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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.

Key words 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[1-3]. 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[4].

In this review, we focus on the 21 PTPRs (including PTPRA, PTPRB, PTPRC, PTPRD, PTPRE, PTPRF, PTPRG, PTPRH, PTPRJ, PTPRK, PTPRM, PTPRN, PTPRN1, PTPRO, PTPRQ, PTPRR, PTPRS, PTPRT, PTPRU, PTPRZ, and PTPRZ1), which are largely homologous in structure and function. PTPRs consist of a transmembrane domain, unequal number of extracellular domains, and intracellular catalytic domains. Immunoglobulin-like domains and fibronectin type III-like domains comprise the extracellular domain of many PTPRs. Twelve of the 21 PTPRs have two catalytic domains arranged in tandem. The catalytic activity mainly resides in the membrane-proximal domain (D1) for many PTPRs with the exception of PTPRA, whose membrane-distal domain (D2) also has some activities[5]. For other PTPRs, the D2 domain has been reported to play an important role in maintaining the stability of the whole protein and regulating protein dimerization[6].

PTPRs are tightly regulated in cell signaling by a variety of mechanisms including post-translational modifications and/or dimerization[7-9]. Reversible oxidation is another important mechanism for regulating PTPR activity. The invariant cysteine residue in the active site of PTPRs has a low pK_a, which makes it susceptible to oxidation[10]. 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 sulfinic or sulfonic acid[11]. 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

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cancers[12]. 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 focus 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.

PTPRT is the most frequently mutated *PTPR* in human cancers. Wang *et al*.[13] reported that *PTPRT* 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 *PTPRT* and all 5 showed reduced phosphatase activity compared with wild-type *PTPRT*, indicating that these are loss-of-function mutations[13]. *PTPRT* 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 *PTPRT* 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

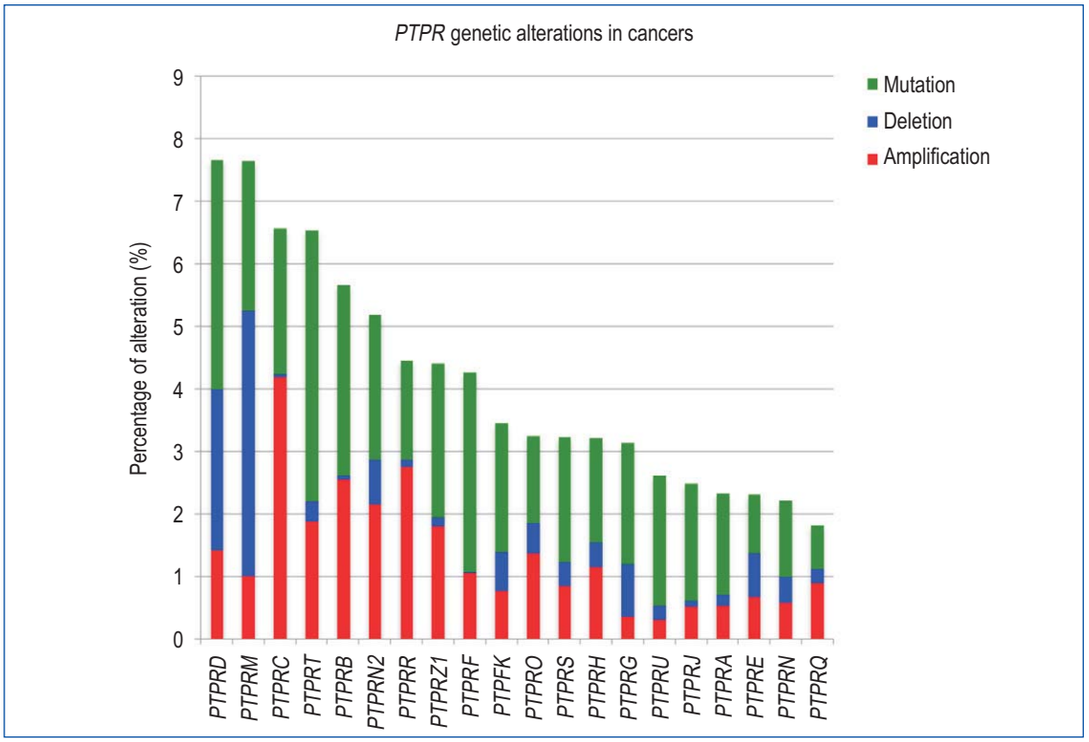

Figure 1. **Receptor-type protein tyrosine phosphatase (*PTPR*) genetic alterations in cancer. Three genetic mechanisms were reported in the Cancer Genome Atlas (TCGA): mutation (green), deletion (blue), and amplification (red). Alterations of 20 *PTPR* family members are summarized across 25 human cancers 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 cystadenocarcinoma, head and neck squamous cell carcinoma, prostate adenocarcinoma, uterine carcinosarcoma, breast invasive carcinoma, adrenocortical carcinoma, cervical squamous cell carcinoma and endocervical adenocarcinoma, glioblastoma multiforme, renal papillary cell carcinoma, lymphoid neoplasm 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. Ratios 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.**

that cancer cells harboring *PTPRD* mutations displayed decreased viability, thus suggesting *PTPRD* acts as a tumor suppressor in these cancers[19,23,24]. Wang *et al*.[13] 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[14].

Behjati *et al*.[25] 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[18,26], GBM[19,24], lung cancer[21,27], metastatic melanoma[28,29], neuroblastoma[30], squamous cell carcinoma of the vulva[31], hepatocellular carcinoma[32], and laryngeal squamous cell carcinoma[33]. In addition, *PTPRF* deletion was reported in pheochromocytomas[34]. Down-regulation of *PTPRF*, considered a tumor suppressor in many cancers, was reported in liver cancer, gastric cancer, and CRC[35].

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[36], gastric cancer[37], nasopharyngeal carcinoma[38], Lynch syndrome CRC[39], childhood acute lymphoblastic leukemia[40], and cutaneous T-cell lymphoma[41]. *PTPRG* expression is negatively correlated with methylation, and when treated with methylation-suppressive agents like 5-aza-2'-deoxycytidine, *PTPRG* expression can be recovered[37,41]. A study of childhood acute lymphoblastic leukemia suggested that *PTPRG* methylation is induced by *Ras* mutations[40].

Promoter hypermethylation is also the primary mechanism of *PTPRO* dysregulation. *PTPRO* hypermethylation has been reported in hepatocellular carcinoma[42,43], colon cancer[44], lung cancer[45], and chronic lymphocytic leukemia[46]. You *et al*.[47] 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[47]. 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)[48]. *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[48]. 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*, *PTPRT*, and *PTPRZ1*. In particular, *PTPRD* was found to be methylated in CRC, breast cancer, HNSCC, and GBM[24]. *PTPRF* hypermethylation is associated with phenobarbital-induced liver tumorigenesis[49], whereas *PTPRJ* hypermethylation was induced by microduplications in 2 patients with early-onset CRC[50]. Moreover, Laczmanska *et al*.[51] 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*, *PTPRR*, and *PTPRQ*, 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% (26 of 150) 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 *PTPRR* mRNA levels than samples without copy number amplifications (**Figure 2**).

PTPRA copy gains have also been reported for some cancers. Junnila *et al*.[52] 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*.[53] 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 G_0 or G_1 phase[53].

Other *PTPR* genes that gain copies in cancer include *PTPRF* and *PTPRH*. *PTPRF* amplification was reported in a small cell lung cancer cell line and has also been observed in liver cancer[18,54]. *PTPRH* is also overexpressed in CRC[55]. Seo *et al*.[55] 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

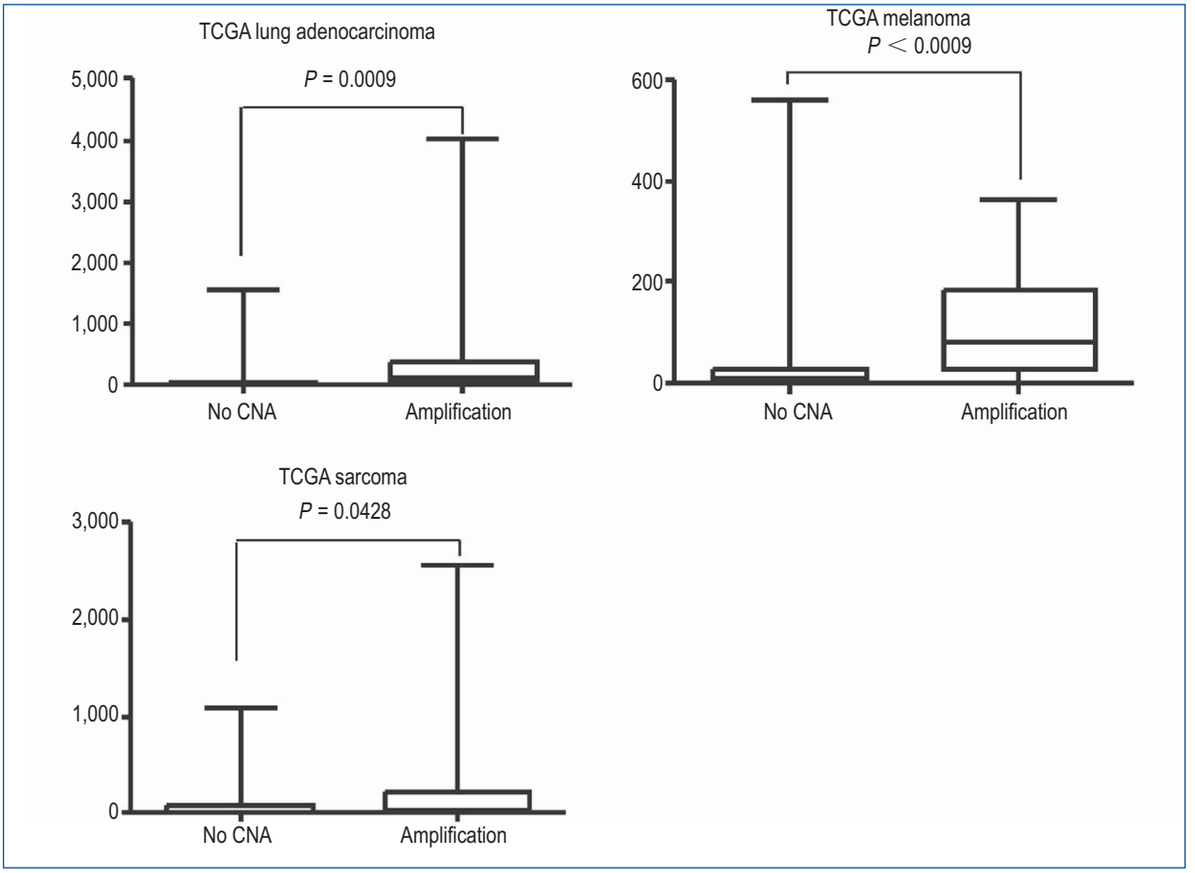

Figure 2. **Protein tyrosine phosphatase receptor type R (*PTPRR*) amplification is associated with *PTPRR* overexpression in lung adenocarcinoma, melanoma, and sarcoma. Unpaired *t* test was used to compare RNAseq values of TCGA samples with and without copy number changes (CNA), namely, 12 lung adenocarcinoma samples with *PTPRR* amplification and 126 samples without copy number alteration, 11 melanoma samples with amplification and 231 without copy number alteration, and 19 sarcoma samples with amplification and 53 without copy number alteration. *PTPRR* mRNA levels were higher in lung adenocarcinomas, melanomas, and sarcomas with amplification compared with those without copy number alterations (respectively, $P = 0.0009$, $P < 0.0001$, $P = 0.0428$).**

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

PTPRA was reported to dephosphorylate c-Src at inhibitory site Y527, thereby inactivating the protein[56]. Ardini *et al*.[53] reported that *PTPRA* overexpression in breast cancer cells inhibited cell growth and caused cells to accumulate in G_0 and G_1 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[57]. Meyer *et al*.[58] found that inhibition of PTPRA reduced the growth of HER2-positive breast cancer cells and decreased Akt phosphorylation.

PTPRA is also an important regulator of cell signaling. PTPRE protein dephosphorylates the C-terminal inhibitory sites of Src, Yes, and Fyn, leading to activation of Src family kinases[59]. Further analysis by Kraut-Cohen *et al*.[60] 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[60].

PTPRA was reported to regulate a candidate tumor suppressor, death-associated receptor kinase (DARK), at pY491/492 coordinately with Src by dephosphorylating or phosphorylating DARK[61]. In a study

in hepatoma cells, Bera *et al*.[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[62].

A study of *PTPRG*'s role as a tumor suppressor revealed that PTPRG inhibited breast tumor formation *in vivo* and that PTPRG up-regulated $p21^{cip}$ and $p27^{kip}$ proteins through the ERK1/2 pathway in a breast cancer cell model[36]. In nasopharyngeal carcinoma, overexpression of PTPRG suppressed tumor growth *in vivo*. PTPRG also induced G_0/G_1 phase arrest through down-regulation of cyclin D1 and stabilization of pRB[38]. 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[63].

PTPRH affects signaling events related to cell proliferation, apoptosis, and survival. Takada *et al*.[64] 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 cortactin[65,66].

In contrast to PTPRJ, PTPRB suppresses angiogenesis by dephosphorylating VEGFR-2 and VE-cadherin and by inhibiting angio-genesis-related signaling[25,67].

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[17,68-71].

Migration, invasion, and metastasis

PTPRA is reported to interact with focal adhesion kinase (FAK) at Y407 in breast cancer[72]. Suppression of PTPRA resulted in increases in FAK phosphorylation, formation of new focal adhesion kinase complexes, and increases in migration. Using colon cancer cells as a model, Krndija *et al*.[73] found that *PTPRA* expression is required for invasion into the chorioallantoic membrane.

Overexpression of *PTPRF* inhibited β-catenin phosphorylation and reduced epithelial cell migration. Overexpression of *PTPRF* also inhibited tumor formation in nude mice[74]. PTPRF 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 glycolsylated CSPGs are absent in the infiltrating GBM tumor cells[75].

PTPRH also plays an important role in migration. Expression of *PTPRH* induced dephosphorylation of $p130^{cas}$, a focal adhesion-associated phosphotyrosyl protein, as well as FAK and $p62^{dok}$ in the integrin signaling pathway. Overexpression of *PTPRH* disrupted the actin-based cytoskeleton and inhibited various integrin-promoted signaling processes[76].

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[77].

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 NCI-60 cancer cell collection[78]. 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*), BMI1 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*)[79]. Recurrence-free survival was worse for patients with the signature compared with those without[79]. 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[80].

PTPRF inhibitors are currently in development. Yang *et al*.[81] 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*.[82] 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. *PTPRJ*'s tumor suppressor role has been investigated in many human cancers including breast cancer[83], pancreatic cancer[84], and colon cancer[85]. Paduano *et al*.[86] identified from a phage display library a PTPRJ agonist peptide that binds and activates PTPRJ, leading to reduced MAPK phosphorylation, increased protein level of cell cycle inhibitor $p27^{Kip1}$, reduced proliferation, and increased apoptosis. Ortuso *et al*.[87] also discovered a PTPRJ 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[12] 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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