## Phylogeny

MAP3K13 (also called LZK) is an evolutionarily conserved mixed-lineage kinase (MLK). It is the functional ortholog of the *C. elegans* DLK-1 and is >95 % identical in the kinase domain to human MAP3K12 (DLK) (Yan & Jin, 2012). In the kinome classification of Manning et al. (2002), the enzyme belongs to the mitogen-activated protein kinase kinase kinase (MAP3K/Ste11) family and, more specifically, to the MLK subfamily that includes the dual-leucine-zipper kinases (Gallo & Johnson, 2002; Bensen & Brognard, 2021). Higher-order grouping is inconsistent, with assignments to either the STE or the TKL branch of the kinome (Manning et al., 2002; Johnson et al., 2023).

## Reaction Catalyzed

ATP + protein substrate ⇌ ADP + phospho-protein substrate  
(Bensen & Brognard, 2021; Gallo & Johnson, 2002; Craig et al., 2008)

## Cofactor Requirements

Mg²⁺ or Mn²⁺ is required for catalytic activity (Bensen & Brognard, 2021; Gallo & Johnson, 2002).

## Substrate Specificity

Kinome-wide profiling places MAP3K13 among kinases that prefer threonine acceptors, a bias linked to an alanine at the DFG+1 position (Johnson et al., 2023). Other studies report preferential phosphorylation of motifs containing hydrophobic leucines near the target residue (Jin & Zheng, 2019) or recognition of canonical S/T-P motifs, as seen for related MLKs (Gallo & Johnson, 2002). Contradictory motif data (+1 glutamine vs. +1 proline preferences) have been noted across different analyses (Johnson et al., 2023; Gallo & Johnson, 2002).

## Structure

The protein comprises an N-terminal kinase domain, two sequential leucine-zipper (LZ) motifs, and a long C-terminal tail (Jin & Zheng, 2019). LZ-mediated homodimerization is essential for activation. The kinase domain contains subdomains I–VII typical of Ser/Thr kinases and VIII–XI characteristic of Tyr kinases (Jin & Zheng, 2019). A structural model (based on DLK) reveals a canonical bilobal fold but a distorted α-helix C caused by a non-consensus Asp, altering an ATP-coordinating salt bridge (Jin & Zheng, 2019). The activation loop harbors regulatory Ser residues, and the extended C-terminus is required for downstream signaling (Jin & Zheng, 2019).

## Regulation

• Activation requires LZ-driven homodimerization and trans-autophosphorylation of the activation loop (Jin & Zheng, 2019; Gallo & Johnson, 2002).  
• Phosphorylation by PKA and AKT further modulates activity (Jin & Zheng, 2019).  
• The E3 ubiquitin ligase RPM-1 negatively regulates the kinase (Chen et al., 2016).  
• An SH3-domain–proline-rich autoinhibitory interaction described for other MLKs is probably retained (Gallo & Johnson, 2002).  
• Rho-family GTPases Rac and Cdc42 can allosterically activate the enzyme (Gallo & Johnson, 2002).

## Function

MAP3K13 is broadly expressed, with prominent levels in brain regions (cerebellar granule and hippocampal neurons) and pancreas (Gallo & Johnson, 2002; Chen et al., 2016; Unknown Authors, 2001). Neuronal activity deprivation can trigger its activation (Chen et al., 2016).  
Downstream: directly phosphorylates MKK4/7 to activate the JNK MAPK cascade (Bensen & Brognard, 2021) and stimulates the IKK complex to modulate NF-κB signaling (Bensen & Brognard, 2021).  
Interacting partners include the scaffold JIP-1, which enhances JNK signaling (Unknown Authors, 2001), and mitochondrial AOP-1, which promotes NF-κB activation (Jin & Zheng, 2019).  
Biological roles encompass cellular stress responses, axon growth and branching, and oncogenic processes (Chen et al., 2016; Bensen & Brognard, 2021).

## Inhibitors

Experimental ATP-competitive inhibitors include:  
• CEP-1347 – pan-MLK inhibitor (Jin & Zheng, 2019).  
• GNE-3511 and GNE-495 – developed for DLK but inhibit MAP3K13 owing to high kinase-domain homology and are brain-penetrant in mice (Jin & Zheng, 2019).

## Other Comments

MAP3K13 dysregulation is linked to neurodegeneration, multiple cancers, and responses to herpes simplex virus infection (Jin & Zheng, 2019). Pharmacological inhibition shows therapeutic benefit in mouse neurological disease models (Jin & Zheng, 2019). High MAP3K13 expression correlates with improved survival in bladder and lung squamous carcinomas but with poorer survival in pancreatic ductal adenocarcinoma and sarcoma (Nguyen et al., 2022). A Map3k13tm1a mutant mouse line is available for in vivo studies (Chen et al., 2016).

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