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Gene Section

Review

EIF4E (eukaryotic translation initiation factor 4E)

Katherine LB Borden, Biljana Culjkovic-Kraljacic, Laurent Volpon

Institute of Research in Immunology and Cancer (IRIC), Department of Pathology and Cell Biology, Universite de Montreal, Pavillion Marcelle-Coutu, Chemin Polytechnique, Montreal, QC, Canada (KLBB, BCK, LV)

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Identity

Other names: CBP, EIF4E1, EIF4EL1, EIF4F, MGC111573

HGNC (Hugo): EIF4E

Location: 4q23

Local order: EIF4E gene covers 51.38 kb, from 100070829 to 100019447 (NCBI 36, March 2006), on the reverse strand.

Gene Card (Weitzmann): GeneLoc location for GC04M100046: starts 100020235 bp from pter and ends 100070139 bp from pter (minus strand).

1 alternative location: Ensembl: Chromosome 4: 99799607-99851786 reverse strand.

DNA/RNA

Description

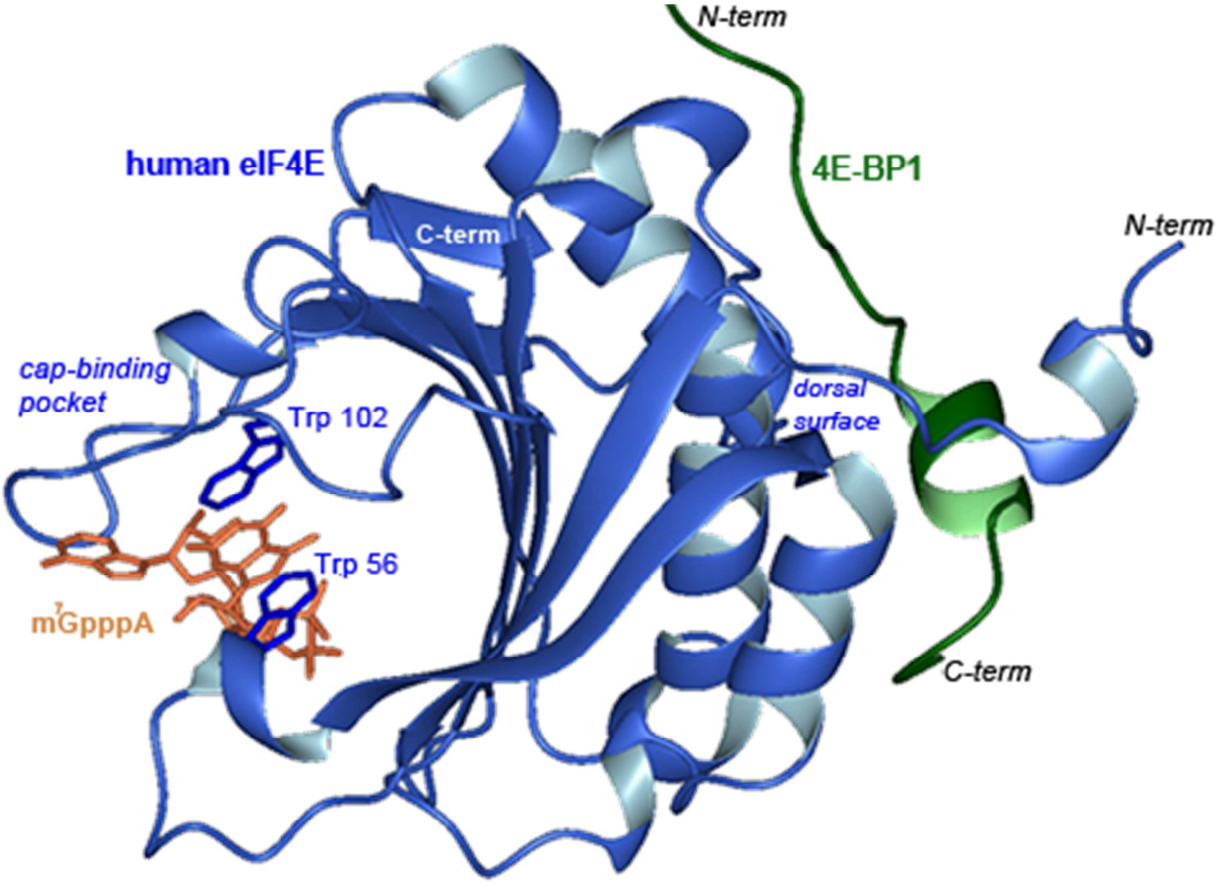
The EIF4E gene spans >50 kbp and contains 8 exons, one of them being alternative. It codes for the major, 4749 nucleotides long transcript variant 1, that codes 217 aa long protein. The longest transcript, variant 2 (4842 nucleotides) contains an additional in-frame exon in 3' coding region compared to variant 1 and codes for a protein (248 aa long, isoform 2) with a longer c-terminus compared to isoform 1. Transcript variant 3 is 3406 nucleotide long and uses an alternative exon for the 5'UTR and 5' coding region that results in translation initiation from a distinct ATG, and an isoform 3, (237 aa) with a longer and distinct N-terminus compared to isoform 1. Transcript variants 2 and 3 are predicted from cDNA sequences, but their expression at mRNA or protein levels was not studied.

Transcription

The promoter of the EIF4E gene lacks a canonical TATA box, but it contains a polypyrimidine element at position -25, named the eIF4E basal element (4EBE) that binds hnRNPK. hnRNPK interacts with TATA-binding protein and recruits it to the promoter, explaining how the 4EBE might replace the TATA box in the EIF4E promoter (Lynch et al., 2005). Mapping of the minimal EIF4E promoter was found to contain CACGTG E box repeats (positions -77 and -232) that are c-myc responsive (Jones et al., 1996; Makhlouf et al., 2001). The same elements overlap for USF binding. Later mapping studies of the 2 kb promoter found AP-1 binding elements involved in EIF4E transcriptional regulation in cardiac muscle cells (Makhlouf et al., 2001) as well as Rel, Myb, NF-kB, SP-1, NF1, STAT, AP-4, ATB and CREB consensus motifs. p53 could also be involved in the regulation of eIF4E-1 expression through its binding to c-myc, thereby preventing c-myc binding to the EIF4E promoter (Gao et al., 1998; Zhu et al., 2005).
It was shown that eIF4E mRNA contains an AU-rich elements in the 3'UTR that is responsible for HuR-mediated binding and stabilization (Topisirovic et al., 2009b).

Pseudogene

Two pseudogenes are mapped so far: EIF4EP1 (also known as EIF4EL2 and dJ1022P6.3), on chromosome 20 (location 20p13), (Entrez Gene ID:



Ternary complex of m7GpppA-eIF4E-4EBP1 peptide. eIF4E (blue) and the 4E-BP1 peptide (green) are shown with the ribbon model. The cap-recognition mode of eIF4E is characterized by a pi-pi sandwiching of the m7G base of the cap (here m7GpppA, orange) by the Trp56 and Trp102 indole rings.

1980), (Pelletier et al., 1991), and EIF4EP2 on chromosome 17 (17q21.32), (Entrez Gene ID: 100113387).
In the report by Gao et al. (1998), numerous intronless eIF4E pseudogenes were found, all containing premature in-frame stop codons.

Protein

Description

eIF4E is a 25 kD cap-binding protein, which exists both in a free form and as part of a multiprotein complex termed eIF4F. The eIF4E protein has two distinct functions. First, the eIF4E polypeptide functions in delivering cellular mRNAs to the eIF4F complex to further facilitate ribosome loading and mRNA translation. The other subunits of eIF4F complex are: eIF4A, a 50 kD polypeptide, ATP-dependent RNA helicase that facilitates melting of the mRNA secondary structure, and eIF4G, a 220 kD scaffolding protein of this complex. Second, eIF4E functions in mRNA export (see below).
The cap-bound form of eIF4E was solved by X-ray crystallography for the human and mouse eIF4E and by NMR solution structure for the yeast homolog. It was shown that each consists of eight-stranded anti-parallel beta-sheets supported by three alpha-helices forming the palm and back of a "cupped" hand (Marcotrigiano et al., 1997; Matsuo et al., 1997; Tomoo et al., 2002). Two Trp residues (Trp56 and Trp102 for human eIF4E) located within a narrow cavity inside the concave surface, hold the guanine residue of the cap-analogue through pi-pi stacking interactions (McCoy et al., 1997; Wieczorek et al., 1997). A third Trp residue (Trp166 in human eIF4E) recognizes the presence of the N^7-methyl group of the cap structure. NMR structure of cap-free eIF4E (apo-eIF4E) exhibits structural differences in the cap-binding site and dorsal surface relative to cap-eIF4E. Alterations in the S4-H4 loop distal to cap binding site seems to be a key in modulating conformational changes of eIF4E upon ligand binding (Volpon et al., 2006).
Although human and S. cerevisiae eIF4E counterparts have only approximately 30% sequence identity, they are functionally conserved and mammalian eIF4Es can rescue the lethality of eIF4E gene disruption in S. cerevisiae (Altmann et al., 1989; Joshi et al., 2002). Amino acid alignments of mammalian eIF4Es with eIF4Es from plants and yeast, coupled with deletion analyses from S. cerevisiae and D. rerio, reveal that the core of eIF4E represented by ~170 amino acids (from

His37 to His200 in human eIF4E) is conserved in all eukaryotes and is sufficient for cap recognition and binding to eIF4G and 4E-BPs (Vasilescu et al., 1996; Robalino et al., 2004), while N- and C-termini are considerably variable both in length and sequence (suggesting that they are dispensable for translation). It is possible that N- and C-termini may be involved in the regulation of eIF4E activity or could affect the stability of the protein (Scheper et al., 2002; Gross et al., 2003). Crystallographic studies of mouse eIF4E bound to either a fragment of eIF4G or 4E-BP1 revealed that His37, Pro38, Val69, Trp73, Leu131, Glu132 and Leu135 (of human eIF4E) interact with eIF4E-binding regions of eIF4G and 4E-BPs (Marcotrigiano et al., 1999). Residues Val69 and Trp73 are found within the phylogenetically conserved part of the consensus sequence. Substitution of Trp73 of mammalian eIF4E to non-aromatic amino acid disrupts ability of eIF4E to interact with eIF4G and 4E-BPs (Ptushkina et al., 1999). Substitution of human eIF4E Val69 for a Gly results in a variant that efficiently binds 4E-BP1, but has reduced capacity to interact with eIF4G and 4E-BP2 (Vasilescu et al., 1996; Ptushkina et al., 1999).

eIF4E undergoes regulated phosphorylation at residue Ser209 (Flynn et al., 1995; Joshi et al., 1995). Mnk1 and Mnk2 are identified as kinases that phosphorylate Ser209, and they are targets for mitogen-activated extracellular signal-regulated kinase and stress/cytokine-activated p38 mitogen-activated protein kinase pathways (Waskiewicz et al., 1997; Wang et al., 1998; Waskiewicz et al., 1999; Scheper et al., 2001). Both enzymes also associate with eIF4G in vivo (Pyronnet et al., 1999; Waskiewicz et al., 1999; Scheper et al., 2001). The structural basis is still not clear as to whether phosphorylation of Ser209 substantially changes the affinity of eIF4E for the cap structure (Minich et al., 1994; Scheper et al., 2002b).

It was shown that eIF4E could be ubiquitinated and degraded in proteasome-dependent manner (Othumpangat et al., 2005; Murata et al., 2006).

Recently, it was suggested that eIF4E could be modified by SUMO1 conjugation (Xu et al., 2010).

Expression

eIF4E is ubiquitously expressed, and its presence is essential for viability of cells or whole organisms (Altmann et al., 1987). The level of expression and phosphorylation status may vary between tissues and cellular differentiation state (Mao et al., 1992; Fahrenkrug et al., 1999; Walsh et al., 2003). It was shown that eIF4E is over-expressed in many types of cancer (see below).

Localisation

eIF4E is localized both in the cytoplasm and the nucleus of the cell. Up to 68% of eIF4E is found in the nucleus of cells from a wide variety of species ranging from yeast to humans (Lejbkowicz et al., 1992; Iborra et al., 2001; Strudwick et al., 2002). Localization of eIF4E can also be dynamic (Fahrenkrug et al., 1999; Strudwick et al., 2002).

Function

In the cytoplasm, eIF4E functions in the rate limiting step of cap-dependent translation initiation (Sonenberg et al., 1998). Here, eIF4E directly binds the 7-methyl guanosine "m^7G cap" structure found on the 5' end of mRNAs, and recruits transcripts to the ribosomes thereby increasing translational efficiency (Pestova et al., 2000; von der Haar et al., 2004). In order for translation to proceed, eIF4E must associate with other factors of the eIF4F complex (eIF4G and eIF4A), as well as the other factors such as the ribosome-bound eIF3 and the poly(A)-binding protein. Once formed, the eIF4F complex is thought to scan 5'-3' from the cap, unwinding any existing secondary structure within the 5'UTR region to reveal the translation initiation codon and to facilitate ribosome loading on the mRNA (Gingras et al., 1999). Importantly, eIF4E effects the translation of some mRNAs, known as eIF4E sensitive, more than other transcripts. When eIF4E is overexpressed, sensitive transcripts have a higher ribosome/mRNA ratio enabling more efficient translation (without modulating mRNA levels in the cytoplasm). Notably, sensitive mRNAs have more highly structured 5'UTRs versus insensitive housekeeping mRNAs such as GAPDH or actin, which contain short, unstructured 5'UTRs (Rhoads et al., 1993; Sonenberg et al., 1998; De Benedetti et al., 1999). Transcripts controlled at this level often code for proteins involved in proliferation such as c-myc, Pim 1, VEGF and ODC (Rhoads et al., 1993; Kevil et al., 1996; Rousseau et al., 1996; Hoover et al., 1997).

In the nucleus, eIF4E functions in the mRNA export of a specific subset of mRNAs, which contain a discrete 50 nucleotides element in their 3'UTR known as the eIF4E sensitivity element (4E-SE) (Rousseau et al., 1996; Culjkovic et al., 2005; Culjkovic et al., 2006; Culjkovic et al., 2007). Many mRNAs sensitive to eIF4E at the export level code for proteins that promote proliferation and survival (such as cyclin D1 and ODC mRNAs). Unlike bulk mRNA export which is TAP/NXF1 dependent, eIF4E dependent mRNA export is CRM1 dependent and requires the 4E-SE and the mRNA export factor LRPPRC (Culjkovic et al., 2006; Topisirovic et al., 2009a).

Thus eIF4E can modulate gene expression at two levels: by exporting mRNAs to the cytoplasm increasing their concentration therein and by enhancing the translational efficiency of transcripts that are already in the cytoplasm. Not all transcripts are affected at both levels. Importantly, eIF4E requires its m^7G cap binding function in order to act in either of these functions.

eIF4E activity is regulated by many proteins. One of the best-characterized regulators of eIF4E is eIF4E binding protein 1 (BP1) (Sonenberg et al., 1998;

Gingras et al., 1999; Zimmer et al., 2000; Wendel et al., 2007). This protein uses a conserved eIF4E binding site to associate with eIF4E, and thereby precludes access of eIF4E to eIF4G and the rest of the translation machinery (Sonenberg et al., 1998). This binding site is defined as follows: YXXXXLPhi (where X is any residue and Phi is a hydrophobic residue). Studies suggest that BP1 increases cap affinity and thereby sequesters both eIF4E and the RNA in question from the translational machinery (von der Haar et al., 2004). Further, endogenous BP1 associates with eIF4E in both the nuclear and cytoplasmic compartments and thus likely modulates eIF4E activity at both the level of translation and mRNA export (Rong et al., 2008). Phosphorylation of 4E-BP1 leads to a reduction in its interaction with eIF4E and thereby, results in increased translational activity of eIF4E. 4E-BP1 phosphorylation is mTOR dependent (Proud, 2007). However, $BP1^{-/-}$ and $BP1^{-/-}BP2^{-/-}$ mice do not develop cancers more readily than controls (Blackshear et al., 1997; Tsukiyama-Kohara et al., 2001; Banko et al., 2006; Le Bacquer et al., 2007), highlighting the importance of redundancy of regulators in the control of eIF4E.

The vast majority of other eIF4E regulators contain the YXXXXLPhi motif like eIF4G and the BPs. These regulators include a set of over 200 homeodomain proteins that contain this motif. Some of these members are negative regulators of eIF4E, such as PRH/Hex. PRH is a nuclear protein that impedes eIF4E's mRNA export function, and its overexpression leads to the cytoplasmic re-distribution of eIF4E (Topisirovic et al., 2003a; Topisirovic et al., 2003b). Other members of this group of homeodomain containing regulators include Emx2, Otx, Engrailed 2, Hox11, Bicoid and HoxA9 (Topisirovic et al., 2005a). HoxA9 can stimulate both the nuclear and cytoplasmic functions of eIF4E (Topisirovic et al., 2005b).

There is also a discrete class of eIF4E regulators that utilize a RING domain to impede eIF4E function. These regulators include the promyelocytic leukemia protein PML, and arenaviral Z proteins from LCMV and Lassa viruses (Lai et al., 2000; Cohen et al., 2001; Ardley et al., 2001). Binding of PML or the Z proteins to eIF4E reduces the affinity of eIF4E for the m^7G cap by up to 100 fold (Nathan et al., 1997; Graff et al., 2003; Topisirovic et al., 2003a). PML is a mostly nuclear protein, and thus primarily inhibits the mRNA export activity of eIF4E (Cohen et al., 2001; Kentsis et al., 2001; Culjkovic et al., 2005; Culjkovic et al., 2006; Culjkovic et al., 2008).

In conclusion, the regulation of eIF4E activity is redundant and multi-factorial. There are tissue specific regulators such as the homeodomain proteins and more ubiquitous regulators such as PML and 4E-BP1. Redundancy of regulators is seen for both the nuclear and cytoplasmic arms of eIF4E activity.

Homology

By analysis of expressed sequence tag sequences, two additional eIF4E-family members in mammals named eIF4E-2 (also known as 4EHP, 4E-LP) and eIF4E-3 were identified (Joshi et al., 2004). They differ in their structural signatures, functional characteristics and expression pattern from eIF4E (eIF4E-1). Like eIF4E-1, eIF4E-2 is expressed in all tissues, with highest levels in the testis, while eIF4E-3 is detectable only in muscles, spleen and lung. Unlike eIF4E-1, eIF4E-2 and eIF4E-3 are not able to rescue the growth of S. cerevisiae lacking a functional EIF4E gene. While both, eIF4E-2 and eIF4E-3 can bind the cap in vitro, eIF4E-2 and eIF4E-3 differ from eIF4E-1 and between each-other in their affinities to 4E-BPs and eIF4G. It is proposed that each eIF4E-family member fills a specialized role in the regulation of recruitment of mRNAs to ribosomes through differences in their ability to bind the cap and/or to interact with eIF4G and 4E-BPs.

Mutations

Note

Autism

Germinal

Genome wide linkage studies in autism patients have shown linkage to the region containing the EIF4E locus on chromosome 4q (Yonan et al., 2003; Schellenberg et al., 2006). Recently, de novo chromosome translocation between 4q and 5q was reported in a boy with classic autism, and a breakpoint site was mapped within a proposed alternative transcript of eIF4E (Neves-Pereira et al., 2009). In the same study, screening of 120 autism families, two unrelated families were found, where in each case both autistic siblings and one of the parents harbored the same single nucleotide insertion at position -25 in the basal element of the EIF4E promoter. EMSA assays and reporter gene studies show that this mutation enhances EIF4E promoter activity by two fold.

Implicated in

Various cancers

Prognosis

eIF4E is overexpressed in many epithelial cell cancers, including breast (Kerekatte et al., 1995; Li et al., 1997; Li et al., 1998; Li et al., 2002; McClusky et al., 2005), colon (Rosenwald et al., 1999; Berkel et al., 2001), bladder (Dickinson et al., 1994; Bochner et al., 1995; Jaeger et al., 1995; Crew et al., 1996; Crew et al., 2000), cervix (Lee et al., 2005; Matthews-Greer et al., 2005), prostate (Graff et al., 2009), lung (Rosenwald et al., 2001; Seki et al., 2002; Jacobson et al., 2006) and squamous cell carcinoma of the head and neck (Nathan

et al., 1997b; Franklin et al., 1999; Nathan et al., 1999a; Nathan et al., 1999b; Sorrells et al., 1999b; Nathan et al., 2000; Chandy et al., 2002; Nathan et al., 2002). Some studies report that eIF4E is overexpressed in almost 100% of tumors of the breast, head and neck, and colon (Kerekatte et al., 1995; Nathan et al., 1999a; Nathan et al., 1999b). Several retrospective studies indicate that eIF4E overexpression is correlated with poor prognosis.

Oncogenesis

It has been demonstrated that eIF4E overexpression is associated with eIF4E gene amplification in both HNSCC and in breast carcinomas (Sorrells et al., 1998; Sorrells et al., 1999a; Sorrells et al., 1999b; Haydon et al., 2000). An increased level of eIF4E gene amplification was observed in invasive carcinomas of the head and neck as compared to benign tumors. Benign tumors only had moderate evidence for gene amplification, while malignant tumors had a 4-15 fold level of amplification. These studies suggest that progression to the malignant phenotype paralleled eIF4E gene amplification and overexpression (Haydon et al., 2000). Also, there was a progressive increase in the degree of eIF4E gene amplification and protein expression when comparisons were made among samples from tumor free margins of resected carcinoma specimens, tumor free regions adjacent to tumor core and tumor core samples (Sorrells et al., 1998). This suggests that molecular events such as eIF4E gene amplification may precede cellular morphological changes, and that surgical margins which appear tumor free microscopically, may have elevated eIF4E protein levels. Thus, eIF4E levels could be used as a marker for prediction of early recurrence. It has been postulated that somewhere in the multi-step pathway of carcinogenesis, elevation of eIF4E is a necessary event in progression of most solid tumors, and that eIF4E does not only reflect the proliferative status of cells but also their malignant properties (Anthony et al., 1996; Nathan et al., 1997b).

Breast cancer

Note

eIF4E overexpression was detected at a range of 3-30 fold in breast carcinomas compared to normal breast tissue (Kerekatte et al., 1995; Li et al., 1997), and eIF4E levels were significantly increased in vascularized malignant ductules of invasive carcinomas (Nathan et al., 1997a). Breast cancer patients with high eIF4E expression (>7 fold relative to normal) experienced a statistically significant poorer clinical outcome with a higher risk for recurrence and cancer related death (Li et al., 1998). There were no correlation between node stage and the degree of 4E overexpression (McClusky et al., 2005).

Prostate cancer

Note

78% of prostate cancer samples in tissue microarray showed elevated eIF4E (Yang et al., 2007). eIF4E was found to be more than 3 times increased at protein level in prostate cancer, and also correlated with worse prognosis (Graff et al., 2008).

Head and neck squamous cell carcinoma (HNSCC)

Note

In the HNSCC, eIF4E levels were found 3 to 22 fold elevated relative to normal controls (Nathan et al., 1997b; Nathan et al., 1999a; Nathan et al., 1999b; Nathan et al., 2000; Nathan et al., 2002). High eIF4E levels in surgical margins are also predictive of increased risk of recurrence in HNSCC (Nathan et al., 1997b; Nathan et al., 1999a; Nathan et al., 2000; Nathan et al., 2002).

Overexpression of eIF4E in >5% of the basal layer of histologically tumor-free surgical margins of HNSCC patients predicted a significantly increased risk of recurrence (Nathan et al., 1999a). This prediction is important for patient outcome, as most HNSCC patients will succumb due to local recurrence (Nathan et al., 1997b; Nathan et al., 2000; Nathan et al., 2002).

Acute myeloid leukemia

Note

In acute myeloid leukemia (AML), elevated eIF4E levels are characteristic of the poor prognosis in M4 and M5 AML subtypes (Topisirovic et al., 2003b). Ribavirin, a competitive inhibitor of the cap was used in the clinical trial to target eIF4E in poor prognosis leukemia patients and led to striking clinical responses including complete and partial remissions (Assouline et al., 2009). This was the first time eIF4E was directly targeted in humans.

Non-Hodgkin lymphoma

Note

Increased level of eIF4E was observed in non-Hodgkin's lymphomas and not in benign lesions (Wang et al., 1999; Mossafa et al., 2006). Here, eIF4E levels correlated with the aggressiveness of these lesions (Wang et al., 1999; Mossafa et al., 2006). Recently it was reported that eIF4E is overexpressed in 40% of mantle cell lymphoma (Inamdar et al., 2009) and that eIF4E is an independent predictor of clinical outcome in MCL patients treated with the R-hyper CVAD regimen.

Hodgkin lymphoma

Note

By immunohistochemical analysis it was shown that eIF4E is elevated in 69% of nodular sclerosis Hodgkin

lymphomas (HL), 75% mixed cellularity HL, and 91% lymphocyte predominant HL (Rosenwald et al., 2008).

Colorectal adenomas and carcinomas

Note

eIF4E protein was found to be 2-6 times increased in tumor samples, and even more in the tumor margins (Rosenwald et al., 1999).

Pancreatic ductal adenocarcinoma

Note

85% of pancreatic ductal adenocarcinoma samples showed high eIF4E staining in cancer tissue. There was no significant correlation between eIF4E expression and age, gender, histopathological grading, lymphatic invasion or lymph node metastasis. Also, there were no significant differences between the high eIF4E expressing group and either the low or moderate eIF4E expressing groups (Mishra et al., 2009).

Lung carcinomas

Note

In bronchioalveolar carcinoma, estimated by immunohistochemistry, eIF4E was found to be 3-8 times elevated (Rosenwald et al., 2001). Analysis of atypical adenomatous hyperplasia and peripheral lung adenocarcinoma samples showed 3.4-7.4 fold of eIF4E protein elevation (Seki et al., 2002). In Another study, 54% of lung adenocarcinoma samples showed high eIF4E expression by immunostaining. Analyses of mRNA and protein from tumor tissues showed 6-10x elevation compared to surrounding normal tissues (Wang et al., 2009). Elevated eIF4E immunostaining was found in 81% of non small cell lung cancer (NSCLC) samples from tissue microarray (Yang et al., 2007).

Another study reported that 91% of NSCLC samples had stronger eIF4E staining than adjacent normal bronchial mucosa. According to subtypes, eIF4E was positive in 88% of adenocarcinoma and 100% cases of squamous cell carcinomas (Khoury et al., 2009). Patients with eIF4E had more than 3 times risk of death than those with negative eIF4E (Khoury et al., 2009).

Bladder cancers

Note

eIF4E was found 4-10 times increased at protein and mRNA levels (Crew et al., 2000).

Brain tumors (oligodendroglial, astrocytomas and meningiomas)

Note

In brain tumors, eIF4E was more than 3 times increased at protein level, being highest in oligodendroglial tumors (Tejada et al., 2009).

Glioblastoma multiforme

Note

In tissue microarray 48% of samples showed elevated eIF4E immunostaining (Yang et al., 2007).

Thyroid carcinoma

Note

Elevated immunostaining especially in aggressive types (Wang et al., 2001).

Cervical cancers

Note

In cervical cancer, eIF4E was found 2-4 fold elevated by immunohistochemical staining (Matthews-Greer et al., 2005). Another study showed 7 fold increased mRNA levels of eIF4E (Van Trappen et al., 2002). Strong immunostaining of eIF4E was found in 21.1% of low-grade cervical intraepithelial neoplasias (CIN) and in 89.5% of high grade CIN, and none in low grade CINs. In another study, 100% of invasive squamous cell carcinoma showed strong eIF4E immunostaining, while mRNA was 2-4 times elevated comparing to normal samples (Lee et al., 2005). No significant difference in eIF4E expression was found between HPV+ and HPV- negative, single or double infected samples (Matthews-Greer et al., 2005).

Ovarian cancers

Note

In tissue microarray 50% of ovarian cancer samples showed elevated eIF4E (Yang et al., 2007). Also, p-eIF4E was increased in 56% analyzed samples (Noske et al., 2008).

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