## Phylogeny

• MAP3K15 (ASK3) is one of three human Apoptosis Signal-regulating Kinases (ASK1/MAP3K5, ASK2/MAP3K6, ASK3/MAP3K15), a sub-family within the MAP3K group of the human kinome (trevelyan2020structurebasedmechanismof pages 32-35).  
• Orthologs are reported in mouse, rat and zebrafish genomes; no ortholog is documented in Drosophila (trevelyan2020structurebasedmechanismof pages 32-35, unknownauthors2024structuralstudiesof pages 20-24).  
• The kinase domain shares 88 % amino-acid identity with ASK1, underscoring close evolutionary relatedness inside the ASK branch (unknownauthors2024structuralstudiesof pages 24-28).

## Reaction Catalyzed

ATP + [protein]-Ser/Thr ⇌ ADP + [protein]-O-phospho-Ser/Thr (kaji2010ask3anovel pages 4-5).

## Cofactor Requirements

Catalytic turnover requires divalent cations, with Mg²⁺ reported as the physiological cofactor for MAP3K family members, including ASK3 (honzejkova2024thecryoemstructure pages 16-17).

## Substrate Specificity

No experimentally validated consensus phosphorylation motif for human MAP3K15 has been published; large-scale kinome profiling did not assign a sequence logo to ASK3 (trevelyan2019mechanismofpreferential pages 1-4, unknownauthors2024structuralstudiesof pages 24-28).

## Structure

Domain organisation  
• N-terminal regulatory segment (residues 1-≈400) predicted to contain a thioredoxin-binding fold analogous to ASK1 (obsilova2021structuralinsightssupport pages 3-4).  
• Central protein kinase domain (≈400-770); Lys681 is the catalytic Lys as shown by loss-of-function K681M mutant (maruyama2016osmoticstressinduces pages 12-13).  
• C-terminal regulatory region with coiled-coil sequences followed by a sterile-alpha motif (SAM, residues ≈1200-1313) (trevelyan2020structurebasedmechanismof pages 1-4).  
3D structural data  
• SAM domain crystal structure solved at 1.80 Å (PDB 6V0M) reveals a classical five-helix SAM fold that assembles into concentration-independent pentameric/hexameric rings via mid-loop:end-helix interfaces (trevelyan2020structurebasedmechanismof pages 4-8).  
• SAXS confirms higher-order oligomers for the SAM domain in solution; oligomerisation is markedly more stable than that of ASK1/ASK2 (trevelyan2020structurebasedmechanismof pages 23-29).  
• Homology modelling predicts an upstream TPR-PH scaffold similar to ASK1, supporting autoregulatory architecture (weijman2017structuralbasisof pages 4-4).  
Catalytic and regulatory features  
• Activation loop and DFG motif are conserved; the C-helix and hydrophobic spines align with canonical serine/threonine kinase architecture in the AlphaFold model (unknownauthors2024structuralstudiesof pages 24-28).  
• SAM-mediated oligomerisation nucleates ASK signalosomes, a prerequisite for kinase activation (trevelyan2020structurebasedmechanismof pages 1-4).

## Regulation

Post-translational modifications  
• ASK3 contains a ubiquitin-like motif that recruits the de-ubiquitinase USP9X, protecting the kinase from proteasomal degradation and promoting oxidative-stress-induced cell death (trevelyan2019mechanismofpreferential pages 35-37).  
• Association with 14-3-3 isoforms modulates subcellular localisation and activity; binding is phosphorylation-dependent (federspiel2016assemblydynamicsand pages 15-15).  
Protein–protein and allosteric control  
• Stable SAM-domain oligomerisation (pentamer/hexamer) is essential for electrophile- and osmotic-stress signalling (trevelyan2020structurebasedmechanismof pages 1-4).  
• A PP6-ASK3 module orchestrates bidirectional cell-volume regulation under osmotic stress (obsilova2021structuralinsightssupport pages 12-13).

## Function

Expression  
• High transcript and protein levels are detected in kidney, brain (including fetal brain) and several other tissues; variant-specific up-regulation occurs in rectum tumours and Alzheimer’s hippocampus, whereas down-regulation is noted in kidney tumours and Alzheimer’s frontal lobe (kaji2010ask3anovel pages 1-2, kaji2010ask3anovel pages 4-5).  
Biological roles and pathways  
• Acts upstream of the p38 and JNK MAPK cascades to mediate stress-induced apoptosis in HeLa cells; siRNA depletion abolishes Fas-, TNF-α- and H₂O₂-triggered cell death (kaji2010ask3anovel pages 6-6).  
• 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, thereby modulating sodium-chloride handling and systemic blood pressure (maruyama2016osmoticstressinduces pages 11-12, trevelyan2019mechanismofpreferential pages 35-37).  
• Forms hetero-complexes with ASK1/ASK2, integrating electrophilic and inflammatory cues within ASK signalosomes (trevelyan2020structurebasedmechanismof pages 1-4).  
Key interactors  
• WNK1, WNK4, PP6, 14-3-3, USP9X (maruyama2016osmoticstressinduces pages 11-12, federspiel2016assemblydynamicsand pages 15-15, trevelyan2019mechanismofpreferential pages 35-37).

## Inhibitors

No small-molecule inhibitors of MAP3K15 have been reported or advanced to clinical evaluation (cuarental2019map3kkinasesand pages 5-6).

## Other Comments

• Ask3-/- mice develop salt-sensitive hypertension, linking kinase loss to dysregulated renal osmotic signalling (cuarental2019map3kkinasesand pages 5-6).  
• Aberrant ASK3 transcript levels are observed in Alzheimer’s disease brain regions and diverse tumours, implicating the kinase in neurodegeneration and oncogenesis (kaji2010ask3anovel pages 1-2).  
• ASK3 contributes to kidney injury and fibrotic responses by modulating stress-activated MAPK pathways (cuarental2019map3kkinasesand pages 6-7).

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