## Phylogeny

Mitogen- and stress-activated protein kinase-1 (MSK1, RPS6KA5) is assigned to the AGC kinase group, RSK family, MSK subfamily of the human kinome (Arencibia et al., 2013). Its N-terminal kinase domain (NTKD) clusters with p70 S6K/p90 RSK isoforms, whereas the C-terminal kinase domain (CTKD) aligns with CaMK/MK2/3, indicating a dual evolutionary origin (Cargnello & Roux, 2011). MSK1 shares ~75 % sequence identity with the paralogue MSK2 and ~40 % with p90 RSKs (Roux & Blenis, 2004). Orthologues occur in zebrafish, Xenopus, Drosophila (JIL-1) and C. elegans, with Drosophila JIL-1 displaying 60–63 % identity over both kinase domains, defining a conserved MSK/JIL-1 clade (Chen, 2017).

## Reaction Catalyzed

ATP + protein-L-Ser/Thr → ADP + protein-O-phospho-L-Ser/Thr (Deák et al., 1998).

## Cofactor Requirements

Mg²⁺ is required for catalytic activity (Cargnello & Roux, 2011).

## Substrate Specificity

Peptide preference: R/K-X-X-S*/T* with an obligatory basic residue at position −3; kinase-wide profiling confirms enrichment for Arg/Lys at −3 and little constraint at +1 (Roux & Blenis, 2004; Cargnello & Roux, 2011).

## Structure

MSK1 is an 802-residue protein comprising an NTKD of the AGC fold, a linker harbouring a hydrophobic-motif Ser360 and MAPK docking site, and a CaMK-like CTKD followed by a bipartite nuclear localisation signal (Roux & Blenis, 2004). Both kinase domains contain conserved VAIK, HRD and DFG motifs; models and RSK homology reveal intact C-helix and regulatory spine (Arencibia et al., 2013). The isolated NTKD crystallises in the canonical bilobal fold with a properly assembled regulatory spine (McCoy et al., 2005). Phosphorylation of Ser212 (NTKD) and Thr581 (CTKD) aligns the spine for catalysis (McCoy et al., 2005). A full-length structure is unresolved, but modelling suggests an autoinhibitory interface that is relieved by MAPK-dependent phosphorylation (Ikuta et al., 2007).

## Regulation

• ERK1/2 or p38 dock to the C-terminus and phosphorylate Ser360 and Thr581, triggering CTKD activation (McCoy et al., 2005).  
• CTKD then autophosphorylates Ser376, Ser381 and NTKD Ser212 for full activation (McCoy et al., 2005).  
• Active NTKD phosphorylates Ser750, Ser752, Ser758 and Thr700; phosphorylation of Thr700 protects Thr581 from phosphatases, stabilising activity (McCoy et al., 2007).  
• 14-3-3 proteins modulate function, although the mechanism is not yet defined (Arencibia et al., 2013).  
• Specific phosphatases remain unidentified (Cargnello & Roux, 2011).  
• Upstream MEK inhibitors (PD98059, U0126, PD184352) and the p38 inhibitor SB203580 prevent the priming phosphorylations and block activation (Deák et al., 1998).

## Function

MSK1 is ubiquitously expressed, with highest levels in brain, heart, placenta and skeletal muscle; the NLS confers constitutive nuclear localisation (Roux & Blenis, 2004). Mitogens (e.g., EGF, phorbol esters) and stresses (UV-C, anisomycin, oxidative stress) activate ERK/p38, which converge on MSK1 (Deák et al., 1998). Nuclear substrates include CREB1 Ser133, ATF1, NF-κB p65 Ser276, STAT3, ETV1, histone H3 Ser10/Ser28 and HMG-14 Ser6, thereby promoting immediate-early gene transcription (Roux & Blenis, 2004). MSK1 competes with RSKs for ERK binding and influences nuclear localisation of upstream MAPKs (McCoy et al., 2005). Msk1⁻/⁻ mice show age-related neurodegeneration, while Msk1/2 double knockouts exhibit hyper-inflammation and cognitive deficits, underscoring roles in neuronal integrity and immune regulation (Chen, 2017).

## Inhibitors

Direct: SB-747651A, H89, BI-D1870, staurosporine, purvalanol A inhibit MSK1 with varying selectivity (Arencibia et al., 2013; Chen, 2017; Ikuta et al., 2007).  
Upstream: SB203580 (p38) and MEK inhibitors PD98059, U0126, PD184352 block activating phosphorylations (McCoy et al., 2005; Deák et al., 1998).

## Other Comments

MSK1 forms part of a negative-feedback loop that limits pro-inflammatory cytokine production downstream of Toll-like receptor signalling and has been linked to neurodegenerative and inflammatory diseases, highlighting therapeutic potential (Arencibia et al., 2013; Chen, 2017; Cargnello & Roux, 2011).

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