## Phylogeny

MAP2K7 belongs to the STE group of the human kinome, clustering within the STE7 family of MAP kinase kinases (Roskoski, 2012; Unknown Authors, 2023; Lacorazza, 2024). It arose through gene-duplication events common to the MAP2K subfamily (Unknown Authors, 2023) and is most closely related to MKK4, sharing ~50–53 % kinase-domain identity, and to the Drosophila ortholog hemipterous (Moriguchi et al., 1997; Katzengruber et al., 2023; Tournier et al., 1997). Orthologs are conserved across vertebrates, including cartilaginous, ray-finned and lobe-finned fish, while the mouse kinase domain shares ~70 % identity with Drosophila hep (Caliz et al., 2022; Wang et al., 2007).

## Reaction Catalyzed

ATP + [a JNK protein] ⇄ ADP + [a phospho-JNK protein] (Caliz et al., 2022; Roskoski, 2012).  
MAP2K7 preferentially phosphorylates the threonine (T183) of the JNK T-P-Y motif, whereas MKK4 favors the tyrosine (Y185) (Katzengruber et al., 2023; Unknown Authors, 2023).

## Cofactor Requirements

Mg²⁺ is required for catalysis (Murakawa et al., 2020).

## Substrate Specificity

Positional scanning peptide-array analysis defined position-specific amino-acid preferences from –3 to +3 around the target threonine (Roskoski, 2012; Johnson et al., 2023). In vivo, MAP2K7 phosphorylates the threonine within the JNK Thr-Pro-Tyr activation motif (Caliz et al., 2022; Katzengruber et al., 2023). MAPKs are generally proline-directed, recognising a +1 Pro residue (Unknown Authors, 2023).

## Structure

Crystal structures (e.g., PDB 6YFZ, 6YG0–6YG7) and AlphaFold models are available (Caliz et al., 2022; Schröder et al., 2020). The protein contains an N-terminal regulatory segment with three D-motifs, a catalytic domain, and a C-terminal DVD domain that binds upstream kinases (Ho et al., 2006; Lacorazza, 2024). The catalytic domain toggles between inactive DFG-out and active DFG-in conformations and displays marked plasticity (Schröder et al., 2020). Activation involves an N-terminal regulatory helix that docks onto the αC helix, stabilising the β3 Lys165–αC Asp182 salt bridge and completing the hydrophobic spine (Schröder et al., 2020; Lacorazza, 2024). A unique Cys218 in the ATP pocket participates in auto-inhibition and can be covalently targeted (Schröder et al., 2020).

## Regulation

Full activation requires dual phosphorylation of Ser271 and Thr275 (and additional Ser287, Thr291) within the SXKAT/SKAKT activation loop by MAP3Ks such as ASK1, TAK1, MEKK and MLK family members (Lacorazza, 2024; Schröder et al., 2020; Unknown Authors, 2023). Phosphorylation-mimetic mutants do not achieve maximal activity without engagement of the N-terminal regulatory helix (Schröder et al., 2020). Auto-inhibited conformations occlude the ATP site until these activating events occur (Schröder et al., 2020).

## Function

MAP2K7 is broadly expressed and localises to cytoplasm and nucleus (Caliz et al., 2022; Tournier et al., 1997, 1999). Acting within the JNK pathway, it converts diverse stress signals (UV, osmotic shock) and inflammatory cytokines (TNF-α, IL-1) into JNK activation (Moriguchi et al., 1997; Caliz et al., 2022). Upstream MAP3Ks phosphorylate MAP2K7; scaffold proteins JIP1–3 stabilise MAP2K7–JNK complexes (Ho et al., 2006; Lacorazza, 2024). Downstream, JNK1-3 phosphorylate transcription factors such as c-Jun and ATF2, influencing AP-1-dependent gene expression that governs proliferation, differentiation, apoptosis, immune responses and development (Ho et al., 2006; Caliz et al., 2022).

## Inhibitors

Peptide inhibitors derived from N-terminal D-sites block JNK binding (Ho et al., 2006). Small-molecule inhibitors include indazole compounds that disrupt the MKK7–TIPRL interaction (Caliz et al., 2022; Schröder et al., 2020), covalent inhibitors targeting Cys218, and the approved drug ibrutinib, which binds an allosteric pocket (Schröder et al., 2020; Murakawa et al., 2020).

## Other Comments

Dysregulated MAP2K7 activity is linked to cancer, inflammatory disorders, neurodegeneration and diabetes, functioning as either tumour promoter or suppressor depending on context (Caliz et al., 2022; Ho et al., 2006; Schröder et al., 2020). The human MAP2K7 gene maps to chromosome 19p13.2, contains 12–14 exons and is alternatively spliced into six isoforms (α1/2, β1/2, γ1/2). β and γ isoforms possess an extended N-terminal D-domain that enhances JNK binding and basal activity relative to α variants (Tournier et al., 1999; Wang et al., 2007).

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