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Gene Section
Review

PEA15 (phosphoprotein enriched in astrocytes 15)

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Identity

Other names: HMAT1, HUMMAT1H, MAT1, MAT1H, PEA-15, PED

HGNC (Hugo): PEA15

Location: 1q23.2

DNA/RNA

Description

According to Entrez Gene, PEA15 maps to NC_000001.10 and spans a region of 10042 bases. PEA15 consists of four exons. Exon 1 and the beginning of exon 2 contain untranslated sequences. The end of exon 2, exon 3, and the beginning of exon 4 contain the coding sequence.

Transcription

Two transcripts, with lengths of 2,5 and 1,7 kb, have been identified. They are identical except for the length of their 3' UTRs.

Pseudogene

No pseudogene of PEA15 known.

Protein

Description

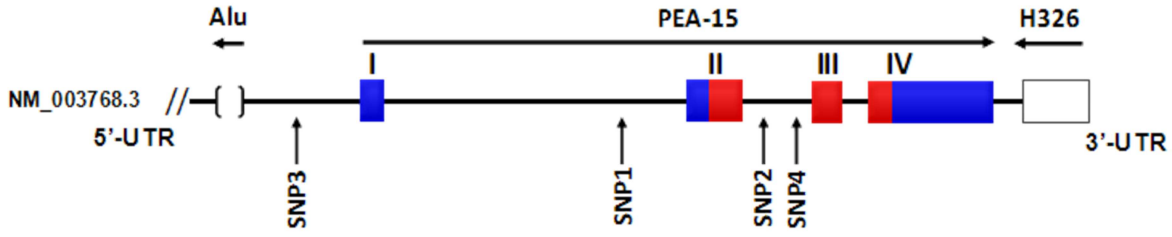
PEA-15 is a 130-amino-acid protein with a predicted molecular mass of 15054 daltons and a calculated isoelectric point of 5.12.

Expression

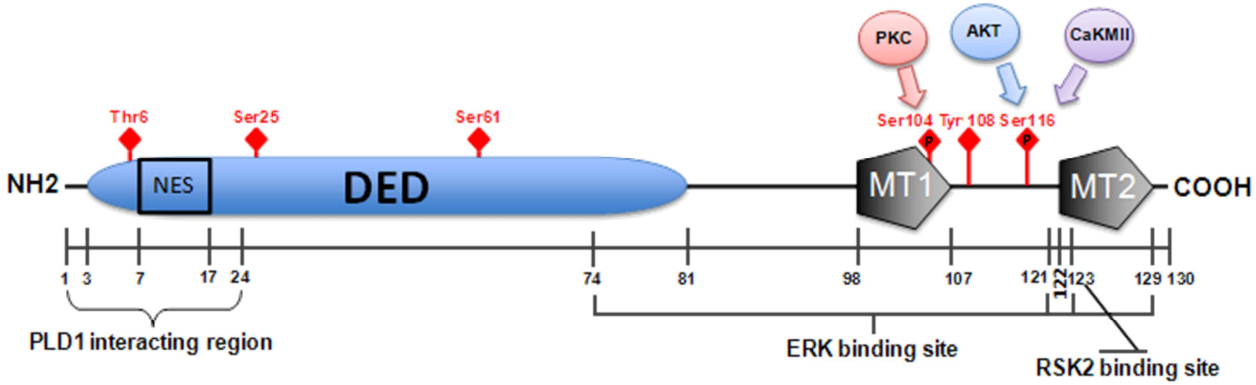
Ovary, breast, brain, placenta, liver, eye, lung, heart, endothelial cells, pancreas, testis, uterus, adrenal gland, prostate gland, kidney, spleen, and astrocytes.

Localisation

Cytoplasm. PEA-15 has a leucine-rich nuclear export sequence (NES), which is required for predominantly localizing in the cytoplasm (Formstecher et al., 2001).



Structure of the human PEA15 gene. Red box: PEA15 coding region; blue box: PEA15 non-coding region; white box: 3' end of H326 region; SNP position: indicated by vertical arrows; Alu element (AA491823) 5' of PEA15: represented by brackets (Wolford et al., 2000, license permission no.: 2907741403264).



DED: death effector domain, amino acid region 3-81, Pfam: PF01335 (Sanger); NES: leucine-rich nuclear export sequence, amino acid region 7-17; MT: microtubule-binding region, amino acid region 98-107, and 122-129; PLD-1 binding region: phospholipase D1 binding site, amino acid region 1-24; ERK binding site: amino acid position 74, 121, 123, and 129; RSK2 binding site: amino acid position 123; Serine 104: phosphorylation site by PKC; Serine 116: phosphorylation site by AKT or CaKMII.

Function

PEA-15 is a ubiquitously expressed protein that exists in non-phosphorylated, mono-phosphorylated, and double-phosphorylated forms (Danziger et al., 1995). PEA-15 does not have an enzymatic domain but serves as a binding molecule in protein complexes. PEA-15 is an endogenous substrate that depends on two distinct serine sites: Ser104, which is phosphorylated by protein kinase C (PKC) (Kubes et al., 1998), and Ser116, which is phosphorylated by Ca2+/calmodulin kinase II (CaMKII) (Kubes et al., 1998) or by AKT (Trencia et al., 2003). At its NH2 terminus, PEA-15 has a PLD-interacting region, which enhances PLD 1 stability and activity (Zhang et al., 2000), and a death effector domain (DED), which enables interaction with DED-containing signaling proteins, including Fas-associated protein with death domain (FADD) and FADD-like IL-1β-converting enzyme (Peter et al., 1999). At its COOH terminus, PEA-15 has a microtubule-binding region, which regulates the stability of tubulins (Danziger et al., 1995).

ERK inhibition. PEA-15 can bind to ERK and sequester it in the cytoplasm. The resulting inhibition of ERK's translocalization into the nucleus blocks ERK-dependent transcriptional activity and cell proliferation (Formstecher et al., 2001).

Apoptosis and anti-apoptosis. PEA-15 interacts with different DED-containing proteins such as FADD and FLICE and inhibits Fas/TNFR1-induced apoptosis by preventing formation of the death-inducing signaling complex (DISC) (Condorelli et al., 1999; Song et al., 2006). On the other hand, under different cellular stresses, PEA-15 acts as a substrate of Omi/HtrA2, which is a proapoptotic mitochondrial serine protease; it results in reducing anti-apoptotic action of Omi/HtrA2 and triggering apoptotic programs (Trencia et al., 2004).

Metabolism. In skeletal muscle and adipose cells, PEA-15 binds to PLD1 and enhances PKC-α activity, thereby inducing resistance to insulin action in glucose uptake (Condorelli et al., 1998).

Invasion. A high expression level of PEA-15 is correlated with low invasive behavior of breast cancer (Glading et al., 2007).

PEA-15's prevention of ERK's nuclear localization results in reduced invasion capability in breast cancer.

Tumorigenicity. In human breast cancers, low levels of PEA-15 expression correlated with high nuclear grade and with negative hormone receptor status.

Overexpression of PEA-15 in breast cancer cells resulted in growth inhibition, reduction in DNA synthesis, and onset of caspase-8-dependent apoptosis (Bartholomeusz et al., 2010). In transgenic mice with overexpression of PEA-15, its expression level had a significant impact on skin tumor development upon chemically induced skin carcinogenesis (Formisano et al., 2005). In in vitro studies, PEA-15 enhanced Ras-MAPK/ERK signaling in the presence of constitutively active H-Ras and drove transformation of kidney epithelial cells (Sulzmaier et al., 2012; Ramos et al., 2000).

Homology

The mouse and human sequences are conserved. In both species, the 3' UTR of the 2,5-kb PEA15 cDNA contains the proto-oncogene MAT1 (Tsukamoto et al., 2000).

Mutations

Note

No known mutations have been reported.

Implicated in

Breast cancer

Note

See above "Invasion" and "Tumorigenicity" sections.

Ovarian cancer

Prognosis

In ovarian cancer, women with high PEA-15-expressing tumors survive longer than those with low PEA-15-expressing tumors, indicating that PEA-15 is a good prognostic marker (Bartholomeusz et al., 2008).

Astrocytic tumors

Prognosis

In astrocytic tumors, decreased PEA-15 expression level was correlated with poor overall survival in patients with high-grade astrocytoma (Watanabe et al., 2010).

Neuroblastoma

Prognosis

High levels of PEA-15 expression correlated with increased survival of patients with neuroblastoma (Gawecka et al., 2012).

Skin tumors

Oncogenesis

PEA-15 increases the susceptibility to chemically induced skin cancer in transgenic mice (Formisano et al., 2005).

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