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Gene Section
Review

CPEB4 (cytoplasmic polyadenylation element binding protein 4)

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Abstract

Review on CPEB4, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

HGNC (Hugo): CPEB4

Location: 5q35.2

Local order: UCSC Genome Browser.

DNA/RNA

Description

CPEB4 gene covers 71.98 kb on human chromosome 5 (5q35.2), between 173315331 and 173387313 (according to hg19-Feb_2009, UCSC).

Transcription

The mRNA of CPEB4 contains 10 exons and 9 introns. Multiple transcript variants encoding different isoforms (10 splice variants) have been found for this gene.

Protein

Description

CPEB4 is a RNA binding protein that belongs to the CPEB-family of proteins. In vertebrates, 4 members (CPEB1, CPEB2, CPEB3, CPEB4) have been identified, CPEBs2-4 are closely related whereas CPEB1 is the most distant member of the family (Wang et al., 2010). All members have a conserved carboxy-terminal region, composed of two RNA Recognition motifs (RRM) and two zinc-finger-like motifs (Hake et al., 1998), and a regulatory highly variable N-terminal domain.
10 different isoforms have been described for CPEB4:
- Isoform a: 729 amino acids, 80.2 kDa protein, RRM motifs: aa 472-563 and aa 580-662.

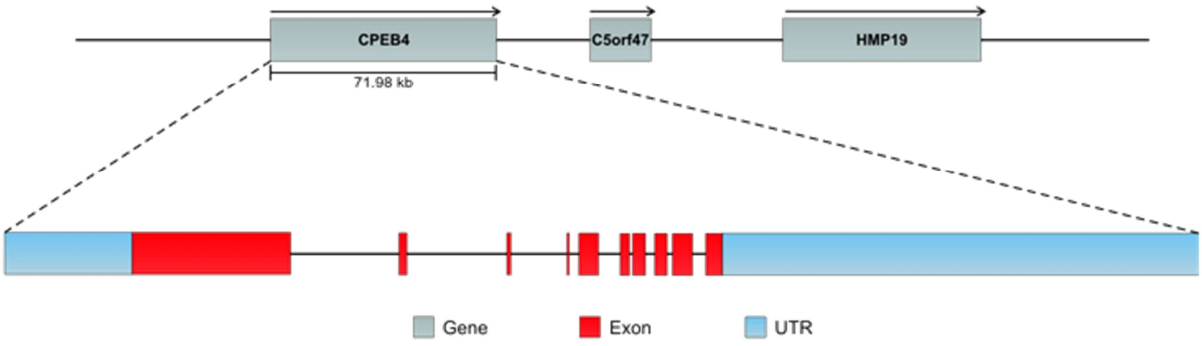

Diagram of the genomic organization of CPEB4.

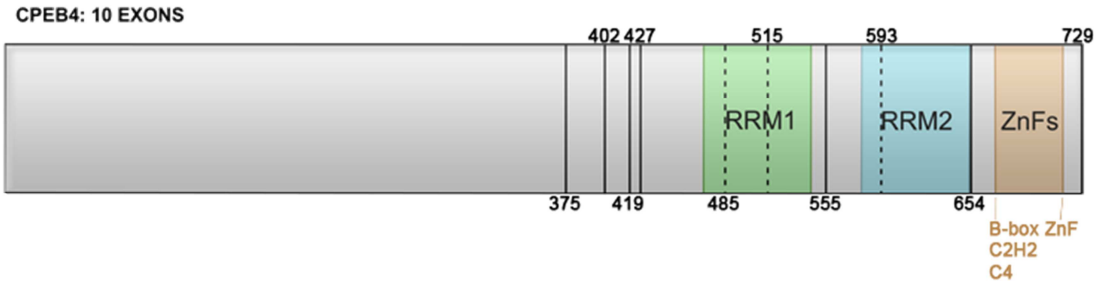

Diagram of CPEB4 protein in scale (Isoform a). CPEB4 presents 2 different RNA Recognition Motifs (RRM1 - green and RRM2 - blue), which recognize U-rich sequences. Moreover, CPEB4 has two Zinc-finger-like motifs (ZnFs - brown). CPEBs share these conserved RNA-binding domain at the C-terminal of the protein.

- Isoform b: Exon 3 skipped, 712 amino acids, 78.3 kDa protein.
- Isoform c: Exon 3 and 4 skipped, 704 amino acids, 77.3 kDa protein.
- Isoform d: Exons 3, 4 and 9 skipped, 639 amino acids, 69.8 kDa protein.
- Isoform e: Exons 3, 4, 5, 6, 7, 8, 9 and 10 skipped, 389 amino acids, 43.1 KDa protein.
- Isoform f: Exons 1 and 4 skipped, 339 amino acids, 38 kDa protein.
- Isoform g: Exons 1, 3 and 4 skipped, 322 amino acids, 36.2 kDa protein.
- Isoform h: Exons 1, 2, 3 and 4 skipped, 295 amino acids, 33 KDa protein.
- Isoform i: Exons 1 (partly) 3, 4, 5, 6, 7, 8, 9 and 10 skipped, 226 amino acids, 25.3 KDa protein.
- Isoform j: Exons 1 (partly) 4, 6, 7, 8, 9 and 10 skipped, 146 amino acids, 16.3 kDa protein.

Expression

CPEBs are widely expressed in different mammalian tissues and tumours and sometimes with overlapping patterns. CPEB4 mRNA is highly expressed in embryonic stages (E14.5) brain, heart, kidney and lung.
Moreover, a lower expression is also present in liver, spleen and ovary (Fernandez-Miranda et al., 2012). At protein level, an upregulation in Pancreatic Ductal Adenocarcinoma (PDA) and glioblastoma (Ortiz-Zapater et al., 2011) has also been described. At RNA level, CPEB4 misregulation is present in several types of cancer: prostate, breast, skin, lung, brain and digestive apparatus (D'Ambrogio et al., 2013) but this misregulation requires further characterization because CPEB4 mRNA is under a strong post-transcriptional regulation.

Localisation

Cytoplasmic Polyadenylation Element Binding protein 4 (CPEB4) is mostly cytosolic, however it has been reported that it can be a nucleus-cytoplasm shuttling protein in neurons, in response to calcium-mediated signalling. In fact, CPEB4 becomes nuclear in response to focal ischemia and when cultured neurons are deprived of oxygen and glucose (Kan et al., 2010).

Function

CPEBs are RNA binding proteins that recognize cis-acting elements named Cytoplasmic Polyadenylation Element (CPE), that are located in the 3'UTR of some mRNAs. They were originally described in Xenopus laevis oocytes, where they control translation of maternal mRNAs during meiosis by regulation of the length of the polyA tail (Hake and Richter, 1994). However, these proteins can be also found in other non-germ cells suggesting other functions for CPEBs (Costa-Mattioli et al., 2009; Mendez and Richter, 2001; Richter, 2007). CPEB4 recognizes the same CPE as CPEB1, although with less affinity (Novoa et al., 2010; Igea et al., 2010). In oocytes, CPEB4 is required for meiotic progression between MI and MII and regulates CSF arrest (Igea et al., 2010). In somatic cells, CPEB4, together with CPEB, regulates mitotic poly(A) tail elongation and is required for cell proliferation (Novoa et al., 2010). Moreover, CPEB4 also plays a role in cancer where overexpression of CPEB4 correlates with increased malignancy, tumour growth and vascularization in pancreatic cancer and glioblastoma (Ortiz-Zapater et al., 2011), suggesting that overexpression of CPEB4 can be a general mechanism in cancer development and that CPEB4 could behave as an oncogene.

Homology

CPEB4 orthologs are also present in other species, such as Mus musculus (Cpeb4), Xenopus laevis (cpeb4), Danio rerio (cpeb4), Drosophila melanogaster (Orb2) and Caenorhabditis elegans (cpb1-2).

Mutations

Note

Relevant point mutations have been described for other members of the CPEB family, such as the point mutation T>C in exon 3 of the CPEB3 mRNA

(rs11186856), which has been associated with a reduced translation efficiency and impaired episodic memory (Vogler et al., 2009). However, even though there are some point mutations described for CPEB4, up to date none of them have been proved to have a functional relevance.

Implicated in

Pancreatic cancer

Note

CPEB4 is overexpressed in human Pancreatic Ductal Adenocarcinoma (PDAC) where it supports tumour growth, vascularization and invasion (Ortiz-Zapater et al., 2011). In addition, knockdown of CPEB4 both in vitro and in vivo causes significant reduction of the malignancy of pancreatic tumor cells, suggesting the use of CPEB4 inhibitors as a PDA therapy.

Disease

The most common type of human pancreatic cancer (95%) is pancreatic ductal adenocarcinoma that is the fifth most common cause of cancer-related deaths worldwide, second only to colon cancer among malignancies of the digestive tract (Siegel et al., 2013). Despite notable efforts to develop novel therapeutic targets, PDA is still highly resistant to therapy, with a median survival of 4-6 months and a 5-year survival rate lower than 5% (Hidalgo, 2010).

Prognosis

CPEB4 expression was specifically upregulated in human pancreatic cancer, correlating with tumor stages. CPEB4 expression is absent in normal pancreas, low in low-grade precursor tumor lesions (PanIN - Pancreatic Intraepithelial Neoplasia), medium in high-grade PanINs and high in well-differentiated PDAC. These data suggest that CPEB4 expression can be a prognostic factor in pancreatic carcinogenesis.

Oncogenesis

CPEB4 has been reported as a master gene involved in the reprogramming of cancer gene expression. The pro-oncogenic functions of CPEB4 originate in the translational activation of mRNAs that are silenced in normal tissue. RNA immunoprecipitation (RIP) analysis, identify more than 800 transcripts significantly enriched in a number of cancer-related cellular functions such as cell signalling molecules (Ras-related, Smad3, PI3 K, CamKII, G-protein coupled-receptor), chromatin-remodelling proteins (i.e. histone deacetylases, MYST histone acetyltransferase), cyclins, apoptosis-related molecules (CASP8, BCL2 binding component 3), stress/inflammation factors (interleukin 32, HIG1, interferon receptor 2, heat shock 70) and genes associated with cell migration/metastasis (MMP-7, tissue plasminogen activator, β-catenin, Twist) (Ortiz-Zapater et al., 2011).

Glioblastoma

Note

CPEB4 is overexpressed in human glioblastoma, increasing its capacity to proliferate and invade. CPEB4 downregulation in vivo correlates with less tumour size, proliferation and vascularization (Ortiz-Zapater et al., 2011).

Disease

Glioblastoma (formerly GlioBlastoma Multiforme, GBM) represents both the most common and most malignant primary brain tumour variant.

Its widely infiltrative growth precludes definitive surgical resection, and its invariably aggressive biological behaviour leads to dismal clinical outcome (Wen et al., 2007).

GBM could arise from a WHO grade II or III astrocytoma (secondary GBM) or emerging in a fully malignant state (primary GBM) (Ohgaki et al., 2005).

Prognosis

CPEB4 is absent in human normal astrocytes but was very abundant in high-grade glioblastoma, suggesting a prognostic value for CPEB4 expression in this tumor.

Ischemic stroke

Note

Ischemic stroke is a leading cause of death and dissability worldwide.

It is produced from a vascular oclussion, which reduces the perfussion of the blood into specific areas of the brain. The subsequent restoration of the blood flow has been demonstrated to exacerbate the damage.

Prognosis

CPEB4 has been described to shuttle to the nucleus of neurons in response to pathological levels of the neurotransmitter glutamate (a hallmark of the ischemic stroke) both in vitro and in vivo. Moreover, the nuclear accumulation of CPEB4 has been associated to an enhanced survival of hippocampal neurons under low levels of oxygen and glucose, pointing to a neuroprotective role of CPEB4 (Kan et al., 2010).

To be noted

Note

Joan Gibert and Héctor Anta contributed equally to this work and share first authorship.

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