1. Phylogeny  
   RPS6KA4, commonly known as MSK2, is a member of the MAPK‐activated protein kinase (MAPKAPK) family and is grouped alongside MSK1 within the dual–kinase domain subfamily of the ribosomal S6 kinase (RSK) superfamily (cargnello2011activationandfunction pages 18-19). MSK2 is evolutionarily conserved across vertebrates and can be traced back to a common ancestor of metazoans, with orthologs identified from mammals to invertebrates such as Drosophila, in which the JIL-1 kinase exhibits structural and functional similarities (roux2004erkandp38 pages 13-14). Phylogenetic studies using genomic homology have classified MSK2 within the AGC kinase group, which also includes other major kinases such as PKA, PKC, and Akt (arul2013arisingcancer pages 2-3). MSK2 and its close paralog, MSK1, share approximately 63% amino acid identity, highlighting their common evolutionary origin and functional redundancy in numerous species (cargnello2011activationandfunction pages 13-15). Furthermore, the dual kinase domain architecture observed in MSK2 is distinct from that of the classical RSK isoforms, reflecting an evolutionary adaptation in response to the need for integration of stress and mitogenic signals in the nucleus (roux2004erkandp38 pages 13-14). The gene encoding MSK2 (RPS6KA4) is mapped to a locus associated with Bardet-Biedl syndrome on human chromosome 11, further illustrating the conservation of genomic organization across species (cargnello2011activationandfunction pages 18-19).
2. Reaction Catalyzed  
   MSK2 catalyzes the transfer of a phosphate group from ATP to specific serine or threonine residues on its protein substrates, following the general reaction: ATP + protein–[L-serine or L-threonine] → ADP + protein–[L-serine/threonine]-phosphate + H⁺ (cargnello2011activationandfunction pages 18-19). This phosphorylation reaction is characteristic of serine/threonine kinases and serves as a molecular switch that modulates the activity, localization, and interaction patterns of substrate proteins (arul2013arisingcancer pages 10-10).
3. Cofactor Requirements  
   The catalytic activity of MSK2, like most protein kinases, depends critically on the presence of Mg²⁺ ions, which coordinate with ATP to enable efficient phosphoryl transfer (jha2025deeplearningcoupledproximity pages 11-11). This cofactor requirement is essential for stabilizing the nucleotide within the active site and promoting the chemical reaction (cargnello2011activationandfunction pages 1-2).
4. Substrate Specificity  
   MSK2 exhibits substrate specificity for serine/threonine residues within consensus motifs that typically contain basic residues in the vicinity of the phosphorylation site, exemplified by an Arg–X–X–pSer/Thr sequence (cargnello2011activationandfunction pages 29-30). Its principal substrates include the transcription factors CREB and ATF1, where MSK2 phosphorylates CREB at Ser133 and ATF1 at Ser63, leading to the recruitment of transcriptional coactivators such as CBP and p300 (cargnello2011activationandfunction pages 18-19). Additionally, MSK2 phosphorylates histone H3 at Ser10—and potentially at Ser28—thus contributing to chromatin remodeling and activation of immediate early genes like c-fos and c-jun (cargnello2011activationandfunction pages 28-29, arul2013arisingcancer pages 10-10). Other substrates of MSK2 include high mobility group proteins, which are involved in the regulation of transcription during stress responses, thereby underscoring its role in modulating gene expression via multiple downstream effectors (roux2004erkandp38 pages 13-14).
5. Structure  
   MSK2 is characterized by the presence of two distinct kinase domains arranged sequentially within a single polypeptide. The N-terminal kinase domain (NTKD) belongs to the AGC kinase family and is primarily responsible for substrate phosphorylation, while the C-terminal kinase domain (CTKD) possesses a calcium/calmodulin-dependent kinase (CAMK)-like fold and functions predominantly in autophosphorylation and activation of the NTKD (cargnello2011activationandfunction pages 18-19, roux2004erkandp38 pages 13-14). In addition to these catalytic domains, MSK2 contains regulatory regions such as a MAPK docking domain that facilitates binding to upstream kinases like ERK1/2 and p38, and a bipartite nuclear localization signal (NLS) that predominantly localizes the enzyme to the nucleus (cargnello2011activationandfunction pages 17-18, roux2004erkandp38 pages 5-8). The activation loop within each kinase domain contains conserved serine/threonine residues whose phosphorylation is critical for full enzymatic activity; for instance, phosphorylation of residues in the linker region, the CTKD activation loop, and a C-terminal site is required to relieve autoinhibition and promote the conformational changes necessary for substrate recognition (cargnello2011activationandfunction pages 18-19, roux2004erkandp38 pages 13-14). Structural studies, including those supported by multiple sequence alignments and crystallographic modeling, have emphasized these conserved motifs as key determinants of the catalytic and regulatory properties unique to the MSK subfamily (modi2019astructurallyvalidatedmultiple pages 12-13).
6. Regulation  
   The activation of MSK2 is tightly regulated by phosphorylation events mediated by upstream mitogen-activated protein kinases (MAPKs), specifically ERK1/2 and p38 MAPK, which directly phosphorylate MSK2 at multiple conserved sites (cargnello2011activationandfunction pages 18-19, roux2004erkandp38 pages 13-14). Unlike the related RSK isoforms, the activation of MSK2 does not require phosphorylation by phosphoinositide-dependent kinase 1 (PDK1) because the NTKD undergoes autophosphorylation once the CTKD has been activated via upstream phosphorylation (cargnello2011activationandfunction pages 17-18, roux2004erkandp38 pages 13-14). Specific phosphorylation sites include a residue in the linker region (commonly Ser360), the activation loop of the CTKD (Thr581), and a C-terminal site (Thr700), with the modification at each site being essential for inducing the conformational changes that result in full catalytic activity (cargnello2011activationandfunction pages 18-19). Furthermore, MSK2’s regulatory mechanism involves interaction with scaffold proteins and regulatory modules that facilitate its activation, and the nuclear localization conferred by its bipartite NLS ensures that phosphorylated substrates, such as CREB and histone H3, are promptly modified to trigger downstream transcriptional responses (cargnello2011activationandfunction pages 17-18, roux2004erkandp38 pages 5-8). Pharmacological inhibition of upstream MAPK pathways using MEK1/2 or p38 inhibitors has been demonstrated to indirectly dampen MSK2 activity, although a highly selective direct inhibitor of MSK2 has not yet been identified (cargnello2011activationandfunction pages 28-29, roux2004erkandp38 pages 14-15).
7. Function  
   MSK2 functions as a serine/threonine kinase that plays a pivotal role in the transduction of mitogenic and stress signals to the nucleus, where it governs gene expression through phosphorylation-dependent mechanisms (cargnello2011activationandfunction pages 19-20). It phosphorylates key transcription factors such as CREB at Ser133 and ATF1 at Ser63, facilitating the recruitment of transcriptional coactivators and the subsequent activation of immediate early genes including proto-oncogenes c-fos and c-jun (cargnello2011activationandfunction pages 18-19, arul2013arisingcancer pages 10-10). Additionally, MSK2 phosphorylates histone H3, specifically at Ser10—and potentially at Ser28—which leads to chromatin remodeling and the displacement of transcriptional repressors, thereby promoting gene activation in response to extracellular stimuli such as UV irradiation, epidermal growth factor (EGF), and anisomycin (cargnello2011activationandfunction pages 28-29, roux2004erkandp38 pages 13-14). MSK2 also influences the activity of the NF-κB pathway by phosphorylating the p65 subunit (RELA) at serine residues to modulate its transcriptional activity, particularly in response to tumor necrosis factor (TNF) (cargnello2011activationandfunction pages 18-19). In immune cells, such as lipopolysaccharide-stimulated primary macrophages, MSK2 acts downstream to regulate the expression of inflammatory cytokines and negative feedback regulators, thereby contributing to the fine-tuning of inflammatory responses (roux2004erkandp38 pages 21-22). The expression of MSK2 is ubiquitous, with notably high levels in tissues such as the brain, heart, and muscle, which is consistent with its role in regulating stress-induced gene transcription and cell survival (cargnello2011activationandfunction pages 17-18).
8. Other Comments  
   No selective direct inhibitors targeting MSK2 have yet been identified, although inhibitors of upstream MAPK pathways, including MEK1/2 and p38 inhibitors, indirectly reduce its activity by preventing the necessary phosphorylation events (cargnello2011activationandfunction pages 28-29, roux2004erkandp38 pages 14-15). MSK2 is implicated in several disease processes due to its central involvement in the regulation of transcription in response to both mitogenic and stress stimuli; aberrant MSK2 signaling has been associated with inflammatory diseases and possibly oncogenesis, given its role in phosphorylating transcription factors and modulating chromatin structure (arul2013arisingcancer pages 10-10, cargnello2011activationandfunction pages 19-20). Additionally, the mapping of the MSK2 gene to the Bardet-Biedl syndrome (BBS1) locus suggests that its dysregulation may contribute to developmental abnormalities, although direct causality with Bardet-Biedl syndrome has not been conclusively demonstrated (cargnello2011activationandfunction pages 18-19). MSK2 also functions non-catalytically in certain contexts, such as the basal inhibition of p53 transcriptional activity, indicating that its role in cellular signaling may extend beyond its enzymatic activity (cargnello2011activationandfunction pages 29-30). Collectively, these features underscore the importance of MSK2 as a key node in MAPK signaling with potential therapeutic relevance, although further studies are required to develop highly specific pharmacological modulators (roux2004erkandp38 pages 21-21).
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