**Abstract**

Eukaryotic elongation factor 2 kinase (eEF-2K) (also known as Calmodulin (CaM)-dependent elongation factor 2 kinase, CaMKIII) is an unusual calcium/calmodulin (Ca²⁺/CaM)-dependent threonine kinase that controls the rate of the elongation phase of protein synthesis through phosphorylating elongation factor 2 (eEF2) (Nairn et al., 1985; Ryazanov 1987; Mitsui et al., 1993; Redpath et al., 1993). Phosphorylation of eEF2 on Thr-56 disrupts the interaction between eEF-2 and the ribosome, leading to reduced protein synthesis. eEF-2K is regulated by phosphorylation by multiple signaling pathways and kinases at 11 different phosphorylation sites (Ryazanov et al., 1988; Carlberg et al., 1990; Abramczyk et al., 2011; Browne et al., 2004; Marshall et al., 2012; Chafouleas et al., 1981; Bowden et al., 2013). Hypoxia, nutrient deprivation and metabolic stress are all known to stimulate eEF-2K through activation of AMPK (Chafouleas et al., 1981). The activity of eEF-2K is increased in rapidly proliferating malignant cells and in cancer specimens, but is absent in normal adjacent tissues (Ashour et al., 2014b). eEF-2K promotes cell proliferation, invasion and tumorigenesis of some cancers. eEF-2K expression (mRNA) correlates with poor patient survival and prognosis (outcome) in some solid tumors, including breast, pancreatic cancer and glioblastoma (Meric-Bernstam et al., 2012). The activity of this kinase is increased in many cancers and may be a potential therapeutic target in some cancers.

**Keywords:** Elongation, protein translation, proliferation, invasion, prognosis, survival, cancer

**Identity**

**Other names:** CaMK-III, eEF-2K, HSU93850

**HGNC (Hugo):** EEF2K

**Location:** 16p12.2

**DNA/RNA**

**Note**

EEF2K gene encodes a Ca²⁺/calmodulin-dependent kinase known as eukaryotic elongation factor-2 kinase (EEF2K).

**Description**

The EEF2K gene is composed of 18 exons. It spans approximately 80.35 kb of genomic DNA.

**Transcription**

This gene encodes 5 transcripts and protein coding transcript (EEF2K-001) has 7388 bp length and this is composed of 725 aa residues. EEF2K-002 is a non sense mediated decay. Other three transcripts (EEF2K-003, -004, -005) do not give rise to proteins.

**Pseudogene**

No pseudogene reported.

**Protein**

**Description**

Human eukaryotic elongation factor-2 kinase is composed of 725 amino acids (105 KDa) alfa-kinase catalytic domain of this protein is located at the section of 76-356. Calmodulin (CaM) binding domain is located close to N-terminal and next to the catalytic domain. The function of the region located...
N-terminal of the CaM-binding site is not well understood but removal of this segment leads to intrinsic autophosphorylation and activity; cause inhibitory effect on the E2F2 activity. Contain 18 phosphorylation sites. Autophosphorylated at multiple residues, Thr-348 is the major site. Towards the C-terminal region, there are four predicted ala-helical regions, and these resemble SEL-1-type repeats. The region lies between SEL-1 type repeats and the C-terminus contains highly reserved sequences. The extreme C terminus is known to be essential for the phosphorylation of eukaryotic elongation factor-2 (eEF2).

**Expression**
Ubiquitously expressed in nomal tissues. Activity is increased in some tumors.

**Localisation**
Cytoplasmic.

**Function**
EEF2K protein belongs to alfa-kinases family of protein kinases. Its activity is dependent to Ca2+/calmodulin kinase and phosphorilates eukaryotic elongation factor-2 (eEF2) at Thr56 and inhibits it association/binding with ribosomes, thus regulates the elongation phase of translation.

**Mutations**
No mutations identified other than SNPs representing normal variations (http://www.hgmd.cf.ac.uk/ac/gene.php?gene=EEF2K)

**Implicated in**

**Breast Cancer**

**Note**
eEF-2K protein expression promotes in breast cancer cell survival, invasion, migration and tumorigenesis (Tekedereli et al., 2012). eEF-2k highly expressed lines compared with normal non-tumorigenic breast epithelium and its expression is associated with poor patient survival and prognosis (Meric-Bernstam et al., 2012).

**Prognosis**
Overexpression of eEF-2k is associated with shorter survival and poor prognosis (outcome) in Estrogen receptor (ER) positive (Tekedereli et al., 2012) and triple negative or ER (-) breast cancer patients (Ozpolat et al in press).

**Pancreatic cancer**

**Note**
eEF-2K protein is significantly overexpressed in pancreatic cancer cell lines and its inhibition lead to inhibition of cell proliferation, in invasion and migration and induces apoptosis (Ashour et al., 2014a; Ashour et al., 2014b).

**Glioblastome multiforme (GBM)**

**Note**
eEF-2K protects cells from nutrient deprivation and in conferring tumor cell adaptation to nutrient deprivation and metabolic stress by blocking translation elongation (Bowden et al., 2013).

**Azheimer’s disease (AD)**

**Note**
Levels of p-eEF2K were found to be significantly increased, and total eEF2 significantly decreased in AD, when compared to controls in the brain tissue. levels of p-MTOR (Ser2481), and EIF4EBP1 (p-4E-BP1) (Thr70 and Ser65) dramatically increase in AD, and are positively significantly correlated with total tau and p-tau proteins.

**Hypertension**

**Note**
eEF2K protein increases in mesenteric artery from spontaneously hypertensive rats (SHR). eEF2K mediates TNF-a-induced vascular inflammation via ROS-dependent mechanism, which is at least partly responsible for the development of hypertension in SHR (Usui et al., 2013).

**References**


Chafouleas JG, Pardue RL, Brinkley BR, Redman JR, Means AR. Regulation of intracellular levels of calmodulin and tubulin in normal and transformed cells. Proc Natl Acad Sci U S A. 1981 Feb;78(2):996-1000


Nairn AC, Bhagat B, Palfrey HC. Identification of calmodulin-dependent protein kinase III and its major Mr 100,000 substrate in mammalian tissues. Proc Natl Acad Sci U S A. 1985 Dec;82(23):7939-43

Redpath NT, Proud CG. Cyclic AMP-dependent protein kinase phosphorylates rabbit reticulocyte elongation factor-2 kinase and induces calcium-independent activity. Biochem J. 1993 Jul 1;293 (Pt 1):31-4

Ryazanov AG. Ca2+/calmodulin-dependent phosphorylation of elongation factor 2. FEBS Lett. 1987 Apr 20;214(2):331-4


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