

Gene Section

Mini Review

DDX5 (DEAD (Asp-Glu-Ala-Asp) box polypeptide 5)

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Identity

Other names: DKFZp434E109,

DKFZp686J01190, G17P1, HLR1, HUMP68, p68

HGNC (Hugo): DDX5

Location: 17q23.3

Note

DDX5/p68 RNA helicase is a member of DEAD box RNA helicases. As an example of a cellular RNA helicase, the ATPase and the RNA unwinding activities of p68 RNA helicase were documented with the protein that was purified from human 293 cells (Iggo and Lane, 1989; Ford et al., 1988; Hirling et al., 1989) and recombinant protein expressed in *E. coli* (Huang and Liu, 2002). The gene is expressed in all dividing cells of different vertebrates (Lane and Hoeffler, 1980; Stevenson et al., 1998). p68 RNA helicase is involved in multiple cellular processes, including gene transcription (Endoh et al., 1999; Rossow and Janknecht, 2003), pre-mRNA processing (Liu, 2002;

Yang et al., 2006), pre-rRNA processing (Jalal et al., 2007), pre-miRNA processing (Fukuda et al., 2007), DNA methylation and de-methylation (Jost et al., 1999), and chromatin remodeling (Carter et al., 2010). A number of different post-translational modifications of p68 are reported, including phosphorylations, sumoylation, and ubiquitylation (Causevic et al., 2001; Yang et al., 2005; Jacobs et al., 2007).

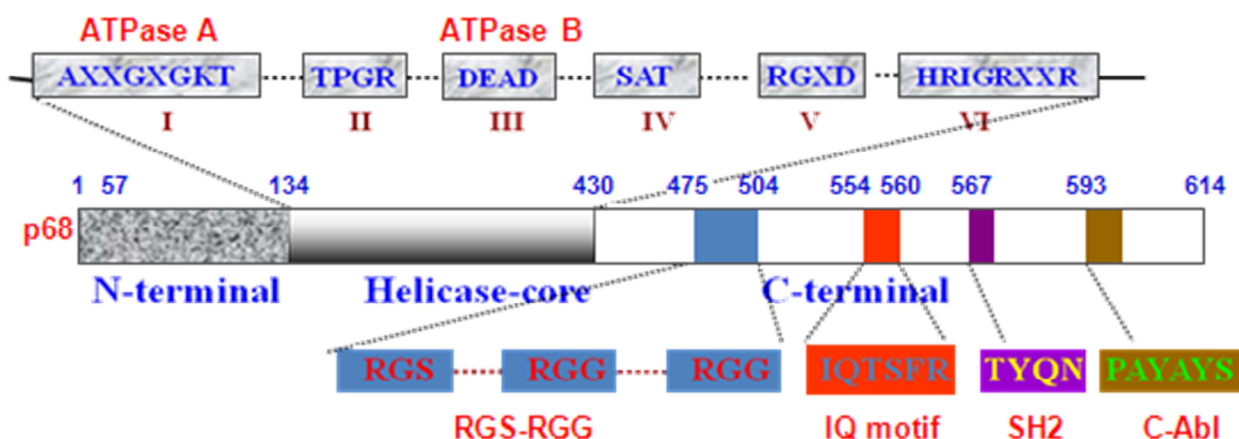
DNA/RNA

Note

DDX5/p68 RNA helicase is expressed in dividing cells of different vertebrates. Transcription of p68 RNA helicase gene generates a single mRNA precursor with 13 exons and 12 introns. Alternative splicing produces two mRNA transcripts, 2.3 kb and 4.4 kb (Rössler et al., 2000). The 2.3 kb mRNA transcript codes full length p68, while no translational product from the 4.4 kb mRNA transcript is detected in cellular and tissue extracts (Rössler et al., 2000).



Diagram of pre-mRNA of p68 RNA helicase. The red bars are exons and the blue thin lines are introns.



Domain structure of p68 RNA helicase. Functional sequence motifs are marked.

Protein

Description

Size of p68; 614 amino acids, 69 kDa.

Expression

Expressed in almost all tissue types. Its expression is increased in cancer cells.

Localisation

Dominately localized in the cell nucleus. It is also found in the cytoplasm in various physiological conditions. p68 is a nucleocytoplasm shuttling protein (Wang et al., 2009).

Function

Pre-mRNA splicing. The protein was demonstrated to associate with spliceosome by mass-spectroscopy and an RNA-protein crosslinking analyses (Hartmuth et al., 2002; Liu et al., 1997; Neubauer et al., 1998). p68 is functionally involved in assemble of the spliceosome by mediating the U1 snRNP and the 5'ss interaction (Liu, 2002). p68 RNA helicase is also shown to regulate the splice site selection in the alternative splicing of several growth related genes, such as c-H-ras and tau (Kar et al., 2011; Guil et al., 2003).

Transcriptional regulation. The protein is shown to involve in transcriptional regulation by different mechanism of actions dependent on each individual regulated gene and biological processes (Stevenson et al., 1998; Endoh et al., 1999; Yang et al., 2005; Kahlina et al., 2004; Wei and Hu, 2001; Warner et al., 2004). p68 may regulate gene transcription by direct interaction with transcription factors or activators, such as p53, ERalpha (Endoh et al., 1999; Bates et al., 2005), or by mediating chromatin remodeling, such as modulating chromatin remodeling complex (Carter et al., 2010).

Epithelial-Mesenchymal-Transition (EMT). p68 becomes phosphorylated at Y593 upon growth factor stimulation by c-Abl. The tyrosine phosphorylation of p68 mediates growth factor stimulated Epithelial-Mesenchymal-Transition (EMT) (Yang et al., 2006).

Other functions. (1) p68 RNA helicase is shown to unwind the human let-7 microRNA precursor duplex. The protein is required for let-7-directed silencing of gene expression (Salzman et al., 2007). p68 is an indispensable part of Drosha complex. Its activity is required for primary miRNA and rRNA processing (Fukuda et al., 2007). (2) It is also demonstrated that the RNA helicases p68/p72 and the noncoding RNA SRA are coregulators of MyoD and skeletal muscle differentiation (Caretta et al., 2006). (3) Phosphorylation of p68 at Thr residues mediates cell apoptosis (Yang et al., 2007).

Homology

Yeast DBP2.

Mutations

Note

Very few mutations of p68 gene were reported. A recent study shows that a S480A mutation in hepatic stellate cells is associated with hepatic fibrosis (Guo et al., 2010).

Implicated in

Colon cancer

Note

p68 expression is significantly increased in colon cancer (Shin et al., 2007). Phosphorylation of p68 at Tyr correlation with colon cancer metastasis (Yang et al., 2006; Yang et al., 2005).

Prognosis

Phosphorylation of p68 at tyrosine can be used as a diagnosis/prognosis marker for cancer.

References

- Lane DP, Hoeffler WK. SV40 large T shares an antigenic determinant with a cellular protein of molecular weight 68,000. *Nature*. 1980 Nov 13;288(5787):167-70
- Ford MJ, Anton IA, Lane DP. Nuclear protein with sequence homology to translation initiation factor eIF-4A. *Nature*. 1988 Apr 21;332(6166):736-8
- Hirling H, Scheffner M, Restle T, Stahl H. RNA helicase activity associated with the human p68 protein. *Nature*. 1989 Jun 15;339(6225):562-4
- Iggo RD, Lane DP. Nuclear protein p68 is an RNA-dependent ATPase. *EMBO J*. 1989 Jun;8(6):1827-31
- Liu ZR, Laggerbauer B, Lührmann R, Smith CW. Crosslinking of the U5 snRNP-specific 116-kDa protein to RNA hairpins that block step 2 of splicing. *RNA*. 1997 Nov;3(11):1207-19
- Neubauer G, King A, Rappsilber J, Calvio C, Watson M, Ajuh P, Sleeman J, Lamond A, Mann M. Mass spectrometry and EST-database searching allows characterization of the multi-protein spliceosome complex. *Nat Genet*. 1998 Sep;20(1):46-50
- Stevenson RJ, Hamilton SJ, MacCallum DE, Hall PA, Fuller-Pace FV. Expression of the 'dead box' RNA helicase p68 is developmentally and growth regulated and correlates with organ differentiation/maturation in the fetus. *J Pathol*. 1998 Apr;184(4):351-9
- Endoh H, Maruyama K, Masuhiro Y, Kobayashi Y, Goto M, Tai H, Yanagisawa J, Metzger D, Hashimoto S, Kato S. Purification and identification of p68 RNA helicase acting as a transcriptional coactivator specific for the activation function 1 of human estrogen receptor alpha. *Mol Cell Biol*. 1999 Aug;19(8):5363-72
- Jost JP, Schwarz S, Hess D, Angliker H, Fuller-Pace FV, Stahl H, Thiry S, Siegmund M. A chicken embryo protein related to the mammalian DEAD box protein p68 is tightly associated with the highly purified protein-RNA complex of 5-MeC-DNA glycosylase. *Nucleic Acids Res*. 1999 Aug 15;27(16):3245-52
- Rössler OG, Hloch P, Schütz N, Weitzenegger T, Stahl H. Structure and expression of the human p68 RNA helicase gene. *Nucleic Acids Res*. 2000 Feb 15;28(4):932-9
- Causevic M, Hislop RG, Kernohan NM, Carey FA, Kay RA, Steele RJ, Fuller-Pace FV. Overexpression and polyubiquitylation of the DEAD-box RNA helicase p68 in colorectal tumours. *Oncogene*. 2001 Nov 22;20(53):7734-43
- Wei Y, Hu MH. [The study of P68 RNA helicase on cell transformation]. *Yi Chuan Xue Bao*. 2001 Nov;28(11):991-6
- Hartmuth K, Urlaub H, Vornlocher HP, Will CL, Gentzel M, Wilm M, Lührmann R. Protein composition of human pre-spliceosomes isolated by a tobramycin affinity-selection method. *Proc Natl Acad Sci U S A*. 2002 Dec 24;99(26):16719-24
- Huang Y, Liu ZR. The ATPase, RNA unwinding, and RNA binding activities of recombinant p68 RNA helicase. *J Biol Chem*. 2002 Apr 12;277(15):12810-5
- Liu ZR. p68 RNA helicase is an essential human splicing factor that acts at the U1 snRNA-5' splice site duplex. *Mol Cell Biol*. 2002 Aug;22(15):5443-50
- Guil S, Gattoni R, Carrascal M, Abián J, Stévenin J, Bach-Elias M. Roles of hnRNP A1, SR proteins, and p68 helicase in c-H-ras alternative splicing regulation. *Mol Cell Biol*. 2003 Apr;23(8):2927-41
- Rosow KL, Janknecht R. Synergism between p68 RNA helicase and the transcriptional coactivators CBP and p300. *Oncogene*. 2003 Jan 9;22(1):151-6
- Kahlina K, Goren I, Pfeilschifter J, Frank S. p68 DEAD box RNA helicase expression in keratinocytes. Regulation, nucleolar localization, and functional connection to proliferation and vascular endothelial growth factor gene expression. *J Biol Chem*. 2004 Oct 22;279(43):44872-82
- Warner DR, Bhattacharjee V, Yin X, Singh S, Mukhopadhyay P, Pisano MM, Greene RM. Functional interaction between Smad, CREB binding protein, and p68 RNA helicase. *Biochem Biophys Res Commun*. 2004 Nov 5;324(1):70-6
- Bates GJ, Nicol SM, Wilson BJ, Jacobs AM, Bourdon JC, Wardrop J, Gregory DJ, Lane DP, Perkins ND, Fuller-Pace FV. The DEAD box protein p68: a novel transcriptional coactivator of the p53 tumour suppressor. *EMBO J*. 2005 Feb 9;24(3):543-53
- Yang L, Lin C, Liu ZR. Phosphorylations of DEAD box p68 RNA helicase are associated with cancer development and cell proliferation. *Mol Cancer Res*. 2005 Jun;3(6):355-63
- Caretti G, Schiltz RL, Dilworth FJ, Di Padova M, Zhao P, Ogryzko V, Fuller-Pace FV, Hoffman EP, Tapscott SJ, Sartorelli V. The RNA helicases p68/p72 and the noncoding RNA SRA are coregulators of MyoD and skeletal muscle differentiation. *Dev Cell*. 2006 Oct;11(4):547-60
- Yang L, Lin C, Liu ZR. P68 RNA helicase mediates PDGF-induced epithelial mesenchymal transition by displacing Axin from beta-catenin. *Cell*. 2006 Oct 6;127(1):139-55
- Fukuda T, Yamagata K, Fujiyama S, Matsumoto T, Koshida I, Yoshimura K, Mihara M, Naitou M, Endoh H, Nakamura T, Akimoto C, Yamamoto Y, Katagiri T, Foulds C, Takezawa S, Kitagawa H, Takeyama K, O'Malley BW, Kato S. DEAD-box RNA helicase subunits of the Drosha complex are required for processing of rRNA and a subset of microRNAs. *Nat Cell Biol*. 2007 May;9(5):604-11
- Jacobs AM, Nicol SM, Hislop RG, Jaffray EG, Hay RT, Fuller-Pace FV. SUMO modification of the DEAD box protein p68 modulates its transcriptional activity and promotes its interaction with HDAC1. *Oncogene*. 2007 Aug 30;26(40):5866-76. Epub 2007 Mar 19.
- Jalal C, Uhlmann-Schiffler H, Stahl H. Redundant role of DEAD box proteins p68 (Ddx5) and p72/p82 (Ddx17) in ribosome biogenesis and cell proliferation. *Nucleic Acids Res*. 2007;35(11):3590-601. Epub 2007 May 7.
- Salzman DW, Shubert-Coleman J, Furneaux H. P68 RNA helicase unwinds the human let-7 microRNA precursor duplex and is required for let-7-directed silencing of gene expression. *J Biol Chem*. 2007 Nov 9;282(45):32773-9. Epub 2007 Aug 27.
- Shin S, Rosow KL, Grande JP, Janknecht R. Involvement of RNA helicases p68 and p72 in colon cancer. *Cancer Res*. 2007 Aug 15;67(16):7572-8.
- Yang L, Lin C, Sun SY, Zhao S, Liu ZR. A double tyrosine phosphorylation of P68 RNA helicase confers resistance to TRAIL-induced apoptosis. *Oncogene*. 2007 Sep 6;26(41):6082-92. Epub 2007 Mar 26.
- Wang H, Gao X, Huang Y, Yang J, Liu ZR. P68 RNA helicase is a nucleocytoplasmic shuttling protein. *Cell Res*. 2009 Dec;19(12):1388-400. Epub 2009 Sep 29.
- Carter CL, Lin C, Liu CY, Yang L, Liu ZR. Phosphorylated p68 RNA helicase activates Snail1 transcription by promoting HDAC1 dissociation from the Snail1 promoter. *Oncogene*. 2010 Sep 30;29(39):5427-36. Epub 2010 Aug 2.

Guo J, Hong F, Loke J, Yea S, Lim CL, Lee U, Mann DA, Walsh MJ, Sninsky JJ, Friedman SL.. A DDX5 S480A polymorphism is associated with increased transcription of fibrogenic genes in hepatic stellate cells. J Biol Chem. 2010 Feb 19;285(8):5428-37. Epub 2009 Dec 17.

Kar A, Fushimi K, Zhou X, Ray P, Shi C, Chen X, Liu Z, Chen S, Wu JY.. RNA helicase p68 (DDX5) regulates tau exon 10

splicing by modulating a stem-loop structure at the 5' splice site. Mol Cell Biol. 2011 May;31(9):1812-21. Epub 2011 Feb 22.

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