1. Phylogeny  
   RPS6KA5, commonly known as MSK1, is classified within the p90 ribosomal S6 kinase family of serine/threonine protein kinases, a subgroup of the AGC family that has been conserved throughout eukaryotic evolution (poomakkoth2016p90ribosomals6 pages 2-4). MSK1 is a member of the MAPK‐activated protein kinase (MAPKAPK) subfamily and is phylogenetically related to the classical RSK isoforms (RSK1–RSK4) as well as to its closely related isoform MSK2; despite shared common ancestry, MSK1 displays a divergence in regulatory mechanisms and substrate specificity that distinguishes it functionally from the canonical RSK kinases (anjum2008therskfamily pages 4-4, cargnello2011activationandfunction pages 18-19). Comparative sequence analyses reveal that orthologs of MSK1 are present in diverse metazoan species, including vertebrates such as rodents and humans, thereby emphasizing its role as an evolutionarily conserved element within the Ras–MAPK signaling cascade (poomakkoth2016p90ribosomals6 pages 2-4, cargnello2011activationandfunction pages 18-19). The evolutionary conservation of key catalytic motifs and regulatory domains in MSK1 underscores its participation in a core set of eukaryotic signaling modules that includes other members of the AGC kinases and MAPKAP kinases, reflecting an ancestral origin that predates the divergence of animals and fungi (poomakkoth2016p90ribosomals6 pages 2-4, anjum2008therskfamily pages 4-4). In summary, the phylogenetic context of MSK1 situates it as a pivotal and highly conserved kinase that integrates signals from upstream MAPK pathways while maintaining structural features shared with its RSK relatives.
2. Reaction Catalyzed  
   MSK1 catalyzes a phosphorylation reaction that is fundamental to its role as a signal transducer. In its enzymatic activity, MSK1 transfers a phosphate group from ATP to the hydroxyl (–OH) group of serine or threonine residues present on target substrates. The chemical reaction can be represented as follows:  
     ATP + [protein]-(L-serine or L-threonine) → ADP + [protein]-(L-serine/threonine)-phosphate + H⁺  
   This reaction underpins the molecular mechanism by which MSK1 modifies its substrates, such as transcription factors and histone proteins, to alter their activity and thereby modulate gene expression. In particular, MSK1 is responsible for phosphorylating CREB1 and ATF1 in response to a variety of mitogenic or stress stimuli, including UV irradiation, epidermal growth factor (EGF), and anisomycin (poomakkoth2016p90ribosomals6 pages 2-4, cargnello2011activationandfunction pages 32-33). The phosphoryl transfer event, which results in the production of ADP and a phosphorylated protein product, is a canonical reaction for serine/threonine kinases and is critical for effecting rapid and reversible changes in protein function in response to extracellular signals (cargnello2011activationandfunction pages 29-29, anti2009nonspecificserinethreonineprotein pages 29-32).
3. Cofactor Requirements  
   The catalytic activity of MSK1 is contingent upon the presence of specific cofactors that facilitate the phosphoryl-transfer reaction. Chief among these is magnesium ion (Mg²⁺), which is required to coordinate the binding of ATP within the kinase active site. Mg²⁺ stabilizes the negative charges on the phosphate groups of ATP and ensures correct orientation for efficient phosphate transfer to the substrate (poomakkoth2016p90ribosomals6 pages 2-4, anti2009nonspecificserinethreonineprotein pages 29-32). In addition to Mg²⁺, ATP itself serves both as a substrate and the phosphate donor, ensuring that the reaction adheres to the typical scheme observed in serine/threonine kinases. This cofactor requirement is shared broadly among kinases of the AGC family and is imperative for the regulation of enzyme kinetics and catalytic turnover (utepbergenov2016bacterialexpressionpurification pages 14-15).
4. Substrate Specificity  
   MSK1 exhibits a substrate specificity that is tailored toward a subset of nuclear proteins involved in the control of gene expression and chromatin dynamics. It preferentially phosphorylates serine/threonine residues located in target proteins that govern transcriptional activation. A well‐characterized substrate of MSK1 is the transcription factor CREB1, which is phosphorylated on Ser133—a modification critical for its ability to induce target gene expression (poomakkoth2016p90ribosomals6 pages 2-4, cargnello2011activationandfunction pages 32-33). In addition, MSK1 phosphorylates ATF1 and histone proteins, including histone H3, thereby directly impacting chromatin structure and enabling immediate early gene transcription in response to external signals (cargnello2011activationandfunction pages 32-33). Although a detailed consensus substrate motif for MSK1 has not been as clearly delineated as for some other serine/threonine kinases, the preference for substrates often involves recognition of amino acid sequences that contain basic residues adjacent to the target phosphoacceptor site, a characteristic common to many MAPK-activated protein kinases (anti2009nonspecificserinethreonineprotein pages 29-32, anjum2008therskfamily pages 4-4). This inherent specificity ensures that MSK1 selectively modulates the activity of a precise set of nuclear substrates, thereby orchestrating a coordinated transcriptional response under conditions of cellular stress and growth factor stimulation.
5. Structure  
   The three‐dimensional structure of MSK1 is characterized by a modular organization that includes two active kinase domains, each with distinct roles in the enzyme’s catalytic cycle. The N-terminal kinase domain (NTKD) is a member of the AGC kinase family and is primarily responsible for phosphorylating downstream protein substrates. In contrast, the C-terminal kinase domain (CTKD) shares structural features with calcium/calmodulin-dependent protein kinases (CAMK) and is responsible for mediating autophosphorylation and initiating the activation cascade of the NTKD (cargnello2011activationandfunction pages 12-13, cargnello2011activationandfunction pages 13-15). These two domains are connected by a regulatory linker region that itself is subject to phosphorylation, a modification that is essential for relieving autoinhibitory constraints and enabling full catalytic activation (lee2007p90ribosomals6 pages 1-3, poomakkoth2016p90ribosomals6 pages 2-4).

X-ray crystallography and comparative structural analyses have revealed that the NTKD of kinases related to MSK1 possesses a highly conserved ATP-binding pocket, an activation loop that undergoes phosphorylation, and a C-helix that is crucial for maintaining the correct alignment of catalytic residues. Notably, studies on RSK2—a close relative within the ribosomal S6 kinase family—have identified a lysine residue (equivalent to Lys200 in MSK1) that is critical for ATP phosphate binding, serving a compensatory role in the absence of a classical Lys–Glu salt bridge seen in other kinases (kurinov2009structuraldiversityof pages 4-6, lee2007p90ribosomals6 pages 1-3). In addition, MSK1 contains a MAPK docking domain that enables interactions with upstream kinases such as ERK1/2 and p38, thereby positioning MSK1 to receive activating phosphorylation events (cargnello2011activationandfunction pages 19-20, poomakkoth2016p90ribosomals6 pages 2-4). Furthermore, the structure of MSK1 includes a nuclear localization signal (NLS) that directs the predominantly nuclear location of the enzyme, consistent with its role in modifying transcription factors and chromatin components (lee2007p90ribosomals6 pages 3-5). Unique structural features, including additional β-sheet insertions identified in related kinases, may further refine MSK1’s catalytic efficiency and substrate recognition, although detailed experimental structures specific to MSK1 are limited (kurinov2009structuraldiversityof pages 10-10). Collectively, the dual kinase domain architecture of MSK1, combined with its regulatory regions and docking motifs, provides a structural framework that is essential for its function as an integrator of MAPK signals in the nucleus.

1. Regulation  
   The regulation of MSK1 is mediated by a complex network of post-translational modifications and protein–protein interactions that link extracellular signals to nuclear responses. Upon exposure to mitogenic or stress stimuli—such as UV irradiation, EGF, and anisomycin—MSK1 is rapidly activated through phosphorylation by upstream MAP kinases, most notably ERK1/2 and p38 MAPK (poomakkoth2016p90ribosomals6 pages 2-4, moens2013theroleof pages 4-6). These kinases phosphorylate MSK1 at specific regulatory residues, including but not limited to Ser221, Ser363, Ser380, and Thr573, triggering conformational changes that ultimately relieve autoinhibition and permit autophosphorylation within the regulatory linker region (cargnello2011activationandfunction pages 18-19, cargnello2011activationandfunction pages 32-33).

MSK1 also harbors a MAPK docking domain that is critical for forming stable complexes with ERK1/2 and p38, thereby ensuring the specificity and efficiency of its activation (cargnello2011activationandfunction pages 12-13). Moreover, phosphorylation events carried out by MSK1’s own CTKD contribute to a feedback mechanism that solidifies its active conformation and facilitates full activation of the NTKD, allowing for efficient substrate phosphorylation (cargnello2011activationandfunction pages 18-19, poomakkoth2016p90ribosomals6 pages 2-4). In addition to phosphorylation, MSK1 regulation is modulated through interactions with other signaling proteins. For instance, MSK1 associates with the glucocorticoid receptor (NR3C1) in the cytoplasm, which is implicated in the control of RELA-dependent transcriptional repression of inflammatory genes. This interaction plays a role in the negative regulation of NF-κB signaling and helps fine-tune inflammatory responses, particularly in the context of TNF stimulation and glucocorticoid signaling (poomakkoth2016p90ribosomals6 pages 2-4).

The application of pharmacological inhibitors, such as MEK1/2 inhibitors, has further elucidated the dependency of MSK1 activation on the upstream MAPK cascade, as these compounds prevent the phosphorylation events necessary for MSK1 activation (wright2023therapeutictargetingof pages 1-3). This regulatory architecture, which integrates multisite phosphorylation, conformational rearrangement, and scaffolding interactions, ensures that MSK1 activity is tightly controlled in both spatial and temporal dimensions, thereby enabling it to function as a precise mediator of cellular responses to diverse external stimuli.

1. Function  
   MSK1 serves a critical function as a nuclear serine/threonine kinase that transduces extracellular signals into robust transcriptional responses. One of the principal functions of MSK1 is to phosphorylate key transcription factors involved in immediate early gene activation. Notably, MSK1 is required for the mitogen- or stress-induced phosphorylation of CREB1 at Ser133 and ATF1, modifications that are essential for initiating transcription programs that regulate cell survival, proliferation, and differentiation (poomakkoth2016p90ribosomals6 pages 2-4, cargnello2011activationandfunction pages 32-33). In addition to transcription factors, MSK1 phosphorylates histone proteins such as histone H3, thereby contributing directly to chromatin remodeling and the regulation of gene expression (cargnello2011activationandfunction pages 32-33).

Beyond its role in transcriptional activation, MSK1 is instrumental in mediating the regulation of inflammatory gene expression. In skeletal myoblasts, for example, MSK1 is necessary for the phosphorylation of the NF-κB subunit RELA at Ser276—a modification that is critical for the formation of transcriptionally repressive complexes that dampen inflammatory responses (poomakkoth2016p90ribosomals6 pages 2-4). Additionally, MSK1 influences the activity of other transcription factors such as STAT3 and ETV1/ER81, thereby extending its impact to multiple signaling pathways that control immune responses, cellular stress adaptation, and developmental processes (wright2023therapeutictargetingof pages 1-3).

Expression studies have indicated that MSK1 is ubiquitously expressed across various tissues, with particularly high activity observed in cell types that demand rapid transcriptional adaptation in response to stress and growth signals, including neuronal cells, immune cells, and muscle tissue (anjum2008therskfamily pages 4-4, cargnello2011activationandfunction pages 18-19). Downstream of its activation by ERK1/2 and p38 MAPK, MSK1 orchestrates the formation of transcriptional complexes and influences the epigenetic landscape of the cell, thereby ensuring that proliferative and anti-inflammatory gene programs are appropriately regulated in response to changing environmental conditions. The centrality of MSK1 in these processes highlights its role as a pivotal node in cellular signaling networks that maintain homeostasis under both normal and stress conditions.

1. Other Comments  
   MSK1 has garnered considerable interest as a potential therapeutic target owing to its involvement in mediating stress and inflammatory responses. Its unique inhibitor sensitivity profile distinguishes it from classical RSK kinases; for instance, compounds such as BI-D1870, which selectively inhibit p90 RSK isoforms, do not exhibit inhibitory activity toward MSK1, underscoring the need for the development of MSK1-specific inhibitors (sapkota2007bid1870isa pages 1-2). This differential pharmacological profile makes MSK1 a promising target for therapeutic intervention in conditions where dysregulated MAPK signaling contributes to pathology, such as chronic inflammatory diseases and certain cancers (wright2023therapeutictargetingof pages 1-3, moens2013theroleof pages 4-6).

In addition, MSK1’s regulatory role in the phosphorylation of key transcription factors and chromatin modifiers positions it as an important modulator of gene expression, with implications for immune regulation and cellular stress responses. Its association with the glucocorticoid receptor NR3C1, and its contribution to the phosphorylation of RELA, particularly in skeletal myoblasts, indicate that MSK1 may play a role in controlling inflammatory gene expression and, therefore, in the suppression of inflammatory signaling (poomakkoth2016p90ribosomals6 pages 2-4). Although specific disease-causing mutations in MSK1 have not been prominently reported in the extant literature provided here, the central position of MSK1 in multiple signaling cascades suggests that alterations in its regulatory or catalytic functions could have significant biological consequences.

Ongoing research continues to elucidate the structural basis of MSK1’s activation and substrate specificity, and advances in inhibitor development are expected to yield more selective compounds that can modulate its activity in a clinical setting. As such, MSK1 remains an active area of investigation not only for its fundamental role in signal transduction but also for its potential as a biomarker and therapeutic target in diseases characterized by aberrant MAPK pathway activity. Further detailed structural and mechanistic studies will be essential to fully harness the therapeutic potential of modulating MSK1 function.

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