Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL

INIST-CNRS

Gene Section
Short Communication

EEF2K (eukaryotic elongation factor 2 kinase)

Bulent Ozpolat, Ozgur Ozkayar

University of Texas-Houston-MD Anderson Cancer Center, Department of Experimental Therapeutics, 1515 Holcombe Boulevard, Unit 422, Houston, TX7730; Bozpolat@mdanderson.org

Published in Atlas Database: January 2016
Online updated version : http://AtlasGeneticsOncology.org/Genes/EEF2KID40411ch16p12.html
Printable original version : http://documents.irevues.inist.fr/bitstream/handle/2042/66071/01-2016-EEF2KID40411ch16p12.pdf
DOI: 10.4267/2042/66071

Abstract

Eukaryotic elongation factor 2 kinase (eEF-2K) (also known as Calmodulin (CaM)-dependent elongation factor 2 kinase,CaMKIII) is an unusual calcium/calmodulin (Ca^{2+}/CaM)-dependent Threonin 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 sides (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. Calmoduline (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 EF2K activity. Contain 18 phosphorylation sites. Autophosphorylated at multiple residues, Thr-348 is the major site. Towards the C-terminal region, there are four predicted alfa-helical regions, and these resemble SEL-1-type repeats. The region lies between SEL-1 type repeats and the C-terminus contains higly reserved sequences. The extreme C terminus is known to be essential for the phosphorylation of eukaryotic elongation factor-2 (eEF2).

Expression

Ubiquitosly 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 repsesenting 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 ist 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' 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

Abramczyk O, Tavares CD, Devkota AK, Ryazanov AG, Turk BE, Riggs AF, Ozpolat B, Dalby KN. Purification and characterization of tagless recombinant human elongation factor 2 kinase (eEF-2K) expressed in Escherichia coli. Protein Expr Purif. 2011 Oct;79(2):237-44

Ashour AA, Gurbuz N, Alpay SN, Abdel-Aziz AA, Mansour AM, Huo L, Ozpolat B. Elongation factor-2 kinase regulates TG2/β1 integrin/Src/uPAR pathway and epithelial-mesenchymal transition mediating pancreatic cancer cells invasion. J Cell Mol Med. 2014 Nov;18(11):2235-51

Browne GJ, Finn SG, Proud CG. Stimulation of the AMP-activated protein kinase leads to activation of eukaryotic elongation factor 2 kinase and to its phosphorylation at a novel site, serine 398. J Biol Chem. 2004 Mar 26;279(13):12220-31

Carlberg U, Nilsson A, Nygård O. Functional properties of phosphorylated elongation factor 2. Eur J Biochem. 1990 Aug 17;191(3):639-45

Chafouleas JG, Pardue RL, Brinkley BR, Dedman 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

Krutsay M. [Nissl staining with cresyl violet]. Z Med Labortech. 1970;11(2):75-6

Leprivier G, Remke M, Rotblat B, Dubuc A, Mateo AR, Kool M, Agnihotri S, El-Naggar A, Yu B, Somasekharan SP, Faubert B, Bridon G, Tognon CE, Mathers J, Thomas R, Li A, Barokas A, Kwok B, Bowden M, Smith S, Wu X, Korshunov A, Hielscher T, Northcott PA, Galpin JD, Ahern CA, Wang Y, McCabe MG, Collins VP, Jones RG, Pollak M, Delattre O, Gleave ME, Jan E, Pfister SM, Proud CG, Derry WB, Taylor MD, Sorensen PH. The eEF2 kinase confers

resistance to nutrient deprivation by blocking translation elongation. Cell. 2013 May 23;153(5):1064-79

Meric-Bernstam F, Chen H, Akcakanat A, Do KA, Lluch A, Hennessy BT, Hortobagyi GN, Mills GB, Gonzalez-Angulo A. Aberrations in translational regulation are associated with poor prognosis in hormone receptor-positive breast cancer. Breast Cancer Res. 2012 Oct 26;14(5):R138

Mitsui K, Brady M, Palfrey HC, Nairn AC. Purification and characterization of calmodulin-dependent protein kinase III from rabbit reticulocytes and rat pancreas. J Biol Chem. 1993 Jun 25;268(18):13422-33

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

Ryazanov AG, Shestakova EA, Natapov PG. Phosphorylation of elongation factor 2 by EF-2 kinase affects rate of translation. Nature. 1988 Jul 14;334(6178):170-3

Tavares CD, O'Brien JP, Abramczyk O, Devkota AK, Shores KS, Ferguson SB, Kaoud TS, Warthaka M, Marshall KD, Keller KM, Zhang Y, Brodbelt JS, Ozpolat B, Dalby KN. Calcium/calmodulin stimulates the autophosphorylation of elongation factor 2 kinase on Thr-348 and Ser-500 to regulate its activity and calcium dependence. Biochemistry. 2012 Mar 20;51(11):2232-45

Tekedereli I, Alpay SN, Tavares CD, Cobanoglu ZE, Kaoud TS, Sahin I, Sood AK, Lopez-Berestein G, Dalby KN, Ozpolat B. Targeted silencing of elongation factor 2 kinase suppresses growth and sensitizes tumors to doxorubicin in an orthotopic model of breast cancer. PLoS One. 2012;7(7):e41171

Usui T, Okada M, Hara Y, Yamawaki H. Eukaryotic elongation factor 2 kinase regulates the development of hypertension through oxidative stress-dependent vascular inflammation. Am J Physiol Heart Circ Physiol. 2013 Sep 1;305(5):H756-68

This article should be referenced as such:

Ozpolat B, Ozkayar O. EEF2K (eukaryotic elongation factor 2 kinase). Atlas Genet Cytogenet Oncol Haematol. 2016; 20(9):478-480.