

Gene Section

Review

EIF3A (eukaryotic translation initiation factor 3, subunit A)

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Published in Atlas Database: November 2010

Online updated version : <http://AtlasGeneticsOncology.org/Genes/EIF3AID40425ch10q26.html>
DOI: 10.4267/2042/45982

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Identity

Other names: EIF3; EIF3S10; KIAA0139; P167; TIF32; eIF3-p170; eIF3-theta; p180; p185

HGNC (Hugo): EIF3A

Location: 10q26.11

DNA/RNA

Description

The eIF3a gene spans over a region of 46 kbp DNA including 22 coding exons and 2 non-coding exons (exon 2 and exon 10).

Transcription

The eIF3a mRNA consists of about 5256 nucleotides with an open reading frame (ORF) of 4149 bases.

Pseudogene

No pseudogene has been identified.

Protein

Description

Structure: The eIF3a protein consists of 1382 amino acid residues with an apparent molecular weight of ~170 kDa as determined using SDS-PAGE (Pincheira et al., 2001b). Its primary sequence contains a PCI (Proteasome, COP9, Initiation factor 3) domain, a

spectrin domain, and a 10-amino acid repeat domain (Pincheira et al., 2001b). It has phosphorylation sites at Ser-881, Ser-1198, Ser-1336 and Ser-1364 (Damoc et al., 2007). The PCI domain spans from amino acid 405 to 495, which contains purely alpha-helix (Pincheira et al., 2001b). Since most of the proteins containing this domain are part of a multi-protein complex, it is tempting to speculate that this domain may be involved in the interaction of eIF3a with other molecules in eIF3 (Hofmann and Bucher, 1998). The spectrin domain, which consists of 112 amino acids, is a sequence almost identical to spectrin, an actin-binding protein (Pascual et al., 1997). Although the exact function of this domain remains unknown, it may be responsible for the binding of eIF3a to actin filaments (Pincheira et al., 2001a). The 10-amino acid repeat domain spanning 925-1172 amino acids is the largest domain of eIF3a. It can be divided into about 25 repeats of DDRGPRRGA (Johnson et al., 1997; Pincheira et al., 2001b). This domain has been suggested to contribute to interaction of eIF4B and eIF3a (Methot et al., 1996).
Regulatory role in gene expression: eIF3a not only functions as a regular translation initiation factor and participates in translation initiation of global mRNAs, it also regulates the translation of a subset of mRNAs which are involved in cell cycle, tumorigenesis and DNA repair (Yin et al., 2010). It has been observed that overexpression of ectopic eIF3a increases the expression of ribonucleotide reductase



Schematic presentation of eIF3a domain structure. Human eIF3a consists of 1382 amino acid residues with three putative domains of PCI, spectrin, and 10-amino acid repeat.

M2 (RRM2) and alpha-tubulin, but decreases that of p27kip without affect their mRNA levels (Dong and Zhang, 2003; Dong et al., 2004). Recently, it has also been found that eIF3a suppresses the synthesis of DNA repair proteins including: XPA, XPC, RPA 14, RPA 32 and RPA 70 KDa (Yin et al., unpublished data). Although the detailed mechanism of eIF3a regulation in translational control is yet to be determined, it is thought that eIF3a may regulate these genes at their 5'- and 3'-UTRs (Dong and Zhang, 2003; Dong et al., 2004).

Binding with other molecule: Since eIF3a is the largest subunit of the eIF3 complex, the interaction between eIF3a and other subunits of eIF3 were intensively studied. It can bind with eIF3b (Methot et al., 1997), eIF3c (Valasek et al., 2002), eIF3f (Asano et al., 1997), eIF3h (Asano et al., 1997), eIF3j (Valasek et al., 1999) and eIF3k (Mayeur et al., 2003). During the translation initiation, the amino terminal domain of eIF3a can bind with 40S protein RPS0A, while the C terminal domain binds with the 18S rRNA (Valasek et al., 2003). Apart from above molecule, eIF3a has also been shown to interact with eIF4B (Methot et al., 1996), actin (Pincheira et al., 2001a), and cytokeratin 7 (Lin et al., 2001).

Expression

eIF3a is ubiquitously expressed in all human tissues (Nagase et al., 1995; Scholler and Kanner, 1997; Pincheira et al., 2001b). However, its expression is higher in proliferating tissues such as bone marrow, thymus and fetal tissues (Pincheira et al., 2001b).

Localisation

eIF3a has been found in both cytoplasmic and membrane fractions and the cytoplasmic eIF3a appears to be phosphorylated at its serine residues (Pincheira et al., 2001a). However, 70-80% of eIF3a is cytoplasmic.

Function

eIF3a has been shown to play important roles in the biological processes: translational initiation (including generation of ribosomal subunit from 80S ribosomes, 43S pre-initiation complex formation and 48S pre-initiation complex formation) (Dong and Zhang, 2006), regulation of mRNA translation (Dong and Zhang, 2003; Dong et al., 2004), differentiation and development (Liu et al., 2007), apoptosis (Nakai et al., 2005), cell cycle regulation (Dong et al., 2009), oncogenesis (Dong and Zhang, 2006; Zhang et al., 2007), and drug response (unpublished observations).

Homology

Centrosomin A and B have strong homology to eIF3a. The spectrin domain is essentially identical to spectrin.

Mutations

Note

Two SNPs (rs10787899 and rs3824830) were found to

be associated with higher risk of breast cancers (Olson et al., 2009).

Implicated in

Breast cancer

Note

eIF3a was overexpressed in breast cancer tissues.

Oncogenesis

The eIF3a was highly expressed in all tested tissues from breast cancer patients compared with normal control tissues, which indicated that it may contribute to the oncogenesis of breast cancer (Bachmann et al., 1997).

Cervical carcinoma

Note

eIF3a was found to be a molecular parameter of predicting cervical carcinoma progression and prognoses.

Prognosis

Patients with high eIF3a expression have better prognosis than those with lower ones, thus it will be useful in predicting cervical cancer prognosis (Dellas et al., 1998).

Gastric carcinoma

Note

eIF3a is an early tumor maker of gastric carcinoma.

Oncogenesis

eIF3a was highly expressed in well differentiated, early invasive stage and no-metastases gastric carcinoma (Chen and Burger, 2004).

Lung cancer

Note

eIF3a is highly expressed in lung cancer compared with normal tissues.

Prognosis

eIF3a expression in human lung cancers negatively correlates with patient response to platinum-based chemotherapy, suggesting that lung cancer patients with higher eIF3a expression level respond better to platinum-based chemotherapy (Yin et al., unpublished findings).

Oncogenesis

eIF3a was over-expressed in all types of human lung cancer. Furthermore, it is ubiquitously highly expressed in proliferating and developing tissues. This suggested eIF3a may be involved in oncogenesis of lung cancer (Pincheira et al., 2001b).

Esophagus squamous-cell carcinoma

Note

eIF3a may be a biomaker of esophagus squamous-cell carcinoma.

Prognosis

Patients with higher eIF3a expression have better

overall survival and fewer tumor metastases than those with lower ones (Chen and Burger, 1999).

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This article should be referenced as such:

Yin JY, Dong Z, Zhang JT. EIF3A (eukaryotic translation initiation factor 3, subunit A). *Atlas Genet Cytogenet Oncol Haematol.* 2011; 15(7):544-546.
