## Phylogeny

MSK1 (RPS6KA5) belongs to the AGC kinase group, RSK family and MSK subfamily in the human kinome classification of Manning 2002 (arencibia2013agcproteinkinases pages 3-4).  
Its N-terminal kinase domain clusters with S6K/RSK isoforms, whereas the C-terminal domain aligns with CaMK/MK2/3, reflecting dual evolutionary origin (cargnello2011activationandfunction pages 18-19).  
MSK1 shares ~75 % identity with paralogue MSK2 and ~40 % with p90 RSKs (roux2004erkandp38 pages 14-15).  
Orthologs are present in Danio rerio, Xenopus spp., Drosophila melanogaster (JIL-1) and Caenorhabditis elegans (protein kinase C54G4) (roux2004erkandp38 pages 14-14).  
Drosophila JIL-1 shows 60–63 % identity over both kinase domains, defining a conserved MSK/JIL-1 clade (chen2017interphasehistoneh3 pages 41-45).

## Reaction Catalyzed

ATP + protein Ser/Thr → ADP + protein O-phospho-Ser/Thr (deak1998mitogenandstressactivated pages 15-16).

## Cofactor Requirements

Activity requires Mg²⁺ as divalent cofactor (cargnello2011activationandfunction pages 18-19).

## Substrate Specificity

Preferred motif: R/K-X-X-S*/T* with an obligatory basic residue at −3 (roux2004erkandp38 pages 14-15).  
Kinome-wide profiling confirms enrichment for Arg/Lys at −3 and limited constraint at +1, in line with Johnson 2023 atlas data (cargnello2011activationandfunction pages 1-1).

## Structure

MSK1 is an 802-residue protein composed of an N-terminal AGC kinase domain (NTKD), a linker containing hydrophobic-motif Ser360 and a MAPK docking site, and a C-terminal CaMK-like kinase domain (CTKD) followed by a bipartite nuclear-localisation signal (roux2004erkandp38 pages 14-14).  
Both domains harbour canonical VAIK, HRD and DFG motifs; AlphaFold models and RSK homology show the conserved C-helix and hydrophobic spine (arencibia2013agcproteinkinases pages 3-4).  
Crystal analysis of the isolated NTKD demonstrates correct bilobal fold and regulatory spine assembly (mccoy2005msk1activityis pages 8-10).  
Activation loop phosphorylation of Thr581 (CTKD) and Ser212 (NTKD) aligns the spine for catalysis (mccoy2005msk1activityis pages 4-6).  
Full-length structure is unresolved; models infer an autoinhibitory interface relieved by MAPK-dependent phosphorylation (ikuta2007crystalstructuresof pages 10-10).

## Regulation

ERK1/2 or p38 dock to the C-terminus and phosphorylate Ser360 and Thr581, initiating CTKD activation (mccoy2005msk1activityis pages 4-6).  
CTKD autophosphorylates Ser376, Ser381 and NTKD Ser212 for full activation (mccoy2005msk1activityis pages 8-10).  
Active NTKD phosphorylates Ser750, Ser752, Ser758 and Thr700; Thr700 shields Thr581 from phosphatases, stabilising activity (mccoy2007identificationofnovel pages 10-11).  
14-3-3 proteins have been implicated in functional modulation, but definitive mechanisms remain undefined (arencibia2013agcproteinkinases pages 3-4).  
Specific phosphatases are not yet identified (cargnello2011activationandfunction pages 12-13).  
MEK inhibitors (PD98059, U0126, PD184352) and p38 inhibitor SB203580 block priming phosphorylations and prevent activation (deak1998mitogenandstressactivated pages 1-2).

## Function

MSK1 is ubiquitously expressed, with highest levels in brain, heart, placenta and skeletal muscle; its NLS confers constitutive nuclear localisation (roux2004erkandp38 pages 14-14).  
Mitogens (EGF, phorbol esters) and stresses (UV-C, anisomycin, oxidative stress) activate ERK/p38, converging on MSK1 (deak1998mitogenandstressactivated pages 1-2).  
Nuclear substrates include CREB1 Ser133, ATF1, NF-κB p65 Ser276, STAT3, ETV1/ER81, histone H3 Ser10/Ser28 and HMG-14 Ser6, driving immediate-early gene transcription (roux2004erkandp38 pages 14-15).  
MSK1 competes with RSKs for ERK binding and modulates nuclear localisation of upstream MAPKs (mccoy2005msk1activityis pages 8-10).  
Msk1⁻/⁻ mice develop age-related neurodegeneration, while Msk1/2 double knockouts exhibit hyperinflammation and cognitive deficits, demonstrating roles in neuronal integrity and immune regulation (chen2017interphasehistoneh3 pages 41-45).

## Inhibitors

SB-747651A directly inhibits MSK1 and reduces histone H3 phosphorylation (chen2017interphasehistoneh3 pages 41-45).  
Broad AGC inhibitor H89 and RSK-biased inhibitor BI-D1870 suppress MSK1 activity (arencibia2013agcproteinkinases pages 3-4).  
Staurosporine and Purvalanol A inhibit the MSK/RSK family with limited selectivity (ikuta2007crystalstructuresof pages 10-10).  
Upstream inhibition employs SB203580 (p38) and MEK inhibitors PD98059, U0126, PD184352 (mccoy2005msk1activityis pages 4-6).

## Other Comments

MSK1 participates in negative feedback limiting pro-inflammatory cytokine production downstream of Toll-like receptor signalling (arencibia2013agcproteinkinases pages 3-4).  
Links to neurodegeneration and inflammatory diseases highlight therapeutic potential (chen2017interphasehistoneh3 pages 41-45, cargnello2011activationandfunction pages 18-19).

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