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PTPN13/PTPL1: an important regulator of tumor aggressiveness.

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Abstract

Protein tyrosine phosphorylation plays a major role in many cellular functions implicated in cancer development and progression, but only a few of the known protein tyrosine phosphatases have yet been clearly classified as oncogenes or tumor suppressors. PTPL1 interacts with tumor-associated proteins, suggesting a link between PTPL1, the *PTPN13* gene product, and tumorigenesis or cancer progression. However, the impact of PTPL1 on cancer is divided between its capacity to counteract the activity of oncogenic tyrosine kinases and its inhibitory interaction with the death receptor, Fas. In this manuscript, we review the PTPL1-interacting proteins implicated in cancer. In addition, we examine the phenotypic arguments concerning both the PTPL1/Fas interaction and the ability of PTPL1 to inhibit signaling from growth factor receptors or oncogenes with tyrosine kinase activity. Finally, we compare the alterations in expression and the genetic and epigenetic arguments supporting an oncogenic or an anti-oncogenic impact of PTPL1.

Author Keywords Cancer ; Fas ; Her2 ; Human papillomavirus 16 ; IRS-1 ; PTPN13 ; PTPL1 ; Src

Introduction

Protein tyrosine phosphorylation plays a major role in many cellular functions, including cell survival, proliferation, differentiation and motility. It is now well established that the dysregulation of intracellular signaling pathways, which triggers these processes, is implicated in cancer development and progression. While much progress has been made over the last 25 years in elucidating the implications of protein tyrosine kinases in signal transduction (for review, see [1]), the role of protein tyrosine phosphatases (PTPs), which were initially believed to be limited in number and considered housekeeping enzymes with broad specificities, has only been addressed within the last decade. Therefore, only a few of the known PTPs have been clearly classified as oncogenes (*PTPN1/* PTP1B - *PTPN11* /SHP-2) or tumor suppressors (*PTPRG* /PTPγ-*PTPRO* /GLEPP1 - *PTPRJ* /DEP1) (for review see [2 –4]).

Among the PTPs with potential roles in carcinogenesis, we are interested in the *PTPN13* gene product, which can impact cancer development through either its capacity to counteract the activity of oncogenic tyrosine kinases or its inhibitory interaction with the death receptor Fas. In this manuscript, we will review the PTPL1-interacting proteins that suggest a link between PTPL1 and tumorigenesis or cancer progression. We will then focus on studies concerning the PTPL1/Fas interaction and the ability of PTPL1 to inhibit signaling from growth factor receptors or oncogenes with tyrosine kinase activity. Finally, we will compare the alterations in expression as well as the genetic and epigenetic arguments that support an oncogenic or anti-oncogenic function of PTPL1. In 1994, the *PTPN13* product was cloned independently by three groups, using different cell models, and is thus referenced as PTP-BAS, hPTP1E or PTPL1 [5 –7]. Moreover, in 1995, Sato *et al.* [8] called it FAP-1 for Fas-associated phosphatase-1 due to evidence of its ability to interact with the death receptor Fas (for review, see[9 –11]). In this manuscript, we will refer to the *PTPN13* product as PTPL1. The physiological functions of PTPL1 are poorly documented. PTP-BL (mouse homologue of PTPL1) KO mice present abnormal regulation of signal transducer and activator of transcription signaling in T cells [12]. Mice that lack PTP-BL PTP activity show mild impairment of motor nerve repair [13], and a significant reduction in the growth of retinal glia cultures from lens-lesioned mice has been observed [14]. Furthermore, we have recently described the role of this phosphatase in adipocyte differentiation [15].

PTPN13 maps to the human chromosomal locus 4q21 [16] and encodes a high-molecular-weight (270 kDa) non-receptor type phosphatase. The phosphatase contains multiple domains, providing numerous potential interfaces. Its first amino terminal domain is a putative kinase non-catalytic C-lobe domain (KIND), which was identified by sequence homology, and the function of which has not yet been experimentally addressed. The next amino terminal domain is a 4.1/ezrin/radixin/moesin (FERM) domain, which is commonly found within a family of peripheral membrane proteins that mediate linkage of the cytoskeleton to the plasma membrane [17]. The FERM domain of PTP-BL, the mouse homologue of PTPL1, was shown to be sufficient for its submembranous distribution [18]. We have shown that PTPL1 is predominantly localized at the apical face of plasma membrane, enriched in dorsal microvilli, when expressed in HeLa cells. By comparing localization of the full-length enzyme to localization of its FERM domain or of a FERM-deleted PTPL1 construct, we established that the PTPL1-FERM domain is necessary and sufficient to direct the wild-type enzyme to the membrane. Two potential phosphatidylinositol 4,5-biphosphate [PtdIns(4,5)P2]-binding motifs were identified within the PTPL1-FERM sequence, and we have shown that mutation of both sites altered PTPL1 localization similarly to deletion of the FERM domain. Using protein-lipid overlays, we

have demonstrated an interaction between the FERM domain of PTPL1 and PtdIns(4,5)P2, which was lost after mutation of the potential PtdIns(4,5)P2-binding motifs [19]. Following this, a study by Kimber *et al* . provided evidence that TAPP1, which binds PtdIns(3,4)P2 and the first PTPL1 PDZ domain (see below), could regulate the membrane localization of PTPL1[20].

Between the FERM domain and the carboxy-terminal catalytic domain, PTPL1 contains five PSD-95/Discs-large/ZO-1 (PDZ) domains, which are protein/protein interaction domains. PTPL1 can, therefore, have numerous partners that can actively participate in the regulation of its phosphatase activity or can permit direct or indirect recruitment of tyrosine phosphorylated PTPL1 substrates.

PTPL1-interacting proteins and cancer

PDZ domains are protein/protein interaction domains able to bind specific C-terminal sequences of proteins [21 –23] as well as other PDZ domains [24], LIM domains (named for the initials of Lin-11, Isl-1, and Mec-3) [25] and ankyrin repeats [26]. With five PDZ domains, PTPL1 presents each type of these interactions. A number of potential PTPL1-interacting partners point to a role for PTPL1 in several steps of tumor progression, such as modification of cell shape, motility and cell signaling, leading to growth or apoptosis, thus indicating a potential role for PTPL1 in cancer and metastasis (Fig.(1)).

Proteins interacting with PDZ-1

The involvement of TAPP1/2 and BP75, two PDZ1 partners, in tumorigenesis has been poorly documented. However, the phosphoinositol 3,4-bisphosphate-binding protein, TAPP1, has been shown to regulate actin cytoskeletal organization by interacting with syntrophins, leading to the blockade of PDGF-induced formation of dorsal circular ruffles [27]. The bromodomain-containing protein BP75 has been reported to bind dishevelled-1 (Dvl-1) and to enhance Wnt signaling in a study by Kim *et al*. They showed that BP75 directly interacts with Dvl-1 in mammalian cells and enhances TCF-dependent gene expression induced by Dvl-1. Specifically, BP75, in cooperation with Dvl-1, was found to facilitate dephosphorylation of glycogen synthase kinase-3β at Tyr216 and consequently, to inhibit its kinase activity. Furthermore, BP75 acted synergistically with Dvl-1 during inactivation of glycogen synthase kinase-3 β and nuclear translocation of β-catenin [28].

PDZ-1, in cooperation with PDZ-5, binds TRPM2, a transient receptor potential (TRP) superfamily member. This receptor is a Ca(2+)-permeable channel, which mediates susceptibility to cell death following activation by oxidative stress, TNFα, or β-amyloid peptide. Co-expression of PTPL1 with TRPM2 in human embryonic kidney-293T cells resulted in significantly reduced tyrosine phosphorylation of TRPM2 and inhibited the rise in $[Ca^{2+}]_i$ and the loss of cell viability in response to H_2O_2 or TNFα treatment. Consistent with these findings, reduction of endogenous PTPL1 expression with small interfering RNA resulted in increased TRPM2 tyrosine phosphorylation, a greater rise in $[Ca^{2+}]_i$ following H_2O_2 treatment, and enhanced susceptibility to H_2O_2 -induced cell death [29].

In addition, PDZ-1 has been shown to bind the inhibitor of nuclear factor κ-B α (IκBα), and inhibition of PTPL1 by expression of a dominant-negative PTPL1 mutant (lacking phosphatase activity) resulted in tyrosine-phosphorylation of IκBα [26]. IκBα is an inhibitor of the transcription factor NFκB. A complex consisting of IκBα and NFκB is formed in the cytosol, preventing NFκB from entering the nucleus. There are two possibilities to dissociate this complex. The first possibility is the phosphorylation of IκBα on Ser32 and 36, resulting in its degradation by the ubiquitin proteasome system. The second is the phosphorylation of IκBα on Tyr42, which leads to dissociation without degradation [30]. Interestingly, the tyrosine phosphorylation site substrate of PTPL1 on IκBα was not identified, and Tyr 305 phosphorylation of IκBα was demonstrated to inhibit NFκB activity [31]. This indicates that, depending on the dephosphorylation site, PTPL1 can activate or inhibit NFκB.

Proteins interacting with PDZ-2

The second PDZ domain of PTPL1 binds two members of the TNFR superfamily. The human cell surface protein Fas was the first protein reported to interact with PTPL1 [8]. It interacts with the PDZ-2 and PDZ-4 domain of PTPL1, and the implication of this interaction on tumorigenesis has been extensively studied and will be discussed in chapter 3. PDZ-2 also interacts with the neurotrophin receptor $p75^{NTR}$. TRAF6-mediated NFκB activation was suppressed by $p75^{NTR}$, and the $p75^{NTR}$ -mediated NFκB suppression was reduced by PTPL1 expression [32]. The latter observation supports the involvement of PTPL1 in modulation of NFκB activity suggested by IκBα dephosphorylation.

Additional proteins known to bind to the PDZ-2 domain are the LIM domain-containing proteins RIL and Trip6/ZRP-1 [25 , 33 , 34]. Reversion-induced LIM (RIL) is a ubiquitously expressed protein but is a target of epigenetic silencing by hypermethylation in a large number of cancer cell lines and tumors derived from various origins, including the breast, liver, and colon. Furthermore, RIL transcription is suppressed in multiple types of human cancer cells, including colon cancer cells, and re-expression of RIL inhibited anchorage-independent growth [35]. These findings strongly suggest that loss of RIL contributes to malignant behavior, and a recent study indicating the involvement of RIL in the regulation of Src activity [36] will be discussed in chapter 4.

The LIM domain-containing protein TRIP6, also known as ZRP-1 (Zyxin-related Protein 1), is a zyxin family member that has been implicated in cell motility and transcriptional control [37]. Originally discovered as a protein interacting with the nuclear thyroid hormone receptor, TRIP6 was later identified as a focal adhesion molecule with the capability to shuttle between the cell surface and nucleus. Through LIM domain-mediated protein-protein interactions, TRIP6 forms complexes with several molecules involved in actin rearrangement, cell adhesion and migration, including p130cas [38] and supervillin [39]. TRIP6/ZRP-1, localized at cell-matrix and cell-cell contact sites, plays a crucial role in coupling the cell-matrix/cell-cell contact signals with Rho GTPase-mediated actin remodeling [40]. Moreover, ectopic expression of TRIP6/ZRP-1 induced invasiveness in MDCK epithelial cells and impaired cell-cell aggregation, at least in part, by uncoupling adherens junctional complexes from the cytoskeleton [41]. For example, LPA stimulation of the LPA2 receptor targets TRIP6 to focal adhesion complexes and promotes c-Src-dependent phosphorylation of TRIP6, which creates a docking site for the Crk Src homology 2 domain, thereby promoting LPA-induced morphological changes and cell migration [42]. Lai *et al* . showed that PTPL1-dependent dephosphorylation inhibited TRIP6 function in LPA-induced cell migration. PTPL1 dephosphorylates phosphotyrosine 55 of TRIP6 *in vitro* and inhibits LPA-induced tyrosine phosphorylation of TRIP6 in cells. This inhibition requires a direct protein-protein interaction between PTPL1 and TRIP6 along with the phosphatase activity of PTPL1. In contrast to c-Src, PTPL1 prevents TRIP6 turnover at sites of adhesions, LPA-induced association of TRIP6 with Crk and TRIP6-mediated promotion of LPA-induced morphological changes and cell migration. These results clearly indicate a negative impact of PTPL1 on cell migration and suggest an inhibitory role of PTPL1 on cancer cell invasiveness that counteracts the oncogenic activity of Src [43].

Another protein strongly linked to cancer, the tumor suppressor protein APC (adenomatous polyposis coli protein), interacts with the PDZ-2 of PTPL1 [44]. The biological effect of this interaction has not yet been addressed, but it is of interest to note that this interaction is restricted to one alternatively spliced variant of the PDZ2 domain.

Proteins interacting with PDZ-3, PDZ-4 and PDZ-5

Only one protein has been shown to interact with PDZ-3. It is protein kinase C-related kinase-2 (PRK2), a cytosolic serine/threonine kinase regulated by the monomeric G-protein rho [45]. PRK2 has not yet been implicated in cancer progression or tumorigenesis, but interaction with PRK2 was shown to inhibit kinase activity of PDK1, the activator of PKB [46]. Furthermore, a role for PRK2 in cell division was demonstrated by Schmidt and collaborators, who showed that PRK2 is required for abscission of the midbody at the end of the cell division cycle and for phosphorylation and activation of Cdc25B, the phosphatase required for activation of mitotic cyclin/Cdk1 complexes at the G2/M transition [47].

In addition to Fas and RIL, which bind to PDZ2 and PDZ4, the fourth PDZ domain interacts with CRIP2 (cysteine-rich intestinal protein 2) [48], PARG1 (PTPL1-associated RhoGAP1) [49], a putative rap2 effector [50] which has been proposed to be a putative tumor suppressor in mantle cell lymphomas [51], and EphrinB1, a transmembrane ligand for B-class Ephrin receptor [52] that controls cell-cell junctions [53].

The fifth PDZ domain of PTPL1 currently has a single known partner, the TRP superfamily member TRPM2, which also binds the first PDZ domain.

Among the numerous described interacting proteins, only a few have been identified as PTPL1 substrates, suggesting a role for these partners in PTPL1 localization or regulation of PTP activity. In addition, a scaffolding protein function for PTPL1 has been suggested by our results concerning the effect of PTP-BL in adipogenesis that is independent of its enzymatic activity.

PTPL1 inhibits Fas receptor mediated apoptosis

The relation between PTPL1 and apoptosis has been addressed by several groups and remains controversial. The first evidence of such a relation was brought up by Sato *et al* . [8] with the demonstration of the interaction of PTPL1 with the carboxy terminal tail of the pro-apoptotic receptor, Fas. In this initial study, it was shown that the apoptotic effect of a Fas agonist antibody was inhibited by 50% in transfected clones of Jurkat cells overexpressing PTPL1. Using an *in vitro* assay inhibiting Fas/PTPL1 binding with a series of synthetic peptides, as well as by a screen of random peptide libraries using the yeast two-hybrid system, the same group showed that the C-terminal three amino acids (SLV) of human Fas were necessary and sufficient for the interaction with the second PDZ domain of PTPL1. Furthermore, direct cytoplasmic microinjection of the (SLV) resulted in the induction of Fas-mediated apoptosis in a colon cancer cell line that expresses both Fas and PTPL1. This observation indicated that an interaction between the C-terminal domain of Fas and the PDZ domain of another protein mediated the inhibition of Fas signal transduction, and the authors proposed that PTPL1 could be this inhibitory protein [54]. Using a peptide-binding assay, Saras *et al* . showed that not only PDZ-2, but also PDZ-4, of PTPL1 interacts with high affinity with peptides derived from the C terminus of Fas. The five most C-terminal amino acid residues of Fas influence the affinity of the interaction. The glutamine and isoleucine residues in the fourth and fifth positions from the C terminus affect the interaction in a negative and positive manner, respectively, and the three C-terminal amino acid residues (SLV) are necessary and sufficient for a high affinity interaction to occur. The valine residue at the C terminus of Fas is essential, and the leucine and serine residues in the 2nd and 3rd positions, respectively, from the C terminus are important for the interactions with PDZ 2 and PDZ 4 of PTPL1 [55]. However, murine Fas

lacks the SLV terminal sequence, and Cuppen *et al* . [56] demonstrated that there was no interaction between murine Fas and PTP-BL (mouse homologue of PTPL1). These data strongly suggest that this interaction, which is not evolutionarily conserved, does not play a crucial role in PTPL1 function. In the same study, Cuppen *et al.* did not observe inhibited Fas-induced apoptosis upon overexpressing PTP-BL in mouse T cell lymphoma cells transfected with human Fas, which interacts with PTP-BL, indicating that this interaction is not sufficient to inhibit Fas transduction in this cell type. [56].

Sato's laboratory has confirmed the interaction between PTPL1 and Fas *in vivo* by co-immunoprecipitation. To investigate the functional role of PTPL1 in Fas-mediated signal transduction, they established stable transfectants of PTPL1 in Jurkat and TMK-1 cells. Apoptosis assays demonstrated that PTPL1 over-expression increased resistance to Fas-induced apoptosis by the anti-Fas antibody CH-11 [57] in these cell lines. Ungefroren *et al* . investigated the functional role of PTPL1 as a potential inhibitor of Fas-mediated apoptosis in pancreatic cancer cells. Stable transfection of the Fas sensitive, PTPL1-negative cell line Capan-1 with PTPL1 cDNA resulted in strongly decreased sensitivity to Fas-induced apoptosis, as measured by DNA fragmentation and caspase-3 activity. The authors then analyzed the subcellular localization of PTPL1 and Fas in order to determine the impact of PTPL1/Fas interaction on Fas localization. Whereas unstimulated cells showed limited colocalization of PTPL1 and Fas, colocalization was increased significantly upon treatment with Fas-ligand. Strong colocalization was observed in intracellular compartments (Golgi apparatus and peripheral vesicular structures). This increase in colocalization was accompanied by a decrease in surface expression of Fas. However, this accumulation of Fas in intracellular stores was not observed in Capan-1 cells, a pancreatic adenocarcinoma cell line lacking PTPL1 expression. Based on the spatial-temporal relationship between PTPL1 and Fas, the authors suggested an interfering role of PTPL1 with the translocation of Fas from intracellular stores to the plasma membrane. [58]. These results were confirmed and extended to melanoma cell lines. Indeed, association of Fas with PTPL1 was shown to attenuate export of Fas to the cell surface in these cell lines and in TIG3 human embryonic lung fibroblasts. In this study, forced expression of PTPL1 reduced cell surface Fas levels and increased the intracellular pool of Fas. The inhibitory effect of PTPL1 on the cell surface expression of Fas was dependent on the presence of the PDZ2 and protein tyrosine phosphatase domain of PTPL1. Moreover, an intact C-terminus of Fas was crucial for the interfering role of PTPL1 in Fas trafficking. Conversely, inhibition of PTPL1 expression by short interfering RNA, or expression of dominant-negative forms of PTPL1, efficiently up-regulated surface expression of Fas [59]. In astrocytoma cells, knockdown of PTPL1 by RNA interference lead to increased apoptosis and increased sensitivity to Fas-induced cell death. In these cells, FasL treatment induced tyrosine phosphorylation of Fas, and PTPL1 dephosphorylates phosphotyrosine 275 [60] in the carboxyl terminus of Fas *in vitro* , which is essential for the Fas/PTPL1 interaction [59].

Unexpectedly, Miyazaki *et al.* , in collaboration with Sato's group, showed that in the colon cancer cell line SW480, overexpression of PTPL1 increased Fas-mediated apoptosis [61]. Conversely, some studies have confirmed the negative action of PTPL1 on Fas-mediated apoptosis in colon cancer, melanoma and myeloid cells using SLV inhibitory peptide [62 , 63], or RNA interference [64 , 65]. Furthermore, the delocalization of Fas from the cell surface to the intracellular compartment was confirmed in melanoma [66] and head and neck cancer [67] where PTPL1 could act via NFκB activation. It is interesting to note that Huang et al [63] in their work on myeloid cells observed a positive effect of SLV inhibitory peptide on apoptosis induction by Fas antibody in murine cells, whereas murine Fas lacks the SLV terminal sequence [56]. This suggests that SLV peptide can induce apoptosis through a mechanism independent from PTPL1/Fas interaction.

The PTPL1/Fas interaction is not the exclusive role of PTPL1 in anti-apoptotic or oncogenic pathways. Indeed, PTPL1 is a direct transcriptional target of EWS-FLI1, a fusion protein expressed in Ewing's Sarcoma Family of Tumors (ESFT) which promotes cell growth and oncogenesis [68]. Reduction of PTPL1 protein levels, using an antisense strategy, leads to highly significant reductions in both anchorage-dependent and anchorage-independent cell growth induced by EWS-FLI1 [68]. PTPL1-depleted ESFT cells also displayed an increased sensitivity to etoposide-induced apoptosis when compared to control cells [68]. Studies are now necessary to identify PTPL1 substrates and PTPL1-modulated pathways in this model.

Negative impact of PTPL1 on cell growth and survival

The positive effects of PTPL1 on apoptosis and suppression of tumor growth affect various pathways initiated by tyrosine kinases, and PTPL1 substrates have been clearly identified in the majority of these pathways (Table 1).

PTPL1 is a pro-apoptotic enzyme in breast cancer

The first evidence of such action of PTPL1 was its involvement in the pro-apoptotic effects of antiestrogens in breast cancer cell lines. Steroidal and non-steroidal antiestrogens, such as tamoxifen, which is currently used in breast cancer adjuvant therapy, inhibit the growth of estrogen receptor-positive cells not only by acting on nuclear receptors as competitors of hormone agonists but also by preventing the mitogenic action of growth factors in the total absence of estrogens [69 , 70]. Inhibition of cell growth, as evidenced by a drastic decrease in the overall cell DNA measurement, correlated with the expression of some protein-tyrosine phosphatases [71]. After cloning all of the antiestrogen-regulated enzymes in MCF7 cells by RT/PCR using degenerated oligonucleotides, we have shown that only two phosphatases, LAR and PTPL1, were up-regulated by these antagonists [72]. While PTPL1 expression has no impact on OH-Tam

antiestrogenic activity, abolition of its expression by antisense transfection completely abrogated its antagonist effect on growth factor action, thus demonstrating that its presence and consequent regulation are crucial in mediating this inhibitory effect [72]. In addition, we have shown that PTPL1 can drastically affect the PI3-kinase/Akt pathway [73]. In wild-type PTPL1-expressing cells, antiestrogen treatment severely reduced IRS-1 and Akt phosphorylation induced by IGF-1 and led to a strong increase in apoptosis (up to 30% of the overall cell population). In contrast, in PTPL1 antisense transfectants, OH-Tam was unable to inhibit the PI-3 kinase pathway or to induce apoptosis, thus demonstrating that PTPL1 affects apoptosis by inhibiting this survival pathway [73]. In a third study, we have shown by complementary approaches, i.e., *in vitro* and *in cellulo* « substrate trapping », dephosphorylation and colocalization experiments, that PTPL1 specifically dephosphorylates insulin receptor substrate-1 (IRS-1). Moreover, our experiments using a dominant-negative mutant and RNA interference confirmed the crucial role of PTPL1 in IRS-1 dephosphorylation. Finally, we reported that PTPL1 expression is sufficient to block the IRS-1/PI3K/Akt signaling pathway, to inhibit the insulin-like growth factor-I effect on cell survival and to induce apoptosis [74].

PTPL1 negatively regulates Her2 malignant signaling

Deregulated Her2 (Human Epidermal Growth Factor Receptor-2) receptor tyrosine kinase drives tumorigenesis and tumor progression in a variety of human tissues. Her2 transmits oncogenic signals through phosphorylation of its cytosolic domain. To study endogenous cellular mechanisms controlling the oncogenic phosphorylation of Her2, Zhu *et al* . screened an siRNA phosphatase library for cellular phosphatases that enhance phosphorylation of the signaling motif of Her2 upon knockdown. The authors found that silencing PTPL1 significantly augmented growth factor-induced phosphorylation of the Her2 signaling domain. Conversely, increased expression of cellular PTPL1 inhibited Her2 phosphorylation, and Her2 formed a stable complex with the “substrate trapping” mutant of PTPL1. In the same study, the authors showed that PTPL1 mutations observed in human cancers [75] inhibited PTPL1 phosphatase activity and promoted Her2 phosphorylation. PTPL1 knockdown or PTPL1 cancer-associated mutants promoted the invasiveness of Her2-overexpressing SKOV3 ovarian cancer cells [76]. Recently, the negative regulation of Her2 signaling by PTPL1 was confirmed by another group studying the silencing of Her3/Her2 signaling by the tumor suppressor Necl-2[77]. The extracellular region of ErbB3, but not ErbB2, interacts with that of Necl-2 without affecting ligand-induced formation of the ErbB3/ErbB2 heterodimer. This interaction reduces the ligand-induced, ErbB2-catalyzed tyrosine phosphorylation of ErbB3 and inhibits the consequent ErbB3-mediated activation of Rac and Akt, resulting in the inhibition of cancer cell movement and survival in A459 or Caco-2 cell lines. Interestingly, the cytoplasmic tail of Necl-2, which interacts with the PTPL1 FERM domain, is involved in its inhibitory action. Knockdown of PTPL1 by siRNA prevents reduction by exogenous expression of Necl-2 of the Her2-catalyzed tyrosine phosphorylation of Her3. These results indicate that PTPL1 is involved in the inhibitory effect of Necl-2 on Her2/Her3 signaling [78]. Interestingly, Her2-activation by EGF up-regulated PTPL1 expression, suggesting a feedback loop in which PTPL1 induced by Her2 activation inhibits this activation [79].

PTPL1 loss is a crucial event of human papillomavirus oncogenic signaling

Human papillomavirus 16 (HPV16) has been associated with head and neck squamous cell carcinoma (HNSCC) in up to 60% of specimens. Immortalization and anchorage-independent growth of human tonsil epithelial cells (HTEC) requires expression of E6 and E7 HPV16 viral genes. However, cells expressing E6 lacking the PDZ binding motif did not cause immortalization or induce anchorage-independent growth. This suggests that the mechanism of oncogenic transformation by E6 in HTECs is dependent on the E6 PDZ binding motif [80]. Spanos *et al.* showed that HPV16 E6 interacts with, and induces the loss of, PTPL1 in a PDZ binding domain-dependent manner. Loss of PTPL1, induced either by the presence of E6 or by a short hairpin RNA strategy, allowed for anchorage-independent growth in mouse and human epithelial cells. Loss of PTPL1 synergized with H-Ras for the invasive growth of xenografts in immune-competent mice. Restoring PTPL1 expression reversed anchorage-independent growth in cells lacking PTPL1 [81]. The same group, in a second study, showed that Her2, which activates Ras, would also cause invasive growth of xenografts of mouse tonsil epithelium (MTE) cell lines stably expressing HPV16 E6 or shPTPL1, but not of MTE cell lines expressing HPV16 E6 with deletion of the PDZ binding motif [82]. Overexpression of Her2, together with HPV16 E6 or shPTPL1 transfection, induced Erk1/2 phosphorylation in this cellular model. Conversely, PTPL1 overexpression in Hek293 cells inhibited Erk1/2 and Mek1/2 activation induced by H-Ras, Her2 or EGF-Receptor transfection. Moreover, a catalytically inactive mutant of PTPL1 was ineffective in the same experiment, indicating that the phosphatase activity of PTPL1 is required for attenuation of MAP Kinase activation [82].

PTPL1 inhibits Src activation

The first connection between PTPL1 and Src was demonstrated through the study of EphrinB phosphorylation and reverse signaling. Indeed, transmembrane EphrinB ligands act as “receptor-like” signaling molecules, which are in part mediated by tyrosine phosphorylation and by engagement with PDZ domain proteins. Src kinase is a positive regulator of EphrinB phosphorylation and phosphotyrosine-mediated reverse signaling. Engagement of the EphB receptor with EphrinB causes rapid recruitment of Src, transient Src activation and phosphorylation of the cytoplasmic domain of EphrinB. In the second step, ephrinB ligands recruit PTPL1 through its PDZ domain and are dephosphorylated. Furthermore, EphrinB and Src are dephosphorylated *in vitro* by the catalytic domain of PTP-BL [83]. Afterwards, reversion-induced LIM (RIL), which is frequently lost in colon and other cancers as a result of epigenetic silencing, was shown to suppress Src activation in a PTPL1-dependent manner. Indeed, RIL interacts and colocalizes with Src and also interacts with

PTPL1. Moreover, knockdown of PTPL1 by siRNA prevents RIL-induced Src inactivation [36]. At the same time, in order to evaluate whether PTPL1 plays a critical role in breast cancer progression, we performed RNA interference experiments in poorly tumorigenic MCF-7 breast cancer cells. PTPL1 inhibition drastically increased tumor growth in athymic mice. However, *in vitro* , PTPL1 did not affect the growth of cells cultivated as cell monolayers on plastic. Therefore, we tested extinction of PTPL1 *in vitro* in more physiological conditions and showed that inhibiting PTPL1 also enhanced cell proliferation on extracellular matrix components (Matrigel and fibronectin) and cell invasion on Matrigel. The Src kinase family plays a major role in the regulation of cell growth induced by cell-matrix interactions in normal and malignant cells [84]. Thus, we hypothesized that PTPL1 regulates breast cancer cell aggressiveness through inactivation of the Src kinase pathway. The inhibition of Src kinase expression drastically blocked the effects of PTPL1 silencing on cell growth. Furthermore, the phosphorylation of Src on tyrosine 419 was increased in PTPL1 knockdown cells, leading to activation of its downstream substrates, Fak and p130cas. Finally, substrate-trapping experiments revealed that Src tyrosine 419 is a direct target of the phosphatase. Thus, we identified PTPL1 as the first phosphatase able to inhibit Src through direct dephosphorylation in intact cells, which could represent a novel mechanism by which PTPL1 inhibits tumor aggressiveness [85].

Other PTPL1 inhibitory actions on cell growth or migration

In addition to the effects of PTPL1 in cancer cells described above, three studies reveal a negative action of PTPL1 on cell growth or migration in normal cells. The first of these studies concerns the interaction between PTPL1 and TRIP6, which was detailed in chapter 2.2 (Proteins interacting with PDZ-2).

The second example is the modulation of pancreatic β-cell proliferation by PTP-BL through an interaction with the Wnt signaling pathway [86]. In pancreatic β-cells, increased expression of HNF1β (Hepatocyte Nuclear Factor lb) led to an enhanced rate of apoptosis and altered regulation of the cell cycle. PTP-BL was identified as an HNF1β-regulated protein in β-cells, and its role was analyzed in INS-1 β-cells. Stably transfected cells were generated, which express either wild-type (WT) or a phosphatase-deficient mutant (PTP-BL-CS) of PTP-BL. Enhanced expression of WT PTP-BL inhibited INS-1 cell growth dose-dependently, but this effect was not observed when PTP-BL-CS was expressed. PTP-BL has been previously reported to interact with components of the Wnt signaling pathway [44], and addition of exogenous Wnt3a resulted in an increase in cell proliferation and a rise in β-catenin levels, consistent with the involvement of this pathway in INS-1 cells. Up-regulation of WT PTP-BL antagonized these responses to Wnt3a, whereas PTP-BL-CS failed to inhibit Wnt3a-induced proliferation. Altogether, these results indicate that PTP-BL plays an important role in the regulation of cell cycle progression in pancreatic β-cells and that it interacts functionally with components of the Wnt signaling pathway [86].

The final study is also concerned with the impact of PTPL1 in pancreatic β-cells, but in regards to an interaction with the IL-4 (interleukin-4) signaling pathway [87]. IL-4 has been reported to mediate a protective effect against the loss of pancreatic β-cells viability after pro-inflammatory cytokines stimulation (IL-1β and interferon-γ). This effect was abrogated by the presence of the PI3K (phosphoinositide 3-kinase) inhibitor, wortmannin, suggesting that activation of the PI3K pathway is involved. Increased tyrosine phosphorylation of STAT6 (signal transducer and activator of transcription 6) also occurred in response to IL-4, and a selective JAK3 (Janus kinase 3) inhibitor reduced the cytoprotective response. Both effects were prevented by overexpression of PTP-BL, indicating that PTP-BL can negatively regulate cell survival of pancreatic β-cells[87].

Alteration of PTPL1 expression or activity in cancer

In addition to the phenotypic changes induced by the overexpression or inhibition of PTPL1, two categories of arguments have been developed to consider PTPL1 as a tumor suppressor or oncogene.

Correlation between PTPL1 expression, transformation, patient survival and resistance to Fas-induced apoptosis

Several laboratories have looked for a correlation between PTPL1 expression and resistance to Fas-induced apoptosis in different cell lines or tissues. Some studies have provided evidence for a high level of PTPL1 mRNA expression in Kaposi's sarcoma [88], pancreatic adenocarcinomas [89] and hepatocellular carcinomas [90] as well as higher expression in T helper cells type 1 (which are resistant to apoptosis) than in T helper cells type 2 (which are sensitive to Fas ligand) [91]. Several groups have shown a positive correlation between PTPL1 expression and resistance to Fas-induced apoptosis in HTLV-I-infected T cell lines [92], ovarian cancer cell lines [93], human pancreatic cancer cell lines [94] and squamous cell carcinomas of the head and neck cell lines [67]. A positive correlation between the percentage of apoptotic tumor cells and the number of FasL-positive tumor infiltrating lymphocytes was observed in PTPL1-negative colon adenocarcinomas, but not in PTPL1-positive ones [62]. Other groups have failed to show any correlation between Fas resistance and PTPL1 expression in colon cancer cell lines [95 –97], prostate cancer cell lines [98], subclones of S49.1 murine T lymphocytes [99], adult T cell leukemia cell lines and Fas-positive human leukemia/lymphoma cell lines [100 , 101], human malignant hematopoietic cell lines [102], ovarian cancer cell lines or cancer specimens [93 , 103]. More recently, Chaudhry *et al.* showed that there was no correlation between PTPL1 expression and apoptosis index in epithelial ovarian cancer after platinum-based chemotherapy [104]. We have evaluated the sensitivity to Fas-mediated apoptosis of three breast cancer cell lines expressing various levels of PTPL1 mRNA: T47D cells, which express high levels of enzyme, wild-type MCF7 cells expressing PTPL1, and the B3 transfectant MCF7 subclone, in which PTPL1

expression has been switched off. T47D cells were sensitive to Fas mediated apoptosis, whereas B3 and MCF7 cells were equally resistant, indicating the absence of a correlation between PTPL1 expression and Fas-sensitivity. Altogether, these studies suggested that in human cells sensitive to Fas-mediated apoptosis, overexpression of PTPL1 inhibits Fas signaling in a cell- and species-specific manner, suggesting the involvement of other partner(s).

The first study addressing PTPL1 expression in normal and cancerous tissue did not permit clear differentiation between normal and cancer tissues. PTPL1 immunostaining was easily detected in numerous normal human tissues, and variable intensities of expression were evident in 123 out of 158 cancers of various origins [105]. Later, Meinhold-Heerlein *et al* . evaluated PTPL1 expression in 95 archival ovarian cancer specimens using tissue-microarray technology. PTPL1 expression was high in normal fallopian tubes and was variable in ovarian cancer, with 93 out of 95 cases containing at least 20% immunopositive cells. This study failed to reveal a significant correlation between PTPL1 immunostaining and response to chemotherapy or survival [93]. Juric et al identified PTPN13 as a marker of yolk sac tumors compared to other germ cell tumors and other common malignant tumors [106]. We analyzed the expression levels of PTP-γ, LAR and its neuronal isoform, and PTPL1 in a training set of RNA from 59 breast tumors using real time PCR methods. We found correlations between the levels of PTPL1, current tumor markers, and survival. We then quantified the expression levels of the selected phosphatase in 232 additional samples, resulting in a testing set of 291 breast tumor RNAs from patients, with a median follow-up of 6.4 years. We observed correlations between the expression of PTPL1 and the differentiation markers. Furthermore, univariate analysis of overall survival demonstrated that PTPL1 was a prognostic factor, together with the progesterone receptor (PR) and node involvement. In multivariate analyses, PTPL1 and PR retained their prognostic value, demonstrating that PTPL1 expression level is an independent prognostic indicator of favorable outcome for patients with breast cancer [107]. Next, we compared PTPL1 expression at the protein level by immunohistochemical analysis of a tissue microarray that contained benign breast tissues, primary infiltrating ductal carcinomas, and 10 matched pairs of primary tumors and lymph node metastases. Although the specimens were heterogeneous, PTPL1 expression in the cancer tissues was significantly lower than in benign tissues, and lymph node metastases showed significantly lower levels of PTPL1 expression than paired primary tumors [85]. At the same time, an analysis of gene expression profiles in response to an mTOR inhibitor in estrogen receptor-positive breast cancer classified PTPL1 in the good prognosis group of genes associated with resistance to the mTOR inhibitor. These results are perfectly consistent with our results indicating that PTPL1 is a prognostic indicator of favorable outcome in patients with breast cancer [107] and that the PI3K/Akt pathway is inhibited in breast cancer cells expressing a high level of PTPL1 [73].

Genetic and epigenetic arguments

Two separate studies indicate genetic polymorphisms in the *PTPN13* gene and susceptibility to a variety of cancers, such as lung squamous cell carcinoma, esophageal cancer [108] and carcinoma of head and neck [109], supporting the link between PTPL1 and tumorigenesis. However, the implications of these polymorphisms on PTPL1 activity are unknown. In clinical human tumors, among the 19 mutations to *PTPN13* that have been reported [75], eight are deletions of the entire catalytic phosphatase domain and two were shown to inhibit phosphatase activity [76]. Furthermore, mutations of the PTPL1 gene were found in 20% of HPV-negative head and neck squamous cell carcinomas [82] and frameshift mutations or mutations affecting the phosphatase domain were identified in hepatocellular carcinomas, suggesting a tumor-suppressive activity of PTPL1 [16]. However, no mutation of the polyadenine tract of PTPN13 was detected in a study addressing 103 colorectal carcinomas [110].

In addition to inactivating mutations in cancer, loss of heterozygosity (LOH) is a hallmark of tumor suppressor genes. *PTPN13* is located in 4q21 [111], a region frequently deleted in ovarian and liver cancers [112 , 112 –114]. Epigenetic regulation of PTPL1 expression was also documented in cancer. In a study using a total of 82 tumor cell lines, Ying *et al* . showed that the expression of PTPL1 was frequently downregulated or silenced in non-Hodgkin's lymphoma (94%, 15 out of 16), Hodgkin's lymphoma (50%, three out of six), breast (30%, three out of 10), gastric (60%, six out of 10) and hepatocellular (67%, eight out of 12) carcinoma cell lines. Methylation was detected by methylation-specific PCR in virtually all of the cell lines with reduced or silenced expression, and in some cell lines, methylation completely silenced the expression of PTPL1 [115]. This result was confirmed in hepatocellular carcinomas, with eight out of 12 tumors (without 4q LOH) presenting significant methylation patterns, i.e., six or more CpGs present in PTPL1 promoter [16].

The last mechanism involved in PTPL1 regulation in cancer is microRNA (miRNA) dysregulation. In a large-scale study identifying miRNA targets on the basis of a strong dysregulation signature of miRNA and mRNA levels between tumor and normal samples, evolutionary conservation of the seed sequence and a strong reverse-correlation of expression level between miRNA and mRNA, PTPL1 was identified as a target of miR185, which was up-regulated in clear-cell renal, kidney and bladder cancers [116]. In contrast, PTPL1 was proposed to be a mir-200c target responsible for Fas-dependent regulation of apoptosis in some cancer cell lines [65]. Indeed, modification of the levels of miR-200 altered the sensitivity of cells to Fas-mediated apoptosis, overexpression of miR-200c induced a loss of PTPL1 expression, and shRNA against PTPL1 restored apoptosis inhibited by an anti-miR-200c [65].

Concluding remarks

The nature of the proteins that PTPL1 interacts with suggests a link between PTPL1 and tumorigenesis or cancer progression. However, in most cases the lack of information about the effects of these interactions prevents the conclusive determination of a positive or negative effect of PTPL1 on tumorigenesis. The positive role of PTPL1 on cell survival has been supported by numerous studies addressing the Fas pathway, suggesting that PTPL1 inhibition can reverse resistance to Fas or carboplatin-induced apoptosis [117]. While Fas itself is finally dephosphorylated, the direct substrate of PTPL1 has not been yet identified in this apoptotic pathway. However, Fas/PTPL1 interaction is essential for this effect and its inhibition using SLV inhibitory peptide can successfully restore apoptosis in some cases. Conversely, PTPL1 can exert positive effects on apoptosis and tumor growth-suppression by affecting various pathways initialized by tyrosine kinases. In the majority of these pathways, the PTPL1 substrates have been clearly identified (Table 1).

It is not surprising that a huge tyrosine phosphatase such as PTPL1 with multiple domains has more than one function depending on the context and tissue. Tissue specificity is clearly insufficient to explain opposite PTPL1 regulatory roles in cancer progression. Indeed, we can observe (Table 2) both positive (↓Apoptosis, ↑cell growth) and negative (↑Apoptosis, ↓ Src activation, ↓ cell growth, ↓ cell invasiveness) impacts of PTPL1 in cancer progression in cells lines established from the same tissue, whenever Fas apoptosis and tyrosine kinases signaling were addressed. This suggests that PTPL1 impact in each cellular context results from the balance between relative influence of Fas and of some tyrosine kinase signaling (Src, IGFI-R, Her2 and unknown substrates). Blockade of Fas-induced apoptosis through diverse mechanisms (loss in Fas expression, p53 mutation...) is a common feature of various tumors, whereas protein tyrosine phosphorylation play a major role in many cellular functions implicated in cancer development and progression. Inhibition of oncogenic tyrosine kinases could therefore constitute the decisive effect of PTPL1 in most cancers in agreement with genetic (mutation and LOH) and epigenetic (methylation) arguments which predominantly support an anti-tumor impact of PTPL1 (Table 3), as do the retrospective clinical studies addressing the prognostic potential of PTPL1 assessment. However, therapeutic strategies that will aim to up-regulate PTPL1 expression or activity will have to take into account the susceptibility of the targeted tumors to Fas-mediated apoptosis. Inhibitors of PTP activity have been evidenced and (or) developed (for inhibitory compound review, see [117]) but no PTP pharmacological activator is presently known underlining the necessity for further studies on the mechanisms by which the expression and the catalytic activity of this phosphatase is regulated.

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Fig. 1

scheme of PTPL1domains and interacting partners. Arrow from the catalytic domain points direct substrates (black) and putative substrates (grey)

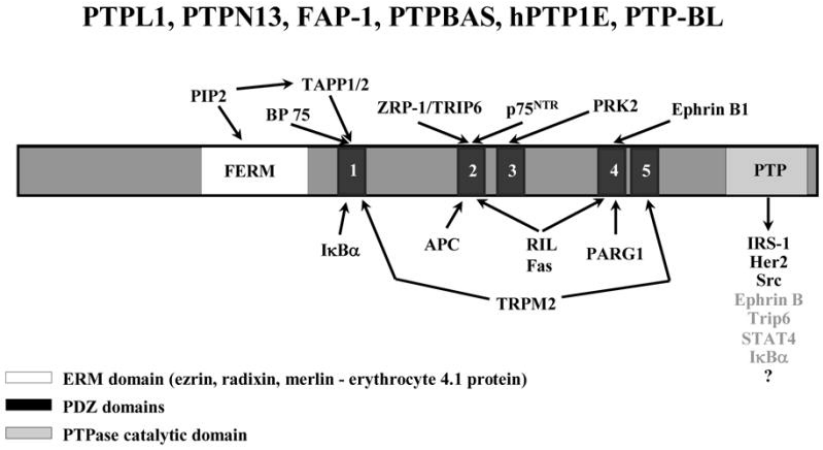

Table 1

Putative substrate of PTPL1 (adapted from *Abaan et al.* 2008 [12]).

Putative substrate	Dephosphorylation		Substrate trapping		Partner (interaction with PTPL1-Wt)	
	in vitro	*in vivo*	*in vitro*	*in vivo*	*in vitro*	*in vivo*
IRS-1	Yes	Yes (transfection full-length dominant negative and PTPL1-Wt, siRNA)	Yes	Yes		
Her2		Yes (transfection full-length PTPL1-WT, si RNA)		Yes		
Src	Yes	Yes (transfection full-length PTPL1-WT, si RNA)	Yes	Yes		Indirect (*via* RIL)
EphrinB1	Yes	Yes (transfection full-length PTPL1-WT)			Yes	Yes (Partial PTPL1)
Trip6	Yes	Yes (transfection full-length PTPL1-WT, si RNA)			Yes	Yes
IκBα	Yes	Yes (partial dominant-negative)			Yes	Yes
STAT4	Yes	Yes (transfection full-length dominant negative and PTP-BL-Wt)				Yes

Table 2

Phenotypic changes that occur upon overexpression or inhibition of PTPL1 expression : organization by tissues and cell lines.

Tissue	Cell lines	Phenotypic Observations	PTPL1 effect
Hematopoietic cells	Jurkat cells	PTPL1 overexpression inhibits Fas apoptosis [8]	↓apoptosis
	U937 myelomono-cytic leukemia cell	SLV inhibitory peptide restores Fas apoptosis [63]	↓apoptosis
Colon	DLD-1	SLV inhibitory peptide restores Fas apoptosis [54]	↓apoptosis
	SW480	PTPL1 overexpression increases Fas apoptosis [61]	↑apoptosis
	HCT-116	Inhibition of PTPL1 expression increases apoptosis induced by Oxaliplatin [64]	↓apoptosis
		Inhibition of PTPL1 expression increases Fas apoptosis [65]	↓apoptosis
		Inhibition of PTPL1 expression prevents RIL-induced Src inactivation [36]	↓ Src activation
	Primary cultured cancer cells	SLV inhibitory peptide restores Fas apoptosis [62]	↓Apoptosis
Stomach	TMK1	PTPL1 overexpression decreases Fas apoptosis [57]	↓apoptosis
Pancreas	Capan-1 pancreatic cancer cells	PTPL1 overexpression decreases Fas apoptosis [58]	↓apoptosis
	Panc89 pancreatic cancer cells	Vanadate induces Fas sensitivity. SLV inhibitory peptide restores Fas apoptosis [58]	↓apoptosis
	INS-1 β-cells pancreatic β-cells	PTPL1 overexpression inhibits INS-1 cell growth and antagonizes Wnt3a proliferative action[86]	↓ cell growth
Melanocytes	FEMX OM431 LU1205	Expression of PTPL1 reduces cell surface Fas level. Inhibition of PTPL1 expression or expression of dominant-negative up-regulate surface Fas levels [59][66]	↓apoptosis
Breast	MCF7	Inhibition of PTPL1 expression fails to restore Fas apoptosis and inhibits antioestrogen-induced apoptosis [73]	↑apoptosis
		PTPL1 overexpression dephosphoryles IRS-1 and inhibits IGF-1 survival signaling [74]	↓ cell growth ↓ cell invasiveness
		Inhibition of PTPL1 expression induces xenograft growth, cell growth on Matrigel, cell invasiveness and Src activation [85]	
	T47D	Inhibition of PTPL1 expression induces cell growth on Matrigel, cell invasiveness and Src activation [85]	↓ cell growth

Brain	D566 Glioblastoma	Inhibition of PTPL1 expression increases Fas apoptosis [60]	↓apoptosis
Ovary	SKOV3	Inhibition of PTPL1 expression promotes invasiveness and Her2 signaling [76]	↓ cell invasiveness
Lung	TIG3 embryonic fibroblasts	Inhibition of PTPL1 expression or expression of dominant- negative up-regulates surface Fas levels [59]	↓apoptosis
	A549	PTPL1 expression is necessary for inhibition by necl2 of Her2 signaling, cell movement and survival [77]	↑apoptosis
Squamous cell carcinomas of the head and neck	PCI-15A Fas resistant	Inhibition of PTPL1 expression increases Fas apoptosis [67]	↓apoptosis
	early-passage human tonsil epithelial cells	Inhibition of PTPL1 expression induces anchorage-independent growth with H-Ras and invasive growth of xenografts. PTPL1 expression reverses anchorage-independent growth in cells lacking PTPL1 [81]	↓ cell growth ↓ cell invasiveness
		Overexpression of Her2 with shPTPL1 transfection induced Erk1/2 phosphorylation. PTPL1 overexpression inhibited Erk1/2 and Mek1/2 activation induced by H-Ras, Her2 or EGF-Receptor transfection [80]	
Ewing's Sarcoma Family of Tumors	TC71	Reduction of PTPL1 protein levels, using an antisense strategy, leads to reductions in both anchorage-dependent and anchorage-independent cell growth induced by EWS-FLI1[68]	↑cell growth
Kidney	HEK293 embryonic cells	Expression of PTPL1 Inhibits LPA induced cell motility [43]	↓ cell invasiveness

Table 3

Alterations of PTPL1 expression or activity in tumor tissues : new arguments for Tumor Suppressor Gene (TSG) or Oncogene (Onco) activity of PTPL1.

	Cancer tissues	Method	Observations	TSG or Onco
Yao H et al 2004	Colon (28 tumors)	IHC	Correlation between apoptotic tumour cells and FasL-positive lymphocytes in FAP-1 negative cancers, but not in FAP-1-positive ones	Onco
Wang et al 2004	Colorectal (211 tumors)	Mutation analysis	Identification of 19 mutations in *PTPN13* gene in tumors among them 8 deleted the catalytic phosphatase domain	TSG
Yeh et al 2006	Liver (24 paired tumorous/non tumorous tissues)	RT/PCR	Significantly decreased expression of FAP-1 in 50% of hepatocellular carcinomas compared with the corresponding nontumorous liver tissues	TSG
	(12 tumors)	Promoter methylation	significant methylation pattern of PTPL1 promoter region in 8 out of 12 hepatocellular carcinomas without 4q21 LOH	TSG
	(70 tumors)	Mutation alanalysis	Missense mutations identified in 7% of primary carcinomas	TSG
Revillion et al 2009	Breast (291 tumors)	RT/PCR	PTPL1 expression level is an independent prognostic indicator of favorable outcome for patients with breast cancer	TSG
Sabine et al 2010	Breast (27 tumors)	Microarray	PTPL1 expression level is in a good prognosis group of genes and is associated with resistance to mTOR inhibitor	TSG
Liu et al 2010	Kidney (25 paired tumorous/non tumorous tissues)	miRNA	PTPL1 is a target of miR185 which is up regulated in clear cell renal cell carcinomas, kidney and bladder cancers	TSG
Glondu-Lassis et al 2010	Breast (5 benign tissues 44 tumors 10 metastases)	IHC	PTPL1 expression in metastases is lower than in cancers and is lower in cancer than in benign tissues.	TSG