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Review

Phosphoinositide phosphatases in cancer cell dynamics—Beyond PI3K and PTEN

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ABSTRACT

Phosphoinositides are a group of lipids that regulate intracellular signaling and subcellular biological events. The signaling by phosphatidylinositol-3,4,5-trisphosphate and Akt mediates the action of growth factors that are essential for cell proliferation, gene transcription, cell migration, and polarity. The hyperactivation of this signaling has been identified in different cancer cells; and, it has been implicated in oncogenic transformation and cancer cell malignancy. Recent studies have argued the role of phosphoinositides in cancer cell dynamics, including actin cytoskeletal rearrangement at the plasma membrane and the organization of intracellular compartments. The focus of this review is to summarize the impact of the activities of phosphoinositide phosphatases on intracellular signaling related to cancer cell dynamics and to discuss how the abnormalities in the activities of the enzymes alter the levels of phosphoinositides in cancer cells.

1. Overview—phosphoinositide metabolism in cancer cells

Phosphoinositides are components of cell membranes that are present in the inner leaflets of plasma membranes and intracellular organelles. They serve as regulators of various intracellular signaling and membrane trafficking [1] (Fig. 1A). Each phosphoinositide has its own unique subcellular localization and undergoes modifications *via* kinases and phosphatases to generate seven species of phosphoinositides: phosphatidylinositol-3-phosphate [PI(3)P], phosphatidylinositol-4-phosphate [PI(4)P], phosphatidylinositol-5-phosphate [PI(5)P], phosphatidylinositol-3,4-bisphosphate [$PI(3,4)P_2$], phosphatidylinositol-3,5-bisphosphate [$PI(3,5)P_2$], phosphatidylinositol-4,5-bisphosphate [$PI(4,5)P_2$], and phosphatidylinositol-3,4,5-trisphosphate (PIP_3) [2] (Fig. 1B). The PI 3-kinase (PI3K)–Akt signaling pathway is a crucial regulator of multiple cellular functions in response to extracellular stimuli such as growth factors, insulin, cytokines, and chemokines [3,4]. PI3Ks are classified into three groups based on their substrate specificities and structures: Class IA and IB PI3Ks phosphorylate $PI(4,5)P_2$ to generate PIP_3 *in vivo*, while Class II and Class III PI3Ks preferentially phosphorylate phosphatidylinositol to generate PI(3)P [5–7]. The hyperactivation of PI3K signaling frequently occurs in a variety of human cancers because of oncogenic mutations in Class I PI3K catalytic subunit p110α and in regulatory subunit p85α; these represent various characteristics of cancers including cell proliferation, anti-apoptosis, cell migration, and invasive phenotypes. Studies have shown that the alteration of PI3K–Akt signaling has a major impact on cancer cell metabolism including increased glycolysis (termed Warburg effect) [8] and redox metabolism [9].

PIP_3 is predominantly generated at the PM by extracellular growth factors and hormonal stimuli from $PI(4,5)P_2$ by PI3K (Fig. 1B). PIP_3 binds to, activates the PH domain of Akt, and induces cell proliferation and anti-apoptotic effects through the activation of the PI3K–Akt signaling pathway (Fig. 2A and Table 1). Abnormalities in this signaling are found in a variety of cancers. For example, *PIK3CA*, the gene that

Abbreviations: ER, endoplasmic reticulum; ERM, ezrin, radixin, and Moesin; ESCC, esophageal squamous cell carcinoma; FA, focal adhesion; FAK, focal adhesion kinase; FEME, fast endophilin-mediated endocytosis; GOLPH3, Golgi phosphoprotein 3; INPP4A, inositol polyphosphate 4-phosphatase type I; INPP4B, inositol polyphosphate 4-phosphatase type II; Lpd, lamellipodin; INPP5J, inositol polyphosphate 5-phosphatase J; INPP5K, inositol polyphosphate 5-phosphatase K; LOH, loss of heterogeneity; N-WASP, neural Wiskott–Aldrich syndrome protein; PDK1, phosphoinositide-dependent kinase 1; PH, plextrin homology; PI, phosphatidylinositol; PI(3)P, phosphatidylinositol-3-monophosphate; PI(4)P, phosphatidylinositol-4-monophosphate; PI(5)P, phosphatidylinositol-5-monophosphate; $PI(3,4)P_2$, phosphatidylinositol-3,4-bisphosphate; $PI(3,5)P_2$, phosphatidylinositol-3,5-bisphosphate; $PI(4,5)P_2$, phosphatidylinositol-4,5-bisphosphate; PIP_3, phosphatidylinositol-3,4,5-trisphosphate; PI3K, PI 3-kinase; PI4K, phosphatidylinositol 4-kinase; PIP5K, phosphatidylinositol 4-phosphate 5-kinase; PIPP, proline-rich inositol polyphosphate 5-phosphatase; PM, plasma membrane; P-Rex, phosphatidylinositol 3,4,5-trisphosphate-dependent Rac exchanger; PTEN, phosphatase and tensin homolog; PX, phox homology; SAC, suppressor of actin; SHIP1, SH2 domain-containing inositol phosphatase 1; SHIP2, SH2 domain-containing inositol phosphatase 2; SKIP, skeletal muscle and kidney enriched inositol polyphosphate phosphatase; SYNJ2, synaptojanin 2; Tks5, tyrosine kinase substrate 5

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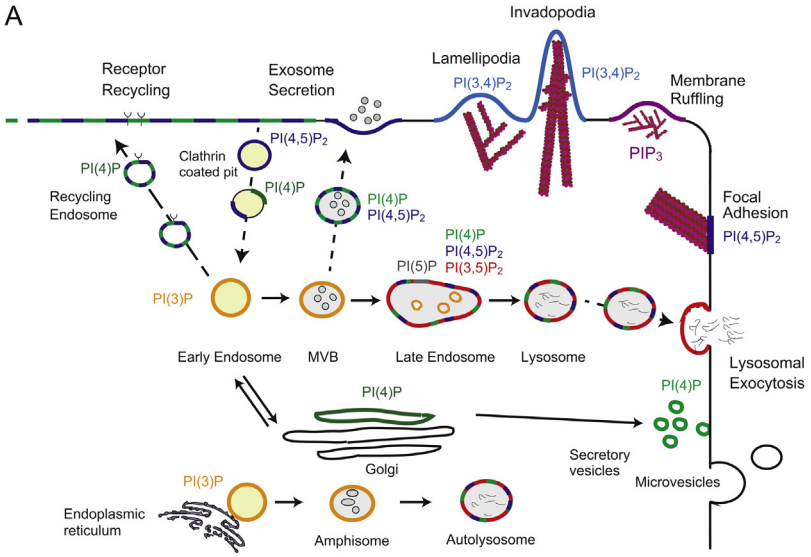

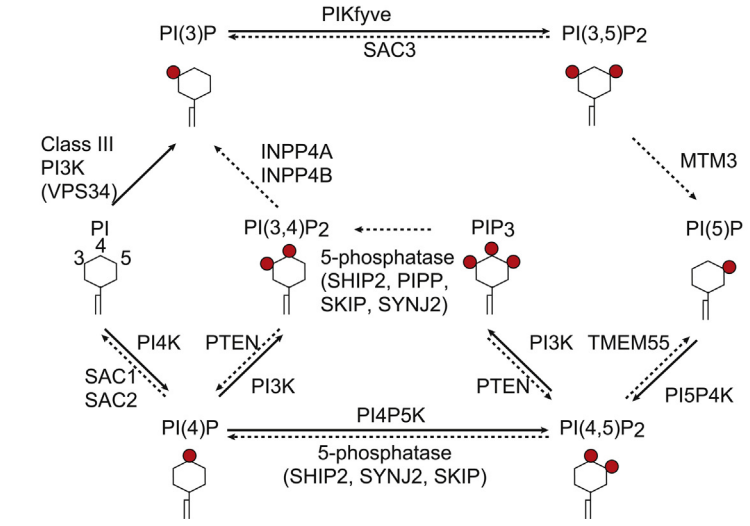

Fig. 1. Intracellular localization of phosphoinositides and the schematic representation of phosphoinositide turnover by phosphoinositide kinases and phosphatases. (A) Intracellular localization of phosphoinositides. PIP_3 and $PI(3,4)P_2$ are predominantly generated at the PM upon the activation of class I PI3K, while $PI(4,5)P_2$ and PI(4)P are identified in the late endosomes, recycling endosomes, lysosomes, and PM. $PI(4,5)P_2$ and PI(4)P are implicated in the regulation of receptor recycling and exosome secretion. PI(3)P is necessary for autophagosome formation and $PI(3,5)P_2$ mediates lysosomal exocytosis through which lysosomal enzymes are secreted out to the extracellular spaces. (B) PIP_3 is generated by PI3K and is dephosphorylated by PTEN to generate $PI(4,5)P_2$. Alternatively, PIP_3 can be hydrolyzed by 5-phosphatases (*e.g.* SHIP2, SKIP, SYNJ2) to generate $PI(3,4)P_2$. $PI(3,4)P_2$ can further be de-phosphorylated either by the 3-phosphatase activity of PTEN to generate PI(4)P or by 4-phosphatase activity to generate PI(3)P.

encodes the catalytic subunit of Class I PI3K, is mutated, activated, and amplified in various human cancers including ovarian, prostate, lung, thyroid, cervical cancers, and glioblastomas [10–13]. Phosphatase and tensin homolog deleted from chromosome 10 (PTEN), a PIP_3 3-phosphatase, is a tumor suppressor that inhibits PI3K signaling and its loss of heterozygosity (LOH) frequently occurs in a wide variety of human cancers [14,15] (Table 1). The loss of PTEN leads to increased PIP_3 and $PI(3,4)P_2$ levels and the subsequent hyperactivation of PI3K–Akt signaling pathway (Fig. 2B); hence, it is now accepted that PI3K, PIP_3, and PTEN play major roles in the regulation of cancer progression. Alternatively, PIP_3 is hydrolyzed by inositol polyphosphate 5-phosphatases to form $PI(3,4)P_2$. $PI(3,4)P_2$ is subsequently hydrolyzed by inositol polyphosphate 4-phosphatases to generate PI(3)P, which terminates PI3K/Akt signaling. The losses of the proline-rich inositol polyphosphate 5-phosphatase (PIPP), a PIP_3 5-phosphatase, and inositol polyphosphate 4-phosphatase (INPP4B), a $PI(3,4)P_2$ 4-phosphatase, respectively, were frequently identified in human cancers [16,17] (Table 1 and Fig. 2B). The loss of INPP4B increases $PI(3,4)P_2$ levels, while the loss of PIPP leads to a decrease in $PI(3,4)P_2$ level and an increase in PIP_3 levels (Fig. 2B). The downregulation of multiple phosphatases such as PIPP, INPP4B, and PTEN that disrupts hydrolysis of PIP_3 and $PI(3,4)P_2$ is a characteristic of some cancer cells. The abnormalities in the expression of multiple phosphoinositide phosphatases may have a cumulative influence on phosphoinositide levels and their downstream signaling. Therefore, the role of phosphoinositides [*e.g.* $PI(3,4)P_2$, $PI(4,5)P_2$, and PI(4)P] and phosphoinositide phosphatases beyond PIP_3 and PTEN should be taken into account in the consideration of the regulatory mechanisms of cancer progression. The roles of PI3K and PTEN in cancer signaling and their clinical implication have been described in many reviews; therefore, we discuss the role of phosphoinositides and other phosphoinositide phosphatases in cancer cell dynamics such as cell migration and invasion.

2. Regulation of cancer cell signaling and dynamics by phosphoinositides

PI(4)P is enriched at the PM and in the Golgi apparatus [18]. It also exists in secretory vesicles, late endosomes, recycling endosomes, autophagosomes, lysosomes [18–21], and in membrane contact sites such as endoplasmic reticulum (ER)–PM junction [22,23] (Fig. 1A). PI(4)P is

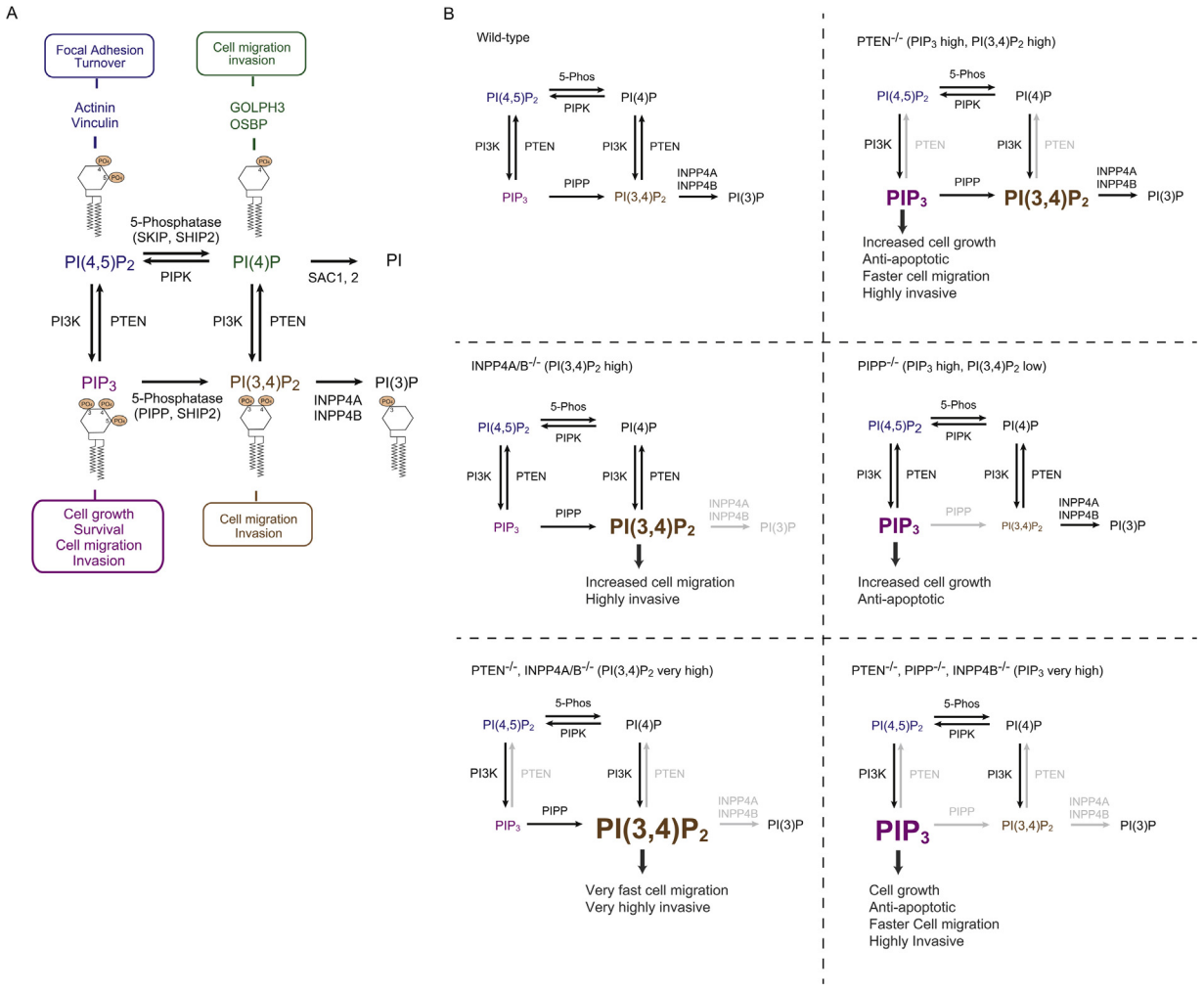

Fig. 2. Alterations in phosphoinositide levels by phosphoinositide phosphatases. (A) The effector proteins that bind to PIP_3, $PI(3,4)P_2$, $PI(4,5)P_2$, and PI(4)P at the PM and in the intracellular organelles related to cancer cell signaling and cancer cell dynamics are shown. PIP_3 and $PI(3,4)P_2$ bind to the PH domain of Akt and PDK-1 that mediates the activation of cancer cell signaling. PIP_3 also facilitates cancer cell migration by binding to Rac1 and GAB1/2. In contrast, $PI(4,5)P_2$ regulates the rearrangement of actin structures by binding with vinculin and talin. (B) The proposed model representing the alterations in phosphoinositide levels and the impacts on cancer cell phenotype *via* the inactivation of PTEN, INPP4A, and PIPP.

mainly generated directly from PI by PI 4-kinases. The PI4KIIα expression is upregulated in a variety of human cancers and it is especially high in malignant melanoma, breast cancer, bladder transitional cell carcinoma, and thyroid papillary carcinoma [24]. The gene encoding PI4KIIIβ is also frequently amplified in breast cancers [25] and approximately 20% of primary human breast tumors show an increase in PI4KIIIβ protein expression [26]. Silencing of PI4KIIIβ in MDA-MB-231 and Hs578t highly invasive breast cancer cells increased cell–cell adhesion and decreased expression of CD44 variant isoforms and cell invasion [27,28]. PI4KIIα generates endosomal PI(4)P and is required for EGF receptor sorting at early endosomes that can affect growth factor signaling in cancer cells [29] (Fig. 1B).

$PI(3,4)P_2$ is considered as the intermediate lipid for the removal of PIP_3 by 5-phosphatases. However, accumulating evidence demonstrates that $PI(3,4)P_2$ is a signaling molecule that directs a distinct branch of the PIP_3-dependent pathway involved in the regulation of a variety of cellular processes, including autoantibody production, insulin sensitivity, neuronal dynamics, macropinocytosis, fast endophilin-mediated endocytosis (FEME), membrane ruffling, lamellipodia, and invadopodia. A number of proteins that specifically bind to $PI(3,4)P_2$, including the tandem PH domain-containing proteins (TAPP1 and TAPP2) and lamellipodin (Lpd), have been characterized. Some PIP_3-binding proteins can also bind to $PI(3,4)P_2$, such as Akt and PDK1 which mediate cell growth and gene transcription of cancer cells (Table 2). The loss of INPP4B leads to an increase in $PI(3,4)P_2$ level decrease in PIP_3 level in PTEN-null triple-negative breast cancer cells [30]. Although $PI(3,4)P_2$ at the PM predominantly derives from PIP_3 dephosphorylation [31,32], it is, in part, synthesized from PI(4)P by Class II PI3Ks mediated clathrin-dependent endocytosis in early endosomes [29].

$PI(4,5)P_2$ is most abundant at the PM, where it regulates actin cytoskeletal rearrangement [33], and recent studies have shown its presence at ER, Golgi apparatus, autophagosomes, caveolae, lysosomes, and endosomes [34–36]. $PI(4,5)P_2$ binds to the effectors (*e.g.* ERM, vinculin, α-actinin, and gelsolin) located at focal adhesions (FAs) and mediates actin cytoskeletal rearrangement such as the turnover of FA (Table 2). The generation of $PI(4,5)P_2$ in FAs by phosphatidylinositol 4-phosphate 5-kinase type Iγ (PIP5KIγ) triggers the activation of focal adhesion kinase (FAK), a major inducer of cancer cell invasion and metastasis, and induces the clustering of FAK to PM [37]. The reduction in $PI(4,5)P_2$ level at the PM by PLCβ1 releases the $PI(4,5)P_2$-binding protein cofilin from its inactive membrane-bound form into the cytosol where it mediates actin turnover, thereby increasing cellular migration and metastasis of breast cancer cells [38]. The effect of $PI(3,4)P_2$ and $PI(4,5)P_2$ at the PM on the cytoskeletal dynamics in cancer cells is discussed as follows.

Table 1
Human phosphoinositide phosphatases associated with cancers.

Approved gene symbol	OMIM number	Location	Approved name	Phosphoinositide phosphatase catalyzed	Developmental disease (OMIM number)	Mutated or loss of heterogeneity in cancer	Downregulated expression in cancer	Upregulated expression in cancer tissue
PTEN	601728	10q23	Phosphatase and tensin homolog (MMAC1, TEP1)	$PI(3,4)P_2 \rightarrow PI(4)P$ $PIP_3 \rightarrow PI(4,5)P_2$	Cowden disease (158350) Lhermitte–Duclos syndrome (158350) Macrocephaly/autism syndrome (605309) Glioma susceptibility 2 (613028)	Lost or mutated in a variety of cancers including Breast, Colon, Prostate, Endometrial, Ovarian cancer, and Glioblastoma Cancer [113]	Downregulated in a variety of cancers including Breast, colorectal, multiple myeloma, and gastric carcinoma [231–234]	
INPP4A	600916	2q11.2	Inositol polyphosphate-4-phosphatase, type I, 107 kDa	$PI(3,4)P_2 \rightarrow PI(3)P$		Mutated in Ductal adenocarcinoma [235]	Oesophageal squamous cell carcinoma [164,173] Hepatocellular carcinoma [174] Lung cancer [164] Bladder cancer [176] Pancreatic cancer [163]	
INPP4B	607494	4q31.1	Inositol polyphosphate-4-phosphatase, type II, 105 kDa	$PI(3,4)P_2 \rightarrow PI(3)P$		Lost in Oesophageal adenocarcinoma [178], Breast cancer [16], Ovarian cancer [16], and Melanoma [162] Mutated or lost in Prostate cancer [117,166]	Melanocytic tumors [32]	Colon cancer [44] Breast cancer [43]
SYNJ2	609410	6q25.3	Synaptojanin 2 (INPP5H)	$PI(4,5)P_2 \rightarrow PI(4)P$				Early colorectal cancer [118] Breast cancer [165]
INPP5J	606481	22q12.2	Inositol polyphosphate-5-phosphatase J (PIPP), PIB5PA	$PI(4,5)P_2 \rightarrow PI(4)P$ $PIP_3 \rightarrow PI(3,4)P_2$		Lost in Melanoma and Breast cancer [141,144,145]	Melanoma [141] Estrogen receptor-negative breast cancers [142,143]	
INPP5K	607875	17p13.3	Inositol polyphosphate-5-phosphatase K, SKIP	$PI(4,5)P_2 \rightarrow PI(4)P$ $PIP_3 \rightarrow PI(3,4)P_2$	Muscular dystrophy, congenital, with cataracts and intellectual disability (617404)		Lung cancer [155] Glioblastoma [116]	Endometrial Carcinoma [152] CPT1-deficient prostate cancer [153] Renal cancer [154] Glioblastoma [116]
INPP5D	601582	2q37.1	Inositol polyphosphate-5-phosphatase, 145 kDa (Src homology-2 domain-containing inositol 5-phosphatase 1, SHIP1)	$PI(4,5)P_2 \rightarrow PI(4)P$ $PIP_3 \rightarrow PI(3,4)P_2$		Mutated in acute myeloid leukemia [120] Lost in Neurofibromatosis type 1 [236]	Adult T cell leukemia/lymphoma [237] Natural killer cell lymphoma [238]	Hodgkin lymphoma [239] Embryonic carcinoma [240] Intraductal papillary mucinous neoplasm [241]
INPPL1	600829	11q23	Inositol polyphosphate phosphatase-like 1, SHIP2	$PI(4,5)P_2 \rightarrow PI(4)P$ $PIP_3 \rightarrow PI(3,4)P_2$	Opsismodysplasia (258480)		Gastric cancer [126] Aggressive squamous cell carcinoma [127]	ER-negative breast cancer [130] Hepatocellular carcinoma tissue [131] Colorectal cancer [132] Non-small cell lung cancer [115] Laryngeal squamous cell carcinoma [133]
INPP5E	613037	9q34.3	Inositol polyphosphate-5-phosphatase, 72 kDa (Joubert syndrome locus 1, JBTS1)	$PI(3,5)P_2 \rightarrow PI(3)P$ $PI(4,5)P_2 \rightarrow PI(4)P$ $PIP_3 \rightarrow PI(3,4)P_2$	Joubert syndrome 1 (213300) Mental retardation, truncal obesity, retinal dystrophy, and micropenis (610156)		Colorectal cancer [117]	

(*continued on next page*)

Table 1 (*continued*)

Approved gene symbol	OMIM number	Location	Approved name	Phosphoinositide phosphatase catalyzed	Developmental disease (OMIM number)	Mutated or loss of heterogeneity in cancer	Downregulated expression in cancer	Upregulated expression in cancer tissue
SAC1M1L	606569	3p21.3	SAC1 suppressor of actin mutations 1-like, hSac1, SAC1	PI(4)P → PI			Breast cancer [28]	
INPP5F	609389	10q26.13	Inositol polyphosphate-5-phosphatase F,Sac2, SAC2	PI(4)P → PI			Chronic lymphocytic leukemia [191]	

The activation of PI3K (p110α and p110β) or the inactivation of PTEN leads to increased PIP_3 levels and the hyperactivation of PI3K–Akt signaling pathway in a variety of cancer cells including luminal breast cancer cells, and treatment with the inhibitors for p110α and p110β leads to tumor regression [39]. Electrospray ionization (ESI) mass spectrometric analysis revealed that a specific PIP_3 subspecies consisting of 38:4 acyl group is predicted in the assessment of susceptibility to PI3K/mTOR dual inhibitor—gedatolisib [37]. Besides Akt activation, PIP_3 directly binds to a number of effector molecules that regulates cancer cell proliferation and cancer cell migration (*e.g.* P-Rex1/2, PDK1, SWAP-70, Tiam1, and WAVE1-3) [40–43] (Table 2). Recent studies have demonstrated that PIP_3 activates multiple downstream effectors *via* PH domain in cancer cell proliferation and migration. PIP_3 recruits BTK to the PM; the activation of PLCγ by BTK triggers calcium mobilization and PKC signaling which then activates NFκB- and NFAT-dependent transcription [44]. Btk also activates Cdc42 and Rac, which control actin remodeling [45]. PDK1 is a constitutively active kinase with two major regulatory domains: a C-terminal PH domain that binds PIP_3 and a PIF-binding pocket within its catalytic domain [46]. The PH domain allows PDK1 to co-localize with Akt at the PM and phosphorylate its activation loop through PIP_3-binding [47]. PDK1 overexpression is frequently observed in a variety of cancers (*e.g.*, prostate and breast cancers), with gene copy numbers that are frequently associated with poor prognosis [48]. PDK1 axis can substitute for Akt in cancer cell survival, migration, and growth, and has emerged as a mechanism of cancer cell resistance to PI3K and Akt inhibitors [49]. An important PIP_3-dependent event, which primarily occurs in cancer cells independently of Akt is Rac (Rac1-3)-dependent actin cytoskeletal rearrangement. PI3K functions as an upstream activator of Rac by stimulating PIP_3-sensitive Rac-GEFs, which include P-Rex1/2, and Sos1 [50,51] (Table 2). The PH domain of Rac-GEFs interacts with PIP_3, which subsequently activates Rac and regulates cytoskeleton reorganization by activating Rac1 effectors, such as p21-activated kinases (PAKs) and Wiskott–Aldrich syndrome protein family verprolin homologs (WAVEs) [52,53]. The expression of P-Rex1 is upregulated in breast cancer, metastatic prostate cancer, and melanoma, and it activates Rac1 to promote cell migration and invasion through lamellipodia formation [54]. The crosstalk between PI3K/Akt signaling axis and Wnt/β-catenin signaling are associated with cancer progression, epithelial-mesenchymal transition (EMT), and metastasis [55] (Table 2). The abnormal activation of PI3K/Akt pathway leads to the activation of the Wnt/β-catenin pathway through the accumulation of nuclear β-catenin by inhibiting GSK-3β in a variety of cancers including gastric, melanoma, breast, and prostate cancer cells [56,57]. SWAP switching B-cell complex 70 kDa subunit (SWAP-70) has an oncogenic function whose mutations are identified in pancreas, large intestine and ovary cancers [58–61]. Expression of SWAP-70 is directly regulated by tumor-suppressive miR-145 in prostate cancer [62]. SWAP-70 is involved in actin cytoskeletal rearrangement through its interaction with Rac1, F-actin, and PIP_3 at the leading edge to regulate cell–cell adhesion, migration and invasion of various type of cells [58,63–68] (Table 2). Together, these signals govern the survival, differentiation, proliferation, and migration. Other phosphoinositides also make an impact on cancer cell phenotype. PI(3)P is localized primarily at the early endosomes and autophagosomes [21,69,70] (Fig. 1). Class III PI3K Vps34 generates PI(3)P and recruits protein complexes such as WIPI1, for phagophore formation (Table 2). PI(5)P is predominantly generated from $PI(3,5)P_2$ by myotubularin-related phosphatase 3 (MTMR3) and serves as a substrate for Type II PI(5)P 4-kinase to generate $PI(4,5)P_2$ [71,72] (Fig. 1B). It helps to regulate actin cytoskeletal rearrangement during cell migration and invasion through the activation of Rac1 in cancer cells [72,73]. Phosphatidylinositol-3,5-bisphosphate [$PI(3,5)P_2$] localizes at multi-vesicular endosomes, endolysosomes, and autophagosomes [74] (Fig. 1B). It helps to regulate lysosomal exocytosis that secretes out lysosomal enzymes to extracellular spaces dependent on calcium-influx through Transient receptor potential mucolipin 1

Table 2
Phosphoinositide-binding proteins related to cancer cell signaling and dynamics.

Phosphoinositides	Effector	Localization	Function	Amplified in cancer
PI(3)P	WIPI1, 2	ER	Autophagy formation	Breast, ovarian and prostate
	PIKfyve	Endosome	Maturation of endosome and autophagosomes	Breast
PI(4)P	GOLPH3	Golgi	Golgi membrane identity	Breast
	OSBP1, ORP5/8	ER–PM junction	Cell proliferation	Pancreatic
$PI(3,5)P_2$	TRPML1	Lysosome	Lysosomal exocytosis	n.d.
$PI(3,4)P_2$	Tks5/FISH	Invadopodia	Invasion	Breast, colon, lung, prostate
	Lamellipodin	Lamellipodia	Cell migration	Breast
$PI(4,5)P_2$	N-WASP	Invadopodia	Invasion	Esophageal squamous cell carcinoma, breast, colon
	Ezrin Radixin Moesin	Adherens junction	Cell–cell adhesion, migration	Prostate, lung, breast
	Vinculin	Focal adhesion	Migration, invasion	Prostate
	Talin	Focal adhesion	Migration, invasion	Oral squamous cell carcinoma
	α-Actinin	Stress fiber, focal adhesion	Migration, invasion	Breast, colon
	Formin	Filopodia	Invasion	Colon, ovarian
	Gelsolin	Actin filaments	Proliferation, migration, invasion	Colon, oral carcinoma
	Arf6	Endosome	Migration, invasion	Prostate, lung
	Dynamin1–3	Clathrin-coated pit	Proliferation, invasion, metastasis	Prostate, colon, breast
$PI(3,5)P_2$ and $PI(4,5)P_2$	Cortactin	Invadopodia	Cell migration, invasion	Breast
$PI(3,4)P_2$ and PIP_3	Akt1,2	PM	Cell growth, anti-apoptosis, cell cycle, glucose metabolism	Breast, prostate, melanoma
	P-Rex1, 2	PM	Cell growth, metastasis	Breast, prostate, melanoma
	PDK1	PM	Cell growth, gene transcription	Breast, prostate, melanoma
PIP_3	Btk	PM	Cell malignancy	Prostate, B-cell lymphoma
	GAB1/2	PM	Proliferation, migration	Breast, ovarian, gastric
	GRP1	PM	Cancer progression, tumor angiogenesis	Colon
	SWAP-70	Leading edge	Cancer progression, invasion, migration	Pancreas, prostate, large intestine, ovarian
	Tiam1	Cell–cell contact, membrane ruffle	Invasion, metastasis	Hepatocellular, colon, breast
	WAVE1-3	Membrane ruffles	Metastasis, migration	Gastric, breast

ER, endoplasmic reticulum; PM, plasma membrane; n.d., not detected.

(TRPML1) channel (Table 2). The excessive release of active lysosomal hydrolases and metalloproteinases compromises the extracellular matrix, thereby facilitating cancer cell migration, invasion, and metastasis [75–78] (Fig. 1A).

3. The influence of phosphoinositide phosphatases on cancer cell dynamics

3.1. PTEN

Intracellular signaling, membrane dynamics, and cytoskeletal rearrangement are dependent on a variety of phosphoinositides as earlier described [79]; hence, alterations in phosphoinositide metabolism *via* LOH, altered expressions, and mutations in genes encoding phosphoinositide kinases and phosphatases are found in tumors and cancer cells (Table 1). PTEN is one of the major tumor suppressors involved in human cancer malignancy. Somatic homozygous mutations and deletions of *PTEN* gene (OMIM 601728, chromosome 10q23.31) are detected in a variety of human cancers, such as glioblastoma [80,81], oligodendroglioma (601728.0029) [82], primary prostate cancer (43%) (601728.0018 and 0019) [83], squamous cell carcinoma (601728.0031) [84], malignant melanoma (601728.0024-0026) [85–87], lung (4-8%) [83,88,89], sporadic endometrial carcinoma (93%) [88], bladder cancer (32%) [90], and breast cancers [89,91–100] (Table 1). PTEN is a 3-phosphatase for PIP_3 [101], whose mutations are identified in Cowden disease (158350) [84,102], and macrocephaly/autism syndrome (605309) [103,104]. The loss of the normal *PTEN* gene copies in cancer cells causes an increase in Akt phosphorylation by an increase in PIP_3 content [105]. In heterozygous $Pten^{+/-}$ mice, the susceptibility to spontaneous tumor formation is associated with an increased Akt activity [106]. Recent findings show that PTEN functions as a major $PI(3,4)P_2$ phosphatase in breast cancer cells and the depletion of PTEN increases $PI(3,4)P_2$ level in a mouse model of prostate cancer [107,108]. Taken together, PTEN functions as a 3-phosphatase for PIP_3 and/or $PI(3,4)P_2$, which contribute to cancer cell phenotypes (Figs. 1B and 2A). The physiological role and molecular implications including the transcriptional and post-transcriptional regulation of PTEN have been described in many studies [109–113].

3.2. Phosphoinositide 5-phosphatases, SHIP1 (INPP5D), SHIP2 (INPPL1), PIPP (INPP5J), SKIP (INPP5K), INPP5E, and SYNJ2

Phosphoinositide 5-phosphatases are a group of ten enzymes that de-phosphorylate the 5-phosphate of $PI(4,5)P_2$ and PIP_3 to generate PI(4)P and $PI(3,4)P_2$, respectively (Fig. 2A). They can act either as anti-oncogenic or as pro-oncogenic because these phosphoinositides influence cancer cell proliferation and dynamics at different steps. Among them, the alterations in the genes encoding SH2 domain-containing inositol phosphatase 1 and 2 (SHIP1 and 2) [114,115], skeletal muscle and kidney-enriched inositol polyphosphate phosphatase (SKIP) [116], proline-rich inositol polyphosphate 5-phosphatase (PIPP) [17], INPP5E [117], and synaptojanin 2 (SYNJ2) [118] have been found in human cancers. SHIP1 dephosphorylates PIP_3 and $PI(4,5)P_2$ and therefore possess both pro-oncogenic and anti-oncogenic roles [119]. SHIP1 functions as a tumor suppressor in acute myeloid leukemia (AML) [120]. Loss of *SHIP1* (OMIM 601582) causes myeloid lung consolidation and inflammation of the ileum, a phenotype that mimics human Crohn's disease [121]. The expression of SHIP1, but not an AML-derived mutant, suppresses the growth of myeloid leukemia cells transplanted in a xenograft transplantation model [120]. In contrast, the treatment of hematopoietic cancer cells with a SHIP1 inhibitor resulted in reduced growth and increased apoptosis, suggesting that SHIP1 has proto-

oncogenic activity [122]. SHIP2, also referred to as inositol polyphosphate phosphatase-like 1 (INPPL1, OMIM 600829), dephosphorylates PIP_3 and $PI(4,5)P_2$, and their homozygous or heterozygous mutations (600829.0001-0009) causes opsismodysplasia (258480) [123–125]. SHIP2 has both pro-oncogenic and anti-oncogenic functions. SHIP2 functions as anti-oncogene whose expression is frequently down-regulated in gastric cancer and aggressive squamous cell carcinoma, which in turn promotes tumorigenesis and proliferation of cancer by the activation of PI3K/Akt signaling [126,127] (Table 1). Mechanistically, SHIP2 de-phosphorylates $PI(4,5)P_2$ and inhibits cell migration through the regulation of $PI(4,5)P_2$-dependent inhibition of FA dynamics in PTEN-deficient 1321 N1 glioblastoma cell lines [128,129]. In contrast, SHIP2 functions as oncogene and its expression is increased in a variety of cancers including ER-negative breast (85%) [130], hepatocellular carcinoma tissue ($p = 0.0014$) [131], colorectal ($p < 0.001$) [132], non-small cell lung cancer ($p < 0.05$) [115], and laryngeal squamous cell carcinoma ($p < 0.001$) [133] (Table 1). High SHIP2 protein expression in non-small cell lung cancer was associated with lymph node metastasis ($p = 0.042$), TNM stage ($p = 0.036$), and 5-year survival rate ($p = 0.046$) [115]. The COSMIC data showed an elevated expression of SHIP2 protein in the breast (11.0%), ovary (13.9%), esophagus (15.2%), and lung cancer (6.28%). Mechanistically, SHIP2 positively regulates cell migration and metastasis in basal-like MDA-MB-231 breast cancer cells [134,135]. It localizes at membrane ruffles, FAs, and invadopodia, where it mediates cancer cell invasion (Fig. 3A–C). As PIP_3 is the preferred substrate, SHIP2 generates $PI(3,4)P_2$ at lamellipodium and induces the development of mature FAs in MDA-MB-231 breast cancer cells [108] (Fig. 3A). SHIP2 generates $PI(3,4)P_2$ at invadopodium, where it recruits Mena, an Ena/VASP family protein, to stabilize and mature into a functional invadopodium [136,137] (Fig. 3B). Thus, the pro-oncogenic and anti-oncogenic roles of SHIP2 in the regulation of cancer development, including actin remodeling, cell adhesion and spreading, receptor endocytosis [129], and apicobasal polarity [138] in specific cancer cell types are growing areas of research [139].

PIPP, also known as inositol polyphosphate-5-phosphatase J (INPP5J), has two proline-rich domains at the N- and C-termini, a central catalytic domain, and a SKIP C-terminal homology (SKICH) domain. PIPP dephosphorylates PIP_3, resulting in $PI(3,4)P_2$ generation (Fig. 2B). PIPP is one of the ten highest ranked genes for predicting the outcomes in human breast cancer [140]; PIPP mRNA expression is lower (25%) in melanoma than in nevi [141] and in estrogen receptor-negative breast cancers than in estrogen receptor-positive cancers [142,143]. The *INPP5J* gene (OMIM 606481) is located on chromosome 22q12, and the allelic loss of this region frequently occurs in ~30% of breast cancers [144,145]. The LOH of D22S1150 and D22S280 mapped

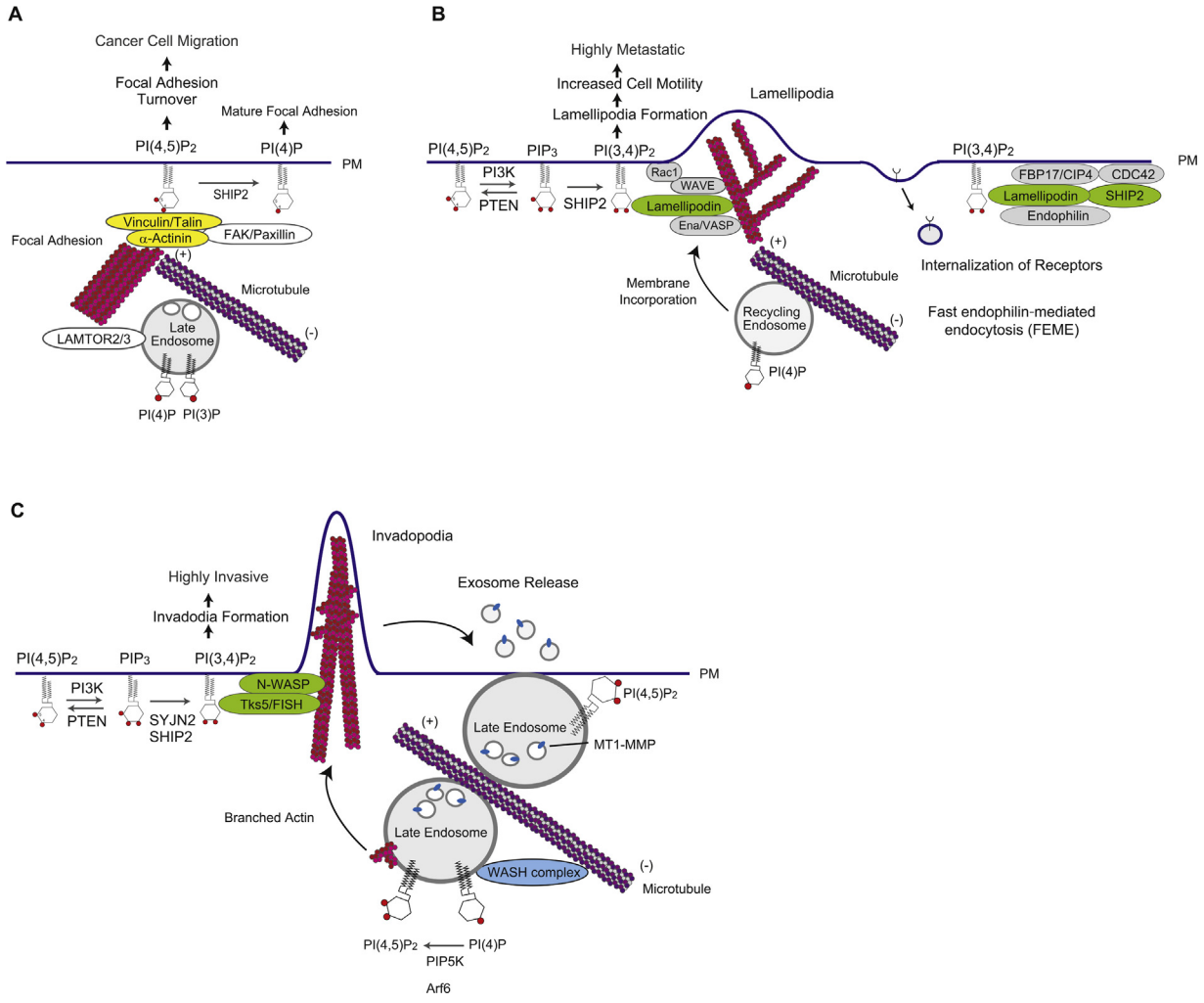

Fig. 3. Schematic representation of the interplay between phosphoinositides and phosphoinositide phosphatases in the regulation of the FA turnover (A), lamellipodia formation (B), and invadopodia formation (C). $PI(4,5)P_2$ stabilizes actin bundling, leading to mature FA formation (A). In contrast, $PI(3,4)P_2$ at the PM recruits Tks5/FISH and Lpd and triggers the formation of lamellipodia (B) and invadopodia (C). It should be noted that $PI(4,5)P_2$-positive MVB-containing late endosomes supply lipid and protein components (*e.g.* branched actin) necessary for invadopodia formation and that PI(4)P-positive recycling endosomes supply membrane lipids required for lamellipodia formation.

close to the PIPP gene, has been detected in 41% and 45% of breast carcinomas, respectively [146]. In breast tumors where PIPP is inactive or suppressed, PIP_3 levels are elevated and Akt1-dependent tumor growth and metastasis are promoted [17]. The expression of PIPP, PTEN, and INPP4A is simultaneously suppressed in cancer cells, which leads to the increase in PIP_3 level and the hyperactivation of PI3K–Akt signaling pathway [141] (Fig. 3B). In contrast, the overexpression of PIPP in ESCC cell lines decreases PIP_3 and Akt phosphorylation and concomitantly suppresses cell proliferation and anchorage-independent growth [147].

SKIP, also referred to as inositol polyphosphate-5-phosphatase K (INPP5K), has an N-terminal 5-phosphatase domain and a SKICH domain at the C-terminus, which dephosphorylates 5-phosphate of PIP_3 and PI(4,5)P_2 *in vitro* [148]. INPP5K negatively regulates insulin-stimulated PI3K–Akt signaling and increases insulin sensitivity in the skeletal muscle of heterozygous mice [149]. Recently, homozygous (607875.0001-0004) and compound heterozygous mutations (607875.0005-0007) in the *INPP5K* gene (OMIM 607875) were found in families with congenital muscular dystrophy, cataracts and intellectual disability (MDCCAID; 617404) [150,151]. The *INPP5K* gene is located at 17p13.3, which is frequently deleted in various tumors including endometrial carcinoma [152]. SKIP expression is higher in endometrial carcinoma than in non-malignant endometrium ($p < 0.0003$) [152], in carnitine palmitoyltransferase (CPT1)-deficient prostate cancer than in normal tissue ($p = 7.74e-6$) [153], and in renal cancer [154] (Table 1). However, it is decreased in lung cancer [155], but is increased and decreased in PTEN-deficient glioblastoma cells [116] (Table 1). This is in line with the large-scale microarray results that showed a higher or lower SKIP expression in glioblastoma than in normal tissue [156,157]. INPP5K gene is one of the three most significant tumor suppressor genes, and its expression is markedly decreased in lung cancer [155]. COSMIC data showed that SKIP expression decreased in lung cancer (9.52%), increased in prostate cancer (4.82%), increased (9.77%) and decreased (8.27%) in ovary cancer in comparison with that in normal tissues.

INPP5E (pharbin, PPI5PIV) is a 5-phosphatase and its mutation causes Joubert syndrome (213300)—a group of disorders characterized by midbrain-hindbrain malformation and is associated with ciliopathies [158]. In colorectal cancer, the upregulation of miR-598 expression promotes cell proliferation and cell cycle progression by suppressing *INPP5E* gene (OMIM 613037) expression [117].

Synaptojanin 2 (SYNJ2) harbors two distinct phosphatase domains: SAC1-like and 5-phosphatase domains which hydrolyze PI(4,5)P_2 and PIP_3 *in vitro* [159]. SYNJ2 controls clathrin-mediated endocytosis and cell growth [118,160,161]. SYNJ2 is a regulator of hair cell survival and its N538K mutation causes progressive hearing loss in mice [162]. *SYNJ2* (609410) is one of the longevity candidate genes; its SNPs (rs12202135) are associated with personality traits [163] and cognitive abilities [164] in the elderly. SYNJ2 expression is amplified in early colorectal cancers ($p < 0.05$) [118] and in breast cancer (4%) [165]. Gene variant (rs9365723) with increased SYNJ2 expression is associated with colorectal cancer risk in Chinese Han population ($p = 0.012$) [166]. In breast cancer, the gain of a region centered at chromosome 6q24 and which contains *SYNJ2* have been reported [165]. The expression of *SYNJ2* correlates with shorter survival of estrogen receptor (ER)-positive patients. SYNJ2 is associated with high tumor grades and cell proliferation, its protein level correlates with that of HER2. In addition, tumors expressing a high level of *SYNJ2* had a predilection to metastasize to bones, pleura, and lungs. Likewise, copy number gain, as well as increased mRNA and protein abundance of SYNJ2 correlates with poor prognosis and aggressive subtypes of breast cancer [165]. SYNJ2 mediates Rac1-regulated cell invasion and migration by regulating invadopodia and lamellipodia formation of SNB19 and U87MG glioma cells [165,167].

3.3. INPP4A and INPP4B

INPP4A and INPP4B are the members of the inositol polyphosphate 4-phosphatase family [168,169] (Fig. 2A). They share 37% sequence homology and consist of an N-terminal C2 domain, a PEST domain, and a C-terminal lipid phosphatase "CX_5R" motif also found in protein tyrosine phosphatases catalytic 4-phosphatase domain [168–170]. A null mutation in *Inpp4a* gene (600916) causes selective neuronal loss in weeble mutant mice, and *Inpp4a*-null mice developed neurodegeneration in the striatum [171,172]. INPP4B is characterized as a 4-phosphatase that hydrolyzes PI(3,4)P_2 to generate PI(3)P [16,80,170], and can also hydrolyze PI(4,5)P_2 and PIP_3 *in vitro*. As Akt binds to and is activated by PM PI(3,4)P_2 and PIP_3, INPP4A and INPP4B are considered tumor suppressors due to their inhibitory action on the PI3K/Akt signaling pathway. Indeed, the tumor suppression effect of INPP4B was first identified in breast cancer [16]. INPP4A acts as a tumor suppressor in bladder, pancreatic, lung, hepatocellular, and esophageal squamous cell cancer [164,173–176]. INPP4B preferentially hydrolyzes PI(3,4)P_2 but can also de-phosphorylates PI(4,5)P_2 and PIP_3 [16,169,177]. LOH of the 4q31.1-3, a gene region of *INPP4B* (607494) was identified in esophageal adenocarcinoma (37%), basal breast tumors (55.6%), ovarian cancers (39.8%), and melanomas (21.6%) [16,175,178]. The gene expression of INPP4B is lost in a cohort of Estrogen receptor (ER)-negative basal-like breast cancers and its reduced expression is associated with high clinical grade, tumor size, and poorer survival rate [179]. In addition, the loss of INPP4B expression in prostate cancer is associated with reduced time for biochemical recurrence and poorer outcomes [180]. INPP4B shRNA knockdown in LNCaP cell lines increased cell proliferation and Akt activation, while its expression in PC-3 cells decreased metastasis [41,181]. Similarly, INPP4B protein expression is progressively decreased in the advanced stages of human melanocytic tumors, and it regulates proliferation, migration, invasion and *in vivo* tumorigenic capacity in melanocytic neoplasm in a PI3K/Akt-dependent manner [32]. INPP4B shRNA knockdown in cancer cell lines increased cell proliferation, motility, anchorage-independent cell growth, xenograft tumor growth, and disrupted mammary acini morphology in a PI3K/Akt-dependent manner [16,179]. The loss of both INPP4B and PTEN in MCF-10A mammary epithelial cells resulted in increased cell senescence, with an enhanced growth of acini in comparison to INPP4B or PTEN single knockdown; hence, the depletion of both INPP4B and PTEN can enhance tumor growth and invasive phenotype [16]. In follicular variant of papillary thyroid carcinoma (FV-PTC), which can invade blood vessels and metastasize to lung or bone, mice lacking the phosphatase domain of INPP4B ($Inpp4b^{\Delta/\Delta}$) or depletion of Inpp4b gene ($Inpp4b^{-/-}$) did not drive tumorigenesis and did not exhibit tumor development *in vivo* [177,182]. However, $Inpp4b^{\Delta/\Delta}$; $Pten^{+/-}$ mice induce malignant thyroid cancers with lung metastases [177]. Furthermore, $Akt2^{-/-}$; $Inpp4b^{\Delta/\Delta}$; $Pten^{+/-}$ mice exhibited milder FV-PTC phenotype and showed an improved lifespan, suggesting the synergistic tumor suppressor function of both INPP4B and PTEN. The depletion of INPP4B and PTEN drives thyroid tumorigenicity through the activation of PIP_3/Akt2 signaling. INPP4B can dephosphorylate PI(3,4)P_2 and PIP_3 in PTEN-null thyroid tissue and the concomitant loss of *Inpp4b* and *Pten* promoted a striking increase in PIP_3 levels [177]. A lower expression of INPP4B is not enough to drive spontaneous tumorigenesis, but the heterozygous PTEN background may help to develop cancer in multiple organs [183]. In this case, the effect of INPP4B deficiency is thought to be derived from an increase in PI(3,4)P_2, which leads to the activation of Akt signaling and an enhancement in cell migration and invasion mediated by binding with Lpd and Tks5/FISH (Fig. 2B).

Although INPP4B tumor suppressor function has been reported *in vivo* and *in vitro* in a variety of cancers, there is emerging evidence showing that INPP4B plays an oncogenic role in certain species of cancers. INPP4B expression was elevated in 66% of colon cancers [44]. INPP4B expression promoted cell proliferation in HTC116 and WiDr

colon cancer cells, and INPP4B knockdown in colon cancer cells reduced murine xenograft tumor size [44]. Mechanistically, in colon cancer cell lines, INPP4B binds and dephosphorylates PTEN leading to PTEN degradation, thereby causing an increase in PIP_3 as well as the activation of PI3K signaling [44]. In colon cancer cells, INPP4B-mediated degradation of PTEN promoted tumor growth and proliferation through PI3K-dependent activation of serum and glucocorticoid-regulated kinase 3 (SGK3) [44]. SGK3 is an oncogenic effector in PIK3CA-mutant breast cancer cells independent of Akt [81], which is activated upon binding of its PX domain to PI(3)P [82]. As INPP4B generates PI(3)P, INPP4B is predicted to trigger SGK3 activation through the hydrolysis of $PI(3,4)P_2$. Indeed, in breast cancer and melanoma cells, increased SGK3 phosphorylation was associated with increased INPP4B protein expression [43,45]. INPP4B knockdown attenuated melanoma cell proliferation and xenograft tumor growth, whereas INPP4B overexpression enhanced cell proliferation and promoted melanocyte anchorage-independent cell growth, in an SGK3-dependent and an Akt-independent manner [45]. The knockdown of INPP4B in cancer cells that expresses high levels of SGK3—MCF-7 and ZR-75-1 breast cancer cells caused a reduced anchorage-independent cell growth, cell migration, 3D colony formation, and mouse xenograft tumor growth [43]. Thus, in cancer cells with high SGK3 expression, INPP4B functions as an activator of PI3K/SGK3 signaling and is required for 3D proliferation, invasive migration, and tumorigenesis *in vivo*. Collectively, INPP4B expression is increased or decreased in different human cancers and INPP4B possesses both pro-oncogenic and anti-oncogenic roles. Mechanistically, INPP4B may have more diverse molecular functions (*e.g.* $PI(3,4)P_2$- and PI(3)P-dependent functions) beyond its role as a negative regulator of PI3K/Akt signaling.

3.4. SAC1 and 2

There are three suppressor of actin (SAC) domain-containing phosphatases in mammals—SAC1, SAC2 (INPP5F), and SAC3 (Fig. 4). SAC1 localizes at the ER, Golgi, ER–PM junctions, and ER–Golgi interface, where it predominantly de-phosphorylates PI(4)P [184,185] (Fig. 2A). Tokuda et al. reported that Golgi PI(4)P level correlates with its invasiveness in breast cancer cells. The attenuation of SAC1 decreased cell–cell adhesion, and caused an increased invasion of MCF7 breast cancer cell line, while the knockdown of PI4KIIIα loosened the cell–cell adhesion and increased the developmental rates of highly invasive MDA-MB-231 breast cancer cells [28]. A PI(4)P effector, Golgi phosphoprotein 3 (GOLPH 3), drives cell migration by promoting Golgi reorientation and directional trafficking to the leading edge in a manner that depends on PI(4)P/GOLPH 3/myosin 18A/F-actin pathway [186]. SAC1 regulates the cell surface expression of CD44 variants and the number of mature FAs of breast cancer cells [27]. This evidence suggests that SAC1 regulates the localization of several Golgi enzymes through PI(4)P hydrolysis, which in turn suppresses the oncogenic activity of GOLPH 3. SAC2 (INPP5F), a PI(4)P 4-phosphatase regulating phagocytosis and endocytosis [187–189], is identified as a prognostic marker for fludarabine-based therapy of chronic lymphocytic leukemia and as a potential tumor suppressor in gliomas [190,191]. However, the role of SAC2 in cancer migration and invasion is still undefined. SAC1 and SAC2 function as anti-oncogenic through PI(4)P de-phosphorylation at intracellular organelles such as Golgi and endosomes. The influence of PI(4)P at the PM on cancer cell signaling and cancer cell dynamics remains to be understood.

4. Influence of local phosphoinositide turnover on cancer cell dynamics, formation of FA, lamellipodia, and invadopodia

The plasma membrane and intracellular organelles have specific phosphoinositide distributions, and they undergo continuous phosphoinositide turnover to regulate organelle dynamics and actin-mediated membrane dynamics in cancer cells. The alterations in phosphoinositide turnover in cancer cell signaling, migration, and invasion, is complex due to the connection between PM dynamics, cytoskeletal dynamics, and intracellular organelle dynamics. The most dynamic events during cancer cell migration and invasion are FA maturation, disassembly, and its turnover [192–197]. The role of phosphoinositides in FA formation and disassembly has been well studied (Fig. 3A). $PI(4,5)P_2$ modulates FA maturation and adhesion strength by binding with talin and vinculin, which subsequently binds to other FA proteins and actin [198]. $PI(4,5)P_2$ is locally generated in newly formed FAs from PI(4)P by PIP5KIγ [199]. $PI(4,5)P_2$ also binds to and activates FAK, thereby promoting the adhesion of cancer cells to the extracellular matrix [200]. Rap1-GTP-interacting adaptor molecule (RIAM1) recruits talin to the PM, and talin caused the depletion of RIAM1 impaired cell migration and cell invasion [158,201,202] with increased tyrosine phosphorylation of Paxillin as a consequence of FA disassembly [203–206]. RIAM1–integrin–talin complex is enriched at the tip of actin protrusions in lamellipodia and filopodia, where it forms a complex with integrins (αIIbβ3 and α5β1) and Lpd [207–209] (Fig. 3B). Lpd binds to and is activated by $PI(3,4)P_2$ and WAVE2 complexes [210], resulting in Rac-WAVE2-Arp2/3-dependent lamellipodia formation and increase in integrin-based cell migration (Fig. 3B). The $PI(3,4)P_2$–Lpd pathway activates lamellipodia formation because the overexpression of the TAPP1 PH domain, which masks $PI(3,4)P_2$, inhibits cell migration [108]. The endosomal system determines the fate of endocytosed cargo, including receptor tyrosine kinases, ensuring that they are recycled back to the cell surface, trafficked to the Golgi by retrograde transport, or sorted to late endosomes and lysosomal degradation [211]. Several studies have shown the involvement of the SHIP2-$PI(3,4)P_2$-Lpd pathway in receptor endocytosis and recycling. First, the SHIP2-$PI(3,4)P_2$-Lpd-endophilin pathway facilitates endocytosis of receptor tyrosine kinases (*e.g.* EGF receptor, VEGF receptor, PDGF receptor, and IGF1 receptor) and G-protein-coupled receptors through fast Endophilin-mediated endocytosis (FEME) [212,213]. The membrane-bound Cdc42 recruits FBP17 and CIP4, which then primes the PM for FEME through the recruitment of SHIP2, Lpd, and endophilin to the protein complex [214]. In addition to lamellipodia formation, local production of $PI(3,4)P_2$ mediates receptor endocytosis through endophilin N-BAR domain-driven membrane curvature formation (Fig. 3B). The roles of recycling endosomes (RE) in cancer cells have been reported. In addition to its role in regulating cell migration through the recycling of specific integrins, [215,216], it also mediates membrane expansion during lamellipodium formation. Taken together, $PI(3,4)P_2$, $PI(4,5)P_2$, PIP_3 (at PM), and PI(4)P (at recycling endosomes) are involved in the regulation of FA turnover and lamellipodia formation (Fig. 3B).

Invadopodia are actin-rich membrane protrusions formed in invasive cancer cells. It is critical for cancer cell invasion through focal degradation of extracellular matrix and metastasis [217]. During metastasis, cancer cells use a unique membrane protrusion, invadopodia, which contains metalloproteases for the degradation of the extracellular matrix [218]. Invadopodia consists of a tyrosine kinase substrate 5 (Tks5)/FISH, N-WASP, cortactin, and Arp2/3 complex [219,220]. Tks5/FISH was originally identified as an Src substrate [221] but was later discovered as an essential factor in podosome/invadopodia formation [222]. It binds to $PI(3,4)P_2$ through the PX domain and N-WASP through the SH3 domains, respectively. Src activates SYNJ2 to generate $PI(3,4)P_2$, which then recruits Tks5/FISH at the PM (Fig. 3C). On the platform of Tsk5/FISH, N-WASP triggers Arp2/3-dependent actin polymerization to form invadopodia. SHIP2 is also recruited to the invadopodia precursor, generates $PI(3,4)P_2$, and induces maturation of invadopodia [137]. Thus, $PI(3,4)P_2$ generated from PIP_3 by SYNJ2 and/or SHIP2 is necessary for Tks5/FISH-mediated stabilization of the precursor and subsequent invadopodia formation (Fig. 3C). In addition to $PI(3,4)P_2$, the local generation of $PI(4,5)P_2$ through Arf6-mediated activation of PIP kinase type Iα (PIP5KIα) recruits several components of invadopodia, including N-WASP, cofilin,

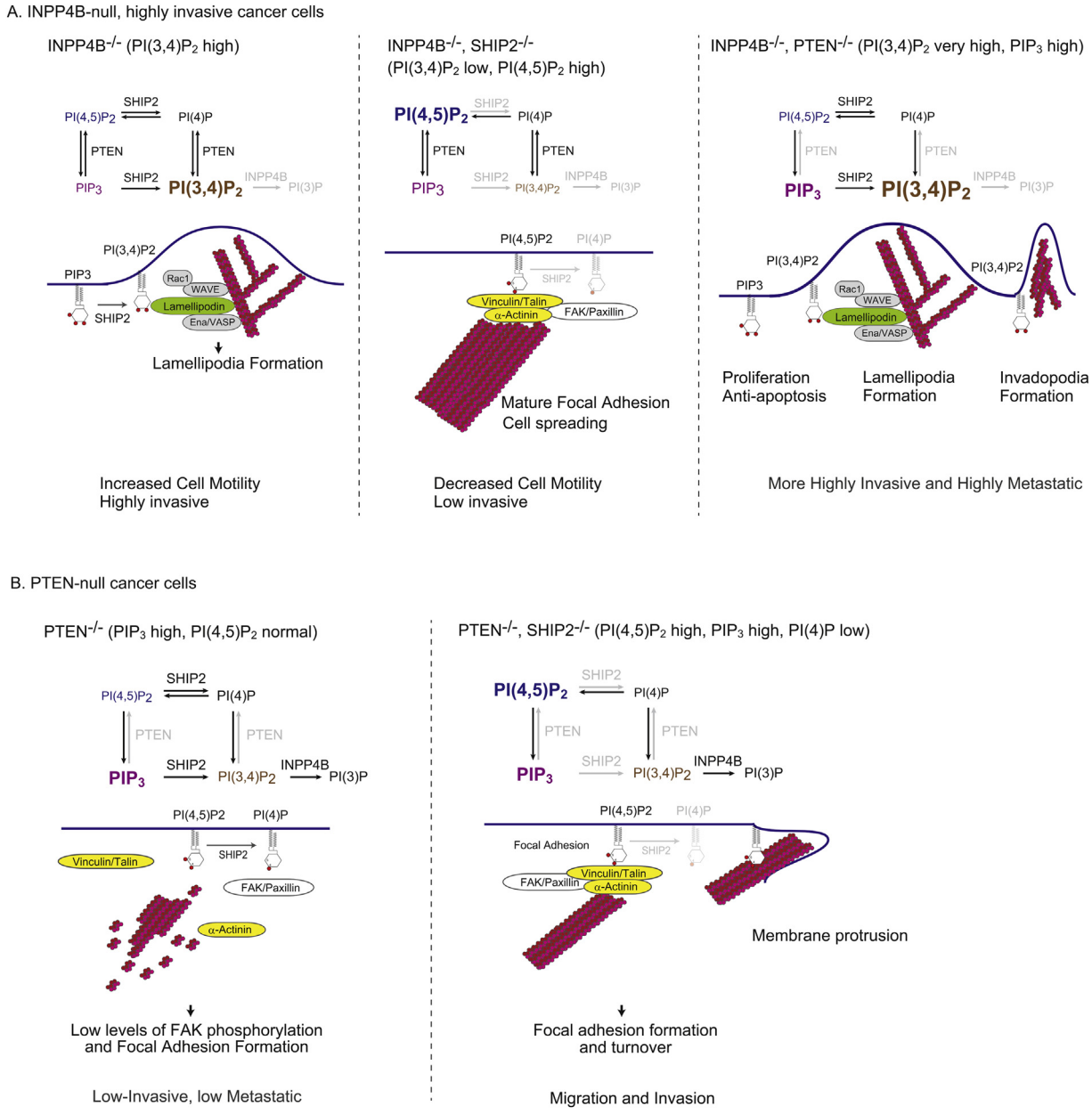

Fig. 4. Inactivation of phosphoinositide phosphatases PTEN, SHIP2, INPP4A/B results in deficient PIP_3 and $PI(3,4)P_2$ metabolism. (A) The proposed model of the pro-oncogenic function of SHIP2. The alteration of phosphoinositides, lamellipodia formation, and invadopodia formation by the depletion of PTEN or SHIP2 in INPP4B-null breast cancer cells (*e.g.* MDA-MB-231 cell). In high $PI(3,4)P_2$ INPP4B-deficient cancer cells, SHIP2 depletion decreased $PI(3,4)P_2$ generation from PIP_3 and subsequently inhibited the formation of lamellipodia and invadopodia. In contrast, PTEN-depletion increased PIP_3 and $PI(3,4)P_2$ levels, leading to an increase in cell proliferation and invasion. (B) The proposed model of the anti-oncogenic function of SHIP2. The alterations in $PI(4,5)P_2$ levels at the FA by the SHIP2 affects FA turnover in PTEN-null cancer cells. The inhibition of SHIP2 suppresses $PI(4,5)P_2$ de-phosphorylation, which leads to the maturation of stable FAs.

and dynamin-2. Arf6 lies at the PM, controls the positioning and tubulation of endosomes to deliver MT1-MMP to invadopodia [223]. PI(4,5)P_2 also serves as a substrate for PIP_3 generation by PI 3-kinase, which in turn activates Akt-dependent invadopodia formation [224]. Taken together, at least three phosphoinositide species, PI(3,4)P_2, PI(4,5)P_2, and PIP_3 are implicated in the formation of invadopodia. Invadopodia appear adjacent to multivesicular late endosomes and exosome secretion, enhancing invadopodia formation and thus triggering invasive behavior [225]. PI(4,5)P_2 at invadopodia offers a site for exosome secretion as well as invadopodia components [226] (Fig. 3C).

5. Distinct function of PI(3,4)P_2, PI(4,5)P_2, PIP_3, and PI(4)P in cancer cell proliferation, migration, and invasion—which phosphoinositide phosphatases regulate local phosphoinositide turnover?

The plasma membrane and intracellular organelles have unique phosphoinositide distributions (Fig. 1), and they undergo continuous phosphoinositide turnover by kinases and phosphatases. These have a great impact on cancer cell dynamics such as cell migration and invasion in both the positive and negative directions. As described earlier, at least four phosphoinositide species—PI(4)P, PI(3,4)P_2, PI(4,5)P_2, and PIP_3, are implicated in cancer cell proliferation, migration, and invasion (Fig. 1B). The potency of anti-oncogenic and pro-oncogenic activity of each phosphoinositide is variable, depending on the cancer cell type

because human cancer cells have varying phosphoinositides levels and their downstream signals. This variability can be explained by the differences in the expression levels and substrate specificity of phosphoinositide phosphatases in cancer cells. For example, as discussed earlier, PTEN acts as a tumor suppressor because it functions as a 3-phosphatase for both PIP_3 and $PI(3,4)P_2$ and it inhibits both PI3K–Akt signaling and PIP_3-dependent cell migration and invasion. Clinical data provide evidence that PIP_3, PTEN, and PI3K–Akt signaling is involved in melanoma metastasis [227]. In contrast, alterations (either increased or decreased expression) or deletions in the number of PIP_3 5-phosphatases, including PIPP, SHIP2, SKIP, and SYNJ2, are involved in tumorigenesis and malignancy in human cancers. 5-phosphatases can act either as a tumor inducer or a tumor suppressor because they hydrolyze PIP_3 and $PI(4,5)P_2$ to generate $PI(3,4)P_2$ and PI(4)P [228]. However, an important question arises—which phosphoinositide phosphatases and which phosphoinositide [*e.g.* PIP_3, $PI(4,5)P_2$, $PI(3,4)P_2$, or others] determine the characteristics of cancer cells. In INPP4B-null MDA-MB-231 cells, the knockdown of SHIP2 induced a slight increase in PIP_3, thus having a minor influence on PI3K–Akt signaling but a significant decrease in $PI(3,4)P_2$ level (Fig. 4A). The silencing of SHIP2 enhanced the FAs and stress fiber formation, resulting in the suppression of cell migration and invasion. By contrast, PTEN deletion triggers FA turnover and aberrant ruffle formation, resulting in the enhancement of cell migration and invasion. Interestingly, SHIP2 knockdown suppressed the phenotype induced by PTEN knockdown, suggesting that $PI(3,4)P_2$ rather than PIP_3 plays a critical role in FA dynamics and cancer cell invasion in MDA-MB-231 cells. SHIP2-depletion does not change PM $PI(4,5)P_2$ level and $PI(4,5)P_2$-dependent FAK phosphorylation but changed Paxillin phosphorylation necessary for FA disassembly [108]. Thus, $PI(3,4)P_2$ [not PIP_3 and $PI(4,5)P_2$] seems to be predominantly involved in cancer cell migration and invasion in INPP4B-null breast carcinoma cells (Fig. 4A). On the contrary, in PTEN-null 1321 N1 glioblastoma cells, SHIP2-depletion increases $PI(4,5)P_2$ level at the PM, which in turn increases FAK phosphorylation and FA length [128]. As described above, $PI(4,5)P_2$ triggers FA formation through the interaction with α-actinin and vinculin and contributes to invadopodia formation through the transport of late endosomes to the cell periphery (Fig. 3A and C). SHIP2 decreases $PI(4,5)P_2$ levels at the PM, which then inhibits cell FA length and cell migration through phosphorylation of FAK in FAs [200]. Although, $PI(3,4)P_2$ is decreased in SHIP2-depleted cells, neither PI3K inhibitors nor Akt inhibitors influence cell migration in these cells [128]. Thus, $PI(4,5)P_2$ [not PIP_3 and $PI(3,4)P_2$] seems to be a preferred substrate for SHIP2 in PTEN-null glioblastomas (Fig. 4B). It should be noted that PIP_3 is a preferred SHIP2 substrate [229], SHIP2 suppression and the hyperactivation of the PI3K–Akt pathway are identified in some cancer cells such as squamous cell carcinoma [127] and gastric cancer [126]. Therefore, the local levels of phosphoinositides [$PI(3,4)P_2$, $PI(4,5)P_2$, PIP_3, and PI(4)P] at the PM may determine the invasiveness of cancer cells, and the phosphoinositide conversion mediated by SHIP2 and PTEN controls FA turnover and invadopodia formation in cancer cells (Fig. 4A and B). Interestingly, cancer phenotype is not a result of an alteration in a single gene. The simultaneous reduction of phosphoinositide phosphatase is frequently observed in human cancers. In human cancers, the expression of miR-508 and miR-3127 is frequently increased in some human cancers, which in turn suppresses the expression of PIPP, PTEN, and INPP4A [147]. The overexpression of miR-508 increased cell proliferation, colony formation, and anchorage-independent cell growth of esophageal squamous cell carcinoma cells [173]. Similarly, the expression of miR-3127 increased the anchorage-independent cell growth of hepatocellular carcinoma [174]. The expression of PTEN, PIPP, and INPP4A/B is simultaneously suppressed by a single miRNA, which leads to the accumulation of PIP_3 and the hyperactivation of PI3K–Akt signaling pathway in cancer cells. It is notable that in INPP4B-null MDA-MB-231 breast cancer cells, in which $PI(3,4)P_2$ levels are high, PTEN suppression leads to an increase in cell migration and invasion while SHIP2 suppression leads to a decrease in these phenotypes. In these cells, SHIP2 mainly contributes to the generation of $PI(3,4)P_2$ and the degradation of $PI(4,5)P_2$, while PTEN depletion leads to increases in $PI(3,4)P_2$ and PIP_3 (Fig. 4B). Taken together, an alteration in the expression of single or multiple phosphoinositide phosphatases affects the intracellular levels of phosphoinositide, and this can be useful in determining cancer cell phenotypes.

6. Conclusion

It had been generally accepted that abnormalities in PI3K and PTEN could cause the hyperactivation of Akt signaling and the induction of cancer cell survival and proliferation, thus leading to the development of tumors. However, recent studies have clarified the importance of all phosphoinositide species in cancer cell migration and invasion through the dynamic membrane and cytoskeletal remodeling. More than 30 species of phosphatases are involved in phosphoinositide turnover; hence, it is not an exaggeration to suggest that the majority of these enzymes have pro-oncogenic and/or anti-oncogenic influences on cancer cell development and invasive phenotypes. The role of these enzymes in cancer cells is more complicated because of their substrate specificities. Among 5-phosphatases, PIPP (together with INPP4A) predominantly acts as a silencer of PI3K–Akt signaling through hydrolysis of PIP_3. The depletion of PIPP (and INPP4A) leads to an accumulation of PIP_3, but not $PI(3,4)P_2$ (Fig. 4B). In contrast, SYNJ2, SHIP2, and SKIP can function either as tumor-suppressors or pro-oncogenes because they can generate PI(4)P and $PI(3,4)P_2$ from $PI(4,5)P_2$ and PIP_3, respectively. In INPP4B-deficient cell with high $PI(3,4)P_2$ level, SHIP2 exerts pro-oncogenic roles through $PI(4,5)P_2$ to $PI(3,4)P_2$ at the PM which then triggers lamellipodia and invadopodia formation. However, in PTEN-deficient cells with high PIP_3 levels, SHIP2 can also act as anti-oncogenic through the inhibition of the PI3K–Akt signaling pathway (Fig. 4B). Therefore, the levels of local phosphoinositides and phosphoinositide phosphatases may determine whether cancer cells become proliferative or invasive. Furthermore, it should be taken into account that intracellular trafficking *via* endosomal recycling and intercellular communication *via* exosome secretion and lysosomal exocytosis are regulated by various phosphoinositides when examining cancer cell proliferation, lamellipodia formation, and invadopodia formation. For example, SHIP2 has an impact on ligand-induced EGFP internalization and degradation through $PI(4,5)P_2$ to $PI(3,4)P_2$ conversion at endocytic coated pit required for endosomal dynamics [230]. Further analysis of the local changes in phosphoinositide levels induced by alterations in phosphoinositide kinases and phosphatases is required to elucidate which phosphoinositide [PIP_3, $PI(3,4)P_2$, $PI(4,5)P_2$, and PI(4)P] predominantly induces the invasive and/or proliferative cancer phenotypes. To develop an appropriate strategy for the treatment of cancer, cancer cells should be classified according to their invasiveness and cell surface expression of receptors, both of which are regulated by phosphoinositide in a very complex manner. Therefore, the identification of phosphoinositide species can help to determine the suitable and appropriate therapies for cancer.

Conflict of interest

The author declares that there are no conflicts of interests.

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