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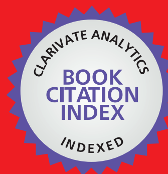

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Chapter

Protein Tyrosine Phosphatases in Tumor Progression and Metastasis: Promoter or Protection?

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Abstract

Reversible phosphorylation of proteins, executed by kinases and phosphatases, is the major posttranslational protein modification in eukaryotic cells, causing them to become activated or deactivated. This intracellular event represents a critical regulatory mechanism of several signaling pathways and can be related to a broad number of diseases, including cancer. Few decades ago, protein tyrosine phosphatases (PTPs) were considered as tumor suppressors. However, nowadays, accumulating evidence demonstrates that a misregulation of PTP activities plays a crucial and decisive role in cancer progression and metastasis. In this chapter, we will focus on the molecular aspects that support the crucial role of PTPs in cancer and in turn make them promising for prediction, monitoring, and rational appropriate therapy selection of individual patients.

Keywords: protein tyrosine phosphatases, cancer hallmarks, tumor suppressor, metabolism, epithelial-mesenchymal transition

1. Introduction

Protein tyrosine phosphorylation plays a key role in cellular biology, once it can create a new recognition site for protein-protein interactions, control protein stability, and specify the protein location, and, more importantly, regulates enzymatic activity. Therefore, this intracellular event represents a critical regulatory mechanism of several signaling pathways and, once it is dysregulated, can be related to a broad number of diseases, including tumor development. Reversible phosphorylation of proteins is controlled reciprocally by both protein tyrosine kinases (PTKs) and protein tyrosine phosphatases (PTPs). These phosphatases are hydrolases that preferentially act on phosphotyrosine residue of a wide range of proteins, having as products dephosphorylated protein at tyrosine residue and inorganic phosphate. PTPs consist of a large protein superfamily with 107 members that can be divided into four families (class I, II, III, and IV) according to differences in the amino acid sequence at their catalytic domains and the amino acid used in the catalytic reaction, cysteine-based PTPs (class 1, 2, and 3) and aspartate-based PTPs (class 4) [1, 2]. So far, most of PTPs have been reported to act as tumor suppressors;

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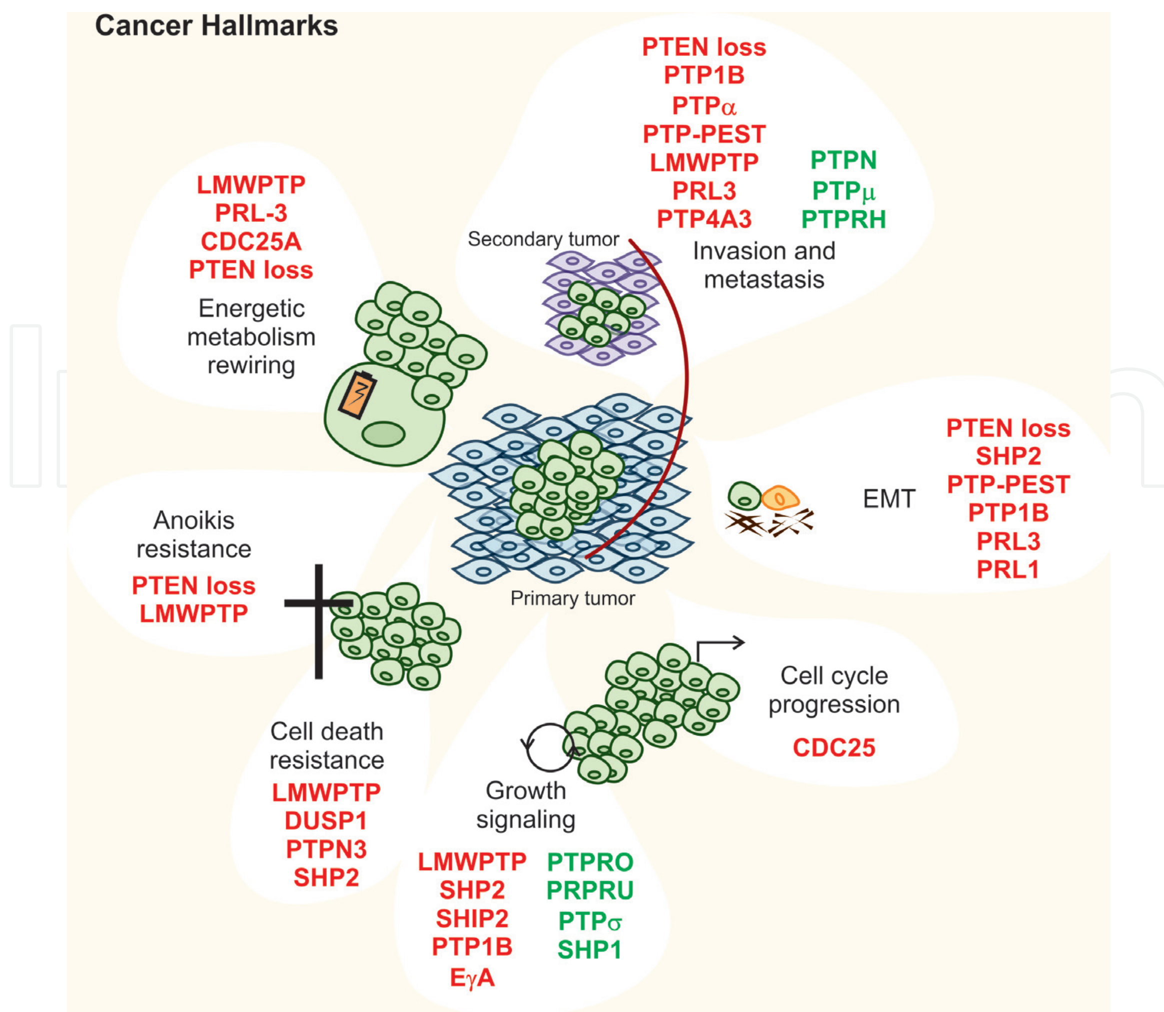

Figure 1.
Schematic overview of the role of PTPs in tumor plasticity. During tumor progression, cells acquire extra mutations and reprogram their metabolism in order to sustain proliferation, migration, and survival. These capacities are in part sustained by key signaling pathways in which PI3K, AKT, MAPK, and mTOR have central roles. In this context, hyperactivation and loss of specific PTPs are crucial for keeping these kinases active.

however, some PTPs can also act as oncogenes depending on the tumor stages or the expression of their interacting partners.

Along human tumor development, cells acquired biological plasticities that were firstly defined by Hanahan and Weinberg, as hallmarks of cancer. These authors proposed some capabilities of cancer cells that contribute for the disease complexity, aggressiveness, and invasiveness: sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, deregulating cellular energetics, avoiding immune destruction, and activating invasion and metastasis [3]. Surprisingly, in the last decade, some reports have shown the relevance of PTPs for tumor cell plasticities. In this chapter we aim to draw an organized picture of the molecular mechanisms by which PTPs take part on tumor biological plasticity acquisition (**Figure 1**).

2. PTPs modulate energetic metabolism in tumors

Under normal conditions, cell metabolism depends on a tightly coordinated regulation of key regulatory enzymes and, consequently, metabolic pathways responsible for converting nutrients into building blocks for synthetic macromolecules, energy production, and biomass. However, cancer cells display efficiency

capacity in reprogramming their metabolism through genetic or epigenetic changes in order to get survival, proliferation, migration, invasiveness, and resistance to death stimuli [5]. In recent years, it has been demonstrated that PTPs display a key role in favoring cancer cell metabolic plasticity.

2.1 PTPs and Warburg effect

Otto Warburg showed that tumor cells substantially metabolize glucose to lactate, even with the availability of oxygen. Under normal conditions, glucose is metabolized to pyruvate by a series of enzymatic steps in the glycolytic pathway, which is subsequently oxidized by the TCA and respiratory chain, generating CO_2, H_2O, and 32 or 34 molecules of ATP per glucose molecule, while in glycolysis, 2 ATPs/glucose are produced. This alteration in glucose metabolism depends on increased transcription of GLUTs, glycolytic enzymes, and oncogenes and increased demand of mitochondrial metabolism for biosynthetic processes [4–6].

Until a few years ago, the importance of protein kinases for the Warburg effect had been focused on several studies. However, recently, in the discovery that PTPs also have relevance in tumor onset and progression, attention has been given to the role of these phosphatases in tumor metabolism, as it is the case of Cdc25A, LMWPTP, PRL-3, and PTEN.

Cdc25A—Until 2016 it was believed that the relevance of Cdc25A in cancer was due to its positive effect on CDK. However, Liang and collaborators [7] performed an elegant study showing the Cdc25A as a positive regulator of PKM2 in human glioblastoma specimens. PKM2 catalyzes the conversion of phosphoenolpyruvate to pyruvate, the last step of glycolysis pathway. These authors described that the EGFR activation triggers the phosphorylation of Cdc25A at Y59 residue, mediated by Src. Consequently, the interaction between Cdc25A and PKM2 is favored at a nuclear compartment, leading to PKM2 dephosphorylation at S37, and in turn induces PKM2-dependent β-catenin transactivation and c-Myc-upregulated expression of the glycolytic genes *GLUT1*, *PKM2*, and *LDHA* [7].

LMWPTP—Our group demonstrated that, in chemoresistant chronic myeloid leukemia cells, the LMWPTP was overactivated and cooperated to Warburg effect. A downregulation of mitochondrial proteins—PDH1, SDHA, and VDAC— was also observed, while GLUT 1 expression and production of lactate were increased [8]. Later on, Lori and colleagues performed a phosphoproteomic analysis of A375 melanoma cells with silenced LMWPTP. These authors identified six possible substrates, of which four, PKM2, GAPDH, α-enolase, and triose phosphate isomerase, take part in the glycolytic pathway. In contrast to the findings reported by Faria and coworkers, it was observed that the inhibition of LMWPTP leads to an inactivation of PKM2, which causes a decrease in glycolytic flux and increase of GLUT1 and hexokinase 2 [8, 9].

PRL-3—It was reported that when colorectal cancer cells (LoVo cell line) overexpress, this phosphatase had an increase of glucose consumption and lactate production in comparison to LoVo cell line wild type. Accordingly, high amount of HK2, PKM2, and LDH were detected when PRL-3 is overexpressed [10]. Importantly, these authors also reported similar results when patient colorectal carcinoma samples were screened. PRL-3 displays a lower expression level in adjacent normal tissue but was overexpressed in colorectal carcinoma lesions. Furthermore, there was a positive correlation between the expression of glycolytic enzymes (GLUT1, HK2, PKM2, LDHA) and PRL-3.

PTEN—In different models (MEFs, prostate cancer cell lines, xenografts, genetically modified mouse and patient prostate cancer samples), the loss of PTEN specifically increases the expression of HK2 [11]. More recently, it was reported that

the knockdown of PTEN in prostate cancer cells (DU145 cell line) leads to an increase of lactate, pyruvic acid, succinic acid, citric acid, fumaric acid, malic acid, and 2-ketoglutarate, in comparison to DU145 wild type [12]. These findings indicate that glycolysis and glutaminolysis pathways are active in prostate cancer DU-145 cells when PTEN is not functional. Accordingly, it was demonstrated that the PTEN higher expression compromises the proliferation and Warburg effect, in melanoma and breast tumor, by dropping the expression of HIF1 and increasing the mitochondrial function, which are, at least in part, caused by decreasing glucose uptake and inhibiting PI3K/mTOR pathway [13–16].

2.2 PTPs and glutamine/lipid metabolism

Some tumor cells become "addicted" to glutamine, once this amino acid can provide energy and substrates necessary for cell division. As a consequence, the tumor increases the mass of tumor cells and controls the potential redox through the synthesis of NADPH [17]. PTEN knockdown, in prostate cancer, reduces the protein level of GLS, enzyme involved in the glutaminolysis pathway, and increases the FASN expression [12]. Tumor cells also exhibit substantial alterations in lipid metabolism. During fast growth and aggressive progression, tumor cells required many metabolic intermediates and coordinate the activation of lipid synthesis leading to membrane formation, energy storage, and second messenger production [17, 18].

3. PTPs favor tumor growth through survival positive regulation, and cell death resistance

While normal cells tightly control the synthesis, secretion of growth factors, and proliferative signaling pathways, in order to ensure cellular homeostasis, cancer cells carry one or more defects along the signaling pathways from extracellular compartment, for example, growth ligands and their receptors, to intracellular mediators, such as PI3K, MAPK, and Akt, which give them survival advantages [19, 20]. In this context, PTPs' overexpression through gene amplification, loss, or inhibition contributes for aberrant signaling and, in turn, promoting tumor cell survival as exemplified below:

CDC25A, CDC25B, and CDC25C—CDC25A regulates cell cycle transition, from G1 to S phase, where it activates the cyclin E/CDK2 complex, whereas the phosphatases CDC25B and CDC25C act in the G2/M phase progression [21, 22]. Deregulations of these enzymes are correlated with imbalance in the cell cycle, genetic instability, and uncontrolled proliferation. In addition, the high expression level of these proteins is related to tumorigenesis [23, 24]. For instance, the overexpression of CDC25A was related to proliferation of breast, colon, hepatocellular, ovarian, lung, and nonmelanoma cancers [25]. Besides propitiating cancer cell proliferation, it was reported that CDC25A modulates Foxo1, consequently activating the expression of matrix metalloproteinase (MMP)-1, key mediator of cell dissemination. Moreover, the CDC25B overexpression was associated with gastric cancer, and its knockdown reduces the proliferation rate of gastric cells [26].

EYA—EYA dephosphorylates tyrosine residues of H2AX, a protein involved with DNA repair that prevents cell death caused by damage to the DNA molecule. Chemical inhibition of EYA phosphatase diminished angiogenesis and tumor growth [27]. WD-repeat-containing protein 1 (WDR1) is a specific substrate of EYA3; thus, this PTP can modulate cytoskeletal reorganization [28]. Another identified substrate of EYA is ERβ, which its dephosphorylation decreases the antitumor potential [29].

LMWPTP—In normal cells, the increase of LMWPTP expression was associated with a reduction of PDGFR phosphorylation, consequently dropping in the mitogenic capacity [30]. However, later on, LMWPTP was described as a positive modulator of Ras-MAPK, FGF, and Eph receptors [31, 32]. It was also reported that the overexpression of LMWPTP contributes for invasive profile and primary sarcoma formation in nude mice [33]. In this context, higher LMWPTP amount (mRNA and protein) in primary human prostate cancer in relation to normal adjacent tissue was found. Interestingly, the high level of mRNA of LMWPTP was detected in lymph nodes, an indication that this phosphatase takes part in the metastasis process [34]. In the same study, 147 patients out of 481 with prostate cancer presented higher expression of LMWPTP and worse clinical outcome [34]. Accordingly, the LMWPTP has been categorized as a potential biomarker for recurrence prediction for prostate cancer [35]. The importance of the LMWPTP in cancer progression was also reported in colorectal cancer. It was demonstrated that the LMWPTP overexpression in colorectal cancer correlated to a higher potential to liver metastasis [36]. Importantly, it was also demonstrated that the LMWPTP knockdown decreases CRC cell survival and sensitizes them to chemotherapy [36].

PTP1B—PTP1B is overexpressed in several cancers, such prostate, ovarian, stomach, and colorectal [37–40]. For instance, in esophagus squamous cell carcinoma, this phosphatase overexpression is directly related to invasion and metastasis [38]. Similar effect was described in lung cancer, which was due to Src and Erk activation. Interestingly, the PTP1B knockdown in colorectal cancer cells decreases proliferation rate by blocking β-catenin signaling, a pathway responsible for supporting the cancer secondary site colonization [39, 41].

SHIP2—SHIP2 positively affects tumor cell proliferation and migration. For instance, it was observed that the overexpression of SHIP2 in colorectal cancer was associated with migration and invasive profile through AKT activation [42].

SHP2 (PTPN11)—SHP2 (PTPN11) propiciates activation of Ras and MAPK triggered by mitogens (insulin, EGF, and lysophosphatidic acid) and cell adhesion. Notably, it has been shown that this phosphatase controls cell shape by contributing to cytoskeletal organization. In addition, SHP2 also regulates integrin-mediated cell adhesion, spreading, and migration. Also, inhibition of SHP2 is accompanied by expressive increase in the numbers of actin stress fibers and focal adhesion contacts. In contrast, overexpression of the SHP2 mutant also increased the strength of cell-substratum adhesion [43]. SHP2 has been considered as a proto-oncogene in several human cancers such as leukemia, glioblastoma, gastric carcinoma, lung cancer, and breast cancer. This phosphatase improves cancer progression and poor prognostic by activation of Ras/Raf/ERK and PI3K/Akt/mTOR pathways [44]. In hepatocellular carcinoma, the overexpression of SHP2 correlates with malignant cancer profile. Accordingly, it was reported that the inhibition of SHP2 diminishes metastasis by inhibition of cell adhesion and migration [45].

During cell transformation to malignancy, tumor cells became expert in overcoming a broad diversity of stresses, such as uncontrolled signaling regulation, starvation, DNA damage, hypoxia, and also anticancer therapy. In this aspect, different researchers have shown that PTPs are involved in tumor cells resistant to chemotherapeutic agents.

DUSP1 or PTPN10—It was shown that DUSP1 inhibits the MAPK (JNK) by dephosphorylation and in turn blocks apoptosis process. This effect might be one of the explanations in which DUSP1 promotes cancer cells escaping from apoptosis. Indeed, it has been reported that DUSP1 is involved in many cancers: gastric intestinal, lung, breast, squamous cell carcinoma, and head and neck [46].

LMWPTP—Our group has reported that in chemoresistant human chronic myeloid leukemia cells (Lucena-1), LMWPTP is around 20-fold more active than in

their sensitive counterpart (K562). Importantly, the knockdown of LMWPTP in Lucena-1 cells reverted chemoresistance to vincristine and imatinib mesylate and culminated in inactivation of Src kinase and Bcr-Abl. Both kinases are well known to have a relevant contribution in leukemogenesis [47].

PTPN3—Wang and collaborators [40] performed a very elegant study, in which they found somatic mutations in six PTPs, including PTPN3, in colorectal, lung, breast, and gastric cancers. Later on, it was reported that PTPN3 induces drug resistance (cisplatin and doxorubicin) in ovarian cancer [48].

SHP2—A study using a RNA interference-based genetic screen in BRAF-mutant colon cancer cells identified the SHP2 as one of the key mediators of intrinsic and acquired resistance. Once this phosphatase maintains the receptor tyrosine kinases activated, even in the presence of BRAF inhibitor, it is still possible to have activation of cell proliferation and survival through involvement of ERK [49].

4. PTPs contribute for metastasis through extracellular matrix remodeling and epithelial-mesenchymal transition

In this chapter subtitle, we will focus on strategies for migration and invasion as part of the metastasis process.

PTPs activate the extracellular matrix remodeling and epithelial-mesenchymal transition. ECM is a three-dimensional noncellular scaffold crucial for life in multicellular organisms which is dynamically and continuously remodeled. ECM is mainly composed of water and almost 300 proteins, for example, collagens (fibrillar forms such as I–III, V, XI and non-fibrillar forms), proteoglycan (aggrecan and glycosaminoglycan such as heparin sulfate and hyaluronic acid), and glycoproteins (especially elastin, laminins, and fibronectin) [50, 51]. This essential component is considered an extremely organized meshwork in a strict contact with cells providing both biochemical and biomechanical support. It is well known that despite the physical support to cells, ECM also modulates cell differentiation, migration, and proliferation [50, 52]. Therefore, abnormal ECM remodeling (exacerbate deposition or degradation) can be observed during pathological conditions such as fibrosis and cancer [50, 52]. In tumor microenvironment, much of the ECM proteins are produced not only by stroma cells, e.g., cancer-associated fibroblasts [52], but also tumor cells can produce ECM proteins [53]. Malignant transformation is characterized by changes in the organization of cytoskeleton resulting in abnormal cell signaling related to cell-cell and to cell-ECM adhesion, a phenomenon termed epithelial-mesenchymal transition (EMT). EMT consists of the loss of epithelial cell characteristics to possess properties of mesenchymal cells. Several studies have shown that the EMT contributes to tumor progression, invasion, metastasis, and acquisition of therapeutic resistance. During the EMT process, the cancer cells acquire a fibroblastic morphology with a positive regulation of mesenchymal markers (N-cadherin, vimentin, and α-actin) and a negative regulation of epithelial cell markers (E-cadherin, ZO-1, claudins, occludins, and cytokeratin) as well as a regulation of transcription factors that are associated with increased migratory capacity (Slug, ZEB1/ZEB2, Twist1/Twist2). These factors bind to the E-cadherin gene promoter and repress it [54–56]. EMT requires a rupture of basement membrane permitting invasion and migration of cancer cells through the ECM, then causing remodeling, and creating a tumor-permissive environment [57].

Characteristic loss of E-cadherin-mediated cell-cell adhesion is commonly found during malignant transformation [58] in which process kinases and phosphatases have key roles [59, 60]. Several PTKs, including SRC and EGFR, phosphorylate the

cadherin-catenin complex on different residues, resulting in a loss of cell adhesion [60]. For instance, PTP1B regulates cadherin-based adhesion by dephosphorylating β-catenin at Tyr654 [61]. In addition to β-catenin, p120-catenin phosphorylation increases binding and affinity to E-cadherin, and PTPμ appears to be a regulator of p120-catenin phosphorylation status, also acts as a scaffold, and recruits similar and regulatory molecules to sites of cell adhesion [61, 62]. SHP2 is also able to bind to cadherin-catenin complex and integrin molecules [62].

Cell migration through ECM requires integrin-mediated adhesion as well as turnover of focal adhesions [63]. A decrease in tyrosine phosphorylation by PTPs is involved in the formation and disassembly of focal adhesions. For instance, PTPα is required for the activation of Src kinase following integrin interaction [64], and the dephosphorylation of p130 CRK-associated substrate, by PTP-PEST, is necessary for disassembly of focal adhesions, enabling cell migration [64]. The relation between PTPs and upstream regulators of cell matrix adhesion and Rho family of small GTPases has also been shown [65]. Most Rho proteins have intrinsic GTPase activity which is stimulated by GTPase-activating proteins (GAPs), and these GAPs are modulated by phosphorylation at tyrosine sites. Consequently, PTPs can influence Rho protein activation through regulating the phosphorylation state of GAPs. Sastry and colleagues showed that PTP-PEST overexpression reduces Rac1 (a kind of G protein) activity resulting in protrusion and retraction during cell migration [66]. On the other hand, SHP2 seems to have some contradictory action, while some literatures reported a RhoA activity inhibition by SHP2 [67] and others suggested a stimulation [43]. In addition, p190RhoGAP, a GAP for RhoA, is a target for SHP-2 and LMWPTP and, in turn, regulating cytoskeletal rearrangement [68].

Metalloproteinases (MMPs) are one of the most important ECM-remodeling enzymes produced by tumoral cells, which are linked to tumorigenesis and metastasis [69]. More recently, it was reported that MMPs promote cell survival, angiogenesis [69], and induction of EMT [70]. Hwang and coworkers [71] observed that the treatment of MCF-7 breast cancer cells with BVT948 (a PTP inhibitor) decreases invasion through suppression of NF-κB-mediated MMP-9 expression. On the converse side, PTPμ knockdowns resulted in elevated adhesion, invasion, and proliferation of breast cancer cells due to activation of ERK and JNK signaling pathway and consequent elevated MMP-9 activity [72]. It was demonstrated that the overexpression of PRL-3 increased the migration and invasion capacity of DLD-1 colorectal cancer cells, which was dependent on the expression of MMP-7 [73]. Maacha and coworkers demonstrated that the contribution of the PTP4A3 for malignancy of uveal melanoma is related to MMP-14 [74]. Yuan and colleagues found that overexpression of PTPN9 reduces invasion and decreases MMP-2 gene expression in MDA-MB-231 cells through inhibition of STAT3 downregulation [75]. Interestingly, still in the context of breast cancer, William Du and his team [76] analyzed the levels of microRNA-24 in patients with breast carcinoma and found higher content of this microRNA in breast carcinoma samples than in benign breast tissue. They also generated constructs expressing miRNA-24 and studied their functions in vivo and in vitro. In vivo experiments in mice indicated that the expression of miRNA-24 enhanced tumor growth, invasion, and metastasis to the lung and decreased survival. Molecularly, in vitro and in vivo experiments showed high EGFR phosphorylation but repressed expression of PTPN9 and PTPRF due to direct target of these phosphatases by miRNA-24. Consistently, they found in patients with metastatic breast carcinoma a higher phosphorylation of EGFR but lower levels of PTPN9 and PTPRF. Another confirmation was the upregulation of MMP-2 and MMP-11 but downregulation of MMP inhibitor (TIMP-2) which supports the roles of miRNA-24 in tumor invasion and metastasis in breast cancer suggesting miRNA-24 as a potential target for cancer intervention. In another

study, Liu and collaborators [41] observed that PTP1B promotes the aggressiveness of brain cancer through decreasing PTEN levels and, consequently, promoting AKT activation and increasing of MMP-2 and MMP-7. Previously, it was reported that PTP1B promotes gastric cancer cell invasiveness through modulating the expression of MMP-2, MMP-9, and MMP-14 [77]. Another interesting study shows the relationship of PTP1B and interruption of cell adhesion and induction of the *anoikis* effect in cancer cells. Inhibition of PTP1B in breast cancer cells leads to cell death and loss of extracellular matrix fixation, leading to negative regulation of cell adhesion proteins and interrupted actin polymerization. They saw that with the inhibition of PTP1B the activity of Src is consequently decreased by the adhesion pathway and motility is impaired [78].

Besides being involved in ECM remodeling by modulating MMP activities, PTPs (PTEN, SHP2, PTP1B, PRL3, PTP1B, PTRB, and PTPN9) have a key role in signaling cascades that promote expression of EMT markers.

DUSP1—It has been reported that the knockdown of DUSP1 culminates in low migratory and invasive efficiency of non-small cell lung cancer (NSCLC). Similar effect was also observed in in vivo model [79].

PTEN—It has been reported that the loss of PTEN or its negative modulation by phosphorylation or microRNA propiciates EMT. For instance, in lung cancer cells, the inactivation of PTEN stimulated the nuclear translocation of β-catenin and transcription factors snail and slug [80]. The authors also observed that the PI3K/AKT/GSK-3β pathway is essential for inducing EMT in PTEN-knocked-down cells. The relation between PTEN and negative regulation of AKT/β-catenin pathway was also described by Li and colleagues in squamous cell carcinoma of the esophagus [81]. It was observed that the glycan-1, a cell surface proteoglycan, promotes cell proliferation by regulating the PTEN/AKT/β-catenin pathway, which culminates in a positive regulation of N-cadherin and β-catenin and a negative regulation of E-cadherin. In colorectal cancer cells, the loss of PTEN is associated with a change in E-cadherin protein expression which was linked to EMT [82]. Wang and co-authors [83] reported that tetraspanin 1 induced liver cancer cell EMT via the PI3K/AKT/GSK-3β pathway. These authors also show that the PTEN repression was fundamental for this process. In addition to the effects reported above, one event that is associated with PTEN induction of EMT is the dysregulation of microRNAs. Studies have shown that PTEN is a target of some microRNAs. Wu and collaborators [84] showed that MiR-616-3p is upregulated in metastatic gastric cancer cells during angiogenesis process, and PTEN was one of the targets of this microRNA. Li [85] also showed that MiR-181-a is associated with lung cancer cell EMT through inhibition of PTEN protein expression. Another strategy to inhibit PTEN is via TGF-β cascade. The phosphorylation of the PTEN C-terminus leads to a conformational change, consequently provoking the loss of membrane binding and downregulation of PTEN phosphatase activity [86].TGF-β derived from the tumor microenvironment induces malignant phenotypes such as EMT and aberrant cell motility in lung cancers, by at least in part, due to inhibition of PTEN by phosphorylation [87].

SHP2—Sun and coworkers reported that IL-6 induces SHP2 activation by phosphorylation, which was required for breast cancer cell EMT stimulation in response to IL-6 [88]. This phosphatase also has a positive connection in lung cancer cell EMT triggered by TGF-β1 [89]. In addition, these authors identified the protein Hook1 as an interactor of SHP2 and classified this protein as an endogenous negative regulator of SHP2. The expression of Snail and Twist1, key mediators of EMT process, has been positively modulated by SHP2 in oral cancer, via its interaction with ERK1/ERK2 [89].

PTP1B—Hiraga and colleagues reported that PTP1B is one of the mediators of pancreatic cancer cell EMT induced by TGF-β [90].

PRL-1—This phosphatase causes activation of AKT, and inhibition of GSK3β, consequently, contributes for elevated levels of Snail expression and decreased E-cadherin expression. In agreement, the high level of this enzyme was associated with more aggressive phenotype and poorer prognosis in hepatocellular carcinoma patients [46].

PRL-3—**PRL-3** activates the PI3K/PKB pathway and promotes EMT by decreasing PTEN protein expression [23]. In addition, it was demonstrated that expression of PRL-3 in hepatocellular carcinoma patients was positively correlated with the expression of MMPs 1, 9, 10, and 12 [46].

PTRB—Overexpression of PTRB has an opposite effect on EMT markers: decreased the expression of E-cadherin and increased the amount of vimentin [91].

5. PTPs that act as tumor suppressors

Tumor suppressors operate in different ways and compartments to limit cell growth and proliferation. Besides the important contribution of PTPs in cancer progression, some PTPs that act as tumor suppressors are described below:

PTEN—Is a central tumor suppressor, mainly due to its negative effect on key pathways related to cell proliferation, survival, and metastasis: PI3K-Akt–mTOR, NF-κB, and HIF [92, 93]. Therefore, the loss of PTEN, which occurs in the major of the tumors, is correlated with tumor aggressiveness and low response to therapy. In prostate cancer studies, PTEN has been shown to ameliorate the malignant phenotype by dephosphorylating the activator residue of PTK6 (Tyr 342), a kinase related to a cancer aggressive phenotype [94]. In addition, other oncogenic kinases, such as PDGFR and FAK, have been reported as a substrate of PTEN [95, 96]. Although the molecular mechanisms by which PTEN acts as a tumor suppressor are well known, until few years ago, there were not a lot of information about the posttranslational regulation of PTEN. Recently, Park and collaborators [97] have reported two mechanisms of PTEN regulation that directly are connected to its tumor suppressor property: (a) deubiquitination by ubiquitin-specific protease 11 (USP11), responsible for increasing the stability of nuclear and cytosolic PTEN; (b) the level and activity of PTEN are also autoregulated by this phosphatase via PI3K-forkhead transcription factor (FOXO)-USP11 cascade [97].

SHP1 (PTPN6)—Has been described as a major negative regulator of MAPK, JAK/STAT, and NF-κB signaling pathways [98, 99]. Therefore, SHP1 activity is inversely related to cancer development. Indeed, the SHP1 expression in stomach cancer is very weak. Accordingly, the overexpression of SHP1 in stomach cancer cell lines induces a decrease of proliferation, migration, and invasion [100]. In addition, Chen and colleagues showed that SHP1 dephosphorylates and inhibits PKM2, a kinase that stimulates proliferation in hepatocellular carcinoma [46].

SHIP1—Is expressed only in hematopoietic-derived cells and acts as a negative modulator of PI3K pathway [101]. It was described that the PTEN and SHIP1 loss is deeply related to lymphoma survival [102].

PTPN9 (PTP-MEG2)—Low expression of this phosphatase predicted poor survival in patients with hepatocellular carcinoma. It was observed that PTPN9 indirectly inhibits activity of STAT3 and STAT5 through direct dephosphorylation of EGFR and HER2, in breast cancer [46]. In addition, the overexpression of PTPN9 decreases the phosphorylation of AKT protein at its activatory residue, which culminated in diminishing the EMT process efficiency [103].

PTPN12 (PTP-PEST)—Regulates oncogenic tyrosine kinases such as HER2 and EGFR and has a role in modulating EMT. Not surprisingly, it has been decreased or lost in human hepatocellular carcinoma tissues, and by using this carcinoma cell

lines as models, it was demonstrated that PTPN12 downregulation stimulated cell migration [46].

FAP-1 (PTPN13)—Downregulates Src-ERK pathway by inhibiting EphrinB1 [104]. FAP-1 can also interact and dephosphorylate Her2, thus reducing the aggressive potential of tumors that have high expression of this receptor [105]. It was also demonstrated that overexpression of this phosphatase caused an upregulation of the epithelial marker, E-cadherin, and downregulated mesenchymal markers such as Snail, Slug, and MMP-9, which are a strong indication that FAP-1 inhibits EMT in hepatocellular carcinoma progression [46].

DUSP2—It has been shown that DUSP2 is involved in P53-induced cell apoptosis; however, this phosphatase is dramatically reduced in different solid tumors compared to their normal counterparts. Accordingly, it was reported that the diminished DUSP2 leads to prolonged ERK phosphorylation, increased drug resistance, as well as an inflammatory response due to overproduction of prostaglandin in colorectal cancer [106]. It was also reported that DUSP2 knockdown in xenograft tumors promotes higher vessel density and metastasis events from colorectal cancer to the liver [107].

PTPRT (PTPρ)—Is commonly mutated in several types of cancer, including colorectal cancer [40]. Many studies have reported the tumor suppressor potential of this PTP, and among the possible substrates of this phosphatase are paxilin and STAT3 [108, 109].

PTPRH—This phosphatase interacts with Grb2 and then modulates Ras pathway activity. Studies have reported that PTPRH blocks cell growth and migration by dephosphorylating proteins associated with focal adhesion, such as p130 [110].

PTPRD—It has been shown that patients with the high level of PTPRD display better long-term survival rate and low chance of liver cancer recurrence. However, the mechanisms underlying this action are not elucidated.

PTP receptor type F (PTPRF)—Is involved in Src kinase inactivation; therefore, it is not surprising that this enzyme is frequently downmodulated in hepatocellular carcinoma patients and upregulation of PTPRF is associated with better prognosis [46].

PTP receptor type O (PTPRO)—Plays as a chronic lymphocytic leukemia, lung, and breast tumor suppressor by inhibiting proliferation and stimulating apoptosis, at least in part, due to STAT3 dephosphorylation [46].

PTP receptor S (PTPσ)—Is an important negative modulator of EGFR. Therefore, the downregulation of this phosphatase has been connected to decreased overall survival and high risk of postoperative recurrence in HCC patients [46].

6. Conclusions

Over the past two decades of research on PTPs, the field has achieved a great progress in understanding the immense role of these phosphatases in cancer progression. Here, we presented an organized picture that clearly shows the participation/contribution of PTPs as key mediators of cancer plasticity, due to their loss of function or overexpression. In summary the above compendium highlights the importance of PTPs not only in cancer progression but also as potential targets for therapeutic interventions. Indeed, during the transition from good to poor outcome of different cancer subtypes, PTPs are extremely plastic, with the capacity to readjust themselves across a wide spectrum of stimuli. This plasticity of PTPs together with the loss of function of PTP suppressors provides tumor cells with all conditions for growth, proliferation, and survival. Illustrative examples are PTEN (loss), LMWPTP, PRL-3, and PTP1B serving as "signaling hubs" that connect different hallmarks (such as sustaining proliferative signaling, evading growth

suppressors, resisting cell death, deregulating cellular energetics, and activating invasion and metastasis). This connection might explain, at least in part, the great capacity of tumor cells' plasticity.

Acknowledgements

Our research on this field has been supported by Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) (grant 2015/20412-7) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) (grant 303900/2017-2).

Conflict of interest

The authors declare no conflict of interest.

Appendices and nomenclature

130 CRK	p130 Crk-associated substrate (member of an adapter protein family that binds to several tyrosine-phosphorylated proteins)
AKT	also known as *protein kinase B (PKB)*, is a serine/threonine-specific protein kinase
Bcr-Abl	tyrosine-protein kinase
Cdc25	dual-specificity phosphatase
CDK2	*cyclin-dependent kinases*
DUSP1 (PTPN10)	dual-specificity protein *phosphatase* 1
DUSP	dual-specificity protein *phosphatase*
ECM	extracellular matrix
EGFR	epidermal growth factor receptor
EMT	epithelial-mesenchymal transition
Eph	ephrin
ERbeta	estrogen receptor beta
ERK	extracellular signal-regulated kinase
Eya	eyes absent
FAK	focal adhesion kinase
FGF	fibroblast growth *factor*
FOXO-1	forkhead box protein O1
GAPDH	glyceraldehyde 3-phosphate dehydrogenase
GAPs	GTPase-activating proteins or GTPase-accelerating proteins
GLS	glutamine synthetase
GLUT	glucose transporter 1
GSK-3beta	glycogen synthase kinase 3 beta
H2AX	H2A histone family member X
HIF	*hypoxia-inducible factor*
HK	hexokinase
JAK	Janus kinase 2
LDHA	lactate dehydrogenase A
LMWPTP	low-molecular-weight protein tyrosine phosphatase, also known as ACP1
MAPK	mitogen-activated protein kinase

MEF	mouse embryonic fibroblast
MMP-1	matrix metalloproteinase-1
mTOR	mammalian target of rapamycin
NFKB	nuclear factor kappa-light-chain-enhancer of activated B cells
PI3K	phosphatidyl inositol-3-kinase
PKM2	pyruvate kinase isozymes M2
PRL-3	phosphatase of regenerating the liver-3, also recognized as PTP4A3
PTEN	phosphatase and tensin homologue
PTKs	protein tyrosine kinases
PTP σ	protein tyrosine phosphatase sigma
PTP μ	protein tyrosine phosphatase
PTP-PEST (PTPN12)	PTP-PEST (PTP—proline, glutamic acid, serine, and threonine rich)
PTP1B	tyrosine-protein phosphatase non-receptor type 1
PTPN3	protein tyrosine phosphatase non-receptor type 3
PTPN11	protein tyrosine phosphatase non-receptor type 11
PTPN13	PTP also referred to as FAP1
PTPN9	tyrosine-protein phosphatase non-receptor type 9
PTPRδ	protein tyrosine phosphatase receptor delta
PTPRF	protein tyrosine phosphatase receptor type F
PTPRH	receptor-type protein tyrosine phosphatase H, also referred to as stomach cancer-associated protein tyrosine phosphatase-1 (SAP-1)
PTPRO	protein tyrosine phosphatase receptor type O
PTPρ	protein tyrosine phosphatase receptor T
PTPs	protein tyrosine phosphatases
Raf	serine/threonine-specific *protein* kinase
Ras	class of protein called small GTPase
Rho	Ras homologue of small *GTPase*
RhoA	Ras homologue of small *GTPase* member A
SHIP1	Src homology 2 (SH2) domain-containing inositol polyphosphate 5-phosphatase 1
SHIP2	Src homology 2 (SH2) domain-containing inositol polyphosphate 5-phosphatase 2
SHP1	Src homology 2 (SH2) domain-containing phosphotyrosine phosphatase, also known as PTPN6
SHP2	Src homology 2 (SH2) domain-containing phosphotyrosine phosphatase 2, also known as PTPN11
Slug	*SNAI2*, a zinc finger transcription factor
Src	proto-oncogene tyrosine-protein *kinase*
STAT3	signal transducer and activator of transcription type 3
TCA	tricarboxylic acid cycle
TGFbeta	transforming growth factor beta
Twist	*Twist*-related *protein*
WDR1	WD-repeat-containing protein 1
ZEB 1/2	zinc finger E-box-binding homeobox ½

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