Sangdun Choi
Editor

Encyclopedia of Signaling Molecules

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SHIP2

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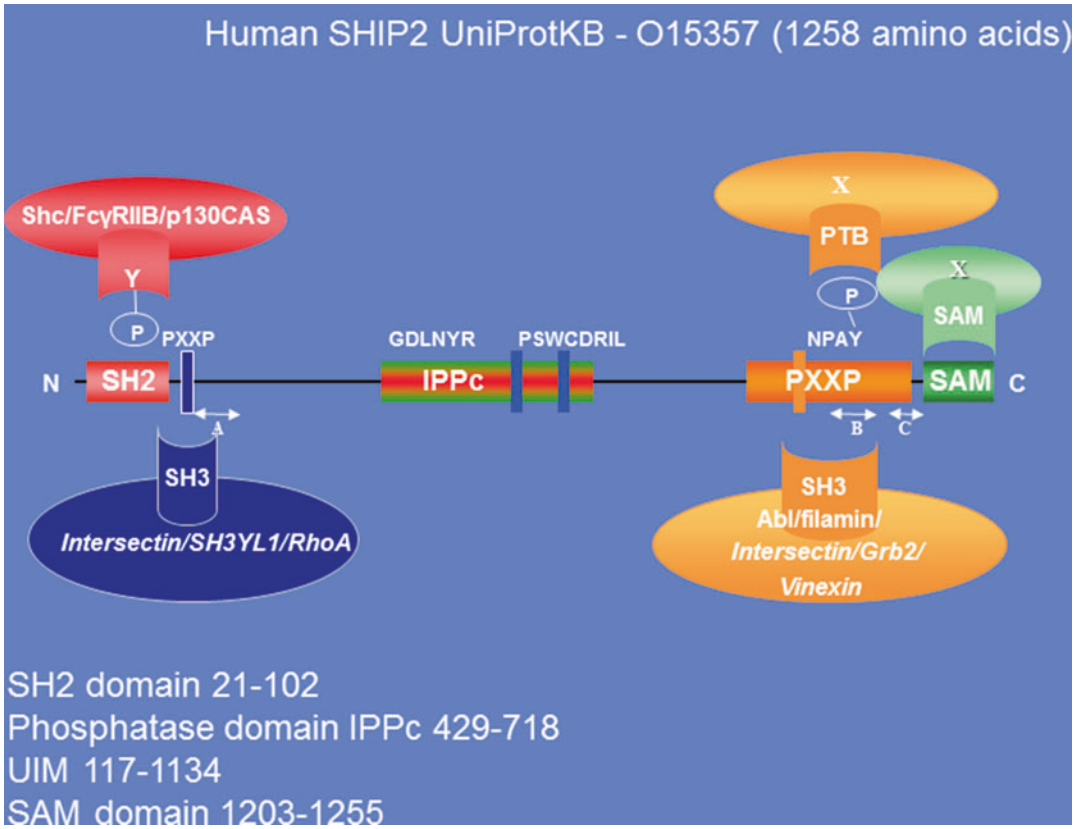
Synonyms

INPPL1; SH2 domain containing inositol phosphate 5-phosphatase type 2

Historical Background

Inositol polyphosphate 5-phosphatase or phosphoinositide 5-phosphatases (or PI 5-phosphatases) are enzymes that can act on inositol phosphates and/or phosphoinositides (PIs) as substrates to dephosphorylate the phosphate at 5 position of the inositol ring (Balla 2013). In human, it consists in a family of ten different isoenzymes (Blero et al. 2007). One of the first isoenzyme to be cloned was OCRL1 which is mutated in the Lowe syndrome and Dent-2 disease (Attree et al. 1992). Our interest in the family of PI 5-phosphatases originated from the cloning of INPP5A (i.e., type 1 inositol 1,4,5-trisphosphate 5-phosphatase), a phosphatase that can act on soluble inositol phosphates, i.e., Ins(1,4,5)P3 and Ins(1,3,4,5)P4 as substrate. At that time, its catalytic domain showed some sequence similarity with OCRL1 and another PI 5-phosphatase INPP5B that was identified by the group of Majerus. This prompted us to design degenerated primers in two conserved regions of the catalytic domains. By PCR reactions on cDNA from the rat brain and those primers, two novel "catalytic" sequences were obtained that we referred to as "51C" (Pesesse et al. 1997) and "51C new" (Drayer et al. 1996). The sequence of "51C" was in the database as "INPPL1" but was not



SHIP2, Fig. 1 SHIP2 interacting domains. SHIP2 domains and interacting partners. The SH2 domain of SHIP2 is capable of binding to phosphorylated tyrosine residue(s) of Shc, the ITIM motif of FcγRIIB receptor in B cells and to p130CAS. The IPPc domain (inositol phosphatidyl phosphatase) has two conserved motifs present in the inositol 5-phosphatase family. The pro-rich region of SHIP2 (PXXP) is recognized by the SH3 domain of the protein kinase Abl. SHIP2 localization to membrane ruffles is mediated by its C-terminal region binding to filamin. Possible PEST regions are indicated as *arrows* and putative interacting partners are indicated in *italic* in the figure. The PXXP motifs within the first PEST sequence (arrow A) are predicted to interact with SH3 domains of intersectin and RhoA. At the C-terminal of SHIP2, two PEST sequences (arrows B and C) were found. The PXXP motifs are predicted to interact with the SH3 domains of vinexin, intersectin, and Grb2. SHIP2 has an NPXY motif, e.g., NPAY. This motif could interact with PTB domains of yet unknown putative partners (e.g., Shc). The sterile alpha motif or SAM domain could interact with other SAM-containing proteins as seen for SAM domains of Eph-related tyrosine kinase receptors (EphrinA2R). SHIP2 UIM, ubiquitin-interacting motif (Xie et al. 2013)

characterized as bonafide Ins(1,4,5)P3 or PI 5-phosphatase (Hejna et al. 1995). After screening human cDNA libraries, full-length cDNAs of "51C" (Pesesse et al. 1997) and "51C new" (Drayer et al. 1996) were isolated. It appeared that the predicted full-length protein for "51C" had 1258 amino acids, but a different sequence in the N- and C-terminal part as compared to "INPPL1" that was reported in the database. In particular "51C" had a SH2 domain at the N-terminal end and a sterile alpha motif (SAM) domain at the C-terminal end of the protein (Fig. 1). At about 1 year earlier, the sequence of SHIP (SH2 domain containing inositol polyphosphate 5-phosphatase type 1) was identified in different laboratories (Damen et al. 1996). This protein was known as a tyrosine-phosphorylated protein identified on SDS gels and largely present in immune cells (particularly macrophages and B cells). As "51C" and SHIP showed 62% sequence identity in the catalytic domain and as both isoenzymes showed the

presence of a SH2 domain, "51C" was referred to as SHIP2 (SH2 domain containing inositol phosphate 5-phosphatase type 2) and "51C new" to as SHIP (also called SHIP1). Contrary to SHIP (SHIP1), SHIP2 was largely expressed in both hematopoietic and non-hematopoietic cells. This was demonstrated, thanks to an antibody made against SHIP2 C-terminal peptide. SHIP2 also shows the presence of proline-rich sequences at both N-terminal and C-terminal end (Fig. 1). A single NPXY site, target of tyrosine phosphorylation, was also present at the C-terminal end (Pesesse et al. 1997).

Two years later, SHIP2 was also identified by mass spectrometry as a 155-kDa tyrosine-phosphorylated protein associated with src homologous and collagen gene (SHC) from p210 (bcr/abl)-expressing hematopoietic cells (Wisniewski et al. 1999).

Catalytic Activity

By comparing different PIs, major substrate of SHIP2 is PI(3,4,5)P3 that is dephosphorylated to PI(3,4)P2 (Giuriato et al. 2002). Once PI(3,4)P2 is produced in cells, it can interact with PH- or PX-domain-containing proteins, some of which being specific for interacting with this lipid (e.g., TAPP1). Therefore SHIP2 could be very important to locally produce a lipid second messenger. For example, it was reported that PI(3,4)P2, produced by SHIP2, could instigate focal adhesions to generate podosomes (Oikawa and Takenawa 2009). The formation of PI(3,4)P2 is cell type dependent and will vary according to tissue/cell PI(3,4)P2 4-phosphatase activities. Although SHIP2 main substrate is considered to be PI(3,4,5)P3, PI(4,5)P2 could be also substrate as shown in isolated enzyme (Giuriato et al. 2002) and in intact cells (Elong Edimo et al. 2016; Nakatsu et al. 2010). The enzyme also recognizes Ins(1,3,4,5)P4 as substrate but with lower catalytic activity (Pesesse et al. 1998) as compared to the ubiquitous type 1 Ins(1,4,5)P3 5-phosphatase (INPP5A). Ins(1,3,4,5)P4 is unlikely to be a physiological substrate of SHIP2.

SHIP2 Functions Evaluated In vivo in Genetically Modified Mice

After human SHIP2 cDNA was obtained, the mouse orthologue was cloned and a first knockout mice model generated. This model resulted from the deletion of a 7.3-kilobase genomic mouse DNA fragment (Clement et al. 2001, 2005). Unfortunately, in addition to exons 19–29 of the *SHIP2* gene, the third (and last) exon of the *Phox2a* gene was also deleted which could conduct in a potential mixed mouse phenotype. Two new constructs resulted in two novel SHIP2 mutated mice that were afterwards generated independently in different laboratories (Dubois et al. 2012; Sleeman et al. 2005). The mice were viable and fertile but showed a decrease in body weight and length (i.e., cell growth). The mice exhibited a rounded head and a shortened snout associated with a rounded and shortened skull. One of the mouse models, expressing a germline catalytically inactive SHIP2 protein, had major defects in development of the muscle, adipose tissue, and female genital tract. Lipid metabolism and insulin secretion were also affected in these mice, but glucose tolerance, insulin sensitivity, and insulin-induced PKB phosphorylation were not (Dubois et al. 2012). In other studies, evidence has been produced to consider SHIP2 as a possible target in type 2 diabetes: by the use of a dominant-negative SHIP2 expressed in liver, inhibition of endogenous SHIP2 improves glucose metabolism and insulin resistance in the diabetic db/db mice (Sasaoka et al. 2006). Whether this effect is SHIP2 specific or could be also observed for other PI 5-phosphatase(s) remains to be established.

The Impact of SHIP2 on PKB Activity

Many studies established that SHIP2, as does PTEN, may influence PKB activity essentially by recognizing PI(3,4,5)P3 as substrate. The impact of SHIP2 on PKB activity is very much cell type dependent. For example, in mouse fibroblasts, PKB activity or PKB phosphorylation (on Ser473 or Thr311 residues) was upregulated

in mouse embryonic fibroblasts deficient for SHIP2 as compared to control cells (Blero et al. 2005). This follows PI(3,4,5)P3 accumulation which was upregulated too in serum-stimulated SHIP2-depleted cells. In this model, PI(3,4)P2 was not detectable as probably rapidly degraded by PI 4-phosphatases. In other cells, PKB activity was downregulated when SHIP2 was repressed. This was observed in colorectal cancer cell lines: PKB phosphorylation was reduced in shSHIP2-derived HCT116 cells as compared to control cells without any change in cell proliferation between the two types of cells (Hoekstra et al. 2016). This could be interpreted as the requirement of PI(3,4)P2 production for full activation of PKB in addition to PI(3,4,5)P3 and suggests that SHIP2, in this model, could have a tumor-initiating role through PKB activation. This contrasts with the ability of SHIP2 to lower PKB activity in PTEN-null glioblastoma U-87 (Taylor et al. 2000) or 1321N1 cells (Elong Edimo et al. 2016). Finally, SHIP2 can also target the MAP kinase pathway. This was reported, for example, in zebrafish and *in vivo*. Inhibiting the expression of SHIP2 in zebrafish leads to an increase in FGF-mediated signaling, including activated MAP kinase signaling (Jurynec and Grunwald 2010).

Understanding SHIP2 Function by Identifying Interactors

In human platelets, thrombin rapidly stimulated SHIP (SHIP1) translocation to the actin cytoskeleton (Giuriato et al. 1997). SHIP2 also shows this effect; however, by comparing the two phosphatases, SHIP2 had a higher affinity for the cytoskeleton (Giuriato et al. 2003). SHIP2-binding partners include a large number of cytoskeletal proteins identified in many different cell models. In this context the actin-binding protein, filamin-A, was one of the first isolated partners of SHIP2 in COS-7 cells (Dyson et al. 2001). The EGF receptor and many other tyrosine-phosphorylated associated receptors (e.g., the FGF or PDGF receptor) were also identified as directly or indirectly interacting with SHIP2 (Erneux et al. 2011). Although direct interaction has been reported for some SHIP2 interactors [e.g., intersectin (Xie et al. 2008)], it is very likely that in many studies the interaction takes part of a complex of proteins as shown for lamellipodin or myosin 1c (Elong Edimo et al. 2016).

The integrin adhesome network components (see http://www.adhesome.org) include membrane receptors, adaptor proteins, actin-associated proteins, tyrosine kinases, phosphatases, and importantly SHIP (or SHIP1) and SHIP2. PTEN is also part of the same network. Interestingly most SHIP/SHIP2 interactors (e.g., intersectin, p130CAS, ABL, RhoA, etc.) identified by biochemical approaches are also part of the focal adhesion intrinsic or associated proteins and related network (Erneux et al. 2011). This supports a role of SHIP2 in many different cytoskeletal-associated mechanisms such as adhesion, migration (Elong Edimo et al. 2016), and also cell polarity (Awad et al. 2013).

SHIP2 Function in Opsismodysplasia

INPPL1 (also referred to as SHIP2) has been found to be mutated in opsismodysplasia (OPS) (OMIM 258480), a severe human chondrodysplasia (Below et al. 2013; Huber et al. 2013). This quite rare autosomal recessive disease is characterized by pre- and postnatal micromelia with extremely short hands and feet of affected children. Mutations in *INPPL1* cause OPS. Mutations could generate premature stop codons, splice sites, and missense mutations in the catalytic domain of SHIP2 but also in other parts of the protein (i.e., the SH2 domain reviewed in Fradet and Fitzgerald 2017). Those mutations could be either homozygous or compound heterozygous mutations. Interestingly, no parents of affected OPS individuals have features of OPS. The mechanism leading to this disease is currently unknown. The fact that mutations could occur outside of the catalytic domain suggests that SHIP2 docking properties have to be considered to account in the mechanism.

Old and New Functions of SHIP2 in Cancer Cells

Changes in the content of PIs are very often observed in cancer cells. Initial reports of Prasad et al. identified an oncogenic role of SHIP2 in breast cancer cells (Prasad et al. 2008). SHIP2 mRNA level is very often upregulated, for example, in colorectal cancer (Hoekstra et al. 2016). SHIP2 protein expression is also increased in colorectal dysplasia and carcinoma as compared to non-dysplastic tissue patients (Hoekstra et al. 2016). Kaplan-Meier survival analysis revealed that high expression of SHIP2 in colorectal cancer is significantly inversely correlated to overall survival. SHIP2 expression had also an impact on cell migration in glioblastoma: depending on the glioblastoma cell type, SHIP2 either positively or negatively modulate cell migration (Elong Edimo et al. 2016). This could be associated to SHIP2 catalytic properties: it appears that in some glioblastoma cells, SHIP2 acts as PI(4,5)P2 5-phosphatase. This is important given that PI(4,5)P2 is also critical in the control of migration and focal adhesion dynamics. Therefore, PI(3,4,5)P3, PI(3,4)P2 and PI(4,5)P2 could be affected by lowering SHIP2 expression in a given cell or by comparing high and low SHIP2 expressing glioblastoma cells (Elong Edimo et al. 2016).

By catalyzing the production of PI(3,4)P2, SHIP2 is also associated to a major control mechanism of invasion in cancer cells. Invadopodia, formed in cancer cells, are specialized structures for extracellular matrix degradation. Recent data point out the involvement of two invadopodial core proteins together with SHIP2 in the mechanism of invadopodia maturation: firstly, the scaffold Tks5 is a target protein for SHIP2 producing PI(3,4)P2 (Sharma et al. 2013). PI(3,4)P2 bound to Tks5 generates a protein complex that anchors the actin nucleation process. Secondly, SHIP2 recruits Mena, an Ena/VASP family actin regulatory protein, to elongate newly nucleated actin filaments. This completely modifies the actin network required for membrane protrusion and further steps of invasion (Rajadurai et al. 2016).

Summary

PI 5-phosphatases participate in the balance of the intracellular concentrations of PIs which have now demonstrated second messenger functions in many human pathologies: the Lowe syndrome, OPS, diabetes, and many types of cancer. This family shows the presence of ten members among which SHIP/SHIP1 and SHIP2. SHIP2 contains N-terminal SH2 domain, a potential phosphotyrosine domain-binding sites (NPXY), N-terminal and C-terminal proline-rich regions with consensus sites for SH3 domain interactions, and a SAM domain at its C-terminal. SHIP2 is both an enzyme that recognizes PI(3,4,5)P3 and PI(4,5)P2 as substrate and also a docking protein for many different proteins and receptors (such as the EGF or FGF receptors). The connection between integrins and the cytoskeleton is mediated by a dynamic network of proteins, the integrin adhesome. SHIP2 is part of this complex. As shown in many different cancer cells, SHIP2 is important for the control of cell migration, adhesion, and invasion, partly (but not only) as PI(3,4)P2 is produced when PI(3,4,5)P3 is used as substrate. Mutations in *INPPL1* (SHIP2) cause OPS, a severe chondrodysplasia in human. Finally, in mice and in zebrafish, SHIP2 has been found to be very important *in vivo* particularly in developmental aspects.

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SHP

► Nr0b2

SHP1

► Nr0b2

SHP-1

► PTPN6

SHP2

► Tyrosine-Protein Phosphatase Nonreceptor Type 11 (PTPN11)

SHP-2

► Tyrosine-Protein Phosphatase Nonreceptor Type 11 (PTPN11)

SHPS-1

► Sirpa

SH-PTP1

► PTPN6

SHPTP2

► Tyrosine-Protein Phosphatase Nonreceptor Type 11 (PTPN11)

SH-PTP2

► Tyrosine-Protein Phosphatase Nonreceptor Type 11 (PTPN11)

SH-PTP3

► Tyrosine-Protein Phosphatase Nonreceptor Type 11 (PTPN11)

sHsp-Kinase

► Mapkap Kinase 2/3 (MK2/3)