## Phylogeny

• Kinome hierarchy: CMGC group → MAPK family → JNK sub-family (rehfeldt2020cjunnterminalkinase pages 11-13).  
• Human paralogs: MAPK8/JNK1 and MAPK9/JNK2 share >90 % identity within the catalytic domain (scapin2003thestructureof pages 1-2).  
• Vertebrate orthologs: Mus musculus Mapk10, Rattus norvegicus Mapk10, Gallus gallus MAPK10, Danio rerio mapk10 (rehfeldt2020cjunnterminalkinase pages 11-13).  
• Non-vertebrate orthologs: Drosophila melanogaster basket (bsk), Caenorhabditis elegans kgb-1, Leishmania major LmMAPK10 (horjales2012thecrystalstructure pages 12-12, rehfeldt2020cjunnterminalkinase pages 11-13).

## Reaction Catalyzed

ATP + {protein}-Ser/Thr → ADP + {protein}-Ser/Thr(P) (kyriakis2012mammalianmapksignal pages 49-50).

## Cofactor Requirements

Catalytic turnover requires two Mg²⁺ ions; Mn²⁺ can substitute in vitro (shaw2008thecrystalstructure pages 7-8, mishra2018newinsightsinto pages 12-13).

## Substrate Specificity

• Primary consensus: (Ser/Thr)-Pro with an obligatory Pro at +1 (wagner2009signalintegrationby pages 2-3, kyriakis2012mammalianmapksignal pages 2-3).  
• Extended ±3 motif derived from high-throughput profiling: Φ-P-(S/T)-P-P-Ψ where Φ is hydrophobic and Ψ is hydrophobic/basic (mishra2018newinsightsinto pages 12-13).  
• Substrate/scaffold docking via the D-recruiting site: basic groove residues 145-169 and acidic ED site 196-204 engage ψ-X-X-φ motifs (rehfeldt2020cjunnterminalkinase pages 11-13).

## Structure

• Single bilobal kinase domain (residues ~48–397) with a β-rich N-lobe and α-helical C-lobe (rehfeldt2020cjunnterminalkinase pages 11-13, mishra2018newinsightsinto pages 1-2).  
• Catalytic motifs: Lys55–Glu111 salt bridge, HRD triad His187-Arg188-Asp189, DFG Asp207-Phe208-Gly209, and activation loop Thr221-Pro222-Tyr223 (kyriakis2012mammalianmapksignal pages 2-3, rehfeldt2020cjunnterminalkinase pages 11-13).  
• Hydrophobic spine spanning the gatekeeper Met146 anchors active conformations (rehfeldt2020cjunnterminalkinase pages 11-13).  
• Unique 12-residue JNK insert (283-328) remodels the MAPK insert, influencing docking (rehfeldt2020cjunnterminalkinase pages 11-13).  
• Crystal structures:  
– Apo/ATP states, PDB 4WHZ, reveal hinge-driven cleft closure (mishra2018newinsightsinto pages 11-12).  
– Inhibitor complex, PDB 1PMV, delineates five subsites in the ATP pocket (rehfeldt2020cjunnterminalkinase pages 11-13).

## Regulation

• Activation: dual phosphorylation of Thr221 by MAP2K7/MKK7 and Tyr223 by MAP2K4/MKK4 downstream of MAP3Ks such as ASK1, DLK and MEKKs (haeusgen2011thebottleneckof pages 3-4, haeusgen2011thebottleneckof pages 9-9, unknownauthors2022jnksastherapeutic pages 33-37).  
• Inactivation: dephosphorylation by DUSP10/MKP5 and DUSP16/MKP7 (rehfeldt2020cjunnterminalkinase pages 11-13).  
• Additional PTMs:  
– Ubiquitination by E3 ligase Itch (rehfeldt2020cjunnterminalkinase pages 11-13).  
– SUMOylation at unspecified lysines (rehfeldt2020cjunnterminalkinase pages 11-13).  
– Palmitoylation targets JNK3 to the Golgi (unknownauthors2022jnksastherapeutic pages 33-37).  
– S-nitrosylation inhibits catalytic activity under nitric-oxide stress (sehgal2013networkmotifsin pages 3-4).  
• Scaffold-mediated control: JIP1-4 and β-arrestin-2 organize MAP3K–MKK–JNK3 modules; β-arrestin-2 employs a “conveyor belt” activation mechanism (unknownauthors2022jnksastherapeutic pages 39-43).  
• Allosteric regulation: ATP binding triggers hinge closure and activation-loop ordering (mishra2018newinsightsinto pages 11-12).

## Function

• Expression: enriched in brain neurons with minor levels in heart and testis (scapin2003thestructureof pages 1-2).  
• Downstream substrates: c-Jun, JunD, ATF2, Elk1 (kyriakis2012mammalianmapksignal pages 2-3), STMN2 (rehfeldt2020cjunnterminalkinase pages 11-13), SCG10 S62/S73 and kinesin-1 S176 (coffey2014nuclearandcytosolic pages 1-2), APP Thr668 (rehfeldt2020cjunnterminalkinase pages 11-13), CLOCK–BMAL1 heterodimer (rehfeldt2020cjunnterminalkinase pages 11-13).  
• Signaling roles: mediates stress-induced AP-1 activation, neuronal apoptosis, cytoskeletal regulation, axonal transport, APP processing and circadian control (scapin2003thestructureof pages 1-2, coffey2014nuclearandcytosolic pages 1-2, rehfeldt2020cjunnterminalkinase pages 11-13).  
• Genetic ablation confers resistance to excitotoxic neuronal death in mice (scapin2003thestructureof pages 1-2).

## Inhibitors

• Compound 589 (type I): IC₅₀ = 0.016 µM for JNK3; exploits Met146/Leu144 hydrophobic recess (rehfeldt2020cjunnterminalkinase pages 11-13).  
• JNK-IN-8 (covalent): nanomolar potency via Cys154 targeting (rehfeldt2020cjunnterminalkinase pages 11-13).  
• AS601245 (ATP-competitive): sub-µM activity, JNK-selective (rehfeldt2020cjunnterminalkinase pages 11-13).  
• CC-930 (tanzisertib): clinical-stage ATP-competitive inhibitor with CNS permeability considerations (rehfeldt2020cjunnterminalkinase pages 11-13).  
• SP600125: broad-spectrum JNK inhibitor used as a neuroprotective probe (coffey2014nuclearandcytosolic pages 1-2).

## Other Comments

• Pathological hyper-activation is implicated in Alzheimer’s, Parkinson’s, Huntington’s disease, amyotrophic lateral sclerosis and cerebral ischemia (mishra2018newinsightsinto pages 12-13, rehfeldt2020cjunnterminalkinase pages 11-13).  
• Disease mutation p.R230C in the activation segment is associated with severe neurodevelopmental disorders (rehfeldt2020cjunnterminalkinase pages 11-13).

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