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Gene Section

Review

PIP5K1A (phosphatidylinositol-4-phosphate 5-kinase type 1 alpha)

Barnabas Nyesiga and Anette Gjörloff Wingren

Biomedical science, Health and society, Malmö University, Malmö, Sweden nyesigabarnabas@gmail.com; anette.gjorloff-wingren@mah.se

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Abstract

Review on PIP5K1A, with data on DNA, on the protein encoded, and where the gene is implicated.

Keywords
PIP5K1A

Identity

HGNC (Hugo)
PIP5K1A

Location
1q21.3

DNA/RNA

Description

The cDNAs encoding the phosphatidylinositol 4-phosphate 5-kinases (PIP5K) were isolated from the human brain using peptide sequences from the erythroid 68-kDa type I PIP5KI (Loijens 1996). A human fetal brain cDNA library was screened leading to isolation of full-length type IA, PIP5K1A cDNAs (Loijens 1996). PIP5K1A is located in the chromosomal region 1q21.3 (Xie 2000), the product of which is predominantly responsible for the synthesis of PtdIns-4,5-P2 (PIP2), a substrate used by PI3K to produce PtdIns-3,4,5-P3 (PIP3) (Shaw 2006). PIP5K1A gene was localized to chromosome 1q22-q24 by fluorescence in situ hybridization (FISH) (Xie 2000).

Transcription

The 549-amino acid protein has a conserved kinase homology domain similar to the rest of the PIP5K family members. Northern blot analysis showed a wide distribution of a PIP5K1A 4.2-kb transcript mostly expressed in skeletal muscle. In addition, high levels of PIP5K1A were also seen in heart, placenta, kidney, and pancreas while low levels of expression were observed in brain, liver, and lung (Loijens 1996). Deletion-mutant analysis was used to determine an approximately 380-amino acid minimal core sequence of mouse PIP5K1A that was sufficient for phosphatidylinositol 4-phosphate kinase activity.

Protein

Figure 1. Schematic representation of human PIP5K1A isoform with the conserved kinase core domain (adopted from Porciello 2016).

Description

PIP5K1A is a 61-kDa protein migrating at about 68 kDa in SDS-PAGE (Fruman 1998). The protein shows 83% and 35% amino acid identity with PIP5K1B and PIP4K2A (PIP5K2A), respectively,

within the conserved kinase homology domain (Loijens 1996). Overall, the PIP5K1A and PIP5K1B proteins are 64% identical and Northern analysis shows the two to have a wide tissue distributions, but greatly differing expression levels. Recombinant, bacterially expressed PIP5KA was observed to have PIP5K activity and to be immunoreactive with erythroid PIP5KI antibodies (Loijens 1996). Furthermore, the authors isolated additional PIP5K1A cDNAs which they suggested represent splicing isoforms. Overexpression of mouse PIP5K1A in COS-7 cells stimulates an increase in short actin fibers and a decrease in actin stress fibers (Ishihara 1998).

PIP5K1A mediate the phosphorylation of phosphatidylinositol 4-phosphate on the D5 position of the inositol ring, thus inducing the production of phosphatidylinositol 4,5-biphosphate (PIP2) (van den Bout 2009). In both humans and mice, all PIP5K isoforms show variation in their sequence by alternative splicing (Ishihara 1998). Three PIP5K1α, four β, and one γ splice variants were identified in humans and eight PIP5K1α, two β, and three γ splice variants are present in mice. (Ishihara 1998).

All PIP5K isoforms α, β, and γ, and splice variants have a highly conserved kinase core domain that consists of 330-380 amino acids (Fig. 1), and a sub-domain called the activation loop, that regulates their activity and subcellular localization (Tuosto 2015). The variables N- and C-termini of PIP5K isoforms are also involved in the regulation of lipid kinase activity and in targeting PIP5Ks to specific cellular compartments (Kwiatkowska 2010). The C-terminal residues (440-562) of PIP5K1A regulate its localization at nuclear speckles (Mellman 2008). The 83 C-terminal amino acids of PIP5K1β are essential for its polarization at the uropod (Lacalle 2007), whereas the N-terminus controls PIP5K1β targeting to the plasma membrane and its dimerization with other PIP5K isoforms (Lacalle 2015). (Ishihara 1998).

The crystal structure of the catalytic domain of zebrafish PIP5K1A has been reported at 3.3Å resolution and the molecule forms a side-to-side dimer (Hu 2015). Mutagenesis study of PIP5K1A indicated two adjacent interfaces for the dimerization and interaction with the DIX domain of the Wnt signalling molecule dishevelled. Much as the interfaces were located distally to the catalytic/substrate-binding site, binding to these interfaces either through dimerization or the interaction with DIX stimulated PIP5K1 catalytic activity. DIX binding additionally enhanced PIP5K1 substrate binding (Hu 2015). (Ishihara 1998).

All the three PIP5K isoforms are expressed by primary T cells (Sun 2011) and they are triggered by phosphatidic acid (PA), which is generated by phospholipase D (PLD), through the hydrolysis of phosphatidylcholine (Jenkins 1994, Moritz 1992). PIP5K1α cooperates with PIP5Kβ and VAV1 in promoting actin polymerization and CD28 signaling functions in human T lymphocytes (Porciello 2016). PIP5K1A localises to the plasma membrane and the Golgi complex, and has also been observed at sites of membrane ruffling induced by the Rho GTPase RAC1 (van den Bout 2009). PIP5K1A in particular is recruited to the plasma membrane in response to several receptors to provide the substrate PIP2 for PLCγ leading to IP3 formation and $Ca2^{+}$ mobilization (Saito 2003, Wang 2008 and Xie 2009). Both PIP5K1α and PIP5Kγ are known to interact and colocalize with phospholipase D 2 (PLD2) at the membrane to stimulate cell adhesion (Divecha 2000, Powner 2005). Some studies have also shown pronounced association of PIP5K1A with nuclear speckles (Chakrabarti 2013) where it may regulate pre-mRNA processing and mRNA export (Barlow 2010).

Function

Treatment of primary cultured astrocytes with gangliosides significantly enhanced PIP5K1α mRNA and protein expression levels (Sang 2010). MicroRNA-based PIP5K1α knockdown strongly reduced ganglioside-induced transcription of proinflammatory cytokines. In addition, PIP5K1α knockdown suppressed phosphorylation and nuclear translocation of NF-kB (Sang 2010).

PIPK-mediated mechanisms regulate microtubule dynamics in neuronal development (Noda 2012). Using immunoprecipitation with an antibody specific to KIF2A, PIPKα was identified as a candidate membrane protein that regulates the activity of KIF2A. Yeast two-hybrid and biochemical assays showed direct binding between KIF2A and PIPKα. Furthermore, the microtubule (MT)- depolymerizing activity of KIF2A was enhanced in the presence of PIPKα in vitro and in vivo.

Implicated in

Prostate cancer

Some studies have shown that overexpression of PIP5K1α in non-malignant PNT1A cells induces the invasive capacity of these cells. An increased expression of major factors that drive cancer cell proliferation and invasion such as VEGF, phosphorylated PTK2 (FAK), TWIST1, and MMP9, was observed in these cells due to PIP5K1α overexpression. PIP5K1α overexpression in these cells led to an increased AKT activity and an increased survival, as well as invasive malignant phenotype. The siRNA-mediated knockdown of PIP5K1α in these cells resulted into a reduced AKT

activity and an inhibition in tumor growth. PIP5K1α, PIP2 and PIP3 are important lipids for membrane structure and actin polymerization, thus increased levels of these lipids may lead to malignant transformation and progression of cancer cells into a more invasive phenotype (Semenas 2014).

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