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Gene Section
Review

RPS6KA1 (ribosomal protein S6 kinase, 90kDa, polypeptide 1)

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Identity

Other names: HU-1; MAPKAPK1A; RSK; RSK1; p90S6K; pp90RSK1
HGNC (Hugo): RPS6KA1
Location: 1p36.11
Local order: Information about the local order of the human RPS6KA1 locus can be found at ensembl.org. Human RPS6KA1 is found on chromosome 1, position 26,744,930-26,774,107, between genes coding for HMGN2 (High-mobility group nucleosome-binding domain-containing protein 2) and ARID1A (AT-rich interactive domain-containing protein 1A).

Note
The commonly used named for RPS6KA1 is RSK1, which will be used hereafter.

DNA/RNA

Note
RSK1 was the first cloned isoform of the p90 ribosomal S6 kinase family, which now contains three other members (RSK2, RSK3 and RSK4).

Description

The genomic size of the entire RSK1 gene is about 45,260 bp and is located on the + strand of chromosome 1. This gene contains 22 coding exons.

Transcription

The length of the transcript is 3,186 bp, from which the open reading frame contains 2,208 bp. While the 5'UTR contains 154 bp, the 3'UTR contains 824 bp.

Pseudogene

No human pseudogene known.

Protein

Description

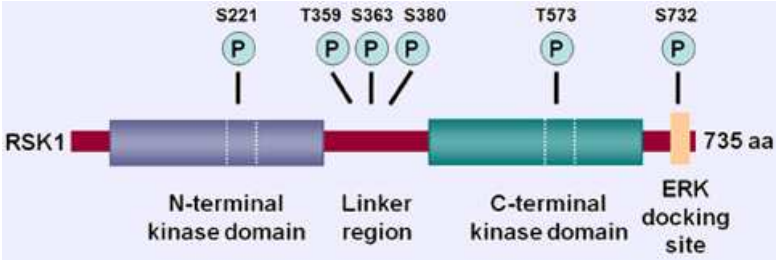
The RSK1 protein consists of 735 amino acids, with an apparent molecular weight of about 85-90 kDa.

Expression

Northern analyses and RNase protection assays revealed that RSK1 is expressed in many tissues, with higher levels in skeletal muscle, kidney, lung, liver, pancreas, spleen, thymus, and brain. Although other RSK isoforms are expressed ubiquitously in the brain, RSK1 is most abundant in the cerebellum. In situ hybridization of mouse embryonic tissues revealed that RSK1 is strongly expressed in regions harbouring highly proliferating cells. These include liver, lung, and thymus, as well as olfactory, respiratory, and gut epithelia.

Localisation

RSK1 is normally present in the cytoplasm, but upon mitogenic stimulation it moves into the nucleus, where it phosphorylates several substrates involved in gene transcription. Within minutes of stimulation, RSK1 was shown to accumulate transiently at the plasma membrane, where it presumably receives additional inputs necessary for activation before nuclear translocation.



The RSK1 protein contains two kinase domains separated by a linker region of about 100 aa. While the N-terminal kinase domain (NTKD) belongs to the AGC family of kinases, the C-terminal kinase domain (CTKD) belongs to the CaMK family. RSK1 activation requires its interaction with ERK1 and ERK2 through its C-terminal ERK docking region, which initiates an ordered phosphorylation sequence leading to the phosphorylation of six serine or threonine residues (S221, T359, S363, S380, T573 and S732).

Function

Mitogenic stimulation of the Ras/ERK pathway leads to the activation of RSK1. RSK1 seems to be a multifunctional ERK effector because it participates in various cellular processes, including nuclear signalling. RSK1 was found to regulate several transcription factors, including SRF, c-Fos, and Nur77. Additional nuclear factors have been shown to be regulated by RSK1, including MITF, estrogen receptor-a nuclear factor (NF)-ATc4 and ER81. RSK1 was shown to interact with the transcriptional coactivator CREB-binding protein (CBP), which, interestingly, binds many trans-cription factors known to be regulated by RSK1. On the basis of the nature of its substrates, RSK1 seems to have important functions in cellular growth control and proliferation. RSK1 may stimulate cell cycle progression through the regulation of immediate early gene products, such as c-Fos, which promotes the expression of cyclin D1 during the G0/G1 transition to S phase. Other proteins through which RSK1 may stimulate proliferation include the cyclin-dependent kinase (CDK) inhibitor p27kip1, the Na+/H+ exchanger NHE-1 and the kinase GSK3. RSK1 has been shown to phosphorylate and inhibit neuronal NO synthase in response to mitogenic signaling. RSK1 may also promote proliferation by regulating cell-growth-related protein synthesis. Indeed, RSK1 was shown to phosphorylate the tumour suppressor proteins TSC2 and LKB1, thereby resulting in increased mTOR signalling and mRNA translation.

Homology

The RSK family contains four human isoforms (RSK1, RSK2, RSK3 and RSK4), which share 65-73% aa identity. RSK-related molecules have also been identified in C. elegans (T01H8.1) and D. melanogaster (RPS6-protein kinase-II), which share around 50% aa identity to human RSK1 and also contain the two kinase domains typical to RSK family members. No RSK homologues have been found in yeast or plant.

Mutations

Somatic

The natural variant K335T has been observed.

Implicated in

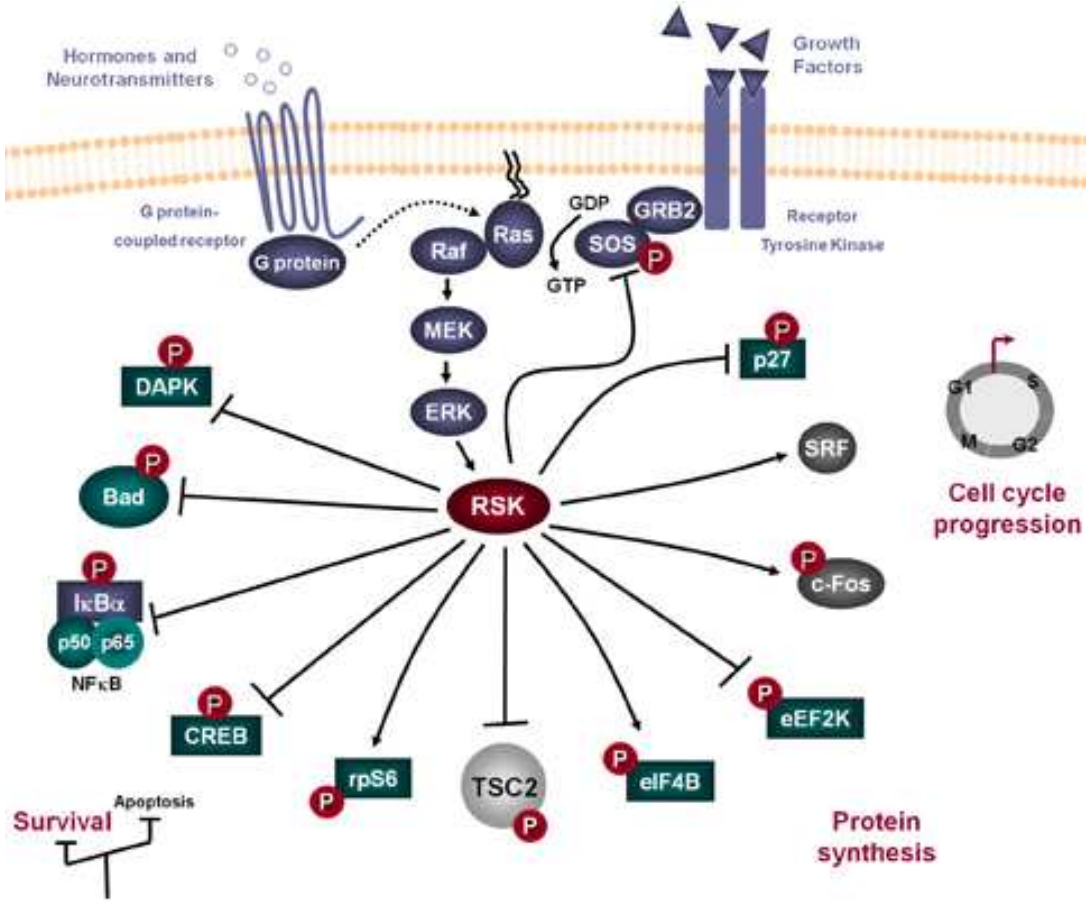
Various cancers

Prognosis

Frequent activation of the Ras/ERK signalling pathway has been reported in a broad range of human cancers including various carcinomas, glioblastomas and hematological malignancies. In some of these tumour types, RSK1 expression has been shown to be increased, such as in cancers of the breast and prostate.

Oncogenesis

RSK1 is an important mediator of survival signals that protect cells from undergoing apoptosis and, thus, is a potentially important therapeutic target. Inhibition of RSK activity using the pharmaco-logical inhibitor SL-0101 was shown to reduce the proliferation rates of breast cancer cells, but not normal breast epithelial cells.



Hyperactivation of RSK has been reported in multiple cancers. Activation of growth factor receptors either by ligand stimulation or receptor overexpression/mutation are common mechanisms that lead to RSK activation. RSK is now known to be a central player in a signalling pathway consisting of many components that have been implicated in tumorigenesis, including upstream Ras GTPases and Raf kinases.

References

Erikson E, Maller JL. A protein kinase from Xenopus eggs specific for ribosomal protein S6. Proc Natl Acad Sci U S A. 1985 Feb;82(3):742-6

Erikson E, Maller JL. Purification and characterization of a protein kinase from Xenopus eggs highly specific for ribosomal protein S6. J Biol Chem. 1986 Jan 5;261(1):350-5

Alcorta DA, Crews CM, Sweet LJ, Bankston L, Jones SW, Erikson RL. Sequence and expression of chicken and mouse rsk: homologs of Xenopus laevis ribosomal S6 kinase. Mol Cell Biol. 1989 Sep;9(9):3850-9

Blenis J, Chung J, Erikson E, Alcorta DA, Erikson RL. Distinct mechanisms for the activation of the RSK kinases/MAP2 kinase/pp90rsk and pp70-S6 kinase signaling systems are indicated by inhibition of protein synthesis. Cell Growth Differ. 1991 Jun;2(6):279-85

Chen RH, Sarnecki C, Blenis J. Nuclear localization and regulation of erk- and rsk-encoded protein kinases. Mol Cell Biol. 1992 Mar;12(3):915-27

Chen RH, Tung R, Abate C, Blenis J. Cytoplasmic to nuclear signal transduction by mitogen-activated protein kinase and 90 kDa ribosomal S6 kinase. Biochem Soc Trans. 1993 Nov;21(4):895-900

Davis IJ, Hazel TG, Chen RH, Blenis J, Lau LF. Functional domains and phosphorylation of the orphan receptor Nur77. Mol Endocrinol. 1993 Aug;7(8):953-64

Sutherland C, Alterio J, Campbell DG, Le Bourdellès B, Mallet J, Haavik J, Cohen P. Phosphorylation and activation of human tyrosine hydroxylase in vitro by mitogen-activated protein (MAP) kinase and MAP-kinase-activated kinases 1 and 2. Eur J Biochem. 1993 Oct 15;217(2):715-22

Hsiao KM, Chou SY, Shih SJ, Ferrell JE Jr. Evidence that inactive p42 mitogen-activated protein kinase and inactive Rsk exist as a heterodimer in vivo. Proc Natl Acad Sci U S A. 1994 Jun 7;91(12):5480-4

Moller DE, Xia CH, Tang W, Zhu AX, Jakubowski M. Human rsk isoforms: cloning and characterization of tissue-specific expression. Am J Physiol. 1994 Feb;266(2 Pt 1):C351-9

Fisher TL, Blenis J. Evidence for two catalytically active kinase domains in pp90rsk. Mol Cell Biol. 1996 Mar;16(3):1212-9

Nakajima T, Fukamizu A, Takahashi J, Gage FH, Fisher T, Blenis J, Montminy MR. The signal-dependent coactivator CBP is a nuclear target for pp90RSK. Cell. 1996 Aug 9;86(3):465-74

Zhao Y, Bjorbaek C, Moller DE. Regulation and interaction of pp90(rsk) isoforms with mitogen-activated protein kinases. J Biol Chem. 1996 Nov 22;271(47):29773-9

Ghoda L, Lin X, Greene WC. The 90-kDa ribosomal S6 kinase (pp90rsk) phosphorylates the N-terminal regulatory domain of IkappaBalpha and stimulates its degradation in vitro. J Biol Chem. 1997 Aug 22;272(34):21281-8

Schouten GJ, Vertegaal AC, Whiteside ST, Israël A, Toebes M, Dorsman JC, van der Eb AJ, Zantema A. IkappaB alpha is a target for the mitogen-activated 90 kDa ribosomal S6 kinase. EMBO J. 1997 Jun 2;16(11):3133-44

Vik TA, Ryder JW. Identification of serine 380 as the major site of autophosphorylation of Xenopus pp90rsk. Biochem Biophys Res Commun. 1997 Jun 18;235(2):398-402

Dalby KN, Morrice N, Caudwell FB, Avruch J, Cohen P. Identification of regulatory phosphorylation sites in mitogen-activated protein kinase (MAPK)-activated protein kinase-1a/p90rsk that are inducible by MAPK. J Biol Chem. 1998 Jan 16;273(3):1496-505

Joel PB, Smith J, Sturgill TW, Fisher TL, Blenis J, Lannigan DA. pp90rsk1 regulates estrogen receptor-mediated transcription through phosphorylation of Ser-167. Mol Cell Biol. 1998 Apr;18(4):1978-84

Palmer A, Gavin AC, Nebreda AR. A link between MAP kinase and p34(cdc2)/cyclin B during oocyte maturation: p90(rsk) phosphorylates and inactivates the p34(cdc2) inhibitory kinase Myt1. EMBO J. 1998 Sep 1;17(17):5037-47

Gavin AC, Ni Ainle A, Chierici E, Jones M, Nebreda AR. A p90(rsk) mutant constitutively interacting with MAP kinase uncouples MAP kinase from p34(cdc2)/cyclin B activation in Xenopus oocytes. Mol Biol Cell. 1999 Sep;10(9):2971-86

Jensen CJ, Buch MB, Krag TO, Hemmings BA, Gammeltoft S, Frödin M. 90-kDa ribosomal S6 kinase is phosphorylated and activated by 3-phosphoinositide-dependent protein kinase-1. J Biol Chem. 1999 Sep 17;274(38):27168-76

Richards SA, Fu J, Romanelli A, Shimamura A, Blenis J. Ribosomal S6 kinase 1 (RSK1) activation requires signals dependent on and independent of the MAP kinase ERK. Curr Biol. 1999 Jul 29-Aug 12;9(15):810-20

Smith JA, Poteet-Smith CE, Malarkey K, Sturgill TW. Identification of an extracellular signal-regulated kinase (ERK) docking site in ribosomal S6 kinase, a sequence critical for activation by ERK in vivo. J Biol Chem. 1999 Jan 29;274(5):2893-8

Takahashi E, Abe J, Gallis B, Aebersold R, Spring DJ, Krebs EG, Berk BC. p90(RSK) is a serum-stimulated Na+/H+ exchanger isoform-1 kinase. Regulatory phosphorylation of serine 703 of Na+/H+ exchanger isoform-1. J Biol Chem. 1999 Jul 16;274(29):20206-14

Frödin M, Jensen CJ, Merienne K, Gammeltoft S. A phosphoserine-regulated docking site in the protein kinase RSK2 that recruits and activates PDK1. EMBO J. 2000 Jun 15;19(12):2924-34

Shimamura A, Ballif BA, Richards SA, Blenis J. Rsk1 mediates a MEK-MAP kinase cell survival signal. Curr Biol. 2000 Feb 10;10(3):127-35

Richards SA, Dreisbach VC, Murphy LO, Blenis J. Characterization of regulatory events associated with membrane targeting of p90 ribosomal S6 kinase 1. Mol Cell Biol. 2001 Nov;21(21):7470-80

Sapkota GP, Kieloch A, Lizcano JM, Lain S, Arthur JS, Williams MR, Morrice N, Deak M, Alessi DR. Phosphorylation of the protein kinase mutated in Peutz-Jeghers cancer syndrome, LKB1/STK11, at Ser431 by p90(RSK) and cAMP-dependent protein kinase, but not its farnesylation at Cys(433), is essential for LKB1 to suppress cell vrowth. J Biol Chem. 2001 Jun 1;276(22):19469-82

Schwab MS, Roberts BT, Gross SD, Tunquist BJ, Taieb FE, Lewellyn AL, Maller JL. Bub1 is activated by the protein kinase p90(Rsk) during Xenopus oocyte maturation. Curr Biol. 2001 Feb 6;11(3):141-50

Wang X, Li W, Williams M, Terada N, Alessi DR, Proud CG. Regulation of elongation factor 2 kinase by p90(RSK1) and p70 S6 kinase. EMBO J. 2001 Aug 15;20(16):4370-9

Frödin M, Antal TL, Dümmler BA, Jensen CJ, Deak M, Gammeltoft S, Biondi RM. A phosphoserine/threonine-binding pocket in AGC kinases and PDK1 mediates activation by hydrophobic motif phosphorylation. EMBO J. 2002 Oct 15;21(20):5396-407

Fujita N, Sato S, Tsuruo T. Phosphorylation of p27Kip1 at threonine 198 by p90 ribosomal protein S6 kinases promotes its binding to 14-3-3 and cytoplasmic localization. J Biol Chem. 2003 Dec 5;278(49):49254-60

Roux PP, Richards SA, Blenis J. Phosphorylation of p90 ribosomal S6 kinase (RSK) regulates extracellular signal-regulated kinase docking and RSK activity. Mol Cell Biol. 2003 Jul;23(14):4796-804

Putz G, Bertolucci F, Raabe T, Zars T, Heisenberg M. The S6KII (rsk) gene of Drosophila melanogaster differentially affects an operant and a classical learning task. J Neurosci. 2004 Nov 3;24(44):9745-51

Roux PP, Ballif BA, Anjum R, Gygi SP, Blenis J. Tumor-promoting phorbol esters and activated Ras inactivate the tuberous sclerosis tumor suppressor complex via p90 ribosomal S6 kinase. Proc Natl Acad Sci U S A. 2004 Sep 14;101(37):13489-94

Roux PP, Blenis J. ERK and p38 MAPK-activated protein kinases: a family of protein kinases with diverse biological functions. Microbiol Mol Biol Rev. 2004 Jun;68(2):320-44

Woo MS, Ohta Y, Rabinovitz I, Stossel TP, Blenis J. Ribosomal S6 kinase (RSK) regulates phosphorylation of filamin A on an important regulatory site. Mol Cell Biol. 2004 Apr;24(7):3025-35

Anjum R, Roux PP, Ballif BA, Gygi SP, Blenis J. The tumor suppressor DAP kinase is a target of RSK-mediated survival signaling. Curr Biol. 2005 Oct 11;15(19):1762-7

Chun J, Chau AS, Maingat FG, Edmonds SD, Ostergaard HL, Shibuya EK. Phosphorylation of Cdc25C by pp90Rsk contributes to a G2 cell cycle arrest in Xenopus cycling egg extracts. Cell Cycle. 2005 Jan;4(1):148-54

Cohen MS, Zhang C, Shokat KM, Taunton J. Structural bioinformatics-based design of selective, irreversible kinase inhibitors. Science. 2005 May 27;308(5726):1318-21

Dumont J, Umbhauer M, Rassinier P, Hanauer A, Verlhac MH. p90Rsk is not involved in cytostatic factor arrest in mouse oocytes. J Cell Biol. 2005 Apr 25;169(2):227-31

Heffron D, Mandell JW. Differential localization of MAPK-activated protein kinases RSK1 and MSK1 in mouse brain. Brain Res Mol Brain Res. 2005 May 20;136(1-2):134-41

Yang TT, Xiong Q, Graef IA, Crabtree GR, Chow CW. Recruitment of the extracellular signal-regulated kinase/ribosomal S6 kinase signaling pathway to the NFATc4 transcription activation complex. Mol Cell Biol. 2005 Feb;25(3):907-20

Chaturvedi D, Poppleton HM, Stringfield T, Barbier A, Patel TB. Subcellular localization and biological actions of activated RSK1 are determined by its interactions with subunits of cyclic AMP-dependent protein kinase. Mol Cell Biol. 2006 Jun;26(12):4586-600

Hauge C, Frödin M. RSK and MSK in MAP kinase signalling. J Cell Sci. 2006 Aug 1;119(Pt 15):3021-3

Kim M, Lee JH, Koh H, Lee SY, Jang C, Chung CJ, Sung JH, Blenis J, Chung J. Inhibition of ERK-MAP kinase signaling by RSK during Drosophila development. EMBO J. 2006 Jul 12;25(13):3056-67

Ranganathan A, Pearson GW, Chrestensen CA, Sturgill TW, Cobb MH. The MAP kinase ERK5 binds to and phosphorylates p90 RSK. Arch Biochem Biophys. 2006 May 15;449(1-2):8-16

Shahbazian D, Roux PP, Mieulet V, Cohen MS, Raught B, Taunton J, Hershey JW, Blenis J, Pende M, Sonenberg N. The mTOR/PI3K and MAPK pathways converge on eIF4B to control its phosphorylation and activity. EMBO J. 2006 Jun 21;25(12):2781-91

Wingate AD, Campbell DG, Peggie M, Arthur JS. Nur77 is phosphorylated in cells by RSK in response to mitogenic stimulation. Biochem J. 2006 Feb 1;393(Pt 3):715-24

Cohen MS, Hadjivassiliou H, Taunton J. A clickable inhibitor reveals context-dependent autoactivation of p90 RSK. Nat Chem Biol. 2007 Mar;3(3):156-60

Roux PP, Shahbazian D, Vu H, Holz MK, Cohen MS, Taunton J, Sonenberg N, Blenis J. RAS/ERK signaling promotes site-specific ribosomal protein S6 phosphorylation via RSK and stimulates cap-dependent translation. J Biol Chem. 2007 May 11;282(19):14056-64

Sapkota GP, Cummings L, Newell FS, Armstrong C, Bain J, Frodin M, Grauert M, Hoffmann M, Schnapp G, Steegmaier M, Cohen P, Alessi DR. BI-D1870 is a specific inhibitor of the p90 RSK (ribosomal S6 kinase) isoforms in vitro and in vivo. Biochem J. 2007 Jan 1;401(1):29-38

Song T, Sugimoto K, Ihara H, Mizutani A, Hatano N, Kume K, Kambe T, Yamaguchi F, Tokuda M, Watanabe Y. p90 RSK-1 associates with and inhibits neuronal nitric oxide synthase. Biochem J. 2007 Jan 15;401(2):391-8

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