and testes (Gallo & Johnson, 2002). Upstream regulators include active Rac1/Cdc42, HPK1, huntingtin, the KIF3/KAP3A motor complex and JIP scaffolds (Nagata et al., 1998; Gallo & Johnson, 2002). Downstream signalling proceeds mainly through MKK4/MKK7 → JNK and MKK3/6 → p38; ERK activation is weak and observed primarily upon over-expression (Gallo & Johnson, 2002). Via these pathways the kinase controls stress-induced apoptosis, cytoskeletal organisation, vesicle transport and developmental morphogenesis (Gallo & Johnson, 2002).

## Inhibitors

Pan-MLK ATP-competitive inhibitors CEP-1347 and CEP-11004 block MAP3K10 activity and suppress downstream JNK signalling (Rana et al., 2013).

## Other Comments

Loss of huntingtin-mediated sequestration in Huntington’s disease unleashes MAP3K10-dependent JNK activation leading to neuronal apoptosis (Gallo & Johnson, 2002). Dysregulated MLK–JNK signalling can enhance tumour cell migration and invasion, making MAP3K10 a prospective therapeutic target in cancer (Rana et al., 2013).

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