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Gene Section

Review

PIP4K2A (phosphatidylinositol-5-phosphate 4-kinase, type II, alpha)

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Abstract

PIP4K2A is a lipid kinase that phosphorylates phosphatidylinositol (PtdIns) 5P, generating PtdIns4,5P2, which is an important precursor to second messengers of the phosphoinositide signal transduction pathways. Recently, studies have indicated that PIP4K2A is involved in the regulation of important biological processes that participate in the malignant phenotype, including cell proliferation, clonogenicity and survival. The present review on PIP4K2A contains data on DNA/RNA, protein encoded and where the gene is implicated.

Keywords: PIP4K2A; cell proliferation; clonogenicity; cell cycle; apoptosis; phosphatidylinositol signaling

Identity

Other names: PIPK, PI5P4KA, PIP5K2A, PIP5KIIA, PIP5KII-alpha

HGNC (Hugo): PIP4K2A

Location: 10p12.2

DNA/RNA

Description

The entire PIP4K2A gene is about 179.7 Kb (start: 22534837 and end: 22714574 bp; orientation: Minus strand) and contains 10 exons.
The PIP4K2A cDNA contains 3.8 Kb.

Figure 1. Schematic primary structure of PIP4K2A protein. The phosphatidylinositol phosphate kinase (PIPK) domain is illustrated. The position of amino acids (aa) are indicated in the figure.

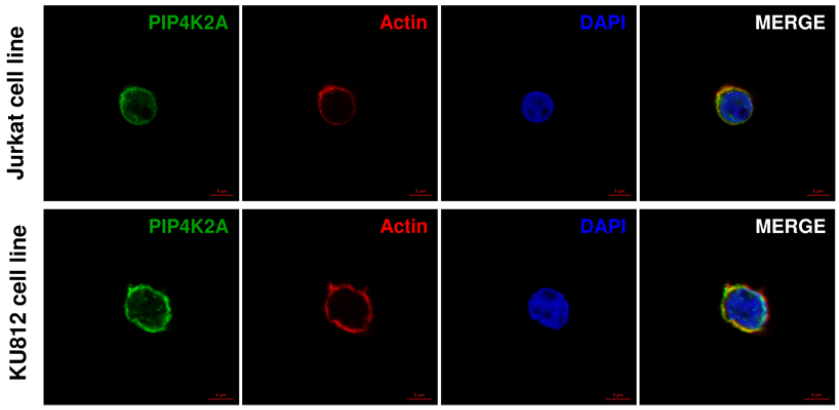

Figure 2. Intracellular localization of PIP4K2A protein in Jurkat and KU812 cells. Confocal analysis of Jurkat (lymphoid leukemia) and KU812 (myeloid leukemia) cells displaying PIP4K2A (green), Actin (red) and DAPI (blue) staining; MERGE shows the overlapped images. Scale bar: 10 or 20 µm, as indicated. Anti-PIP4K2A (sc-100406) was from Santa Cruz Biotechnology, Phalloidin (A12379) and DAPI (P-36931) was from Life Technologies (Carlsbad, CA, USA). Personal data.

Protein

Description

PIP4K2A protein consists of 406 aminoacids with a molecular weight of 53 kDa and has a conserved phosphatidylinositol phosphate kinase (PIPK) domain in the C-terminal region. The schematic representation of PIP4K2A protein is illustrated in Figure 1.

Expression

Ubiquitous.

Localisation

PIP4K2A is predominantly located in the cytoplasm. However, in some cell types PIP4K2A was found in both nucleus and cytoplasm (Figure 2).

Function

PIP4K2A belongs to the class II of the phosphatidylinositol-5-phosphate 4-kinase family, and major function of these proteins is to recognize the phosphatidylinositol (PtdIns) phosphorylated at position five (PtdIns5P) and phosphorylate inositol ring in position four, to generate a new lipid messenger, the phosphatidylinositol-4,5-bisphosphate (PtdIns4,5P2) (Figure 3).

The PtdIns4,5P2 plays an important role in phosphoinositide signaling, participating in several cell processes, including vesicle transport, cell proliferation, adhesion, apoptosis and nuclear events (revised in McCrea and De Camilli, 2009). The acknowledgment about the functions of PIP4K proteins in cellular mechanism is still under construction and recent findings suggest that this protein family is strongly involved in oxidative stress and cellular senescence (revised in Fiume, et al., 2015).

In contrast, the specific functions of PIP4K2A are poorly elucidated, and seems to vary according to cell type and stimulus.

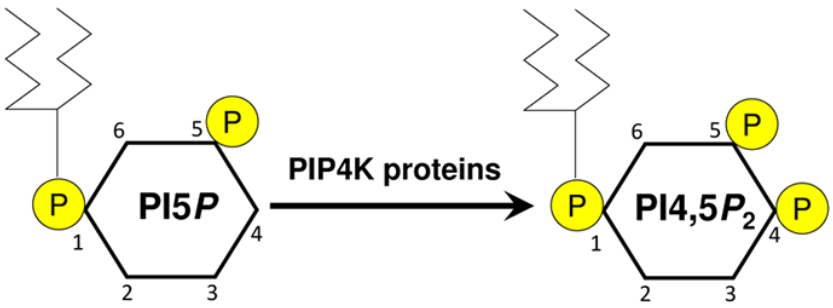

Figure 3. PIP4K proteins function. PIP4K2A belongs to the class II of the Phosphatidylinositol-5-phosphate 4-kinase (PIP4K) family, which recognize the phosphatidylinositol phosphorylated at position five (PI5*P*) and phosphorylate inositol ring in position four to generate the phosphatidylinositol-4,5-bisphosphate (PI4,5P_2) .

% Identity for: *Homo sapiens* PIP4K2A	Symbol	Protein	DNA
vs. P. troglodytes	PIP4K2A	100	99.9
vs. M. mulatta	PIP4K2A	100	98.7
vs. C. lupus	PIP4K2A	100	91.8
vs. B. taurus	PIP4K2A	99.3	92.6
vs. M. musculus	Pip4k2a	98.3	89.5
vs. R. norvegicus	Pip4k2a	97.5	87.9
vs. G. gallus	PIP4K2A	93.6	84.5
vs. X. tropicalis	pip4k2b	93.2	80.9
vs. D. rerio	pip4k2aa	87.6	76.8

Table 1. Comparative identity of human PIP4K2A with other species (Source: http://www.ncbi.nlm.nih.gov/homologene)

For instance, PIP4K2A silencing reduces cell survival in THP1 cells (an acute myeloid leukemia cells) (Jude, et al., 2015), but not in K562 cells (a chronic myeloid leukemia cell line) (Peretti de Albuquerque Wobeto, et al., 2014), whereas its overexpression reduces clonogenicity and sensibility to oxidative stress in O2OS cells (Jones, et al., 2013).
PIP4K2A was initially identified in erythrocytes (Ling, et al., 1989) and its expression was found to be upregulated during erythroid differentiation (Peretti de Albuquerque Wobeto, et al., 2014, Zaccariotto, et al., 2012), suggesting a potential participation in cell differentiation.
Of note, among the PIP4K proteins, which include PIP4K2A, PIP4K2B and PIP4KC, PIP4K2A has been reported as having the highest kinase activity (Bultsma, et al., 2010).
PIP4K2A might also form heterodimer with PIP4K2B and result in PIP4K2A nuclear translocation (Bultsma, et al., 2010, Wang, et al., 2010).

Homology

PIP4K2A shares high homology with the other members of the PIP4K protein family, including PIP4K2B and PIP4K2C. PIP4K2A also shares high homology among different species (Table 1).

Mutations

Somatic

Recurrent mutations in the PIP4K2A gene are rare, 68 substitution missense, 1 substitution nonsense, 19 substitution synonymous, 2 insertion frameshift and 4 deletion frameshift mutations are reported in COSMIC (Catalogue of somatic mutations in cancer; http://cancer.sanger.ac.uk/cancergenome/projects/cosmic).

Implicated in

Acute Leukemia

Wobeto and colleagues (Peretti de Albuquerque Wobeto, et al., 2014) reported that PIP4K2A is a nuclear and cytoplasm protein widely expressed in myeloid leukemia cell lines, and that PIP4K2A inhibition induces hemoglobin production and slightly decreases cell proliferation, but does not modulate apoptosis in K562 cells. Using a targeted knockdown screen for phosphoinositide modulator genes as approach, Jude and colleagues (Jude, et al., 2015) identified PIP4K2A as an important gene for proliferation, clonogenicity and survival of acute myeloid leukemia cells. In this work, the sensibility

to PIP4K2A inhibition was modulated by CDKN1A (p21) and mTOR activation. Szczepanek and colleagues (Szczepanek, et al., 2012), using ex vivo drug sensitivity experiments and DNA microarray analysis in childhood acute lymphoblastic leukemia

cells, found that PIP4K2A gene signature was associated with drug resistance for vincristine, thioguanine, melphalan and doxorubicin.
Recently, our research group (Lima, et al., 2015) observed that PIP4K2A expression was reduced in a panel of myeloid and lymphoid leukemia cells when compared with normal leukocytes.
Similar PIP4K2A expression prolife was observed in acute lymphoblastic leukemia patients compared with healthy donors.
In our study, HEL cells, a myeloid leukemia cell line that presents very low levels of p21, and Namalwa cells, a lymphoid leukemia cell line, that presents constitutive PI3K/AKT activation, did not show any modulation regarding cell proliferation, clonogenicity and apoptosis upon PIP4K2A silencing (Lima, et al., 2015).

Myelodysplastic syndromes

In a cohort of 54 untreated patients with myelodysplastic syndromes (MDS) was observed a reduction of PIP4K2A expression in ≥5% bone marrow blats MDS patients group and an association between low expression of PIP4K2A and high blast percentage.
Interestingly, MDS patients with low levels of PIP4K2A (stratified by tertiles) presented reduced overall survival by univariate analysis (Lima, et al., 2015).

Breast cancer

Emerling and colleagues (Emerling, et al., 2013), using immunohistochemistry and western blot, reported that PIP4K2A is highly expressed in primary samples and cell lines from breast cancer. In this study, PIP4K2A plus PIP4K2B silencing reduced cell proliferation and tumor growth and induced cell senescence of null, but not of p53 wild type, breast cancer cell lines.
Of note that triple knockout mice for PIP4K2A, PIP4K2B and TP53 presented reduced tumor burden and increased tumor free survival compared with Tp53 knockout mice (Emerling, et al., 2013).

Osteosarcoma

Using the osteosarcoma cell line, U2OS cells, Jones and colleagues (Jones, et al., 2013) observed that induction of oxidative stress inhibits PIP4K2A activity and PIP4K2A overexpression reduces clonogenic cell growth.
In contrast, PIP4K2A overexpression increased cell viability in response to oxidative stress in U2OS cells (Jones, et al., 2013).

To be noted

PIP4K2A knockout has been reported in several organisms, including fly, worm, fish and mouse, and different phenotypes has been described. In Drosophila and zebrafish, PIP4K2A orthologue protein knockout resulted in strong defective development (Gupta, et al., 2013, Elouarrat, et al., 2013). In Caenorhabditis elegans, PIP4K2A orthologue protein knockout did not lead to developmental defects, but increased oxidative stress (Fiume, et al., 2015). In mice, Pip4k2a knockout did not present any aberrant phenotype (Emerling, et al., 2013).

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