Atlas of Genetics and Cytogenetics in Oncology and Haematology

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Gene Section

Review

HNRNPD (heterogeneous nuclear ribonucleoprotein D (AU-rich element RNA binding protein 1, 37kDa))

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Identity

Other names: AUF1; AUF1A; HNRPD; P37; hnRNPD0

HGNC (Hugo): HNRNPD

Location: 4q21.22

DNA/RNA

Note

Differential splicing of a single HNRNPD transcript results in four isoforms: p37, p40, p42 and p45.

Description

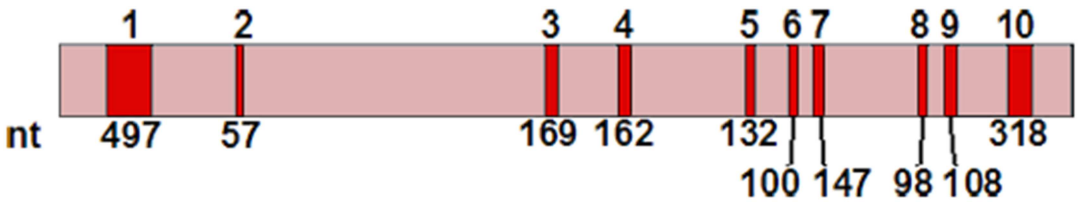
HNRNPD gene is composed of 10 exons, ranging in size from 57 to 497 nt. Eight of 10 exons are localised within the coding region. Exon 1 contains 5' UTR and encodes N-terminal part of the AUF1 protein. Exon 2 encodes the 19-aminoacid insertion of the N-terminal part of the first RNA-binding domain (RBD). This insertion is localised only in isoforms p40 and p45. Exons 3-6 encode the rest of the first RBD, the N-terminal half of the second RBD, the C-terminal half of the second RBD and the glutamine rich region, respectively. Exon 7 encodes the 49-aminoacid insertion localised only in isoforms p42 and p45. The smallest isoform p37, lacks exon 2 and 7. Exon 8 encodes the C-terminal part common to all isoforms and part of the 3' UTR. A TAA nonsense codon is also localised within this exon. Exon 9 contains two additional in-frame stop codons and encodes an alternatively spliced, 107 nt part of the 3' UTR. Exon 10 encodes the rest of 3' UTR and contains an AATAAA polyadenylation signal.

Transcription

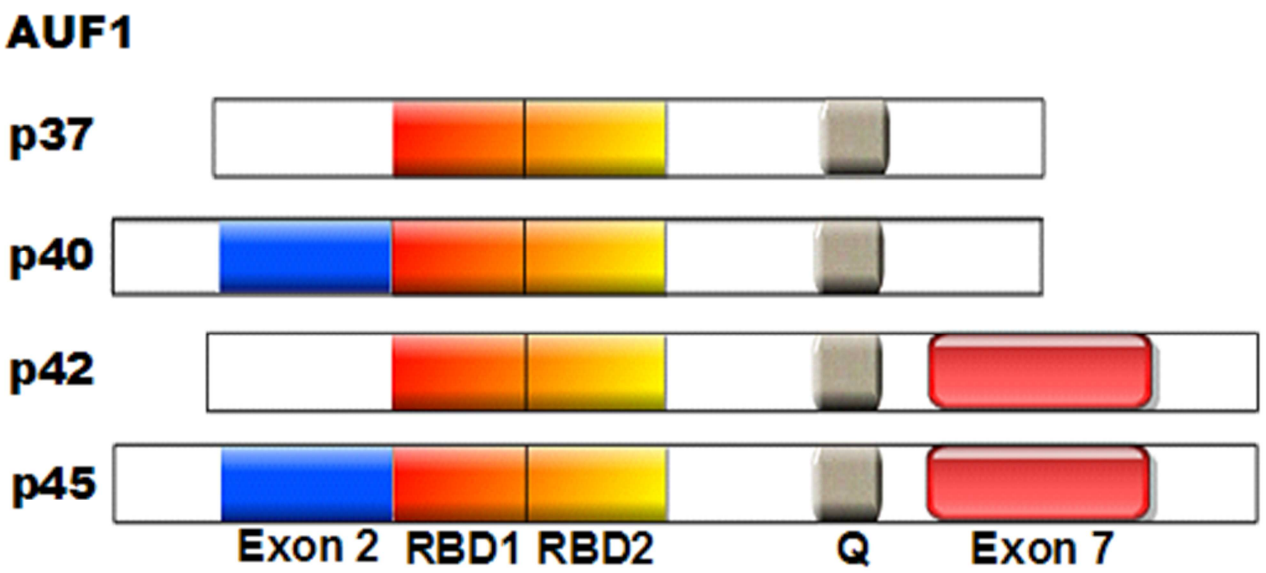
Transcription initiation sites were not exactly identified, but there is a TATAA box 175 nt upstream of the 5' end of the human cDNA clone with the longest 5' UTR. The first ATG codon is located in exon 1, at least 250 nt from the 5' end of mRNA.

Pseudogene

One pseudogene according to RefSeq was localised. Localisation: Xq12.



Structure of the human HNRNPD gene. Exon positions (red) and sizes (nt-nucleotides) are labelled.



Structure of HNRNPD (AUF1) proteins; RBD1-2, RNA binding domains; Q, glutamine rich element; HNS, Exon 2, 19 amino acids; Exon 7, 49 amino acids.

Protein

Description

The family of HNRNPD (AUF1) proteins distinguishes a 37 kDa (p37) core protein, a 40 kDa protein (p40) containing an N-terminal 19 amino acid insertion (exon 2), a 42 kDa protein (p42) exhibiting a C-terminal 49 amino acids insertion (exon 7), and a 45 kDa protein (p45) with insertions of both exon 2 and exon 7. Presence or absence of these alternatively spliced exons confers distinct biological properties to individual AUF1 isoforms. Presence of exon 7 not only affects nucleo-cytoplasmic distribution, but also blocks ubiquitination of p42 and p45. In contrast, the lack of exon 7 targets p37 and p40 to the ubiquitin proteasome pathway, where both isoforms serve as substrates in decay reaction. This results in rapid and selected decay of adenylate-uridylate rich elements (AREs) containing mRNAs. Importantly, absence of exon 2 in p37 and p42 is associated with high affinity binding of these isoforms. The smallest AUF1 isoform p37 posses the strongest mRNA binding affinity, which for other isoforms decreases in following rank of order: p37>p42>p45>p40.

Expression

AUF1 is expressed early in the development. High levels of AUF1 proteins were found in lymphoid tissues, such as spleen and thymus, and lower levels in brain and fetal liver. In adult liver AUF1 was undetectable. In spleen and thymus extracts, isoforms p40 and p45 were more abundant than p37. Isoforms p45 and p40 were most abundant in brain and in fetal liver, respectively. Both mentioned organs lacked expression of p37.

Localisation

AUF1 is predominantly nuclear and is able to shuttle between nucleus and cytoplasm. In the nucleus, AUF1 is found within stable ribonucleoprotein complexes; in the cytoplasm, AUF1 binds to target mRNAs and is often co-localised with the exosome.
The triggering of AUF1-mediated degradation is consistent with changes of cellular localisation of this protein. Previous studies demonstrated that blocking of ARE-mediated mRNA decay by heat shock, down-regulation of the ubiquitin-proteasome pathway or by inactivation of the E1 ubiquitinating enzyme all resulted in hnRNPD movement to the nucleus of human HeLa cells. However, the cellular factors and/or events involved in regulating these different activities for AUF1 remain to be defined.

Function

AUF1 is involved in processes of apoptosis, tumorigenesis and development by its interactions with AREs bearing mRNAs. It is able to bind both single stranded DNA and RNA, especially transcripts bearing AREs in their 3' UTR. AUF1 may bind AREs of all classes (I, II and III) and its over-expression noticeably influences the stability of ARE containing mRNAs. AUF1 appears to enhance target mRNA decay, a process that is closely related to the ubiquitination and targeting of AUF1 to the proteasome. AUF1 target mRNAs encode mitogenic, immune response, cancer-associated, stress response, and cell cycle regulatory proteins such as c-fos, c-jun, c-myc, egr-1, interleukins, iNOS, DNMT1, p21, p27, hsp70, MnSOD, catalase, cyclin D1, and cdc25. It was reported that increased level of AUF1 in human erythroleukemic K562 cells, especially isoforms p37AUF1 and p42AUF1, induced ARE-directed mRNA degradation.

AUF1 itself does not possess enzymatic activity but may interact and recruit other proteins, including lactate dehydrogenase (LDH), stratifin, ubiquitin-conjugating enzyme E2I, RNA binding proteins NSEP-1, NSAP-1 and IMP-2. NSEP-1 was demonstrated to possess an endoribonuclease activity.

Homology

The human and murine HNRNPD proteins are highly conserved and revealed similarity of 98.9%. The differences are mainly restricted to the N-terminal portion of the protein.
The human HNRNPD locus maps to 4q21, and the murine Hnrnpd locus maps to the F region of chromosome 3.

Mutations

Note
Not known in human.

Implicated in

Oral squamous cell carcinoma (OSCC)

Note
The higher expression of HNRNPD, HNRNPK, MutS homolog 2 (MSH2) and grainyhead-like 2 (GRHL2), and subsequently increased activity of human telomerase reverse transcriptase (hTERT) were detected in OSCC cells when compared to normal cells, which do not exhibit hTERT activity. RNAi mediated knock-down of HNRNPD, MSH2 and GRHL2 resulted in decreased proliferation rates and hTERT promoter activity. Down-regulation of HNRNPK reduced only proliferation of the cells without affecting the hTERT promoter activity.

Mediated growth arrest of cancer cells

Note
Prostaglandin A_2 (PGA_2) is an experimental anti-cancer agent associated with reduced levels of cyclin D1 and decreased proliferation of cancer cells. Employment of PGA_2 induced AUF1 expression and resulted in destabilisation of cyclin D1 mRNA in non small cell lung cancer (H1299) and breast carcinoma (MCF-7) cells. The other breast carcinoma cell line MDA-MB-453, bearing a large deletion in cyclin's D1 3'UTR, responded with unaltered cyclin D1 mRNA upon PGA2 treatment.

Thyroid carcinoma

Note
AUF1 was demonstrated as a new, additional marker for thyroid carcinoma. Increased cytoplasmic AUF1 levels were found in dividing thyroid carcinoma cell lines and in most malignant thyroid carcinoma tissues. Furthermore, by immunohistochemistry and subcellular fractionation of thyroid tissues it has been shown that cytoplasmic expression of AUF1 in benign and malignant tissues was significantly increased when compared to normal thyroid tissues. Furthermore, logarithmic nuclear/cytoplasmic ratio of total AUF1 expression in normal, goiter, adenoma and follicular thyroid carcinoma decreased with tissue malignancy.
Stable and transient suppression of AUF1 by RNAi in thyroid carcinoma cells resulted in decreased proliferation rates accompanied by increased levels of cell cycle inhibitors and reduced expression of cell cycle promoters.

Lung cancer

Note
Cytosolic levels of AUF1 and HuR proteins were found to be significantly increased in lung hyperplasia and neoplasia, both in vitro and in vivo. Normal peripheral lung tissues expressed significantly lower levels of cytosolic AUF1 and HuR when compared with lung tumors.

Sarcomas

Note
Overexpression of AUF1 isoform p37 led to development of sarcomas accompanied by induction of c-myc, c-fos, c-jun and cyclin D1 mRNAs in tumor tissues comparing with non-neoplastic control tissues. Furthermore, sarcomas revealed decreased levels of TNFa and GM-CSF mRNAs, and no significant differences in VEGF expression were detectable.

Melanoma with increased expression of interleukin 10 (IL-10)

Note
Elevated levels of IL-10 in melanoma cells resulted in decreased cytosolic AUF1 levels as compared with normal melanocytes.

Hepatitis C virus (HCV) mediated hepatitis, liver cirrhosis and hepatocellular carcinoma

Note
Overexpression of HNRNPD (especially isoforms p37 and p45) resulted in enhanced translation of internal ribosome entry site (IRES) of HCV, further processed into 10 or more viral proteins. In contrast, HNRNPD knock-down significantly reduced its translation and hampered infection by HCV.

Anaplastic large cell lymphoma (ALCL)

Note
Approximately 80% of anaplastic lymphoma kinase (ALK)-positive lymphomas express the fusion protein called nucleophosmin-anaplastic lymphoma kinase (NPM-ALK) causing constitutive activation of ALK tyrosine kinase and abnormal induction of down-stream signaling resulting in malignant transformation. It was demonstrated that AUF1 is co-localised with NPM-ALK in the same cytoplasmic loci and was hyperphosphorylated in NPM-ALK expressing cells. AUF1 hyperphosphorylation was associated with

elevated stability of several target mRNAs encoding proteins crucial for cell proliferation and cell survival such as c-myc, and cyclin D1, cyclin A2, cyclin B1, and cyclin D3.

Cardiac hypertrophy and heart failure

Note

Experimental animals and patients with cardiac hypertrophy and heart failure revealed abnormalities in myocardial relaxation, which are related with reduced levels of sarco(endo)plasmic reticulum calcium ATPase 2a (SERCA2a) gene expression. AUF1 was identified to interact with SERCA2a 3' UTR predominantly in nucleus. This suggests that AUF1-mediated decay of SERCA2a mRNA starts within the nucleus and further continues during shuttling to the cytoplasm.

Expression of cardiac myocyte Kv4 channels is reduced in hypertrophy and leads to reduce in the transient outward current. Studies in vitro demonstrated that employment of angiotensin II may recapitulate these effects and is accompanied by up-regulation of AUF1, which in turn binds and destabilises Kv4 mRNA.

Secondary hyperparathyroidism

Note

It was demonstrated that AUF1 mRNA levels were repressed in secondary hyperparathyroidism patients with nodular growth of the gland. It is worth to notice that secondary hyperparathyroidism results in increased levels of parathyroid hormone (PTH), demonstrated to be a target for AUF1. PTH mRNA contains AREs in its 3' UTR.

Replicative senescence

Note

AUF1 was identified as a critical mediator of senescence events. Reduction of AUF1 level occurred with replicative senescence and contributed to stabilisation and elevated expression of ARE-bearing p16 mRNA in senescence-phenotype cells.

UVC irradiation-induced apoptosis

Note

AUF1 levels increased upon UVC irradiation-induced apoptosis and correlated with reduction of ARE-containing bcl-2 mRNA.

Mammary gland differentiation

Note

It was demonstrated that AUF1 translocation from cytoplasm to the nucleus correlates with mammary gland differentiation, induction of milk production and inhibition of proliferation. Participation of AUF1 in those processes was lactogenic hormone signals-dependent.

Systemic rheumatic diseases

Note

AUF1 proteins were identified as novel autoantigens in systemic lupus erythematosus (SLE) and other associated autoimmune rheumatic disorders. Autoantibodies to AUF1 were found in 33% of SLE patients, 20% of patients with rheumatioid arthritis, 17% of patients with mixed connective tissue disorders and below 10% of patients with other related rheumatic diseases. Healthy controls were AUF1 autoantibodies negative.

References

Zhang W, Wagner BJ, Ehrenman K, Schaefer AW, DeMaria CT, Crater D, DeHaven K, Long L, Brewer G. Purification, characterization, and cDNA cloning of an AU-rich element RNA-binding protein, AUF1. Mol Cell Biol. 1993 Dec;13(12):7652-65

Chen CY, Shyu AB. AU-rich elements: characterization and importance in mRNA degradation. Trends Biochem Sci. 1995 Nov;20(11):465-70

Buzby JS, Lee SM, Van Winkle P, DeMaria CT, Brewer G, Cairo MS. Increased granulocyte-macrophage colony-stimulating factor mRNA instability in cord versus adult mononuclear cells is translation-dependent and associated with increased levels of A + U-rich element binding factor. Blood. 1996 Oct 15;88(8):2889-97

Dempsey LA, Li MJ, DePace A, Bray-Ward P, Maizels N. The human HNRPD locus maps to 4q21 and encodes a highly conserved protein. Genomics. 1998 May 1;49(3):378-84

Lafon I, Carballès F, Brewer G, Poiret M, Morello D. Developmental expression of AUF1 and HuR, two c-myc mRNA binding proteins. Oncogene. 1998 Jul 2;16(26):3413-21

Wagner BJ, DeMaria CT, Sun Y, Wilson GM, Brewer G. Structure and genomic organization of the human AUF1 gene: alternative pre-mRNA splicing generates four protein isoforms. Genomics. 1998 Mar 1;48(2):195-202

Loflin P, Chen CY, Shyu AB. Unraveling a cytoplasmic role for hnRNP D in the in vivo mRNA destabilization directed by the AU-rich element. Genes Dev. 1999 Jul 15;13(14):1884-97

Blaxall BC, Dwyer-Nield LD, Bauer AK, Bohlmeyer TJ, Malkinson AM, Port JD. Differential expression and localization of the mRNA binding proteins, AU-rich element mRNA binding protein (AUF1) and Hu antigen R (HuR), in neoplastic lung tissue. Mol Carcinog. 2000 Jun;28(2):76-83

Gouble A, Morello D. Synchronous and regulated expression of two AU-binding proteins, AUF1 and HuR, throughout murine development. Oncogene. 2000 Nov 9;19(47):5377-84

Lin S, Wang W, Wilson GM, Yang X, Brewer G, Holbrook NJ, Gorospe M. Down-regulation of cyclin D1 expression by prostaglandin A(2) is mediated by enhanced cyclin D1 mRNA turnover. Mol Cell Biol. 2000 Nov;20(21):7903-13

Xu N, Chen CY, Shyu AB. Versatile role for hnRNP D isoforms in the differential regulation of cytoplasmic mRNA turnover. Mol Cell Biol. 2001 Oct;21(20):6960-71

Gouble A, Grazide S, Meggetto F, Mercier P, Delsol G, Morello D. A new player in oncogenesis: AUF1/hnRNPD overexpression leads to tumorigenesis in transgenic mice. Cancer Res. 2002 Mar 1;62(5):1489-95

Lapucci A, Donnini M, Papucci L, Witort E, Tempestini A, Bevilacqua A, Nicolin A, Brewer G, Schiavone N, Capaccioli S. AUF1 Is a bcl-2 A + U-rich element-binding protein involved in bcl-2 mRNA destabilization during apoptosis. J Biol Chem. 2002 May 3;277(18):16139-46

Laroia G, Sarkar B, Schneider RJ. Ubiquitin-dependent mechanism regulates rapid turnover of AU-rich cytokine mRNAs. Proc Natl Acad Sci U S A. 2002 Feb 19;99(4):1842-6

Laroia G, Schneider RJ. Alternate exon insertion controls selective ubiquitination and degradation of different AUF1 protein isoforms. Nucleic Acids Res. 2002 Jul 15;30(14):3052-8

Pioli PA, Hamilton BJ, Connolly JE, Brewer G, Rigby WF. Lactate dehydrogenase is an AU-rich element-binding protein that directly interacts with AUF1. J Biol Chem. 2002 Sep 20;277(38):35738-45

Brewer G, Saccani S, Sarkar S, Lewis A, Pestka S. Increased interleukin-10 mRNA stability in melanoma cells is associated with decreased levels of A + U-rich element binding factor AUF1. J Interferon Cytokine Res. 2003 Oct;23(10):553-64

Moraes KC, Quaresma AJ, Maehnss K, Kobarg J. Identification and characterization of proteins that selectively interact with isoforms of the mRNA binding protein AUF1 (hnRNP D). Biol Chem. 2003 Jan;384(1):25-37

Sarkar B, Lu JY, Schneider RJ. Nuclear import and export functions in the different isoforms of the AUF1/heterogeneous nuclear ribonucleoprotein protein family. J Biol Chem. 2003 Jun 6;278(23):20700-7

Lal A, Mazan-Mamczarz K, Kawai T, Yang X, Martindale JL, Gorospe M. Concurrent versus individual binding of HuR and AUF1 to common labile target mRNAs. EMBO J. 2004 Aug 4;23(15):3092-102

Blum JL, Samarel AM, Mestril R. Phosphorylation and binding of AUF1 to the 3'-untranslated region of cardiomyocyte SERCA2a mRNA. Am J Physiol Heart Circ Physiol. 2005 Dec;289(6):H2543-50

Enokizono Y, Konishi Y, Nagata K, Ouhashi K, Uesugi S, Ishikawa F, Katahira M. Structure of hnRNP D complexed with single-stranded telomere DNA and unfolding of the quadruplex by heterogeneous nuclear ribonucleoprotein D. J Biol Chem. 2005 May 13;280(19):18862-70

Santamaría I, Alvarez-Hernández D, Jofré R, Polo JR, Menárguez J, Cannata-Andía JB. Progression of secondary hyperparathyroidism involves deregulation of genes related to DNA and RNA stability. Kidney Int. 2005 Jun;67(6):2267-79

Suzuki M, Iijima M, Nishimura A, Tomozoe Y, Kamei D, Yamada M. Two separate regions essential for nuclear import of the hnRNP D nucleocytoplasmic shuttling sequence. FEBS J. 2005 Aug;272(15):3975-87

Wang W, Martindale JL, Yang X, Chrest FJ, Gorospe M. Increased stability of the p16 mRNA with replicative senescence. EMBO Rep. 2005 Feb;6(2):158-64

Fawal M, Armstrong F, Ollier S, Dupont H, Touriol C, Monsarrat B, Delsol G, Payrastre B, Morello D. A "liaison dangereuse" between AUF1/hnRNPD and the oncogenic tyrosine kinase NPM-ALK. Blood. 2006 Oct 15;108(8):2780-8

He C, Schneider R. 14-3-3sigma is a p37 AUF1-binding protein that facilitates AUF1 transport and AU-rich mRNA decay. EMBO J. 2006 Aug 23;25(16):3823-31

Nagaoka K, Tanaka T, Imakawa K, Sakai S. Involvement of RNA binding proteins AUF1 in mammary gland differentiation. Exp Cell Res. 2007 Aug 1;313(13):2937-45

Torrisani J, Unterberger A, Tendulkar SR, Shikimi K, Szyf M. AUF1 cell cycle variations define genomic DNA methylation by regulation of DNMT1 mRNA stability. Mol Cell Biol. 2007 Jan;27(1):395-410

Paek KY, Kim CS, Park SM, Kim JH, Jang SK. RNA-binding protein hnRNP D modulates internal ribosome entry site-dependent translation of hepatitis C virus RNA. J Virol. 2008 Dec;82(24):12082-93

Skriner K, Hueber W, Süleymanoglu E, Höfler E, Krenn V, Smolen J, Steiner G. AUF1, the regulator of tumor necrosis factor alpha messenger RNA decay, is targeted by autoantibodies of patients with systemic rheumatic diseases. Arthritis Rheum. 2008 Feb;58(2):511-20

Zhou C, Vignere CZ, Levitan ES. AUF1 is upregulated by angiotensin II to destabilize cardiac Kv4.3 channel mRNA. J Mol Cell Cardiol. 2008 Dec;45(6):832-8

Kang X, Chen W, Kim RH, Kang MK, Park NH. Regulation of the hTERT promoter activity by MSH2, the hnRNPs K and D, and GRHL2 in human oral squamous cell carcinoma cells. Oncogene. 2009 Jan 29;28(4):565-74

Pautz A, Linker K, Altenhöfer S, Heil S, Schmidt N, Art J, Knauer S, Stauber R, Sadri N, Pont A, Schneider RJ, Kleinert H. Similar regulation of human inducible nitric-oxide synthase expression by different isoforms of the RNA-binding protein AUF1. J Biol Chem. 2009 Jan 30;284(5):2755-66

Trojanowicz B, Brodauf L, Sekulla C, Lorenz K, Finke R, Dralle H, Hoang-Vu C. The role of AUF1 in thyroid carcinoma progression. Endocr Relat Cancer. 2009 Sep;16(3):857-71

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