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Gene Section
Review

PHLDA3 (Pleckstrin Homology-Like Domain, family A, member 3)

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Abstract

Review on PHLDA3, with data on DNA, on the protein encoded, and where the gene is implicated.

Keywords
PHLDA3; Tumor suppressor; Apoptosis; Hypoxia

Identity

Other names: TIH1

HGNC (Hugo): PHLDA3

Location: 1q32.1

Location (base pair)
Starts at 201464284 and ends at 201469171 bp from pter (GRCh38.p12 - 21/12/2017)

Note
PHLDA3 was mapped to human chromosome 1q32.1 and consist of 4,888 base pairs, starting at base pair 201464284 and ending at base pair 201469171 from the p-terminus, it is a TP53 responsive gene and is required for TP53-dependent apoptosis (Frank et al., 1999; Kawase et al., 2009). This gene is a member of the Pleckstrin Homology-Like Domain A family, which includes PHLDA1, PHLDA2, and PHLDA3. PHLDA3 downregulation has been correlated with DNA hypermethylation in some types of cancer as prostate (Mahapatra et al., 2012) and neuroendocrine tumors, and also with TP53 mutation in neuroendocrine tumors and mammary carcinomas (Ohki et al., 2014; Takikawa and Ohki, 2017; Christgen et al., 2012; Leszczynska et al., 2015). The DNA of PHLDA3 contains 3 exons and encodes a 2.74 kb mRNA with a coding region of 383bp.

DNA/RNA

Description

DNA size: 4,888 kb; 3 exons

Transcription

mRNA size: 2734bp NM_012396.4. Three transcript variants encoding different isoforms and three non-coding transcripts variants have been descript for this gene.
NM_012396 - Homo sapiens pleckstrin homology-like domain, family A, member 3 (PHLDA3), transcript variant 1, mRNA-> NP_036528. Transcript size: 2734bp. Translation length: 127 residues.
https://www.ncbi.nlm.nih.gov/nuccore/NM_012396.4 - 28 May, 2015. Variant 1 encodes the functional protein.
NR_073080 - Homo sapiens pleckstrin homology like domain family A member 3 (PHLDA3), transcript variant 2, non-coding RNA. Transcript size: 1625 bp. https://www.ncbi.nlm.nih.gov/nuccore/NR_073080.1 - 23 - Dec - 2018
ENST00000367311.4 - Homo sapiens pleckstrin homology like domain family A member 3 (PHLDA3), transcript variant, protein coding,

mRNA -> NP_036528, NM_012396. Transcript size: 2640 bp Translation length: 127 residues. http://www.ensembl.org/id/ENST00000367311.4
ENST00000367309.1 - Homo sapiens pleckstrin homology like domain family A member 3 (PHLDA3), transcript variant, protein coding. Transcript size: 896 bp. Translation length: 127 residues.
http://www.ensembl.org/id/ENST00000367309.1
ENST00000485436.1 - Homo sapiens pleckstrin homology like domain family A member 3 (PHLDA3), transcript variant, non-coding RNA. Transcript size: 661 bp.
http://www.ensembl.org/id/ENST00000485436.1
ENST00000497057.1 - Homo sapiens pleckstrin homology like domain family A member 3 (PHLDA3), transcript variant, non-coding RNA. Transcript size: 582 bp.
http://www.ensembl.org/id/ENST00000497057.1

Protein

NP_036528.1. Molecular weight: 13.9 kDa, 127 aa. https://www.ncbi.nlm.nih.gov/protein/NP_036528. 1 - 23/Dec/18

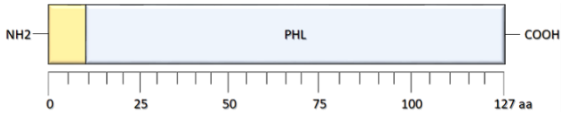

Figure 1. Schematic representation of the PHLDA3 protein structure. The structure of the PHLDA3 protein is composed mainly of the pleckstrin like-domain (PHL).

Description

PHLDA3 is a 13.9kDa protein, composed of 127 amino mostly comprised of the PHL domain (120aa) (Frank et al., 1999). PHLDA3 PHL domain confers to this protein the ability of binding specifically to membrane lipids. According to in vitro binding assay, PHLDA3 protein binds to a wide combination of phosphatidylinositol phosphate (PIP): (PI(3)P, PI(4)P, PI(5)P, PI(3,4)P2, PI(4,5)P2, PI(3,5)P2 and PI(3,4,5)P3) (Kawase et al., 2009; Saxena et al., 2002). PHLDA3 has been reported as an AKT1 (Akt) pathway inhibitor and associated with tumor suppression (Kawase et al., 2009).

Expression

A RNA-seq performed in different tissue samples shown that PHLDA3 is broadly expressed in adrenal, appendix, brain, colon, duodenum, endometrium, esophagus, fat, gall bladder, heart, kidney, liver, lung, lymph node, ovary, pancreas, placenta, prostate, salivary gland, skin, small intestine, spleen, stomach, testis, thyroid and urinary bladder tissue (Fagerberg et al., 2014). PHLDA3 expression has been shown to be modulated by promoter methylation in prostate cancer and TP53 mutations in human infiltrating lobular breast cancer cells (Christgen et al., 2012; Mahapatra et al., 2012). Also, besides TP53 it was described that XBP1 transcription factor is implicated in PHLDA3 induction upon ER stress (Han et al., 2016).
PHLDA3 was identified as a gene modulated by ochratoxin A (OTA) induced genotoxicity, it was upregulated in renal outer medulla cells after treatment with the renal carcinogen OTA in response to DNA damage. In other toxicogenomics studies, PHLDA3 was also proposed as a potential biomarker (Ellinger-Ziegelbauer et al., 2008; Furihata et al., 2018; Hibi et al., 2013; Uehara et al., 2008).

Localisation

PHLDA3 is primarly localized at the plasmatic membrane due its specificity binding to membrane phosphoinositides but can also be find in the cytoplasm and extracellular content.

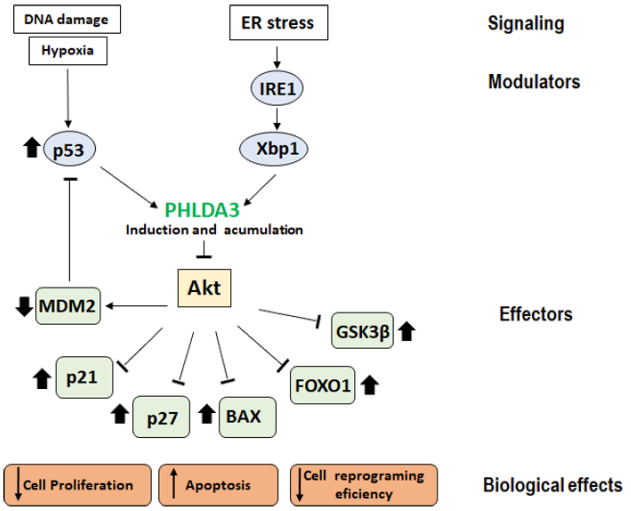

Figure 2 - Schematic diagram of the modulators and biological effects of PHDA3 expression. PHLDA3 is a p53-target gene activated in response to DNA damage and hypoxia. The gene can also be activated by Xbp1 in response to endoplasmic reticulum stress (ER stress). PHLDA3 induction leads to Akt pathway inhibition by binding to phosphoinositide competition leading to increased apoptosis and proliferation, and decreased cell reprograming efficiency.

Function

Murine PHLDA3 was first identified in 1999 and was designated Tih1 as the closest paralog of the imprinted gene Ipl (Frank et al., 1999). It was reported as a tumor suppressor gene. PHLDA3 protein function is still being studied, but it was reported as an AKT1 (Akt) pathway repressor by preventing Akt-binding to membrane lipids. Thus, PHLDA3 is a TP53 regulated repressor of Akt signaling by binding competition, so inhibits Akt activity via competitive binding to PIP3 (Kawase et al., 2009) and thereby acts as a dominant-negative form of Akt contributing to TP53-dependent apoptosis. It was reported that active TP53 localizes to the transcription start site of PHLDA3 and transcriptionally activates this gene. PHLDA3 was upregulated by hypoxia (Leszczynska et al., 2015), and there is a clear accumulation of TP53 at the response elements identified in PHLDA3, demonstrating direct transactivation of these genes in response to hypoxia in colorectal carcinoma, non-small-cell lung carcinoma, and nontumor lung fibroblast cells. It was observed after cisplatin treatment in testicular germ cell-derived human embryonal carcinoma cells that PHLDA3 and other genes downstream targets of TP53 are involved in response to DNA damage and events leading to cell death (Kerley-Hamilton et al., 2005).

In renal tubular cells, cisplatin increases PHLDA3 in kidneys' tubules and in urinary content suggesting PHLDA3 protein as a kidney injury marker since it is urine-detectable (Lee et al., 2014; Lee, Kang, and Kim 2015).

Furthermore, PHLDA3 exhibited statistically significant changes in gene expression in liver samples of rats treated with genotoxic hepatocarcinogens, suggesting that it may be a candidate marker gene for differentiating genotoxic hepatocarcinogens from non-genotoxic hepatocarcinogens (Suenaga et al., 2013). There is evidence that PHLDA3 is involved in zebrafish embryogenesis since PHLDA3 overexpression disrupted hemangioblast specification and affected intersegmental vessel development (ISV). It was suggested that overexpression of PHLDA3 inhibits ISV development by blocking the activation of AKT, it is supported by data showing a reversal of ISV defects induced by phlda3 overexpression upon Akt constitutively active form expression (Wang et al., 2018). In induced pluripotent stem cells (iPSC) PHLDA3 was expressed at a lower level and reduced gradually during the process of iPSCs generation; reprogramming efficiency was inhibited by PHLDA3 overexpression. Evidence supports that the mechanism by which PHLDA3 promotes decrease iPSC generation efficiency involves Akt- GSK3B activation during the reprogramming process (Qiao et al., 2017). Photoreceptor injury induced PHLDA3 expression in microglia, the resident macrophage in the CNS, data provide insights into the participation of PHLDA3 in the activation status of microglia under pathological conditions (Koso et al., 2016). PHLDA3 was the most significantly affected gene by thrombin knockout in zebrafish embryos but PHLDA3 function in embryonic development is still unclear (Day and Jagadeeswaran, 2009).

The process of endomitosis consists of several rounds of DNA synthesis without division and leading to polyploidization in megakaryocytes. Downregulation of TP53-target genes in TP53 knock-down megakaryocytes supports the hypothesis that TP53 suppresses polyploidization during megakaryocytic differentiation by arresting DNA synthesis and inducing apoptosis. PHLDA3 together with other genes was identified as a gene through which TP53 mediates these biological effects in megakaryocytes (Apostolidis et al., 2012).

Homology

PHLDA3 gene is highly conserved in Euteleostomi and homologs have been found in P.troglodytes, M.mulatta, M.musculus, R.norvegicus, G.gallus and D.rerio.

Implicated in

Tumor suppressor

PHLDA3 represses Akt activity and Akt-regulated biological processes including insulin-mediated glucose transport, protein and glycogen synthesis, proliferation, cell growth, differentiation, and survival. Pancancer genomics analyses of human cancer shown that TP53 mutation is significantly related to PHLDA3, TNFRSF10B and PTEN downregulation. Thus, a TP53 mutation may cause tumor development due to the loss of basal TP53 target expression together with the TP53 mutant inability to active stress-responsive genes as PHLDA3 (Pappas et al., 2017). PHLDA3 suppresses neuroendocrine tumorigenicity and deficiency of this gene results in islet resistance to oxidative stress leading to increased proliferation, cell death prevention and improved insulin-releasing function without causing tumors. It was also observed in PHLDA3-deficient islet enhanced activation of Akt in response to hypoxia, thereby inducing signaling pathways of apoptosis inhibition, and cellular growth and survival (Sakata et al., 2017). It was observed after cisplatin treatment in testicular germ cell-derived human embryonal carcinoma cells that PHLDA3 and other genes downstream targets of TP53 are involved in response to DNA damage and events leading to cell death (Kerley-Hamilton et al., 2005). PHLDA3 was identified as a gene modulated by ochratoxin A (OTA) induced genotoxicity, it was upregulated in renal outer medulla cells after treatment with the renal carcinogen OTA in response

to DNA damage. In other toxicogenomics studies, PHLDA3 was also proposed as a potential biomarker (Uehara et al., 2008; Ellinger-Ziegelbauer et al., 2008; Hibi et al., 2013; Furihata et al., 2018).

Fusion genes

PHLDA3/ MYBPH (1q32.1/1q32.1). Cancer type: Breast Cancer (FusionGDB ID: 26994).

PHLDA3/ PFKM (1q32.1/ 12q13.11) Cancer type NOS (FusionGDB ID: 26995).

Prostate cancer

The association of PHLDA3 and prognosis of cancer patients is still under investigation. Some studies have found that downregulation of PHLDA3 in cancer worsens the prognosis of patients diagnosed with cancer. In prostate cancers, for example, reduced expression of PHLDA3 is found in 22% of the patients in the study. Furthermore, microarray analysis performed to evaluate the global methylation profiling of prostate cancer patients with clinical recurrence revealed significant DNA methylation of PHLDA3 in the patients with clinical recurrence (Mahapatra et al., 2012).

Solid cancers (prostate cancer, breast cancer, pancreatic cancer and lung neuroendocrine tumors, lung cancer, gastric cancer, melanoma, sarcomas, ovarian cancer, and colorectal cancer).

Prognosis:

The association of PHLDA3 and prognosis of cancer patients is still under investigation. Some studies have found that downregulation of PHLDA3 in cancer worsens the prognosis of patients diagnosed with cancer. Microarray analysis to evaluate a global methylation profiling of prostate cancer patients with clinical recurrence revealed significant DNA methylation of PHLDA3 in the patients with clinical recurrence (Mahapatra et al 2012).

In silico analysis using Oncomine datasets showed that underexpression of PHLDA3 together with INPP5D, SULF2, BTG2, CYFIP2 and KANK3, a hypoxia-inducible TP53-dependent group of genes, was significantly associated with a poor clinical outcome in patients with breast, lung, gastric, melanoma, sarcoma, ovarian, and colorectal cancers. Individually no relation of their expression with patient prognosis was observed, suggesting that their concomitant regulation is the relevant factor for clinical outcome in these tumors. A meta-analysis on METABRIC data confirmed that lower expression of these group of genes correlated with TP53 mutation status and was associated with poor patient outcome in overall survival over 12 years in breast cancer patients (Leszczynska et al., 2015).

Furthermore, PHLDA3 downregulation was consistently observed in cells with PHLDA3 LOH and associated with pancreatic neuroendocrine tumors at an advanced stage, whereas lack of LOH was related to lower tumor grades (Ohki et al., 2014; Takikawa Ohki, 2017).

Also, loss of PHLDA3 associated with protein expression downregulation is frequently found in primary lung cancer (Kawase, T. et al., 2009). Reduced expression of PHLDA3 is also found in 22% of prostate cancers (Soung, et al., 2011). Furthermore, Low PHLDA3 expression is associated with poor prognosis and postoperative tumor progression and recurrence in patients with oesophageal squamous cell carcinoma (ESCC) (Muroi, et al., 2015).

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