Gene Section
Mini Review

PHLPP1 (PH domain leucine-rich repeat protein phosphatase 1)
Audrey K O’Neill, Alexandra C Newton
(AKO, ACN)

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Identity
Other names: PHLPP; KIAA0606; MGC161555; PLEKHE1; SCOP
HGNC (Hugo): PHLPP1
Location: 18q21.33

DNA/RNA

Description
The gene for PHLPP1 is located at 18q21.33. It encompasses two different splice variants: PHLPP1alpha and PHLPP1beta. PHLPP1alpha spans 154 kb and includes 16 exons. The PHLPP1beta gene is identical to the PHLPP1alpha gene except that it has a much (~1.5 kb) longer exon 1 and a slightly shorter exon 2. Including the new exon 1, the PHLPP1beta gene is 265 kb in length. PHLPP1 is one of two separate genes in the PHLPP gene family; the second gene, PHLPP2, is located at 16q22.3.

Transcription
The PHLPP1alpha and PHLPP1beta transcripts are identical except for exon 1 and the beginning of exon 2. The PHLPP1alpha transcript is 4617 bp; the PHLPP1beta transcript is 6155 bp.

Protein

Description
The PHLPP1alpha and PHLPP1beta proteins both contain a pleckstrin homology (PH) domain, a series of leucine-rich repeats (LRR), a PP2C phosphatase domain, and a C-terminal PDZ (post synaptic density protein [PSD95], Drosophila disc large tumor suppressor [DlgA], and zonula occludens-1 protein [zon-1]) binding motif. In addition, PHLPP1beta has a putative Ras association (RA) domain near its N-terminus. PHLPP1alpha is composed of 1205 amino acids and has a molecular weight of approximately 133 kDa, while PHLPP1beta has 1717 amino acids and a molecular weight of approximately 185 kDa. (The related isoform PHLPP2 has a domain structure similar to that of PHLPP1beta).

Expression
PHLPP1 is expressed in most human cancer cell lines and all mouse tissues examined so far. PHLPP1beta appears to be more abundant than PHLPP1alpha. Rat PHLPP1beta (termed SCOP for Suprachiasmatic nucleus circadian oscillatory protein) is also expressed in the suprachiasmatic nucleus, where its mRNA expression oscillates in a circadian fashion.
PHLPP1 (PH domain leucine-rich repeat protein phosphatase 1)

Localisation
PHLPP1 appears to be localized throughout the cell.

Function
PHLPP1 is a phosphatase that specifically dephosphorylates the hydrophobic motif (HM) of Akt and conventional/novel PKC isoforms. HM phosphorylation is important for the function of both kinases. For Akt, phosphorylation at serine 473, the HM site, allows full activation of the kinase and subsequent phosphorylation of its downstream substrates. For PKC, phosphorylation of the HM (serine 660 in PKCbetaII) increases protein stability; once the HM is dephosphorylated, two other important regulatory sites on the kinase (the activation loop and the turn motif) are rendered more sensitive to dephosphorylation by other phosphatases. The dephosphorylated PKC is then shunted to the detergent-insoluble fraction of the cell, where it is degraded. PHLPP1 therefore functions to decrease the activity of both Akt and PKC, albeit by different mechanisms.

While PHLPP1 and its family member PHLPP2 have similar functions, their specificity for Akt isoforms differs. PHLPP1 preferentially binds and dephosphorylates Akt2 and Akt3, resulting in decreased phosphorylation of a set of Akt targets that includes GSK-3beta, TSC2, and FoxO, as well as and GSK3alpha. PHLPP2, on the other hand, binds and dephosphorylates Akt1 and Akt3, resulting in downregulation of an overlapping yet distinct set of downstream targets: GSK-3beta, TSC2, and FoxO, as well as TSC2 and p27.

Interestingly, PHLPP1’s regulation of its protein substrates appears to be regulated by its protein-protein interaction domains. PHLPP1 lacking a C-terminal PDZ ligand is unable to dephosphorylate Akt, whereas deletion of PHLPP1’s PH domain decreases its ability to dephosphorylate PKC.

Since PHLPP1 downregulates the pro-survival kinase Akt, it is not surprising that this phosphatase plays roles in apoptosis and suppression of cellular proliferation. siRNA-mediated reduction of PHLPP1 causes increased apoptosis in a number of cell lines, whereas overexpression of PHLPP1 decreases proliferation in LN229, a glioblastoma cell line, and suppresses its ability to form tumors in nude mice. PHLPP1 also regulates the phosphorylation and activity of ERK; it has been suggested to interact directly with the nucleotide-free form of K-Ras and thus suppress the Ras/Raf/MEK/ERK pathway. This pathway is important for the regulation of learning and memory, and overexpression of rat PHLPP1beta in the hippocampus of transgenic mice abolishes memory for novel objects. In addition, training for hippocampus-based learning prompts calpain protease-mediated degradation of PHLPP1. Together, these results suggest that proper regulation of PHLPP1 in certain neurons is crucial for memory formation.

Homology
PHLPP is a highly conserved phosphatase; its earliest orthologue is the yeast protein CYR1. In addition to a PP2C phosphatase domain, a leucine-rich repeat, and a Ras association domain, CYR1 contains an adenylate cyclase domain near its C-terminus. Though invertebrates have only one PHLPP gene, most vertebrates have genes for both PHLPP1 and PHLPP2.

Mutations
Somatic
One glioblastoma multiforme sample was found to have a mutation in the catalytic domain of PHLPP1 (M738T in the PHLPP1a transcript). This tumor sample presented with mutations in several other known tumor suppressors, including PTEN and Rb.

Implicated in
Glioblastoma multiforme
Oncogenesis
PHLPP1 overexpression in human LN229 cells limits their ability to form tumors in a xenograft model. Various human glioblastoma cell lines respond to PHLPP1 knockdown with increased Akt phosphorylation. In addition, mRNA expression of both PHLPP1 and PHLPP2 are decreased by around 30% in patient glioblastoma samples (relative to normal brain).
Colorectal cancer

Cytogenetics

18q21.33, the chromosomal locus containing the gene for PHLPP1 as well as the putative tumor suppressors BCL2 and Maspin, commonly undergoes loss of heterozygosity in colon cancers.

Oncogenesis

Overexpression of PHLPP1 or PHLPP2 in the human colon cancer cell lines HCT-116 and HT29 causes decreased expression of PKC and decreased phosphorylation of Akt. Cells overexpressing PHLPP exhibit decreased proliferation and were less able to induce tumors in nude mice. Conversely, DLD1 cells, which express high levels of PHLPP, respond to PHLPP1 or PHLPP2 knockdown with increased Akt phosphorylation, PKC stability, and proliferation.

Leukemia

Disease

Chronic lymphocytic leukemia, chronic myelogenous leukemia

Oncogenesis

PHLPP1 mRNA expression is frequently reduced to undetectable levels in patients with chronic lymphocytic leukemia (CLL). About 50% of CLL patients have loss of chromosomal region 13q14, and about 50% of these show drastically reduced PHLPP1 expression. In chronic myelogenous leukemia (CML), PHLPP mRNA levels may also be decreased, albeit by a different mechanism. Bcr-Abl, the fusion protein responsible for CML, downregulates PHLPP1 and PHLPP2 mRNA levels; decreasing PHLPP levels interferes with the efficacy of Bcr-Abl inhibitors, including Gleevec, in CML cell lines.

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