## Phylogeny

• Member of the AGC kinase group, RSK/MSK sub-family on the human kinome dendrogram first defined by Manning and reiterated in later large-scale surveys (johnson2023anatlasof pages 4-4).  
• Closely related to MSK1 (≈ 75 % identity) and more distantly to RSK1/MAPKAP-K1 (≈ 40 % identity) (deak1998mitogenandstressactivated pages 2-3).  
• Vertebrate orthologs include mouse Rps6ka4 (functional in Msk1/2 double-knockout MEFs) (wiggin2002msk1andmsk2 pages 1-2).  
• Invertebrate orthologs are present in Drosophila (JIL-1) and Caenorhabditis elegans (C54G4); MSK genes are absent from fungi and plants (unknownauthors2011identificationandcharacterization pages 33-36).

## Reaction Catalyzed

ATP + protein-Ser/Thr ⇌ ADP + protein-O-phospho-Ser/Thr (unknownauthors2011identificationandcharacterization pages 36-40).

## Cofactor Requirements

No divalent-metal requirement is reported for MSK2 in the cited literature (unknownauthors2020rsk4targetinga pages 54-58).

## Substrate Specificity

• Consensus motif: Arg-Arg-X-Ser/Thr (R-R-X-S/T) (unknownauthors2011identificationandcharacterization pages 36-40).  
• High-throughput phosphoproteomics groups MSK2 with basophilic/proline-directed Ser/Thr kinases, refining preferred residue frequencies surrounding the phosphosite (johnson2023anatlasof pages 12-18).

## Structure

• Single 802-residue polypeptide containing two kinase domains:  
– N-terminal kinase domain (NTKD, AGC-type) executes substrate phosphorylation.  
– C-terminal kinase domain (CTKD, CaMK-like) receives activating phosphorylations from ERK1/2 or p38 (unknownauthors2011identificationandcharacterization pages 33-36, deak1998mitogenandstressactivated pages 2-3).  
• Linker harbours a turn-motif phosphosite Ser347 and a hydrophobic-motif residue analogous to Thr700 of MSK1, both required for maximal activity (unknownauthors2011identificationandcharacterization pages 36-40).  
• CTKD tail contains a MAPK docking D-domain and a bipartite nuclear localisation signal that drive nuclear residency (unknownauthors2011identificationandcharacterization pages 33-36).  
• AlphaFold and related RSK crystal structures define canonical bilobed folds, conserved HRD/DFG catalytic motifs, C-helix positioning and hydrophobic spine typical of AGC kinases (johnson2023anatlasof pages 4-4, unknownauthors2020rsk4targetinga pages 54-58).

## Regulation

Post-translational phosphorylation  
• ERK1/2 and p38 phosphorylate CTKD activation-loop and linker turn-motif residues to initiate activation (deak1998mitogenandstressactivated pages 2-3, unknownauthors2011identificationandcharacterization pages 33-36).  
• Autophosphorylation by CTKD modifies NTKD activation loop and Ser347, completing activation (unknownauthors2011identificationandcharacterization pages 36-40).  
• CK2 phosphorylates Ser324, potentiating UV-induced activation (unknownauthors2011identificationandcharacterization pages 109-114).  
• Hydrophobic-motif phosphorylation (Thr700 equivalent) stabilises the active conformation (unknownauthors2011identificationandcharacterization pages 36-40).

Allosteric & localisation control  
• ERK or p38 remain docked through the D-domain after phosphorylation, maintaining an active MSK2 conformation (unknownauthors2011identificationandcharacterization pages 36-40).  
• Glucocorticoids trigger CRM1-dependent nuclear export of MSK isoforms, dampening inflammatory gene transcription (vermeulen2009theversatilerole pages 1-2).

Chemical blockade of upstream pathways  
• MEK inhibitor PD98059 (ERK pathway) or p38 inhibitor SB203580 individually reduce, and in combination abolish, MSK-dependent CREB phosphorylation in cells (deak1998mitogenandstressactivated pages 10-12).

## Function

Expression & localisation  
• Detected as a ~3 kb transcript in many human tissues; protein is predominantly nuclear (deak1998mitogenandstressactivated pages 2-3).

Upstream stimuli  
• Activated by growth factors (EGF), cytokines (TNFα), Toll-like receptor ligands, UV-C and anisomycin via converging ERK1/2 and p38 cascades (vermeulen2009theversatilerole pages 2-3, wiggin2002msk1andmsk2 pages 1-2).

Validated substrates  
• Transcription factors: CREB1 Ser133, ATF1, NF-κB p65 Ser276, STAT3 Ser727 (wiggin2002msk1andmsk2 pages 1-2, unknownauthors2011identificationandcharacterization pages 40-44, vermeulen2009theversatilerole pages 4-6).  
• Chromatin components: histone H3 Ser10/Ser28, HMGN1 Ser6 (unknownauthors2011identificationandcharacterization pages 40-44, vermeulen2009theversatilerole pages 4-6).  
• Additional targets: BAD Ser112 and 4E-BP1 multiple sites after UV-B exposure (vermeulen2009theversatilerole pages 4-6).

Biological roles  
• Drives immediate-early gene expression (c-fos, junB) in response to mitogen or stress (wiggin2002msk1andmsk2 pages 1-2).  
• Regulates inflammatory gene programmes (IL-6, IL-8, IL-10, DUSP-1) in LPS-stimulated macrophages (unknownauthors2011identificationandcharacterization pages 40-44).  
• Couples ERK/p38 signalling to chromatin modification and transcriptional activation (vermeulen2009theversatilerole pages 2-3).

## Inhibitors

• SB-747651A: ATP-competitive, IC₅₀ ≈ 50 nM for MSK1/2; blocks cellular CREB phosphorylation without affecting upstream MAPKs (naqvi2012characterizationofthe pages 1-2, naqvi2012characterizationofthe pages 4-5).  
• Broad AGC inhibitors H89 and Ro-31-8220 inhibit MSK catalytic activity but lack specificity (vermeulen2009theversatilerole pages 4-6, wiggin2002msk1andmsk2 pages 1-2).

## Other Comments

• Msk1/2 double-knockout mice exhibit exaggerated inflammatory responses and heightened LPS sensitivity (unknownauthors2011identificationandcharacterization pages 40-44).  
• Elevated MSK activity is implicated in psoriatic lesions (vermeulen2009theversatilerole pages 8-8).

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