## Proposed EC/sub-subclass:

Not specified in the provided material

## Accepted name:

Mitogen-activated protein kinase 9 (MAPK9)

## Synonyms:

JNK2; c-Jun N-terminal kinase 2; Stress-activated protein kinase (SAPK) isoform

## Phylogeny

MAPK9/JNK2 belongs to the c-Jun N-terminal kinase (JNK) subgroup of the mitogen-activated protein kinase (MAPK) family. Three vertebrate paralogues arose from duplication of a single ancestral JNK gene: MAPK8/JNK1, MAPK9/JNK2 and MAPK10/JNK3. These isoforms share >85 % sequence identity (Bogoyevitch & Kobe, 2006; Zeke et al., 2016). JNK2 is ubiquitously expressed, whereas JNK3 is largely restricted to brain, heart and testes (Barr & Bogoyevitch, 2001; Bogoyevitch & Kobe, 2006). Alternative splicing yields p46 and p54 variants that differ in C-terminal length and tissue distribution (Zeke et al., 2016). JNKs are classified as stress-activated protein kinases within the CMGC group of Ser/Thr kinases, a conserved signaling module from yeast to humans (Bogoyevitch & Kobe, 2006; Zeke et al., 2016).

## Reaction catalyzed

ATP + L-seryl/threonyl-[protein] ⇄ ADP + H⁺ + O-phospho-L-seryl/threonyl-[protein] (Barr & Bogoyevitch, 2001; Zeke et al., 2016)

## Cofactor requirements

Mg²⁺ is essential for ATP binding and phosphoryl transfer (Barr & Bogoyevitch, 2001).

## Substrate specificity

JNK2 is a proline-directed Ser/Thr kinase that preferentially phosphorylates the S/T-P consensus motif (Barr & Bogoyevitch, 2001; Bogoyevitch & Kobe, 2006; Cicenas et al., 2017). Docking motifs (D-domains) in substrates and scaffold proteins enhance recognition. Key substrates include transcription factors c-Jun and ATF2, mitochondrial and cytoplasmic apoptosis regulators (Bcl-2, Bcl-xL, Mcl-1, Bad, Bim, Bax) and signalling adaptors such as IRS1/2 (Barr & Bogoyevitch, 2001; Bogoyevitch & Kobe, 2006; Zeke et al., 2016).

## Structure

MAPK9/JNK2 adopts the canonical two-lobed protein-kinase fold with a glycine-rich loop, catalytic loop and αC-helix. The activation loop contains the Thr-Pro-Tyr (TPY) motif required for dual phosphorylation-dependent activation (Barr & Bogoyevitch, 2001; Heo et al., 2004). Surface common-docking and hydrophobic grooves bind D-motif-containing partners, including the scaffold JIP1 (Zeke et al., 2016). Alternative splicing alters the C-terminal extension (p46 vs p54), influencing regulatory interactions (Bogoyevitch & Kobe, 2006; Zeke et al., 2016).

## Regulation

Activation requires dual phosphorylation of the TPY motif by MAP2Ks MKK4 (Tyr site) and MKK7 (Thr site) (Barr & Bogoyevitch, 2001; Fleming et al., 2000; Cargnello & Roux, 2011). Scaffold proteins such as JIP1 assemble MAP3Ks, MAP2Ks and JNK2, ensuring signal fidelity and spatial control (Willoughby et al., 2003; Heo et al., 2004). Activity is reversed by dual-specificity phosphatases (e.g., MKP1, MKP5) (Zeke et al., 2016). Feedback phosphorylation of adaptor or upstream proteins fine-tunes signaling, and additional post-translational modifications and auto-phosphorylation events modulate kinase output (Barr & Bogoyevitch, 2001; Zeke et al., 2016).

## Function

MAPK9/JNK2 transduces a wide spectrum of stress signals (UV, cytokines, osmotic and oxidative stress) to regulate gene expression, apoptosis, immune responses, epithelial barrier integrity, circadian rhythms and neuronal development (Barr & Bogoyevitch, 2001; Bogoyevitch & Kobe, 2006; Zeke et al., 2016).  
• Expression: broadly expressed across tissues (Barr & Bogoyevitch, 2001).  
• Upstream kinases: MAP3Ks activate MKK4/MKK7, which activate JNK2.  
• Downstream substrates/partners: c-Jun, ATF2, TP53, YAP1, Bcl-2 family proteins, IRS1/2; scaffold JIP1 coordinates signaling (Bogoyevitch & Kobe, 2006; Zeke et al., 2016).  
• Pathways: regulates AP-1 transcription, mitochondrial apoptosis, T-cell receptor signaling (Th1 differentiation), Wnt/β-catenin suppression and CLOCK-BMAL1 circadian components (Barr & Bogoyevitch, 2001; Bogoyevitch & Kobe, 2006; Zeke et al., 2016).

## Inhibitors

SP600125 is a widely used ATP-competitive JNK inhibitor with limited isoform selectivity; CEP-1347 has been examined clinically for neurodegenerative indications (Cicenas et al., 2017; Heo et al., 2004; Bogoyevitch & Kobe, 2006).

## Other Comments

Dysregulated JNK2 activity is implicated in neurodegeneration, cancer, metabolic and inflammatory disorders. Scaffold interactions (e.g., JIP1) and disease-linked signaling outputs highlight MAPK9/JNK2 as a potential therapeutic target (Bogoyevitch & Kobe, 2006; Zeke et al., 2016).

## References

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