## Phylogeny

MAP3K15 (ASK3) is one of the three human Apoptosis Signal-regulating Kinases (ASK1/MAP3K5, ASK2/MAP3K6, ASK3/MAP3K15) that form a distinct branch within the MAP3K family of the human kinome (Trevelyan et al., 2020). Orthologues are documented in mouse, rat and zebrafish, but not in Drosophila (Trevelyan et al., 2020; “Structural studies…”, 2024). The catalytic domain shares ~88 % amino-acid identity with ASK1, highlighting their close evolutionary relationship (“Structural studies…”, 2024).

## Reaction Catalyzed

ATP + [protein]-Ser/Thr ⇌ ADP + [protein]-O-phospho-Ser/Thr (Kaji et al., 2010).

## Cofactor Requirements

Catalysis requires a divalent cation; Mg²⁺ is reported as the physiological cofactor for MAP3K family members, including ASK3 (Honzejková et al., 2024).

## Substrate Specificity

No experimentally validated consensus phosphorylation motif has been defined for human MAP3K15. Large-scale kinome profiling failed to assign a sequence logo to ASK3 (Trevelyan et al., 2019; “Structural studies…”, 2024).

## Structure

• N-terminal regulatory segment (residues 1–≈400) predicted to contain a thioredoxin-binding fold analogous to ASK1 (Obsilová et al., 2021).  
• Central serine/threonine kinase domain (≈400–770); Lys681 acts as the catalytic lysine (Maruyama et al., 2016).  
• C-terminal region comprises coiled-coil sequences followed by a sterile-alpha motif (SAM, ≈1200–1313) (Trevelyan et al., 2020).

3-D data  
– SAM domain crystal structure at 1.80 Å (PDB 6V0M) reveals a canonical five-helix fold that forms pentameric/hexameric rings via mid-loop:end-helix interfaces (Trevelyan et al., 2020).  
– SAXS confirms higher-order SAM oligomers in solution; oligomerisation is more stable than that of ASK1/ASK2 (Trevelyan et al., 2020).  
– Homology modelling predicts an upstream TPR-PH scaffold similar to ASK1, supporting an autoregulatory architecture (Weijman et al., 2017).  
– Conserved activation loop, DFG motif, C-helix and hydrophobic spines align with canonical kinase architecture (“Structural studies…”, 2024).  
– SAM-driven oligomerisation nucleates ASK signalosomes, a prerequisite for kinase activation (Trevelyan et al., 2020).

## Regulation

Post-translational modifications  
• A ubiquitin-like motif recruits the de-ubiquitinase USP9X, shielding ASK3 from proteasomal degradation and promoting oxidative-stress-induced cell death (Trevelyan et al., 2019).  
• Phosphorylation-dependent association with 14-3-3 isoforms modulates localisation and activity (Federspiel et al., 2016).

Protein–protein / allosteric control  
• Stable pentamer/hexamer SAM oligomers are essential for electrophile- and osmotic-stress signalling (Trevelyan et al., 2020).  
• A PP6–ASK3 module coordinates cell-volume recovery during osmotic stress (Obsilová et al., 2021).

## Function

Expression  
High transcript and protein levels occur in kidney and brain (including fetal brain). Variant-specific up-regulation is seen in rectum tumours and Alzheimer’s hippocampus, whereas down-regulation appears in kidney tumours and Alzheimer’s frontal lobe (Kaji et al., 2010).

Biological roles  
• Acts upstream of the p38 and JNK MAPK cascades to mediate stress-induced apoptosis; siRNA depletion blocks Fas-, TNF-α- and H₂O₂-triggered cell death (Kaji et al., 2010).  
• Functions as an osmotic-stress sensor in kidney epithelia: activates p38-MAPK–MK signalling leading to WNK4-Ser575 phosphorylation and suppresses the WNK1–SPAK/OSR1 axis, influencing NaCl handling and blood pressure (Maruyama et al., 2016; Trevelyan et al., 2019).  
• Forms hetero-complexes with ASK1 and ASK2, integrating electrophilic and inflammatory cues within ASK signalosomes (Trevelyan et al., 2020).

Key interactors  
WNK1, WNK4, PP6, 14-3-3, USP9X (Maruyama et al., 2016; Federspiel et al., 2016; Trevelyan et al., 2019).

## Inhibitors

No small-molecule inhibitors of MAP3K15 have been reported or advanced to clinical evaluation (Cuarental et al., 2019).

## Other Comments

• Ask3⁻/⁻ mice develop salt-sensitive hypertension, linking kinase loss to dysregulated renal osmotic signalling (Cuarental et al., 2019).  
• Aberrant ASK3 transcript levels are observed in various tumours and Alzheimer’s disease brain regions, implicating the kinase in oncogenesis and neurodegeneration (Kaji et al., 2010).  
• ASK3 contributes to kidney injury and fibrotic responses through stress-activated MAPK pathways (Cuarental et al., 2019).

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