Clinical Cancer Research

Molecular Pathways: Targeting Protein Tyrosine Phosphatases in Cancer

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Abstract

The aberrant activation of oncogenic signaling pathways is a universal phenomenon in cancer and drives tumorigenesis and malignant transformation. This abnormal activation of signaling pathways in cancer is due to the altered expression of protein kinases and phosphatases. In response to extracellular signals, protein kinases activate downstream signaling pathways through a series of protein phosphorylation events, ultimately producing a signal response. Protein tyrosine phosphatases (PTP) are a family of enzymes that hydrolytically remove phosphate groups from proteins. Initially, PTPs were shown to act as tumor suppressor genes by terminating signal responses through the dephosphorylation of oncogenic kinases. More recently, it has become clear that several PTPs overexpressed in human cancers do not suppress tumor growth; instead, they positively regulate signaling pathways and promote tumor development and progression. In this review, we discuss both types of PTPs: those that have tumor suppressor activities as well as those that act as oncogenes. We also discuss the potential of PTP inhibitors for cancer therapy. *Clin Cancer Res; 23(9); 2136–42. ©2017 AACR.*

Background

Signal transduction is a complex process that transmits extracellular signals effectively through a cascade of events involving protein phosphorylation/dephosphorylation to produce a broad spectrum of signal responses. Protein phosphorylation, mediated by protein kinases, is a reversible posttranslational modification that leads to the activation of signal transduction pathways involved in cell biological processes, such as growth, proliferation, metabolism, differentiation, and cell death. Uncontrolled activation of these pathways results in abnormal cell growth and proliferation leading to tumorigenesis. Dephosphorylation of proteins is mediated by protein tyrosine phosphatases (PTP) that lead to the termination of signaling pathways, resulting in the inhibition of growth, proliferation, and differentiation. In normal cells, the balance between the activation and termination of signaling pathways is accomplished through coordination between these protein kinases and phosphatases, which subsequently controls the amplitude and duration of a signal response. Loss or disruption of the balance of signal pathways is implicated in many human diseases. Dysregulation of this balance in human cancers is due to the hyperactivation of protein kinases or loss of PTPs, which dephosphorylate oncogenic protein kinases. Our recent study was the first report to extensively profile the expression of PTPs altered in human breast cancer samples (1). In this review, we will discuss tumor suppressor and oncogenic PTPs in cancer and discuss the current status of PTP inhibitors for cancer therapy.

PTPs belong to a superfamily of enzymes that hydrolytically remove phosphate groups from proteins (2). Genome sequencing studies have shown that the human genome includes more than 100 genes that encode PTPs (3, 4). These enzymes function as holoenzymes and share a consensus sequence (known as the HCX_5R motif, where X is any amino acid) in the active site of the enzyme (5). PTPs are classified on the basis of their cellular localization, specificity, and function. Cellular localization determines whether PTPs are grouped as receptor-type PTPs (PTPR), which are localized to the plasma membrane, or non-receptor–type PTPs (PTPN), which are localized in the cytosol. Similarly, based on their specificity, PTPs are grouped into either tyrosine-specific phosphatases or dual-specific phosphatases (which remove a phosphate group from tyrosine and/or serine/threonine residues).

PTPs are broadly classified into two groups based on their function: tumor suppressor PTPs or oncogenic PTPs. These tumor suppressor/oncogenic PTPs may belong to the other groups described above based on their cellular localization and specificity. The loss of tumor suppressor PTP function is often observed in cancer due to gene deletions, mutations, and epigenetic modifications, such as promoter methylation. Loss of these tumor suppressor PTPs leads to the hyperactivation of signaling pathways and promotes tumorigenesis. PTEN is the most frequently mutated phosphatase, leading to hyperactivation of the PI3K signaling pathway in many human cancers. Similar to PTEN, underexpression of inositol polyphosphate-5-phosphatase J (INPP5J) is observed in triple-negative breast cancer (TNBC), and increases *in vivo* PI3K/Akt signaling and oncogene-induced transformation and tumor growth while reducing metastasis in mouse models (6).

Phosphatases as Tumor Suppressors

Several tumor suppressor PTPs have been identified whose loss has been shown to promote tumorigenesis, growth, and

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Table 1. Tumor suppressor PTPs and cancer

PTP	Cancer	Mechanism for reduced expression	Altered signaling pathway	Reference
PTEN	Prostate and breast	Mutations and deletions	PI3K	7–10
INPP5J	Breast	Transcriptional repression	PI3K	2
SHP1	Leukemia and lymphomas	Methylation of promoter	JAK/STAT signaling	27, 28
DEP1	Breast and colon	Mutations and deletions	FLT3, Erk1/2, and Akt signaling	11, 12
PTPRF PTPRG PTPRT PTPN3 PTPN13 PTPN14	Colon, breast, and lung	• Somatic mutations • Deletions • Methylation of promoter regions	• PDGF, Akt, and PLC • JAK and integrin • STAT3 and paxillin • EGFR/MAPK signaling • Src signaling • YAP signaling	17
PTPN12	Breast	Mutations	EGFR, HER2, and mTOR	18
PTPRK	Colon and lymphoma	Methylation of promoter	EGFR and Akt signaling	19, 20
DUSP6	Leukemia, lung, and liver	Methylation of promoter	MAPK signaling	27
DUSP4	Breast, pancreas, and thyroid	Copy number loss	MAPK, JNK, Rb, and NF-κB	13–16
PTPRO	Leukemia, lung, and breast	Methylation of promoter	P53/FOXM1	24–26

metastasis in *in vitro* and *in vivo* models (Table 1). The first tumor suppressor phosphatase identified was PTEN, which was found to be frequently lost or mutated in many human cancers at high frequency (reviewed in refs. 7, 8). PTEN dephosphorylates phosphoinositide substrates, which leads to inhibition of the AKT/PKB kinase cascade. Mutation or loss of PTEN results in unopposed activation of AKT, leading to growth promotion and tumor development. Laboratory studies have shown that deletion of PTEN in normal cells promotes transformation of these cells (9) and that PTEN-deficient mice develop cancers (10).

More recently, other tumor suppressor phosphatases have been identified. These include DEP1 [also known as PTP receptor (PTPR) type J] that is frequently deleted or mutated in many human cancers, including breast and colon cancers (Table 1; ref. 11). Loss of DEP1 is associated with increased growth factor receptor signaling and promotes cell growth (12). Recently, Mazumdar and colleagues identified dual specificity phosphatase 4 (DUSP4) as the most commonly underexpressed protein phosphatase in estrogen receptor–negative (ER^-) breast cancers, and showed that ectopic expression of DUSP4 inhibits the growth and invasive properties of ER^- breast cancer cells by dephosphorylating growth-promoting signaling proteins (13). Similarly, loss of DUSP4 promotes the progression of intraepithelial neoplasms into invasive carcinoma in the pancreas (14). Moreover, loss of DUSP4 activates the activation of the MAPK pathway, thereby promoting a stem cell–like phenotype and dampening the response to neoadjuvant therapy in breast cancer (15, 16).

Further studies identified loss-of-function mutations in six other PTPs in several human cancers (including colorectal, lung, breast, and gastric cancer): PTPRF, PTPRG, PTPRT, PTP nonreceptor type (PTPN) 3 (PTPN3), PTPN13, and PTPN14 (Table 1; ref. 17). Expression of the wild-type form of these mutated genes suppresses the growth of colon cancer cells (17).

Sun and colleagues identified PTPN12 as a tumor suppressor through a genetic screen and showed that PTPN12 inactivation promotes the transformation of mammary epithelial cells through activation of the EGFR/HER2 signaling axis (Table 1; ref. 18). In addition to gene deletions and inactivating mutations, loss of tumor suppressor PTP function may be due to loss of expression by epigenetic modifications in the promoter region. Analysis of the methylation patterns of CpG islands within the promoter regions has revealed that loss of PTPRF, PTPRM, and PTPRK expression is due to hypermethylation in leukemia samples (19). Loss of PTPRK leads to hyperactivation of Akt signaling and promotes colon cancer progression (20). PTPRK also functions as a tumor suppressor by inhibiting the phosphorylation of EGFR (21) and STAT3, and subsequently inhibiting tumor growth and invasive ability (22).

Hypermethylation of promoter regions may suppress the expression of several other tumor suppressor phosphatases. Promoter methylation silences the expression of DUSP6 in primary pancreatic cancers (23) and PTPRO in hepatocellular carcinoma, lung cancer, and leukemia (Table 1; ref. 24). Overexpression of PTPRO induces antiproliferative/transformational and apoptotic properties in leukemia and lung cancer cells (25), and PTPRO promoter methylation is a predictive marker for poor prognosis in $HER2^+$ breast cancer patients (26). Hypermethylation of the SHP1 (PTPN6) promoter has been reported in leukemias/lymphomas, and treatment with a DNA methylation inhibitor reactivated SHP1 expression. Loss of SHP1 is associated with both clinical stage and pathogenesis of leukemia and lymphomas (27). DNA methylase I and STAT3 signaling mediate the silencing of SHP1 expression (28).

Phosphatases as Oncogenes

Recent studies have demonstrated that PTPs can also function as oncogenes to promote tumor development (Table 2). The expression of these oncogenic PTPs is aberrantly elevated in

Table 2. Oncogenic PTPs and cancer

PTP	Cancer	Expression	Altered signaling pathway	Reference
SHP2 (PTPN11)	Breast, leukemia, and gliomas	Overexpression and activating mutations	EGFR/Ras/MAPK	29–35
PTP1B (PTPN1)	Ovarian, gastric, prostate, and breast	Overexpression	Src/Ras/Erk and PI3K/Akt	36–43
PTP4A3 (PRL3)	Breast, gastric, and colon	Overexpression	PDGF, integrin, and EphA signaling	1, 44–46

several human cancers, which lead to tumor formation, growth, and metastasis, ultimately leading to diminished survival.

Src-homology 2 (SH2) domain containing protein tyrosine phosphatase 2 (SHP2), also known as PTPN11, was the first oncogenic PTP to be reported (Table 2). Despite sharing homologous structure and sequence with the tumor suppressor SHP1 (PTPN6), SHP2 functions as an oncogene, and its overexpression has been reported in human leukemia (29) and breast cancers (30). Activating SHP2 somatic mutations were initially identified in patients with Noonan syndrome; however, these mutations are associated with childhood (but not adult) malignancies, such as chronic myelomonocytic leukemia (~35%) and acute myeloid leukemia (31). SHP2 contains two SH2 domains: a PTP catalytic domain, and a C-terminal domain with tyrosine phosphorylation sites and a proline-rich domain that mediate protein–protein interactions. SHP2 is a PTPN that, contrary to tumor suppressor PTPs, positively regulates cell signaling pathways activated by growth factors, cytokines, and hormones and promotes cell growth, motility, differentiation, and survival. Upon EGF stimulation, EGFR activates SHP2 through growth factor receptor bound protein 2 (GRB2)–associated binding protein 1 (GAB1; ref. 32), and several studies have demonstrated that activated SHP2 promotes the Ras/ERK pathway by dephosphorylating RasGAP, a negative regulator of Ras activation (33). A recent study by Bunda and colleagues demonstrates that SHP2 activates the Ras signaling pathway in glioma by dephosphorylating Ras at tyrosine residue 32, which blocks Ras–Raf binding (34). In addition, SHP2 inhibition reduces the growth and invasiveness of breast cancer cells by inhibiting the Ras/ERK and PI3K/Akt signaling pathways (35).

PTP1B, a non-receptor–type oncogenic PTP, also known as PTPN1, is involved in growth factor signaling (Table 2). The *PTP1B* gene is frequently amplified in ovarian, gastric, prostate, and breast cancers and correlates with poor prognosis (36–39). Knockdown of PTP1B reduces cell growth and induces both cell-cycle arrest and apoptosis. Knockdown of PTP1B reduces migration and invasion by reversing the epithelial–mesenchymal transition (EMT) process (40). PTP1B expression is elevated in HER2-transformed human breast epithelial cells and tumors. Knockout of PTP1B or use of a pharmacologic PTP1B inhibitor delays the onset of mammary tumor formation and reduces lung metastasis in the MMTV Her2/NeuT mouse model by reducing Ras/MAPK and Akt signaling (41). Furthermore, tissue-specific overexpression of PTP1B alone induces mammary tumorigenesis (41). Consistently, the elevated PTP1B expression promotes cell proliferation and metastasis in non–small cell lung cancer through the activation of the Src/Ras/ERK and PI3K/Akt signaling pathways (42). However, in contrast to its oncogenic role, PTP1B can also function as a tumor suppressor, as genetic depletion of PTP1B has been shown to accelerate lymphomagenesis in p53-null mice (43).

PTP4A3, another oncogenic PTP (also known as PRL3), is highly expressed in breast, colon, gastric, and liver cancers and has been shown to play an important role in cell proliferation and metastasis (Table 2). Src-dependent phosphorylation of PTP4A3 promotes cell motility and invasion through the activation of Rho (44). In contrast, tyrosine phosphatome analysis has revealed that overexpression of PTP4A3 induces aberrant Src activation, suggesting that PTP4A3 works both downstream and upstream of Src (45). Furthermore, PDGF, integrin, and Eph receptors are key players in PTP4A3-overexpressing cells (45). PTP4A3 directly binds integrin-beta 1, suggesting an involvement in focal adhesion signaling.

den Hollander and colleagues (2016) explored the expression levels of PTPs in 102 human breast cancer samples to identify PTPs that are differentially overexpressed in TNBC. In this study, 146 PTPs were differentially expressed in TNBC as compared with ER^+ breast cancer samples. Nineteen of these PTPs were significantly upregulated and 27 were downregulated in TNBC. Of these 19 upregulated PTPs, the growth of triple-negative compared with ER^+ breast cancer cells was significantly reduced with the knockdown of six PTPs: PTP4A3, phospholipid phosphatase 3 (PPAP2B), discs large homolog associated protein 5 (DLGAP5), cell division cycle 25B (CDC25B), phosphoserine phosphatase (PSPH), and translocase of inner mitochondrial membrane 50 (TIMM50; Table 2). Further screening of these PTPs through anchorage-independent growth assays and cell-cycle progression analyses demonstrated that knockdown of PTP4A3 was found to have the greatest suppression of cell growth. In addition, analysis of publicly available breast cancer datasets revealed that PTP4A3 expression is significantly elevated in TNBC samples, and *in silico* analysis revealed that increased PTP4A3 expression is due to gene amplification in 29% of basal-like breast cancers. Depletion of PTP4A3 reduced TNBC tumor growth *in vivo* by reducing proliferation marker (Ki67), phospho-ERK1/2, and p38 levels while increasing apoptotic markers (1). Highly elevated PTP4A3 expression is also associated with enhanced tumor formation and metastasis by reducing tumor-initiating cells in colon cancer mouse models (46). Collectively, these studies demonstrate that oncogenic PTPs play a critical role in tumor initiation, progression, and metastasis by enhancing signaling pathways and serving as valuable targets for cancer therapy.

Clinical–Translational Advances

It is now clear that several types of human cancer are associated with abnormal PTP signaling. PTPs fall into two broad groups: tumor suppressing and oncogenic phosphatases, with tumor suppressor PTP expression lost in cancers and oncogenic PTP expression elevated in cancers. Increasing evidence highlights the physiologic importance of PTPs in tumor initiation, growth, and invasiveness and has consequently fueled interest in developing PTP-targeted therapies for treating cancer. The concept of targeting PTPs for human diseases initially arose from the discovery that genetic depletion of PTP1B increases insulin sensitivity and resistance to high fat diet–induced obesity (47).

As the disruption and/or loss of tumor suppressor PTP function in cancer is due to gene deletions, mutations, or epigenetic modifications, it is not feasible to reactivate the function or expression of tumor suppressor PTPs that are deleted at both loci. Somatic mutations inactivate six of the PTPs in colon cancer, and there are no drugs currently available that reactivate the wild-type function of these mutant PTPs. The last subset of tumor suppressor PTPs is silenced due to epigenetic modifications (e.g., hypermethylation of the prompter region); however, the specific DNA methylases and/or methyltransferases must be identified to develop DNA methylation inhibitors capable of reactivating PTP expression and thereby serving as potential agents for cancer therapy. To date, the FDA has approved one DNA methylation inhibitor, 5-Aza-cytidine (nucleoside analogue), for the treatment of hematologic malignancies. The expansion of the application of this drug to other cancers with epigenetically silenced tumor

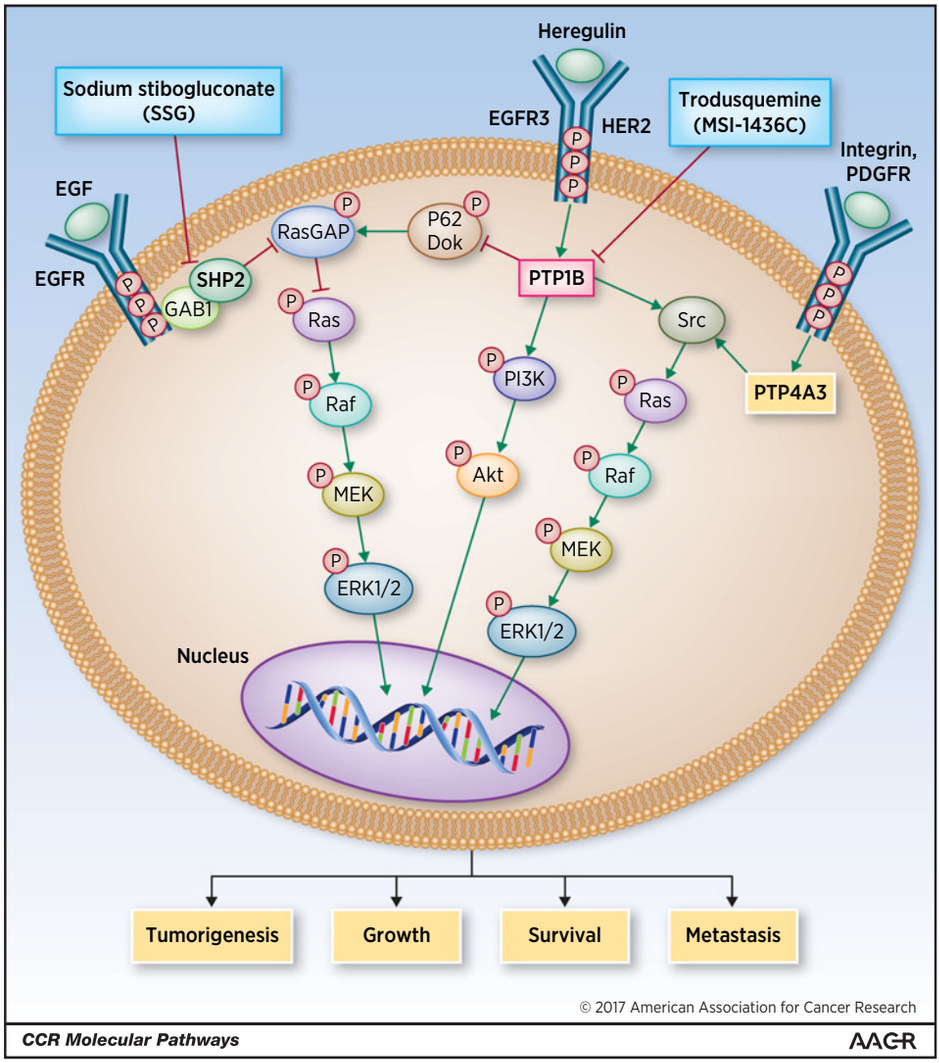

Figure 1.
Targeting molecular pathway. Activation of oncogenic PTPs (SHP2, PTP1B, and PTP4A3) by growth factor receptors promotes tumorigenesis, growth, survival, and metastasis through activating Ras/Raf/MAPK and PI3K/Akt pathways in several human cancers. Targeting these phosphatases reduces tumor formation, growth, survival, and metastatic potential.

suppressor PTPs could greatly impact future cancer therapy and possibly cancer prevention.

Overexpression of oncogenic PTPs has been shown to be critical for tumor development, growth, and metastasis, as evidenced by reduced tumor formation, growth, and lung metastasis in PTP1B knockout MMTV-Her2 mice (39). Similarly, several other studies have demonstrated the importance of oncogenic PTPs, including SHP2 and PTP4A3, in a variety tumor types, as discussed above.

Inhibitors of oncogenic phosphatases

Although oncogenic PTPs are attractive molecules for the development of targeted therapies, the development of PTP inhibitors remains challenging. Selectivity poses a major challenge in developing PTP inhibitors due to the high level of conservation in the active site of both tumor suppressor and oncogenic PTP subtypes. Thus, the inhibitors that target the active sites of oncogenic PTPs also inhibit tumor suppressor PTPs in normal healthy tissues of patients and potentially result in adverse side effects. However, these adverse side effects could be resolved by designing selective PTP inhibitors that bind to regions located externally to the PTP active site.

The oncogenic role of PTP1B has been well characterized using both *in vitro* and *in vivo* models for various human cancers. In 2003, Xie and colleagues reported the first potent PTP1B inhibitor (48). Using a second nonconserved aryl phosphate–binding site adjacent to the active site of PTP1B, Xie and colleagues developed bidentate ligands as PTP1B inhibitors. These bidentate ligands bind to both the active site and a unique adjacent aryl phosphate–binding site. These bidentate PTP1B inhibitors are the most potent inhibitors of PTP1B to date (K_i value, 2.4 nmol/L), providing as much as 1,000- to 10,000-fold selectivity for PTP1B as compared with other PTPs; however, the initial PTP1B inhibitor did not affect cancer cell growth due to a lack of cell permeability properties (48). Therefore, this bidentate ligand was modified with a fatty acid moiety, thereby increasing its cell membrane permeability; the resulting analogue of this compound is highly active in blocking PTP1B and shows remarkable antigrowth effects in several cancer cell lines (49). A number of additional PTP1B inhibitors have also been developed in recent years. Scapin and colleagues developed benzotriazole inhibitors of PTP1B with an IC_{50} of 5 nmol/L; unfortunately, these inhibitors had limited cell permeability (50). Another compound, difluoromethyl phosphonate, developed at Merck, has been shown

Table 3. PTP inhibitors and clinical trials[a]

PTP inhibitor	PTP	Sponsor	CT identifier	Disease	Clinical trial
Trodusquemine	PTP1B	Genaera	NCT00606112	Type II diabetes and obesity	Phase I completed
MSI-1436C	PTP1B	Northwell Health	NCT02524951	Metastatic breast cancers	Phase I (recruiting)
SSG	SHP2	U.S. Army Medical Research and Materiel Command	NCT00662012	Leishmaniasis	Phase I completed
SSG	SHP2	Case Comprehensive Cancer Center	NCT00498979	Stage IV melanoma	Phase I completed
SSG	SHP2	MD Anderson Cancer Center	NCT00629200	Advanced solid tumors	Phase I completed

[a]Data obtained from ClinicalTrials.gov.
Abbreviation: CT, ClinicalTrials.gov.

to significantly delay tumor formation and prevent lung metastasis in MMTV-Her2 mice (41). Through high-throughput screening analyses using enzymatic assays, Wyeth-Ayerst research has identified a potent PTP1B inhibitor, ertiprotafib (51). This drug entered clinical trial for patients with type II diabetes but was stopped after phase II testing showed toxicity concerns. Recently, Genaera developed a noncompetitive PTP1B inhibitor, trodusquemine (MSI-1436C), with an IC_{50} of 1 μmol/L and a 200-fold sensitivity over TCPTP, a tumor suppressor PTP homologous to PTP1B (Fig. 1; Table 3). This drug has been tested in a phase I trial for the treatment of type II diabetes (NCT00606112), and a phase II trial is currently in development (52). Given the significant role of PTP1B in cancer, MSI-1436C is now being tested in a phase I clinical trial for the treatment of metastatic breast cancer (NCT02524951).

As SHP2 overexpression is associated with several human cancers, inhibitors of the SHP2 oncogene also represent attractive agents for the treatment of cancers. However, similar to the specificity issues associated with PTP1B inhibitors, SHP2 inhibitors face problems with selectivity due to the high sequence similarity between SHP2 and SHP1, which functions as a tumor suppressor in opposition to SHP2. Although several research groups and pharmaceutical companies are actively developing SHP2 inhibitors, there are currently no SHP2-specific inhibitors. Sodium stibogluconate (SSG) is a potent inhibitor of both SHP2 and SHP1 and has been used for treating leishmaniasis (Fig. 1; Table 3; ref. 53). SSG represents the first SHP2 drug to enter the clinical trial setting and was studied in combination with IFNα-2b for the treatment of patients with advanced solid tumors, lymphoma, or melanoma. IFNα-2b has been approved by the FDA for the treatment of solid tumors, including advanced melanoma. SHP2 is a negative regulator of IFN signaling pathways, and inhibition of SHP2 by SSG sensitizes IFNα-refractory melanoma tumors to IFNα-2b (54, 55). More recently, Kundu and colleagues identified a quinone-type SHP2 inhibitor with a higher potency than SSG; their studies have shown promising results in both cell-based assays and preclinical melanoma mouse models (56). SSG is currently being tested in a phase I clinical trial for the treatment of leishmaniasis (NCT00662012), stage IV melanoma (NCT00498979), and advanced solid tumors (NCT00629200). Chen and colleagues (in 2015) identified a novel SHP2 inhibitor, fumosorinone (derived from fungi), which selectively inhibits SHP2-dependent signaling and inhibits EGF-induced invasion *in vitro* (57). Similarly, Bunda and colleagues have shown that pharmacologic inhibition of SHP2 by a salicylic acid–based SHP2 inhibitor attenuates growth and progression of gliomas (34, 58).

Future of Phosphatase Inhibitors for Cancer Therapy

Recent research has demonstrated that oncogenic PTPs are attractive candidates for the development of targeted therapies for multiple cancer types. However, the development of specific PTP inhibitors has been challenging, resulting in a lack of effective and safe PTP inhibitors for clinical use. The results of a phase I trial with the SHP2 inhibitor SSG showed that patients with advanced solid tumors and stage IV melanoma well tolerated the concentrations of 900 and 1,200 mg/m^2, respectively (59, 60). Similarly, positive results from the ongoing phase I clinical trial of the PTP1B inhibitor MSI-1436C, defining its safety and tolerability in treating metastatic breast cancer patients, will be instrumental to the translation of this drug to the clinical setting. Although several additional phosphatases have also been shown to be attractive targets for cancer therapy, further research is required to identify specific critical sites located outside the active sites to successfully develop highly specific PTP inhibitors for cancer therapy.

Recent advances in the study of phosphatases in cancer have demonstrated that phosphatases are critical growth-regulatory molecules that are as potentially "druggable" as kinases. However, the fact that many phosphatases are constitutively active and that they are often regulated by subunits or binding partners makes targeting them much more difficult than kinases. The biologic results reviewed here demonstrate that inhibition of oncogenic phosphatases can suppress the growth of human cancers. The challenge now for the scientific and pharmaceutical communities is to discover effective and safe methods to target these cancer-promoting molecules. Once this challenge is overcome, a whole new class of drugs for cancer treatment will become available to treat many life-threatening cancers.

Disclosure of Potential Conflicts of Interest

P.H. Brown is a consultant/advisory board member for Susan G. Komen Foundation. No potential conflicts of interest were disclosed by the other authors.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A. Mazumdar
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): P.H. Brown
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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M.I. Savage, P.H. Brown
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