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Gene Section
Review

EIF4EBP1 (Eukaryotic translation initiation factor 4E binding protein 1)

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Identity

Other names: BP-1; 4EBP1; 4E-BP1; PHAS-I; MGC4316

HGNC (Hugo): EIF4EBP1

Location : 8p12

DNA/RNA

Description

The EIF4EBP1 gene codes for 4E-BP1, one member of a family of small proteins that act as repressors of translation. The gene is 29.86 Kb in length and contains three exons, comprising nucleo-tides 1-217, 218-397 and 398-859 of the mature mRNA.

Transcription

Activity of the promoter of the EIF4EBP1 gene is regulated by the Forkhead-O1 (FOXO1) transcript-tion factor (Southgate et al., 2007). Over-expression of FOXO1 enhances the levels of 4E-BP1 mRNA and protein. The consequent accumulation of the hypophosphorylated form of 4E-BP1 impairs overall protein synthesis. There is evidence that activity of the phosphatidylinositol 3-kinase (PI3K) and MAP kinase pathways can negatively regulate the transcription of EIF4EBP1 (Azar et al., 2008), possibly via the transcription factor Egr-1 (Rolli-Derkinderen et al., 2003). Conversely, EIF4EBP1 transcription is positively regulated by ATF4 in response to cell stress (Yamaguchi et al., 2008).

Pseudogene

Two pseudogenes with homology to 4E-BP1 exist in the human genome, located at 14q11.2 (LOC768328) and 22q12 (EIF4EBP1P), with the latter pseudogene present on the antisense strand of the gene locus encoding chromodomain helicase DNA binding protein 8 (CHD8).

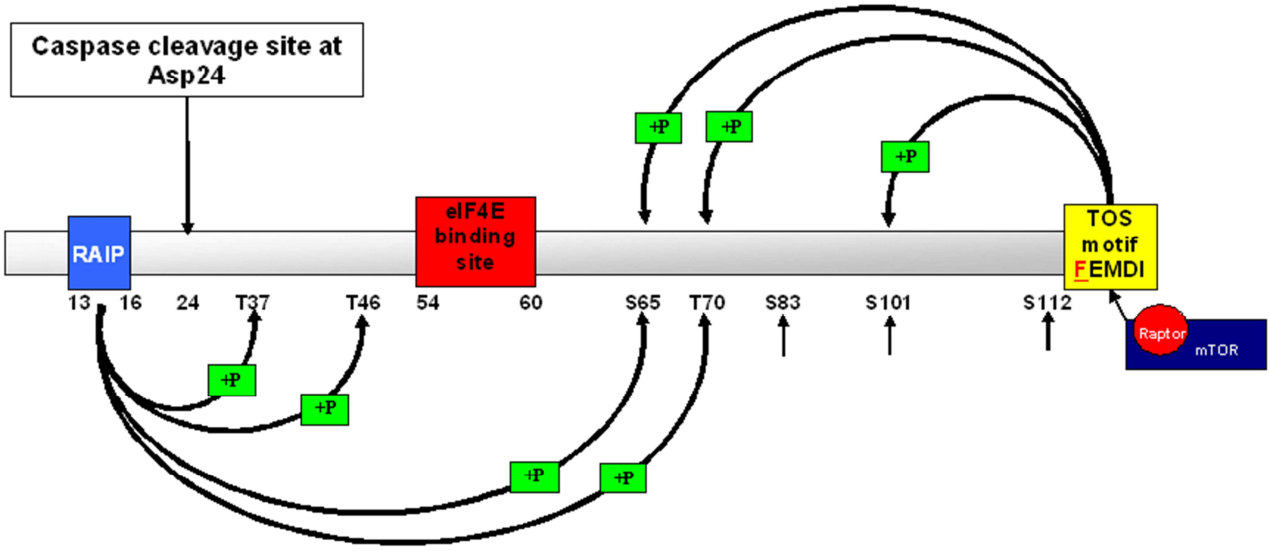
Protein

Description

Human 4E-BP1 is a 118 amino acid protein (119 amino acids including the initiating methionine) and is encoded by an mRNA containing 877 nucleotides (including a short poly(A) tail). The mRNA has a 72 nucleotide 5' untranslated region and a 448 nucleotide 3' untranslated region. The coding region comprises nucleotides 73-429. The protein can be reversibly phosphorylated at Thr^{37}, Thr^{46}, Ser^{65}, Thr^{70}, Ser^{83}, Ser^{101} and Ser^{112} in response to a variety of physiological stimuli.

Expression

4E-BP1 is ubiquitously expressed, although its presence is not essential to the viability of cells or the organism as a whole (Le Bacquer et al., 2007). The level of expression and state of phospho-rylation of the protein may influence cellular phenotype, with high levels of phosphorylated 4E-BP1 in breast, ovary, and prostate tumours being associated with malignant progression and an adverse prognosis (Armengol et al., 2007).



The diagram illustrates key regulatory features of the human 4E-BP1 protein, including the RAIP and TOS motifs that are important for the phosphorylation of the protein at Thr^{37}, Thr^{46}, Ser^{65}, Thr^{70} and Ser^{101} by the Raptor/mTOR complex (Eguchi et al., 2006; Lee et al., 2008). Additional phosphorylation sites have been identified at Ser^{83} and Ser^{112}. The region required for binding of 4E-BP1 to initiation factor eIF4E and a site of cleavage of the protein by caspases in apoptotic cells are also shown. (Diagram adapted from an original prepared by Dr C. Constantinou).

Conver-sely, hypophosphorylated 4E-BP1 may have an anti-oncogenic role due to its inhibitory effect on eIF4E.

Localisation

4E-BP1 is present in both cytoplasm and nucleus. The hypophosphorylated protein in the latter compartment can sequester eIF4E within the nucleus under conditions of physiological stress (Rong et al., 2008).

Function

The members of the 4E-BP family of proteins act by binding to the mRNA cap-binding protein eukaryotic initiation factor 4E (eIF4E), in compe-tition with another initiation factor, eIF4G, that is essential for polypeptide chain initiation. Thus the availability of eIF4E for translation of cap-dependent mRNAs is limited by the extent to which this factor is sequestered by the 4E-BPs.

4E-BP1 is reversibly phosphorylated at multiple sites (see diagram above), in response to several physiological signals that promote translation (Proud, 2004; Wang et al., 2005; Proud, 2006). Such phosphorylations lower the affinity of 4E-BP1 for eIF4E and result in the dissociation of the two proteins, thereby enhancing the level of active eIF4E and promoting the translation of capped mRNAs, most likely in a selective manner (Averous et al., 2008). Conversely, physiological stresses and other conditions that inhibit translation - e.g. exposure of cells to cytokines of the TNFalpha family (Lang et al., 2007; Jeffrey et al., 2006) or activation of the tumour suppressor protein p53 (Tilleray et al., 2006; Constantinou and Clemens, 2007) - cause dephosphorylation of 4E-BP1 and increase binding of the latter to eIF4E. 4E-BP1 is also susceptible to other post-translational modifications, notably specific proteolytic cleavages (Tee and Proud, 2002; Constantinou et al., 2008) and phosphorylation-dependent ubiqui-tination (Elia et al., 2008). Although 4E-BP1 is not essential to viability the protein (together with its homologue 4E-BP2) is important for regulation of adipogenesis and insulin resistance (Le Bacquer et al., 2007). The 4E-BPs have also been reported to play a role in myelopoiesis (Olson et al., 2008). There is a major role for 4E-BP1 in the responses of cells to hypoxia, which promotes dephosphorylation of the protein (Koritzinsky et al., 2006; Connolly et al., 2006). It is likely that this response implements hypoxia-induced changes in gene expression at the translational level (Magagnin et al., 2008; Barnhart et al., 2008).

Homology

4E-BP1 was identified alongside another member of the eIF4E-binding protein family designated 4E-BP2 (Pause et al., 1994). A further homologue has also been identified, 4E-BP3 (Poulin et al., 1998), and these proteins respectively share 55.7% identity (82.0% similarity) and 50.8% identity (66.9% similarity) with 4E-BP1. All share the central eIF4E binding motif and are capable of competing with the eIF4G proteins for binding to eIF4E.

CLUSTAL 2.0.10 multiple sequence alignment:

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4E-BP1    MSGGSSCSQTP--SRAIPATRRVVLGDGVQLPPGDYSTTPGGTLFSTTPGGTRIIYDRKF 58
4E-BP2    MSSSAGSGHQPSQSRAIPT-RTVAISDAAQLP-HDYCTTPGGTLFSTTPGGTRIIYDRKF 58
4E-BP3    MSTST--------SCPIP-------GGRDQLP-DCYSTTPGGTLYATTPGGTRIIYDRKF 44
          ** .:        * .**       ..  ***   *.*******::**************

4E-BP1    LMECRNSPVTKTPPRDLPTIPGVTSPSS--DEPPMEASQSHLRNSPEDKRAGGEESQFEM 116
4E-BP2    LLDRRNSPMAQTPPCHLPNIPGVTSPGTLIEDSKVEVNNLNNLNNHDRKHAVGDDAQFEM 118
4E-BP3    LLECKNSPIARTPPCCLPQIPGVTTP------PTAPLSKLEELKEQETEEEIPDDAQFEM 98
          *:: :***:::***  ** *****:*      .    .: .  :. : :.   :::****

4E-BP1    DI 118
4E-BP2    DI 120
4E-BP3    DI 100
          **
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Mutations

Note

No mutations have been identified.

Implicated in

Breast cancer

Prognosis

Elevated expression of eIF4E in human cancer often correlates with poor prognosis (Culjkovic et al., 2007). Likewise, expression of phosphorylated 4E-BP1 (which is inactive as an inhibitor of eIF4E) is associated with malignant progression and an adverse prognosis in breast, ovary, and prostate tumours (Armengol et al., 2007).

Oncogenesis

Because 4E-BP1 is an antagonist of the oncogenic initiation factor eIF4E (Avdulov et al., 2004), it might be anticipated that 4E-BP1 could function as a pro-apoptotic tumour suppressor protein. However it has been reported that a majority of large advanced breast cancers overexpress 4E-BP1 (Braunstein et al., 2007). The latter may contribute to tumourigenesis (in combination with over-expressed eIF4G) by promoting a hypoxia-activated switch in selective mRNA translation that enhances angiogenesis and tumour cell growth and survival.

Breakpoints

Note

Although no breakpoints within the 4E-BP1 gene locus have been identified, the chromosomal region containing 4E-BP1 (8p11-12) is frequently rear-ranged in breast carcinomas. However, microarray profiling of the genes within these regions in breast tumours and cell lines shows that rearrangements of the chromosome do not correlate with significantly changed 4E-BP1 mRNA expression (Gelsi-Boyer et al., 2005).

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