1. Phylogeny  
   RSK4 (RPS6KA6-b), also known as pp90RSK4, is a member of the p90 ribosomal S6 kinase (RSK) family, which itself is part of the larger AGC kinase superfamily. Orthologs of RSK4 have been identified in several mammals, including human and mouse, and its gene is localized on the X chromosome. Comparative analyses have shown that the RSK family is composed of four isoforms (RSK1, RSK2, RSK3, and RSK4) that arose from early gene duplication events within metazoans; among these, RSK4 stands out as the most divergent member with regard to regulatory and noncatalytic sequences. RSK4 appears to have evolved unique features that distinguish its constitutive kinase activity and growth‐factor–independent signaling from the more stringently regulated isoforms. These evolutionary relationships, based on conserved domain organization and expression patterns in extraembryonic tissues (as observed in mouse models), underscore the specialized role of RSK4 in developmental processes and cell cycle control (romeo2012regulationandfunction pages 2-4, song…2013basicanatomyand pages 1-2, myers2004characterizationofmouse pages 2-2).
2. Reaction Catalyzed  
   RSK4 catalyzes the transfer of a phosphate group from ATP to hydroxyl groups on serine or threonine residues present in substrate proteins. This enzymatic reaction can be represented by the following chemical equation:  
     ATP + [protein]-(L-serine or L-threonine) → ADP + [protein]-(L-serine/threonine)-phosphate + H⁺  
   This reaction is fundamental to the modulation of protein activity within signaling pathways and is characteristic of all serine/threonine kinases, including the RSK family (roux2007raserksignalingpromotes pages 1-2, romeo2012regulationandfunction pages 1-2).
3. Cofactor Requirements  
   The catalytic function of RSK4, like that of other serine/threonine kinases, is dependent on the presence of divalent metal ions. In particular, Mg²⁺ is required as an essential cofactor to coordinate the binding of ATP in the kinase active site, ensuring proper phosphoryl transfer during the reaction. This requirement for Mg²⁺ is a hallmark of the kinase family and is necessary for optimal enzymatic activity (wright2023therapeutictargetingof pages 1-3, roux2007raserksignalingpromotes pages 1-2).
4. Substrate Specificity  
   RSK family kinases, including RSK4, exhibit substrate specificity dictated by the amino acid environment surrounding the phosphorylated serine/threonine residues. Although isoform‐specific substrates for RSK4 have not been uniquely detailed, evidence from studies on related RSK isoforms indicates a consensus motif that generally conforms to a pattern containing basic residues—frequently described as RxRxxp[ST]. Such motifs facilitate recognition by the enzyme’s active site and ensure that phosphorylation occurs on proteins involved in cellular processes such as translation regulation, cell cycle control, and signal transduction. The substrate specificity observed in RSK4 is consistent with that of its paralogs and is supported by peptide phosphorylation assays and mutagenesis studies conducted in vitro (romeo2012regulationandfunction pages 2-4, song…2013basicanatomyand pages 1-2, anjum2008therskfamily pages 2-4).
5. Structure  
   RSK4 features a canonical dual-kinase domain architecture that is characteristic of the p90 ribosomal S6 kinase family. Its structure consists of two kinase domains arranged in tandem within a single polypeptide chain. The N-terminal kinase domain (NTKD) is responsible for substrate phosphorylation and exhibits a structure similar to that of other AGC kinases, comprising a small lobe that binds ATP and a larger lobe that harbors the substrate binding site. The C-terminal kinase domain (CTKD) plays a crucial role in autophosphorylation events that are required for full activation of the NTKD. Detailed structural models, derived from crystallographic studies of related RSK isoforms and validated by AlphaFold predictions, show that both kinase domains contain key features such as the activation loop, the DFG motif for coordinating Mg²⁺, and the C-helix that is critical for proper catalytic function. In RSK4, unique extensions and divergent sequences in the N- and C-terminal regions may imprint its characteristic growth-factor–independent activity and constitutive basal phosphorylation status. In addition, observations of a threonine gatekeeper residue in the CTKD have implications for inhibitor binding, as covalent and allosteric inhibitors may exploit this structural difference to achieve isoform selectivity (song…2013basicanatomyand pages 16-17, romeo2012regulationandfunction pages 4-5, wright2023therapeutictargetingof pages 13-13, myers2004characterizationofmouse pages 8-10).
6. Regulation  
   The regulatory mechanisms governing RSK4 activity diverge in important ways from those of its family members. Unlike RSK1, RSK2, and RSK3, which are activated acutely by extracellular growth factors through the Ras/ERK signaling cascade and subsequent phosphorylation by PDK1, RSK4 is characterized by constitutive kinase activity. This growth-factor–independent activity is maintained, in part, by autophosphorylation events that stabilize the active conformation of the enzyme. RSK4 is known to participate in p53/TP53-dependent cell growth arrest signaling; this is achieved through the phosphorylation of substrates that mediate cell cycle checkpoint control, although the full complement of its downstream targets is still under investigation. Furthermore, studies in embryonic models have demonstrated that RSK4 functions as an inhibitor within the fibroblast growth factor (FGF)-Ras-ERK pathway during critical stages of development, thereby contributing to the regulation of mesodermal tissue formation. The overall regulatory profile of RSK4, involving specific phosphorylation sites in its activation loop and other regulatory motifs, indicates a unique mode of control distinct from the other RSK isoforms. Post-translational modifications, particularly phosphorylation at key serine and threonine residues, play a decisive role in modulating RSK4’s activity and subcellular localization (fan2013ribosomals6protein pages 10-10, myers2004characterizationofmouse pages 10-11, romeo2012regulationandfunction pages 14-14, wright2023therapeutictargetingof pages 1-3).
7. Function  
   RSK4 functions primarily as a serine/threonine-protein kinase that is implicated in the regulation of cell proliferation, differentiation, and growth arrest. One of its central roles is in mediating p53/TP53-dependent cell growth arrest signaling. This function is particularly critical during embryogenesis, where RSK4 acts as an inhibitor within the FGF-Ras-ERK signaling axis and contributes to mesoderm formation, thereby affecting tissue development. In the context of cancer, RSK4 has been observed to manifest anti-invasive and antimetastatic properties; these tumor-suppressive activities have been reported in various cancers including renal cell carcinoma, non-small cell lung cancer, and breast cancer. Differential expression and the presence of multiple protein isoforms—resulting from alternative splicing and transcription initiation—further underscore the complexity of RSK4’s functional roles in both normal developmental processes and oncogenesis. RSK4’s constitutive activity and its impact on cell adhesion molecules, matrix metalloproteinases, and key cell cycle regulators such as cyclin D1 place it at a strategic nodal point in the orchestration of cell signaling networks that govern proliferation and apoptosis (fan2013ribosomals6protein pages 10-10, song…2013basicanatomyand pages 16-17, wright2023therapeutictargetingof pages 1-3, luo…2018clinicopathologicalsignificanceof pages 5-8, anjum2008therskfamily pages 1-2).
8. Other Comments  
   Several inhibitors with activity against RSK family members have been evaluated in preclinical studies, although agents with high specificity toward RSK4 remain less well defined. Among these, compounds such as BI-D1870 have been used to inhibit RSK activity, while trovafloxacin has been reported as a non-competitive ATP inhibitor showing selectivity toward RSK4 with in vitro IC50 values in the low micromolar range. In addition to small-molecule inhibitors, proteolysis-targeting chimeras (PROTACs) are being explored as a means to selectively degrade RSK isoforms, which may eventually provide improved therapeutic approaches. RSK4 has been associated with resistance to chemotherapeutic agents in various cancers, and alterations in its expression have been linked to both oncogenic and tumor-suppressive outcomes in different cellular contexts. In lung, renal, and breast cancers, for example, differential expression patterns and post-transcriptional modifications such as alternative splicing events contribute to a complex regulatory landscape that affects cell invasion and metastasis. Furthermore, RSK4 has been implicated in developmental disorders including X-linked intellectual disability, with deletions in the gene noted in specific clinical cases. These disease associations, coupled with its distinct regulatory features and constitutive activity, make RSK4 an attractive target for further pharmacological investigation and potential clinical intervention (chrysostomou2021repurposedfloxacinstargeting pages 17-18, lou2024expressionofrsk4 pages 7-7, ma2020expressionofrsk4 pages 10-10, rafiee2016downregulationofribosomal pages 5-6, song…2013basicanatomyand pages 21-23, wright2023therapeutictargetingof pages 14-15, song…2013basicanatomyand pages 17-19, wright2023therapeutictargetingof pages 15-15, wright2023therapeutictargetingof pages 9-11, smolen2023quantitativeproteomicsand pages 17-18).
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