PRKCI (protein kinase C, iota)

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Identity

Other names: DXS1179E: nPKC-iota: PKCI
HGNC (Hugo): PRKCI
Location: 3q26.2

Local order
The PRKCI gene is located between the polyhomeotic homolog 3 gene in centromeric position and the SKI-like oncogene in telomeric position (according to GeneLoc).

DNA/RNA

Description
The PRKCI gene is composed of 18 exons and spans 83618 bases on the plus strand.

Transcription
The PRKCI transcript (NM_002740) contains 4884 bases and the open reading frame spans from 239 to 2029.

Pseudogene
There is a single exon pseudogene mapped on chromosome X.

Protein

Description
PKCι consists of 596 amino acids and has a molecular mass of 68262 Da.
PKCι is a member of the PKCs, a diverse family of lipid dependent serine/threonine kinases.
PKCι activity can be regulated by lipid second messengers (ceramide, phosphatidylinositol 3,4,5-P3, and phosphatidic acid), phosphoinositide-dependent kinase (PDK1), tyrosine phosphorylation and specific protein-protein interactions.
The PB1 domain within the N-terminal regulatory domain mediates protein-protein interactions between PKCι and other PB1 domain containing proteins such as ZIP/p62 (Hirano et al., 2004; Puls et al., 1997), Par-6 (partitioning-defective 6) (Joberty et al., 2000; Lin et al., 2000; Noda et al., 2001; Qiu et al., 2000) and MEK5 (MAPK (mitogen-activated protein kinase)/ERK (extracellular-signal-regulated kinase) kinase 5) (Diaz-Meco and Moscat, 2001; Hirano et al., 2004). In the inactive state, the PKCι PS is positioned in the substrate binding cavity in the kinase domain and is displaced upon PKCι activation.
Exon-intron structure of the PRKCI gene. Blue vertical bars correspond to exons, green bar represents 5'UTR and orange 3'UTR.

Schematic diagram showing the domain structure of PKCι. PB-1 Phox-Bem1; PS: auto-inhibitory pseudosubstrate sequence.

Phosphatidylserine binds the C1 domain to anchor PKCι to the membrane. The PKCι catalytic domain is subdivided into the C3 and C4 domains that mediate ATP-binding and substrate binding.

**Expression**

PKCι is widely expressed with varying levels in different tissues (Selbie et al., 1993).

**Localisation**

PKCι is mainly expressed in the cytoplasm. PKCι is translocated to the cell membrane in response to second messengers and colocalizes with p62/ZIP in lysosome-targeted endosomes (Sanchez et al., 1998). Src phosphorylation leads to translocation of PKCι into the nucleus (White et al., 2002) where it forms a complex with Cdk7 (Win and Acevedo-Duncan, 2008).

**Function**

PKCι is a lipid-dependent, serine/threonine kinase. PKCι participates a number of signaling pathways that regulate cell survival (Sanz et al., 1999; Wooten et al., 1999; Xie et al., 2000), differentiation (Wooten et al., 2000), polarity (Joberty et al., 2000), and microtubule dynamics in the early secretory pathway (Tisdale, 2002).

**Homology**

PRKCI is highly evolutionarily conserved. PKCι and PKCζ exhibit 72% overall amino acid sequence homology and 86% identity within the kinase domain. PKCι shows less homology with the other PKC isoform, with less than 53% identity in the highly conserved catalytic domain (Selbie et al., 1993).

**Mutations**

**Germinal**

No germline mutations in the PRKCI gene have been reported.

**Somatic**

The PKCι gene is amplified as part of the 3q26 amplicon in lung (Regala et al., 2005b), esophageal (Yang et al., 2008) and ovarian (Eder et al., 2005; Zhang et al., 2006) cancers. A P118L mutation was found in a metastatic melanoma sample (Greenman et al., 2007).

**Implicated in**

**Various cancers**

Note

PKCι overexpression has been observed in numerous human cancers including cancers of the lung (Regala et al., 2005b), pancreas (Scotti et al., 2010), stomach (Takagawa et al., 2010), colon (Murray et al., 2004), esophagus (Yang et al., 2008), liver (Du et al., 2009), bile duct (Li et al., 2008), breast (Kojima et al., 2008), ovary (Weichert et al., 2003; Eder et al., 2005; Zhang et al., 2006), prostate (Ishiguro et al., 2009), and brain (Patel et al., 2008). PKCι is itself an oncogene, which appears to be activated through tumor-specific overexpression. In addition, however, PKCι is activated downstream of other oncogenes including oncogenic Ras, Bcr-Abl and Src.

**Non Small Cell Lung Cancer (NSCLC)**

**Prognosis**

Elevated levels of PKCι expression correlate with poor clinical outcome in NSCLC patients (Regala et al., 2005b).

**Cytogenetics**

The PRKCI gene is amplified as part of the 3q26 amplicon in NSCLC.

**Oncogenesis**

PKCι is an oncogene in NSCLC. PRKCI is amplified as part of the 3q26 amplicon in NSCLC and amplification drives PKCι overexpression in NSCLC cell lines and primary NSCLC tumours. PKCι is required for transformed (anchorage-independent) growth and invasion of human NSCLC cells (Frederick et al., 2008; Regala et al., 2005a). Disruption of the Prkci gene inhibits oncogenic Kras induced expansion and transformation of tumor-initiating, lung stem-like cells. Consequently, genetic loss of Prkci dramatically
inhibits Kras-initiated hyperplasia and subsequent lung tumor formation in vivo. PKCi enhances resistance of NSCLC to NNK-induced apoptosis by phosphorylating the pro-apoptotic protein BAD (Jin et al., 2005). PKCi forms an oncogenic complex with Par6 that activates a Rac1-Mek-Erk signaling axis that drives the transformed growth and invasion of NSCLC cells in vitro (Frederick et al., 2008; Regala et al., 2005a) and tumorigenicity in vivo (Regala et al., 2005a). PKCi and the oncogene ECT2 are genetically linked through coordinate gene amplification as part of the 3q26 amplicon in NSCLC tumors (Justilien and Fields, 2009). PKCi phosphorylates Ect2 and forms an oncogenic PKCi-Par6-Ect2 complex that drives NSCLC cell transformation by activating Rac1 (Justilien and Fields, 2009; Justilien et al., 2011). Expression of MMP10 is regulated through the PKCi-Par6-Rac1 signaling axis and MMP10 represents a key downstream effector in PKCi mediated transformation in lung cancer cells that is required for transformed growth and invasion (Frederick et al., 2008). PKCi also regulates expression of COPB2, ELF3, RFC4, and PLS1 in primary lung adenocarcinoma (Erdogan et al., 2009). The PKCi inhibitor aurothiomalate (ATM) disrupts the PB1-PB1 domain interaction between PKCi and Par6 and inhibits PKCi-mediated Rac1 activation and blocks anchorage-independent growth of NSCLC cells in vitro and tumorigenicity in vivo (Erdogan et al., 2006; Stallings-Mann, 2006).

Colon cancer

Oncogenesis
PKCi expression is elevated in human colon tumors, AOM-induced colon tumors in mice (Murray et al., 2004) and intestinal tumors in APCMin/+ mice (Murray et al., 2009; Oster and Leitges, 2006). Expression of caPKCi in the colonic epithelium of mice led to an increase in the number of AOM-induced colon tumors, and promoted tumor progression from benign adenoma to malignant intramuscular carcinoma (Murray et al., 2004) PKCi is required for oncogenic Ras-mediated transformation of the intestinal epithelium in vitro and in vivo. PKCi is also required for the formation of intestinal tumors in APCMin/+ mice (Murray et al., 2009).

Pancreatic cancer

Prognosis
PKCi overexpression predicts poor survival in pancreatic cancer patients (Scotti et al., 2010).

Oncogenesis
PKCi is significantly overexpressed in human pancreatic cancer. Knock down of PKCi expression using lentiviral-mediated shRNA blocked transformed (anchorage-independent) growth and invasion of human Pancreatic Ductal Adenocarcinoma (PDAC) cells (Scotti et al., 2010). Disruption of PKCi expression also blocks tumorigenicity of PDAC cell tumors injected orthotopically into the pancreas (Scotti et al., 2010). Analysis of human PDAC cells after orthotopic injection into the mouse pancreas revealed that PKCi-deficient tumor cells yielded significantly smaller tumors and significantly fewer metastases to the kidney, liver, diaphragm and mesentery (Scotti et al., 2010). The Rac1-MEK/ERK1/2 signaling axis is required for PKCiota-mediated transformed growth and cellular invasion of PDAC cells (Scotti et al., 2010).

Ovarian cancer

Prognosis
PKCi expression is a strong predictor of survival when combined in a multi-variate analysis with tumor cyclin E expression (Eder et al., 2005).

Cytogenetics
The PRKCI gene is amplified as part of the 3q26 amplicon in ovarian cancer (Eder et al., 2005).

Chronic myelogenous leukemia

Oncogenesis
PKCi is highly expressed in human K562 leukemia cells and functions as a survival gene in chronic myelogenous leukemia (CML). The chimeric tyrosine kinase oncogene Bcr-Abl activates a Ras/Mek/Erk signaling pathway that stimulates PKCi expression through an Elk1 transcription factor site in the proximal promoter of PKCi (Gustafson et al., 2004). Bcr-Abl activation of PKCi is necessary and sufficient to mediate apoptotic resistance to chemotherapy in K562 CML cells (Murray and Fields, 1997).

Gliomas

Oncogenesis
PKCi is overexpressed in glioblastoma multiforme. PKCi is required for survival and chemoresistance of glioblastoma cells. Genetic disruption of PKCi expression results in sensitization of glioblastoma cells to cisplatin (Baldwin et al., 2008). RNAi mediated depletion of PKCi also blocks the proliferative and invasive properties of glioma cell lines in vitro (Baldwin et al., 2008; Patel et al., 2008). PKCi promotes survival in glioblastoma cells through attenuation of p38 mitogen-activated protein kinase signaling that protects these cells against cytotoxicity to chemotherapeutic agents (Baldwin et al., 2008).
Esophageal cancer

Cyto genetics
PRKCI gene is amplified as part of the 3q26 amplicon (Yang et al., 2008).

Oncogenesis
PRKCI is amplified in 53% of esophageal squamous cell carcinomas (ESCC) and PKC\textit{iota} protein expression correlated with PRKCI gene amplification in these tumors (Yang et al., 2008). Examination of clinicopathologic features of ESCC tumors revealed a significant correlation between PRKCI expression and larger tumor size, later stage and lymph node metastasis suggesting that PRKCI overexpression is a hallmark of tumor progression and metastasis in ESCC (Yang et al., 2008).

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