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Gene Section
Review

PEBP1 (phosphatidylethanolamine binding protein 1)

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Identity

Hugo: PEBP1
Other names: HCNP; HCNPpp; PBP; PEBP; PEBP-1; RKIP
Location: 12q24.23

DNA/RNA

Description

The gene is composed of 4 exons spanning a region of 9,520 base pairs.

Transcription

The mRNA contains 1507 nucleotides. Alternative splicing has not been described. In prostate cancer cell lines RKIP transcription is repressed by Snail through an E-box in its promoter. Promoter methylation does not seem to cause loss of RKIP expression.

Pseudogene

RKIP has two putative pseudogenes located on chromosomes 2 and 14. These are intronless sequences with no verified expression to date.

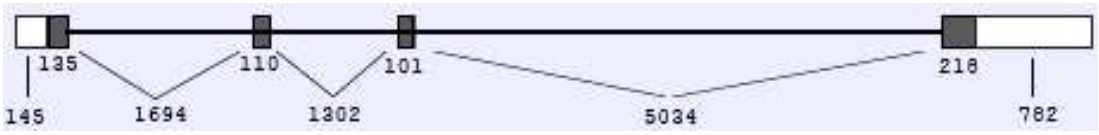
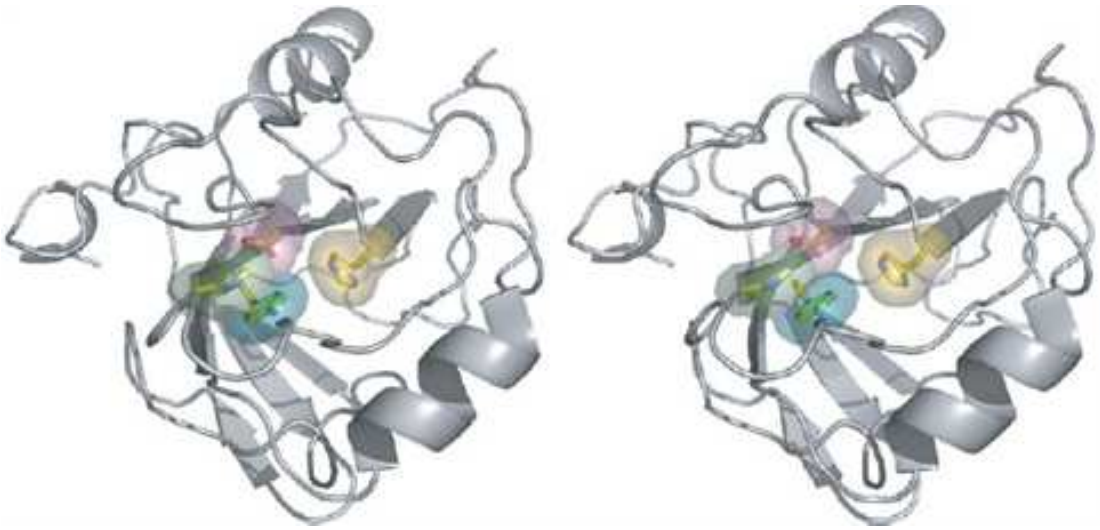


Diagram of the RKIP gene. Exons are depicted as filled boxes and untranslated regions are unfilled boxes. Introns are represented as lines between exons. Intron, exon, and untranslated region sizes are described in base pairs.



Stereo view of the human RKIP structure prepared with Pymol (Delano, 2002). Pocket residues H86 (left), H118 (right), D70 (top) and Y120 (bottom) are indicated.

Protein

Note: RKIP belongs to a highly conserved family of phospholipid-binding proteins, which have been recognized and studied for several years as PEBP. These proteins are represented in eukaryotes, bacteria, and archae. One of the interesting properties of some PEBP family members is that they are cleaved at the N-terminus to release an undecapeptide which has been named hippocampal cholinergic neurostimulating peptide (HCNP).

Description

RKIP is an 187 amino acid protein with a molecular mass of 21-23 kDa. The crystal structures of human, bovine and plant PEBPs are solved revealing no homologies to domains of known functions. The structure of RKIP features a b-fold formed by two anti-parallel b-sheets, a small C-terminal aba element, and a cavity at the surface, which could accommodate a small anion such as a phosphoryl group (see diagram above). Amino acids forming this cavity are conserved among all PEBP family members and constitute the PEB motif.

Expression

RKIP and its mammalian homologs are widely expressed in tissues; it has been detected in lung, oviduct and ovary, mammary glands, uterus, prostate epithelium, thyroid, mesenteric lymph node, megakaryocytes of the heart; spleen, liver, and epididymis, testis, spermatids, Leydig cells, steroidogenic cells of the adrenal gland zona fasiculata, small intestine, plasma cells, and neural cells such as brain oliodendricytes, Schwann cells, and Pukinje cells.

Localisation

RKIP is localized in the cytoplasm and at the plasma membrane.

Function

RKIP inhibits the Raf/MEK/ERK cascade. Identified as a Raf-1 interacting protein in a yeast two-hybrid screen, RKIP was found to inhibit phosphorylation and activation of MEK by Raf-1. RKIP inhibits the phosphorylation of the N-region of Raf-1 by (21-activated kinase) Pak and Src family kinases thereby inhibiting activation of Raf-1. PKC phosphorylation of RKIP following GPCR stimulation causes its release from Raf-1. Classical and atypical PKCs can phosphorylate RKIP at serine 153 causing dissociation of the Raf-1 kinase domain and RKIP, indicating that PKC can mediate ERK activation through RKIP. Once free from Raf-1, RKIP was shown to bind GRK-2 and block its activity, promoting and enhancing G protein signaling and MEK/ERK signaling.

RKIP appears to support macrophage differentiation via inhibition of the NFKB pathway. RKIP inhibits the NF-kappaB pathway through interaction with NIK, TAK1, and IKK. RKIP was a novel effector of apoptosis signaling; this may occur by modulation of the NF-kappaB pathway and/or the regulation of the spindle checkpoint via Aurora B kinase and the spindle checkpoint by RKIP. RKIP regulation of Aurora kinase B and the spindle checkpoint through Raf-1/MEK/ERK signaling influences cell cycle fidelity.

RKIP has serine protease activity. Purified RKIP was found to inhibit the serine proteases thrombin, chymotrypsin, and neuropsin.

HCNP, the N-terminal fragment of RKIP, may play a role in phospholipid organization of the myelin sheath and septal cholinergic development of the hippocampus. HCNP can act on frog cardiac mechanical performance, exerting a negative inotropism. Results of these experiments suggest that RKIP/HCNP may be a new endocrine factor that regulates cardiac physiology. RKIP downregulation may be associated with the congenital heart disease manifested in Down syndrome. RKIP downregulation was found in the rat right ventricle and in the interventricular septum upon cardiac remodeling.

RKIP has been found in the male reproductive tract with implications in the organization of sperm membranes during spermiogenesis. It has been identified as a decapacitation factor in mouse spermatozoa. RKIP and other proteins inhibited progesterone-induced acrosome reaction and zona pellucida binding of sperm.

Homology

No significant sequence homology to other proteins. Humans have two known family members, RKIP and PEBP4. RKIP has high sequence identity to mouse, rat, bovine, and monkey phosphatidylethanolamine binding proteins.

Implicated in

Breast cancer

Oncogenesis

Immunohistochemical examination of breast cancer lymph node metastases showed significant loss of RKIP protein expression compared to normal breast duct epithelia and primary tumors. There was a weak negative correlation between RKIP expression and apoptosis in breast tumors that did not have associated lymph node metastases.

Low levels of RKIP may allow cancer cells to evade apoptosis. Breast cancer cell lines expressing low levels of RKIP undergo apoptosis following ectopic RKIP addition or Taxol treatment, which induced RKIP expression.

Prostate cancer

Prognosis

Decreased protein expression of RKIP may be a prognostic marker in prostate cancer, with low RKIP levels indicating early PSA failure.

Oncogenesis

Low levels of RKIP may protect cancer cells against apoptosis. Tumorgenic prostate cancer cell lines expressing low levels of RKIP increase their RKIP expression following treatment with a chemotherapeutic drug, sensitizing the cells to apoptosis. Cell lines with higher RKIP expression can be made resistant to apoptosis when RKIP is knocked down.

RKIP is downregulated in prostate cancer progression and metastasis. Modulation of RKIP expression in prostate cancer cell lines changes invasive ability in vitro as well as development of metastases in vivo, with loss of RKIP corresponding to increased invasiveness and metastatic spread. MEK/ERK activation was associated with low or decreased RKIP expression in vitro, and vice-versa.

RKIP mRNA can activate interferon-inducible 2',5'-oligoadenylate synthetases (OAS), leading to RNase L activation. RNase L deficiency in prostate cancer cell lines (PC3, Du145, LNCap) is associated with resistance to apoptosis through OAS activation.

Melanoma

Note: RKIP mRNA and protein expression is reduced in melanoma cell lines versus normal melanocytes. AP-1 activation and ERK1/ERK2 phosphorylation decreased in Mel Im cells stably transfected with RKIP compared to control transfected cells. Immunohistochemical analyses showed reduced RKIP in primary melanoma versus normal normal skin, and further reduction in melanoma metastases. RKIP may act by inhibiting B-Raf kinase activity, as demonstrated in melanoma cell lines in vitro.

Hepatocellular carcinoma

Note: Hepatocellular carcinoma cell lines and HCC liver tissue showed decreased RKIP expression as compared to primary human hepatocytes or adjacent peritumoral tissues. Low RKIP expression was correlated with increased ERK activation and modulation of RKIP expression antagonized MAPK signaling in vitro.

Colorectal cancer

Note: Loss of RKIP, as studied in tissue microarrays of MMR-proficient and deficient colorectal cancer samples, was a marker of tumor progression and metastasis. Diminished RKIP expression was significantly positively associated with worse survival.

Insulinoma / Islet neoplasia

Note: Insulinomas showed decreased or absent RKIP expression as compared to normal nearby islets. β-cell line HIT-TI5 proliferation, but not apoptotis, was inhibited by RKIP.

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