## Phylogeny

• Member of the mixed-lineage kinase (MLK) subfamily within the STE group of MAP3Ks in the human kinome (gallo2002mixedlineagekinasecontrol pages 2-3).  
• Clusters with paralogs MAP3K9 (MLK1), MAP3K11 (MLK3) and MAP3K21 (MLK4); adjacent branches include MAP3K12 (DLK) and MAP3K13 (LZK) (modi2019astructurallyvalidated pages 19-22).  
• Orthologs are conserved from vertebrates (murine and rat MLK homologs) to invertebrates such as Drosophila Slipper and C. elegans MLK, underscoring an evolutionarily preserved JNK-activating module (gallo2002mixedlineagekinasecontrol pages 1-2).

## Reaction Catalyzed

ATP + protein-Ser/Thr → ADP + protein-Ser/Thr-P (hirai1997mstmlk2amember pages 1-1).

## Cofactor Requirements

No divalent-cation requirement has been experimentally documented in the referenced studies (sapkota2013thetgfβinducedphosphorylation pages 6-7).

## Substrate Specificity

• Peptide-library profiling places MAP3K10 in a MAP3K-specific cluster that disfavors acidic residues at −2/−3, prefers hydrophobic or Gln at +1, and shows a modest bias toward threonine as the phospho-acceptor (johnson2023anatlasof pages 2-3).  
• Direct protein substrates include MAP2Ks SEK1/MKK4 and MKK7, phosphorylated by MAP3K10 on their activation-loop Thr/Tyr sites (hirai1997mstmlk2amember pages 1-1).

## Structure

• Domain layout: N-terminal SH3, catalytic kinase domain, central leucine-zipper (LZ), C-terminal CRIB motif and proline-rich tail (gallo2002mixedlineagekinasecontrol pages 3-4).  
• SH3 domain crystal structures (PDB 5K28, 5K26, 6AQB) reveal two distinct peptide-binding pockets (kokoszka2018identificationoftwo pages 1-2).  
• LZ-mediated homodimerisation juxtaposes activation loops, enabling trans-autophosphorylation required for full activity (gallo2002mixedlineagekinasecontrol pages 3-4).  
• No full-length or kinase-domain crystal structure is available; structural features are inferred from conserved bilobal architecture shared across MLKs (gallo2002mixedlineagekinasecontrol pages 1-2).

## Regulation

• Autophosphorylation of the activation loop following LZ-driven dimer formation is essential for catalytic activity (gallo2002mixedlineagekinasecontrol pages 3-4).  
• HPK1 phosphorylates the activation loop, further enhancing activity (gallo2002mixedlineagekinasecontrol pages 8-9).  
• JNK phosphorylates C-terminal Ser/Thr residues, providing negative feedback that modulates stability and activity (gallo2002mixedlineagekinasecontrol pages 8-9).  
• GTP-bound Rac1/Cdc42 binds the CRIB motif, relieving SH3 autoinhibition and recruiting the kinase to membranes (gallo2002mixedlineagekinasecontrol pages 4-5).  
• Prenylation promotes transient membrane association during signalling (gallo2002mixedlineagekinasecontrol pages 4-5).  
• Wild-type huntingtin sequesters MAP3K10; dissociation from polyglutamine-expanded huntingtin releases and activates the kinase (gallo2002mixedlineagekinasecontrol pages 8-8).

## Function

• High expression in brain, skeletal muscle and testes (gallo2002mixedlineagekinasecontrol pages 3-4).  
• Upstream regulators: active Rac1/Cdc42, HPK1, huntingtin, KIF3/KAP3A motor complex and JIP scaffolds (nagata1998themapkinase pages 1-2).  
• Downstream targets: MKK4/MKK7 → JNK and MKK3/6 → p38; weak ERK activation under over-expression (gallo2002mixedlineagekinasecontrol pages 1-2).  
• Governs stress-induced apoptosis, cytoskeletal organisation, vesicle transport and developmental morphogenesis via JNK/p38 pathways (gallo2002mixedlineagekinasecontrol pages 8-8).

## Inhibitors

Pan-MLK inhibitors CEP-1347 and CEP-11004 block MAP3K10 activity and downstream JNK signalling (rana2013mixedlineagekinasecjun pages 1-2).

## Other Comments

• Huntington’s disease: loss of huntingtin sequestration unleashes MAP3K10-driven JNK activation leading to neuronal apoptosis (gallo2002mixedlineagekinasecontrol pages 8-8).  
• Cancer: dysregulated MLK-JNK signalling promotes migration and invasion, positioning MAP3K10 as a therapeutic target (rana2013mixedlineagekinasecjun pages 3-5).

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