## Phylogeny

• Kinase group: CaMK-like branch → MAPK-activated protein kinase (MAPKAPK) family → MK2/3 sub-family (cargnello2011activationandfunction pages 12-13).  
• MAPKAPK3 shares ≈75 % amino-acid identity with MAPKAPK2 and ≈46 % with MAPKAPK5, confirming its closest paralogue is MAPKAPK2 (unknownauthors2014mitogenactivatedproteinkinaseactivated pages 22-28).  
• Documented orthologs span Mus musculus, Rattus norvegicus, Danio rerio, Xenopus species, Drosophila melanogaster and Caenorhabditis elegans, retaining ~60 % sequence similarity in invertebrates (unknownauthors2014mitogenactivatedproteinkinaseactivated pages 22-28).  
• A conserved basic D-domain embedded in the C-terminal tail mediates docking to p38α/β and atypical ERK3/4 MAPKs, illustrating evolutionary conservation of MAPK→MAPKAPK interaction motifs (cargnello2011activationandfunction pages 9-10).

## Reaction Catalyzed

ATP + [protein]-Ser/Thr → ADP + [protein]-O-phospho-Ser/Thr (unknownauthors2014mitogenactivatedproteinkinaseactivated pages 69-72).

## Cofactor Requirements

Catalysis requires Mg²⁺ to coordinate ATP within the active site (unknownauthors2014mitogenactivatedproteinkinaseactivated pages 28-31).

## Substrate Specificity

• Preferred consensus: Φ-X-Arg-X₂-Ser, where Φ is a bulky hydrophobic residue (unknownauthors2014mitogenactivatedproteinkinaseactivated pages 69-72).  
• Basic residues at −3/−2 positions enhance recognition, paralleling MAPKAPK2 selectivity (cargnello2011activationandfunction pages 21-23).  
• Verified cellular substrates include HSP27/HSPB1, tristetraprolin (TTP/ZFP36), CREB, HSF-1, TAB3, keratins-18/20, RCSD1 and hnRNP A1 (cheng2010high‐resolutioncrystalstructure pages 1-2, unknownauthors2014mitogenactivatedproteinkinaseactivated pages 69-72).

## Structure

• Domain organisation: N-terminal proline-rich SH3-binding segment → catalytic kinase domain (residues ~45-350) → C-terminal regulatory tail containing bipartite NLS (KK-X₁₀-KRRKK) and phosphorylation-regulated NES (MTSALATMRV) (unknownauthors2014mitogenactivatedproteinkinaseactivated pages 22-28).  
• Crystal structure: 1.9 Å MK3-pyrrolopyridinone complex (PDB 2JBO) displays canonical bilobal fold; key catalytic residues Lys73 (β3), Glu84 (αC) and Asp187 (HRD) align for phosphotransfer (cheng2010high‐resolutioncrystalstructure pages 1-2).  
• P-loop (Gly51-Gly56, GXGXXG) caps the nucleotide and exhibits conformational flexibility (cheng2010high‐resolutioncrystalstructure pages 1-2).  
• Activation segment (DFG→APE) harbours the regulatory threonine analogous to Thr222 in MK2; additional regulatory residues correspond to Ser272 and Thr334 of MK2 (unknownauthors2014mitogenactivatedproteinkinaseactivated pages 28-31).  
• Structural homology with MK2 underpins use of MK3 as a surrogate template for inhibitor design (cheng2010high‐resolutioncrystalstructure pages 1-2).

## Regulation

• Upstream kinases: stress-activated p38α/β phosphorylate the activation-loop threonine and auxiliary sites within the C-lobe and hinge, generating full catalytic activity (unknownauthors2014mitogenactivatedproteinkinaseactivated pages 28-31).  
• Alternative pathway: group I PAKs → ERK3/ERK4 → MAPKAPK3 defines a PAK-ERK3/4-MK3 cascade (unknownauthors2014mitogenactivatedproteinkinaseactivated pages 69-72).  
• Docking: basic D-domain within the NLS mediates high-affinity binding to p38; phosphorylation near this motif modulates complex stability (cargnello2011activationandfunction pages 9-10).  
• Phosphorylation-dependent exposure of the NES drives stress-induced nuclear export; dephosphorylated kinase remains predominantly nuclear (unknownauthors2014mitogenactivatedproteinkinaseactivated pages 22-28).

## Function

• Expression: ubiquitous across tissues, although overall abundance and catalytic output are lower than MAPKAPK2 (unknownauthors2014mitogenactivatedproteinkinaseactivated pages 22-28).  
• Biological roles: mediates cytokine (TNF, IL-6) production, regulates endocytosis, cell migration, chromatin remodelling and transcription during stress responses (unknownauthors2014mitogenactivatedproteinkinaseactivated pages 69-72).  
• HSP27 phosphorylation disrupts sHSP oligomers, reducing chaperone capacity under oxidative stress (unknownauthors2014mitogenactivatedproteinkinaseactivated pages 69-72).  
• Phosphorylation of tristetraprolin stabilises pro-inflammatory mRNAs, linking MK3 to TNFα regulation (cheng2010high‐resolutioncrystalstructure pages 1-2).  
• Dynamic localisation: full-length isoform is nuclear in quiescent cells and translocates to cytoplasm upon stress; a shorter splice variant lacking NLS/NES is constitutively cytoplasmic (unknownauthors2014mitogenactivatedproteinkinaseactivated pages 22-28).  
• Signalling network: upstream p38α/β and ERK3/4; downstream substrates include HSP27, TTP, CREB, HSF-1, TAB3, keratins-18/20, RCSD1 and hnRNP A1 (unknownauthors2014mitogenactivatedproteinkinaseactivated pages 69-72, cheng2010high‐resolutioncrystalstructure pages 1-2).

## Inhibitors

• A high-affinity pyrrolopyridinone compound co-crystallised with MK3 occupies the ATP hinge region (cheng2010high‐resolutioncrystalstructure pages 1-2).  
• Additional ATP-competitive and emerging allosteric inhibitors targeting the p38-MK2/3 axis are under preclinical exploration for anti-inflammatory therapy (unknownauthors2014mitogenactivatedproteinkinaseactivated pages 69-72).

## Other Comments

• MK3 contributes to inflammatory and cardiac stress pathways; MK2-null mice studies show MK3 partially compensates for TNFα regulation, underscoring its therapeutic relevance in inflammation (cheng2010high‐resolutioncrystalstructure pages 1-2, unknownauthors2014mitogenactivatedproteinkinaseactivated pages 69-72).

References

1. (unknownauthors2014mitogenactivatedproteinkinaseactivated pages 69-72): Mitogen-activated protein kinase-activated protein kinase 5-Structure, function and inhibition
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4. (unknownauthors2014mitogenactivatedproteinkinaseactivated pages 22-28): Mitogen-activated protein kinase-activated protein kinase 5-Structure, function and inhibition
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