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

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Identity

Other names: AUFI; AUFI-A; HNRPD; P37; hmRNPD0
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 AUFI 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.
**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 A2 (PGA2) is an experimental anti-cancer agent associated with reduced levels of cyclin D1 and decreased proliferation of cancer cells. Employment of PGA2 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 rheumatoid 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.

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