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Gene Section
Review

ZFP36L1 (zinc finger protein 36, C3H type-like 1)

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Identity

Hugo: ZFP36L1
Other names: Berg36; BRF1; cMG1; ERF1; TIS11B
Location: 14q24.1
Note: The rat clone of ZFP36L1, cMG1, was the first cloned member of the tristetraprolin (TTP, TIS11, NUP475, GOS24) family of CCCH tandem zinc finger proteins. There are 4 mammalian members of this family, TTP, ZFP36L1, ZFP36L2 (TIS11D, ERF2, BRF2), and ZFP36L3. ZFP36L3 is the only family member that is rodent-specific. These proteins have been shown to bind (via their conserved tandem zinc finger domain) directly to class II AU-rich elements (ARE) in the 3'-untranslated region (UTR) of mRNA leading to deadenylation and destabilization of the mRNA.

DNA/RNA

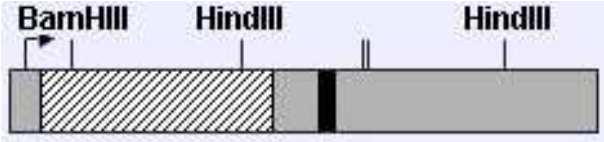

Diagram of the human ZFP36L1 gene. Exons are represented by gray boxes; intron by the hatched box. The translation start site is indicated by the arrow and the translation stop site by the double line. The dark box represents the CCCH tandem zinc finger domain.

Description

The human ZFP36L1 has 2 exons spanning 5411 bp on chromosome 14 (NC_000014.7; NT_026437.11). The first exon, which is small (186 bp), is separated from the larger second exon (2834 bp) by a 2388 bp intron.

Transcription

3022 bp human transcript (NM_004926.2) with 1014 bp (338 amino acids) of coding region.

Pseudogene

None known.

Protein

Description

Human ZFP36L1 is a 338 amino acid protein with a predicted molecular weight of 36.3 kDa.

Expression

In the adult mouse, expression appears to be ubiquitous. Based on northern blots, mRNA expression is highest in mouse kidney, spleen, ovary and lung, with lower levels of expression in thymus and heart, and still lower levels in brain, liver and testis. In the embryonic mouse, mRNA was barely detectable at embryonic day 7.5 (E7.5), but increased dramatically by E9.5 and E10.5. In situ hybridization histochemistry demonstrated that there was high level expression in the allantois at E8.0, immediately before fusion with the chorion. Expression is also seen in mouse embryonic stem cells.

Localisation

Transfection studies using a GFP-tagged protein have shown diffuse cytoplasmic expression. There is good evidence that the protein can shuttle between the nucleus and the cytoplasm in a CRM1 (nuclear export receptor)-dependent, leptomycin B-inhibitable manner.

Function

ZFP36L1 is a member of the TTP (ZFP36) family of CCCH tandem zinc finger proteins. These proteins have been shown to bind to target mRNAs through their AU-rich elements present in the 3'-untranslated regions of the mRNA.
The binding of these proteins to mRNA leads to deadenylation and destabilization of the mRNA. All four family members have been shown to bind directly

to single stranded RNA probes (RNA gel shift assays), destabilize target mRNA (co-transfection assays), and deadenylate ARE-containing RNA probes (cell-free deadenylation assays). Physiological target mRNAs have been identified for TTP which include tumor necrosis factor alpha (TNF), granulocyte-macrophage colony stimulating factor (GM-CSF), interleukin-2b (IL-2), and immediate early response gene 3 (IER3, IEX-1, gly96).
To date, one physiological target mRNA has been identified for ZFP36L1; however, this target mRNA is not destabilized by ZFP36L1 (see below).
Two reports of ZFP36L1 knockout mice have been published. In one report, knockout embryos died around embryonic day 11 mainly due to failure of chorioallantoic fusion. When fusion did occur, there was increased apoptosis throughout the neural tube, as well as placental failure due to atrophy of the trophoblast layers. In a second report, knockout embryos also died at mid-gestation and exhibited extraembryonic and intraembryonic vascular abnormalities and heart defects. In the developing placenta, the extraembryonic mesoderm failed to invaginate the trophoblast layer. This phenotype was associated with an elevated expression of vascular endothelial growth factor (VEGF)-A (in the embryo and in mouse embryonic fibroblasts). This elevated level of expression was not due to increased stability of the VEGF-A mRNA, but rather due to enhanced association with polyribosomes.
This is in contrast to a prior report using co-transfection studies showing that ZFP36L1 was able to bind to two AU-rich motifs in the 3' UTR of VEGF mRNA that led to destabilization of the mRNA. Mouse ZFP36L1 has been shown to interact with 14-3-3 proteins in a phosphorylation-dependent manner. This interaction causes ZFP36L1 to be sequestered in the cytoplasm preventing it from regulating mRNA decay. Several studies have suggested that ZFP36L1 may function as a pro-apoptotic protein.

Homology

Four members of the TTP family of CCCH tandem zinc finger proteins, TTP (ZFP36), ZFP36L1, ZFP36L2 and the rodent-specific ZFP36L3, have been identified. They all share a highly conserved tandem zinc finger domain.

Mutations

Note: Eight polymorphisms have been identified. The functional significance of these polymorphisms has not been determined.
1) G change into T at base 644 in the 5' UTR.
2) AG change into GC at base 706 in the first coding region.
3) G change into A at base 729 in the intron.
4) C change into CC at base 772 in the intron.
5) A change into G at base 804 in the intron.
6) G change into C at base 845 in the intron.
7) G change into A at base 3685 in the second coding region.
8) C change into A at base 3915 in the second coding region.

Implicated in

Cisplatin sensitivity in head and neck squamous cell carcinoma (HNSCC)

Note: A common feature in HNSCC is cisplatin sensitivity. Microarray analysis identified mouse ZFP36L1 to be differentially expressed by cisplatin treatment. Cisplatin-sensitive HNSCC cell lines expressed elevated levels of ZFP36L1 compared to cisplatin-resistant HNSCC cell lines. Downregulation of ZFP36L1 (using antisense oligonucleotides) in cisplatin-sensitive cell lines made the cells cisplatin-resistant. Conversely, overexpression of ZFP36L1 reverted cisplatin-resistant cells to cisplatin-sensitive cells. There was an inverse correlation between the expression levels of ZFP36L1 and the human inhibitor of apoptosis protein-2, cIAP2 (Birc3, baculoviral IAP repeat-containing 3). Increased expression of ZFP36L1 also correlated with increased caspase-3 activity and increased cisplatin-induced apoptosis. These results suggested that expression of ZFP36L1 enhanced cisplatin sensitivity in HNSCC cells by reducing cIAP2 mRNA levels.

t(8;21) translocation

Note: The AML1-MTG8 fusion transcription factor generated by t(8;21) translocation is thought to affect the normal regulation of genes that are needed for differentiation and proliferation of hematopoietic progenitors leading to acute myelogenous leukemia (AML). ZFP36L1 was identified as an up-regulated gene in t(8;21) leukemic cells suggesting that it may be important to AML1-MTG8-mediated leukemogenesis.

Human T-lymphotropic virus 1 (HTLV-1)

Note: ZFP36L1 expression is also up-regulated in human T-lymphotropic virus 1(HTLV-1)-infected cells. HTLV-1 is associated with adult T-cell leukemia/lymphoma and the Tax oncoprotein encoded by the 3' region of HTLV-1 has been proposed to dysregulate the expression of many genes that are important for cell proliferation. The Tax transactivator was shown to bind to two ZFP36L1 upstream elements (a novel transcription factor-binding site labeled BRF1 Tax-responsive site or BTRS and a second consensus cAMP-responsive site or CRE).

Various cancers

Note: Increased expression of ZFP36L1 has been seen in several cancers including lymph node (+) primary breast tumors and hepatocellular carcinomas. Increased

expression has also been demonstrated in a number of the NCI 60 panel of human cancer cell lines. These include the mammary gland cancer cell lines BT549, MDA-MB-231, and NCI/ADR-RES; ovarian cell lines OVCAR-5, OVCAR-8 and SK-OV-3; lung cell line NCI-H226; skin cell lines LOXMVI, M14, MALME-3M, and SK-MEL-2; brain cell lines SF268 and SF295; prostate cell line PC-3; kidney cell lines A498, ACHN, CAKI-1, SN12C, TK10, and UO31; and colon cell line HT29.

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