Receptor-type protein tyrosine phosphatases in cancer

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Abstract
Protein tyrosine phosphatases (PTPs) play an important role in regulating cell signaling events in coordination with tyrosine kinases to control cell proliferation, apoptosis, survival, migration, and invasion. Receptor-type protein tyrosine phosphatases (PTPRs) are a subgroup of PTPs that share a transmembrane domain with resulting similarities in function and target specificity. In this review, we summarize genetic and epigenetic alterations including mutation, deletion, amplification, and promoter methylation of PTPRs in cancer and consider the consequences of PTPR alterations in different types of cancers. We also summarize recent developments using PTPRs as prognostic or predictive biomarkers and/or direct targets. Increased understanding of the role of PTPRs in cancer may provide opportunities to improve therapeutic approaches.

Keywords: Receptor-type protein tyrosine phosphatases (PTPRs), cancer, mutation, deletion, amplification, promoter methylation

Signaling pathways are coordinately controlled by a balance between activators, such as protein tyrosine kinases (TKIs), and inactivators, including protein tyrosine phosphatases (PTPs). To date, cancer biology and drug development has primarily focused on TKIs, with relatively little understanding about the contribution of PTPs to regulate signal transduction in cancer cells\textsuperscript{[1,3,5,7-9,11-13]}. In the human genome, the 107 PTPs can be divided into four families according to differences in the amino acid sequence of catalytic domains and in evolutionary development: class I cysteine-based PTPs, class II cysteine-based PTPs, class III cysteine-based PTPs, and Asp-based PTPs. The largest family of the four, the 99-member class I cysteine-based PTPs, can be further grouped into two subfamilies: tyrosine-specific, or classical, PTPs, which include 21 receptor-type PTPs (PTPRs) and 17 non-receptor PTPs (NRPTPs); and VH1-like dual-specificity phosphatases, which are more diverse and contain substrates in addition to pTyr\textsuperscript{[12,13]}. In PTP1B, the sulfenic acid, which is displayed when the cysteine is oxidized, is converted to a cyclic sulfenamide structure to prevent further irreversible changes of cysteine to sulfonic acid\textsuperscript{[12,13]}. The inactive sulfenamide structure can be reverted to cysteine with reducing agents, thus providing a reversible mechanism of PTPR activation.

Tyrosine phosphorylation has a crucial role in the regulation of physiological processes such as cell proliferation, differentiation, adhesion, and migration, which are closely relevant to human diseases, especially cancer. Genetic and epigenetic alterations such as copy number changes, mutation, and promoter methylation contribute to the expression level and/or function of PTPR proteins. Numerous PTPRs are reported to be involved in a variety of...
cancers[13]. Although PTPRs share similar basic structures and the conserved cysteine in active sites, individual PTPRs have specific targets and thereby play different roles in cancer. This review focuses on the impact of PTPR alterations across a spectrum of cancers and the clinical implications of targeting PTPRs therein.

**Genetic and Epigenetic Alterations of PTPRs**

Genetic alterations that are frequently seen in cancers include mutation, copy number loss/deletion, and copy number amplification. Gain-of-function mutations can increase the activity of an oncogene, and loss-of-function mutations may silence a tumor suppressor gene. Of the 21 PTPRs, 20 are mutated in multiple cancers, per The Cancer Genome Atlas (TCGA) data (summarized in Figure 1). Mutation appears to be the most common mechanism by which PTPRs are genetically modified when compared with copy number amplification or loss.

*PTPR* is the most frequently mutated *PTPR* in human cancers. Wang et al.[13] reported that *PTPR* was mutated in 27% of colorectal cancers (CRCs), 17% of gastric cancers, and 18% of lung cancers. They tested the functional consequences of 5 mutations in the catalytic domains of *PTPR* and all 5 showed reduced phosphatase activity compared with wild-type *PTPR*, indicating that these are loss-of-function mutations[13]. *PTPR* mutation has also been reported in other cancers including head and neck squamous cell carcinoma (HNSCC)[14], acute myeloid leukemia[15], and T-cell large granular lymphocytic[16]. Functional analysis of *PTPR* mutation in HNSCC revealed that normal function, signal transducer and activator of transcription 3 (STAT3) dephosphorylation, was abrogated for the mutant protein[17].

*PTPRD* is the second most commonly mutated *PTPR* across all human cancers. *PTPRD* mutation has been reported in cutaneous squamous cell carcinoma[18], glioblastoma multiforme (GBM)[19], melanoma[19], CRC[20], HNSCC[14], and lung cancer[21,22]. Functional studies of *PTPRD* mutation in neuroblastoma, melanoma, and GBM showed that mutation inactivated the function of *PTPRD* and

![Figure 1. Receptor-type protein tyrosine phosphatase (PTPR) genetic alterations in cancer. Three genetic mechanisms were reported in the Cancer Genome Atlas (TCGA); mutation (green), deletion (blue), and amplification (red). Alterations of 22 *PTPR* family members are summarized across 25 human cancers studied to date (all TCGA, provisional). Including skin cutaneous melanoma, lung adenocarcinoma, gastric adenocarcinoma, bladder urothelial carcinoma, lung squamous cell carcinoma, uterine corpus endometrial carcinoma, sarcoma, colorectal adenocarcinoma, ovarian serous epithelial carcinoma, head and neck squamous cell carcinoma, prostate adenocarcinoma, uterine sarcoma, breast invasive carcinoma, adenocortical carcinoma, soft tissue sarcoma, prostate adenocarcinoma and endocervical adenocarcinoma, glioblastoma multiforme, renal papillary cell carcinoma, lymphoid neoplasms diffuse large B-cell lymphoma, renal chromophobe, hepatocellular carcinoma, acute myeloid leukemia, pancreatic adenocarcinoma, brain lower grade glioma, renal clear cell carcinoma, and thyroid carcinoma. Relative were generated using the number of cases altered by each mechanism divided by the total number of cases examined in each cancer that contain the specific alteration.](image-url)
that cancer cells harboring PTPRD mutations displayed decreased viability, thus suggesting PTPRD acts as a tumor suppressor in these cancers. Wang et al. [15] also reported 6% (3%) PTPRF mutations in CRCs, 1% (9%) in lung cancer, and 1% (9%) in breast cancer. PTPRF mutation was also reported in HNSCC. [16]

Behjati et al. [20] reported 14 PTPRB mutations in 10 of the 39 angiosarcomas studied. In tumors that were secondary and/or had MYC amplification, which is a radiation-associated biomarker of secondary angiosarcoma, the PTPRB mutation rate was up to 45% (10 of 22 cases). PTPRB inhibits angiogenesis, and inactivating mutations of PTPRB are considered driver events in angiosarcoma.

Copy number loss/deletion is common in cancers. Homozygous deletion usually contributes to loss of function of tumor suppressor genes. Many PTPRs negatively regulate cell proliferation, migration, and invasion, and homozygous deletion of these PTPRs may contribute to carcinogenesis. One of the most frequently deleted PTPRs is PTPRD. Homozygous or heterozygous loss of this gene has been reported in cutaneous squamous cell carcinoma [15,16,18], GBM [18,24], lung cancer [25-27], metastatic melanoma [28], neuroblastoma [30], squamous cell carcinoma of the vulva [31], hepatocellular carcinoma [32], and laryngeal squamous cell carcinoma [33]. In addition, PTPRD deletion was reported in pheochromocytomas [25]. Down-regulation of PTPRF, considered a tumor suppressor in many cancers, was reported in liver cancer, gastric cancer, and CRC [30].

Promoter methylation is an epigenetic mechanism of regulating gene expression. Tumor suppressors are often silenced by promoter hypermethylation in cancer. Promoter methylation is also an important mechanism for PTPR inactivation in cancer. PTPRG is hypermethylated in multiple cancers including breast cancer [34], gastric cancer [35], nasopharyngeal carcinoma [36], Lynch syndrome CRC [37], childhood acute lymphoblastic leukemia [38], and cutaneous T-cell lymphoma [39]. PTPRG expression is negatively correlated with methylation, and when treated with methylation-suppressive agents like 5-aza-2’-deoxycytidine, PTPRG expression can be recovered [34,36]. A study of childhood acute lymphoblastic leukemia suggested that PTPRG methylation is induced by Ras mutations [38].

Promoter hypermethylation is also the primary mechanism of PTPRO dysregulation. PTPRO hypermethylation has been reported in hepatocellular carcinoma [40,43], colon cancer [40], lung cancer [41], and chronic lymphocytic leukemia [42]. You et al. [43] explored the potential of PTPRO as a biomarker in esophageal squamous cell carcinoma. They found PTPRO methylation in 75.0% (27 of 36) of solid tumors and 36.1% (13 of 36) of matched peripheral blood samples, whereas no PTPRO methylation was observed in normal peripheral blood from 10 healthy subjects, suggesting PTPRO methylation is an epigenetic biomarker for noninvasive diagnosis of esophageal squamous cell carcinoma [43]. A study of breast cancer showed that PTPRO methylation was associated with lymph node involvement (P = 0.014), poorly differentiated histology (P = 0.037), depth of invasion (P = 0.004), and HER2 amplification (P = 0.001) [44]. PTPRO methylation was detected in 54% (53 of 98) of breast tumors and 34% (33 of 98) of matched peripheral blood samples from patients with breast cancer but in none of the normal peripheral blood samples from 30 healthy individuals [44]. Taken together, PTPRO methylation may represent a biomarker for noninvasive diagnosis and a prognostic factor in breast cancer.

Other PTPRs reported to be hypermethylated in cancer include PTPRD, PTPRF, PTPRJ, PTPRM, PTPRR, and PTPRZ1. In particular, PTPRD was found to be methylated in CRC, breast cancer, HNSCC, and GBM [16]. PTPRF hypermethylation is associated with phenobarbital-induced liver tumorigenesis [45], whereas PTPRJ hypermethylation was induced by microduplications in 2 patients with early-onset CRC [46]. Moreover, Lacmanska et al. [47] reported hypermethylation of PTPRM, PTPRR, PTPRT, and PTPRZ1 in sporadic CRC compared to non-cancer people.

Copy number amplification generally leads to gene overexpression and protein activation and is a common genetic alteration of oncogenes. Several PTPR genes, including PTPRC, PTPRD, and PTPRR, are reportedly amplified in human cancers. PTPRC has the highest proportion of copy number amplifications among the PTPR genes, based on data for all cancers in the TCGA database. More specifically, PTPRC is amplified in 4.1% (212 of 5,130) of tumor samples across 16 cancers including 11.2% (108 of 962) of breast cancer samples and 13.6% (27 of 199) of liver cancer samples. PTPRQ and PTPRR amplifications were detected in a respective 8.7% (13 of 150) and 17.3% (28 of 160) of sarcoma samples in the TCGA repository. Furthermore, in samples in the TCGA repository, melanomas, lung adenocarcinomas, and sarcomas with PTPRR copy number amplifications have higher PTPR mRNA levels than samples without copy number amplifications [48].

PTPRA copy gains have also been reported for some cancers. Junnila et al. [49] conducted an array-based analysis of gene expression and copy number levels using gastric cancer samples and then validated the results using the affinity capture-based transcript analysis (TRAC assay) and real-time quantitative reverse transcription-polymerase chain reaction (qRT-PCR). In their study, PTPRA copy number gain was detected in 5 of 13 primary gastric tumors and 3 of 7 gastric cell lines, and PTPRA overexpression was associated with copy number gain. Ardini et al. [50] reported PTPRA overexpression in 29% of breast cancers and found that high expression of PTPRA was associated with low tumor grade and positive estrogen receptor status. Furthermore, PTPRA overexpression in breast cancer cells inhibited cell growth, causing accumulation of cells in G0 or G1 phase [50].

Other PTPR genes that gain copies in cancer include PTPRF and PTPRH. PTPRH amplification was reported in a small cell lung cancer cell line and has also been observed in liver cancer [51,52]. PTPRH is also overexpressed in CRC [53]. See et al. [54] found no PTPRH expression in normal colon tissue but detected overexpression in 11.8% (2 of 17) of adenoma samples and 40% (19 of 48) of adenocarcinoma samples, suggesting overexpression of PTPRH may occur late in CRC tumorigenesis. Overall, the functional consequences of PTPR gene amplification are not well understood.

In summary, PTPR dysregulation in cancer occurs through several mechanisms. These include mutation, which is the most common mechanism; deletion and promoter methylation, which
cause PTPR inactivation; and gene amplification, though the functional consequences and role of this mechanism require further study.

PTPR Regulation of Cell Signaling in Cancer

PTPRs play important roles in controlling cell signaling. Thus, dysregulation of PTPRs leads to signaling alterations.

Cell proliferation, apoptosis, and survival

PTPR was reported to dephosphorylate c-Src at inhibitory site Y527, thereby inactivating the protein. Ardini et al. reported that PTPRA overexpression in breast cancer cells inhibited cell growth and caused cells to accumulate in G₀ and G₁ phase, suggesting PTPRA plays a tumor suppressor role in breast cancer. In estrogen-receptor-negative breast cancer cell lines as well as colon cancer cell lines, siRNA-mediated knockdown of PTPRA reduced Src activity and induced apoptosis. Meyer et al. found that inhibition of PTPRA reduced the growth of HER2-positive breast cancer cells and decreased Akt phosphorylation.

PTPR is also an important regulator of cell signaling. PTPRE dephosphorylates the C-terminal inhibitory sites of Src, Yes, and Fyn, leading to activation of Src family kinases. Further analysis by Kraut-Cohen et al. reveals that, in the absence of activated HER2, PTPRE inhibits the activity of Shc and thus indirectly inhibits the mitogen-activated protein kinase (MAPK) pathway. However, in the presence of HER2, HER2 binds to the PTB domain of Shc and blocks the interaction of PTPRE to Shc, leading to Src activation.

PTPR was reported to regulate a candidate tumor suppressor, death-associated receptor kinase (DARK), at py491/492 coordinately with Src by dephosphorylating or phosphorylating DARK. In a study...
in hepatoma cells, Bera et al.\textsuperscript{[35]} found that cell-cell contact during cell proliferation activated PTPRF, which in turn inhibited extracellular related kinase (ERK)-dependent signaling. In prostate cancer, overexpression of PTPRF decreased cell survival, inhibited insulin-like growth factor-1 receptor (IGF-1R) phosphorylation, and enhanced poly (ADP-ribose) polymerase (PARP) cleavage in the presence of neuroendocrine-derived medium\textsuperscript{[34]}.

A study of PTPRG's role as a tumor suppressor revealed that PTPRG inhibited breast tumor formation in vivo and that PTPRG up-regulated p21\textsuperscript{WAF1} and p27\textsuperscript{KIP1} proteins through the ERK1/2 pathway in a breast cancer cell model\textsuperscript{[34]}. In nasopharyngeal carcinoma, overexpression of PTPRG suppressed tumor growth in vivo. PTPRG also induced G0/G1 phase arrest through down-regulation of cyclin D1 and stabilization of pRB\textsuperscript{[34]}. Furthermore, PTPRG is considered a tumor suppressor in chronic myeloid leukemia. In addition to interacting with breakpoint cluster region/ABL proto-oncogene 1, non-receptor tyrosine kinase (BCR/ABL) and v-crk avian sarcoma virus CT10 oncogene homolog-like (CRKL) through its intracellular domain, PTPRG, when overexpressed, inhibited BCR/ABL-dependent signaling, whereas down-regulation of PTPRG increased colony formation in chronic myeloid leukemia models\textsuperscript{[35]}.

PTPRH affects signaling events related to cell proliferation, apoptosis, and survival. Takada et al.\textsuperscript{[34]} reported that PTPRH induced apoptotic cell death by at least two potential mechanisms, based on their results using a fibroblast cell line model: inhibiting Akt and integrin-linked kinases, which are both downstream of phosphoinositide 3-kinase (PI3K), and activating caspase activity.

PTPRJ regulates Src activity. Namely, after phosphorylation at Y1311 and Y1320 in a Src- and Fyn-dependent manner, PTPRJ then dephosphorylated the Y529 inhibitory site of Src, activated it, and caused vascular endothelial growth factor (VEGF)-induced phosphorylation of vascular endothelial (VE)-cadherin and contactin\textsuperscript{[34,35]}.

In contrast to PTPRJ, PTPRB suppresses angiogenesis by dephosphorylating VEGFR-2 and VE-cadherin and by inhibiting angio-genesis-related signaling\textsuperscript{[34,35]}.

STAT3 is an important regulator of cell proliferation and survival. Two PTPRs regulate STAT3 phosphorylation at Y705. When mutated, deleted, or hypermethylated in cancer, PTPRT and PTPRD drive hyperactivation of STAT3, which is accompanied by cell proliferation and, likely, migration in multiple cancers\textsuperscript{[73-75]}. \hfill

Migration, invasion, and metastasis

PTTPA is reported to interact with focal adhesion kinase (FAK) at Y407 in breast cancer\textsuperscript{[72]}. Suppression of PTTPA resulted in increases in FAK phosphorylation, formation of new focal adhesion kinase complexes, and increases in migration. Using colon cancer cells as a model, Kndija et al.\textsuperscript{[35]} found that PTTPA expression is required for invasion into the chorioallantoic membrane.

Overexpression of PTTPF inhibited β-catenin phosphorylation and reduced epithelial cell migration. Overexpression of PTTPF also inhibited tumor formation in nude mice\textsuperscript{[34]}. PTTPF has been implicated to connect noninfiltrating GBM tumor cells to the extracellular glycosylated chondroitin sulfate proteoglycans (CSPGs) which serve as the central organizer of GBM tumor microenvironment. Those glycosylated CSPGs are absent in the infiltrating GBM tumor cells\textsuperscript{[75]}.

PTPRH also plays an important role in migration. Expression of PTPRH induced dephosphorylation of p130\textsuperscript{Src}, a focal adhesion-associated phosphotyrosyl protein, as well as FAK and p62\textsuperscript{FAK} in the integrin signaling pathway. Overexpression of PTPRH disrupted the actin-based cytoskeleton and inhibited various integrin-promoted signaling processes\textsuperscript{[36]}.

Overexpression of PTPRJ decreased platelet-derived growth factor receptor (PDGFR) signaling by dephosphorylation and inhibition of the MAPK pathway. However, PTPRJ overexpression also caused a redistribution of cadherin and β-catenin, which results in aberrant cell-substratum interactions\textsuperscript{[27]}.

In conclusion, PTPR alterations collectively play an important role in modulating cell signaling, leading to effects on proliferation, apoptosis, survival, migration, invasion, and metastasis.

Clinical Implications

Few drugs available to date directly target PTPRs. Several studies have investigated the clinical implication of PTPRs in the setting of cancer treatment. PTPRC is reportedly related to response to radiotherapy in the NC1-60 cancer cell collection\textsuperscript{[76]}. A recent report describes a 7-gene signature that predicts relapse and survival for early stage cervical carcinoma, namely PTPRF, ubiquitin-like 3 (UBL3), fibroblast growth factor 3 (FGF3), BM1 proto-oncogene, polycomb ring finger (BMI1), platelet-derived growth factor receptor, alpha polypeptide (PDGFRA), replication factor C (activator 1) 4 (RFC4), and nucleolar protein 7 (NOL7)\textsuperscript{[35]}. Recurrence-free survival was worse for patients with the signature compared with those without\textsuperscript{[77]}. Notably, because PTPRF controls β-catenin signaling, the PTPRF extracellular domain was studied and confirmed as a novel plasma or tissue-based biomarker in prostate cancer\textsuperscript{[36]}.

PTPRF inhibitors are currently in development. Yang et al.\textsuperscript{[35]} used a high-throughput screening assay to identify potential inhibitors of the PTPRF D1 and found that 1 of the 8 candidates showed specificity to PTPRF and was an effective inhibitor. Ajay et al.\textsuperscript{[35]} used in silico assays, including pharmacophore mapping and 3D database searching, followed by SADMET-based virtual screening, docking analysis, and toxicity studies, and discovered 8 nontoxic PTPRF inhibitors. PTPRF's tumor suppressor role has been investigated in many human cancers including breast cancer\textsuperscript{[35]}, pancreatic cancer\textsuperscript{[34]}, and colon cancer\textsuperscript{[36]}. Paduano et al.\textsuperscript{[36]} identified from a phage display library a PTPRF agonist peptide that binds and activates PTPRF, leading to reduced MAPK phosphorylation, increased protein level of cell cycle inhibitor p27\textsuperscript{KIP1}, reduced proliferation, and increased apoptosis. Ortuso et al.\textsuperscript{[35]} also discovered a PTPRF agonist peptide, PTPRJ-pep19.4, and determined that the peptide inhibited in vitro tube formation, ERK1/2 phosphorylation, and proliferation in breast cancer cells but had no effect on primary normal human mammary endothelial cells.

Although there is limited clinical data on drugs that directly target PTPRs, PTPRs have been investigated as biomarkers for treatment
or prognosis in different cancers. In addition, PTPR inhibitors and agonists are under development. Challenges in the development of PTPR-targeted therapies include the homology of PTPR catalytic domains and the susceptibility of the active site of most PTPRs to oxidation. Further research is needed on the effect of current and emerging drugs in vivo.

In conclusion, PTPRs are a group of PTPs that share great structural similarity and play key roles in cell signaling. Alterations of these phosphatases, whether by mutation, deletion, amplification, or promoter methylation, are reported to cause aberrations in crucial cellular pathways related to proliferation, apoptosis, survival, migration, and invasion, suggesting these PTPRs are critical components in carcinogenesis. Therefore, efforts to determine how best to target PTPRs are warranted.

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