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Role of Protein Tyrosine Phosphatases in Cancer

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Abstract

Protein phosphorylation and dephosphorylation are complex enzymatic reactions that are performed by the concerted action of protein kinases and phosphatases, respectively. Deregulation of such coordination due to loss or gain of a single component of the process can result in disease conditions that include, but are not limited to, neoplastic transformation, developmental, autoimmune, and metabolic disorders. Unlike many protein tyrosine kinases that function as oncoproteins, protein tyrosine phosphatases (PTPs) could impart positive or negative effect on cell proliferation. Although past studies have suggested a potential role for PTPs in cancer, the molecular mechanisms of the altered activity/level of these enzymes and the pathological manifestations of these modifications in diseases, particularly in cancer, have not been critically analyzed. This chapter is a comprehensive survey of the alterations of PTPs and the implications of the growth, proliferation, and apoptosis phenotypes attributable to the altered function of this family of phosphatases in cancer. Further, the potential applications of different therapeutic approaches to rectify the adverse effects of alterations in expression of the phosphatase genes and of the phosphatase activity in cancer are discussed.

I. Introduction

Protein phosphorylation plays an important role in several cellular processes, including differentiation, cell growth, adhesion, motility, and apoptosis. Cascading events involving phosphorylation and dephosphorylation of proteins are responsible for transfer of signals from a cell's exterior to its ultimate target in the cytoplasm or nucleus. The membrane proximal signaling generally involves tyrosine phosphorylation, which is regulated by the concerted actions of protein tyrosine kinases (PTKs) and protein tyrosine phosphatases (PTPs). Aberrations in this fine-tuned regulation of protein phosphorylation can result in altered cellular processes like uncontrolled cell growth, a dedifferentiated phenotype, defective apoptosis (all characteristics of neoplastic disease), and in some cases also increased cell migration (characteristic of metastatic disease). PTKs comprise a majority of the dominant known oncogenes. Further, somatic mutations in tyrosine kinases account for a large number of cancers (1). PTKs have thus been implicated in oncogenic transformation. Since PTPs catalyze the reverse reaction, it was logical to assume that some PTPs would act as tumor suppressors. However, unlike the PTKs, PTPs can act as positive or negative regulators of signal transduction pathways. They can either activate tyrosine kinases or counteract their activity by dephosphorylating the kinase itself or its downstream target. PTPs are, therefore, a complex group of enzymes whose function is dependent on the availability of their functional partners.

The sequencing of the human genome has helped identify 107 PTP-coding genes of which only 81 are active protein phosphatases. Similarly, of the 90 genes coding for PTKs only 85 are catalytically active. Further, both PTPs and PTKs are distributed almost equally in tissues. It is, therefore, conceivable that both group of enzymes share some substrate

specificities and that both are equally important in maintaining optimal protein phosphorylation levels. Although the function of a few PTKs as oncogenes has been accepted, there is still no defined role for PTPs in cancer. The PTP superfamily can be subdivided into three major families based on their structure, function, and sequence: (i) tyrosine-specific or "classical" phosphatases, (ii) dual-specificity phosphatases (DUSP), and (iii) low-molecular-weight phosphatases (LMW-PTP). In addition to their phosphatase activity on tyrosine and serine/threonine residues of the same protein, some phosphatases with structural similarity to DUSPs also dephosphorylate lipids (2). In fact the phosphatase PTEN (phosphatase and tensin homologue), often classified as a DUSP, derives its well-established tumor suppressor property from its phospholipid phosphatase activity (3). On the contrary, the cdc25 family of proteins also classified as DUSPs is frequently overexpressed in several different cancers and is thought to circumvent the cell cycle checkpoints facilitating cell proliferation [See (4) for a review]. Additionally, several other members of the DUSPs function as either tumor suppressors or oncogenes [See (5) for a review]. There is only one known *LMW-PTP* gene that gives rise to four different isoforms as a result of alternate splicing. Its upregulation during contact inhibition and the antagonistic role in PDGF stimulated cell growth suggest that it is a protein capable of inducing growth arrest [reviewed in (6)]. The classical PTPs can be further divided into two groups, receptor-type protein tyrosine phosphatases (RPTPs) and nonreceptor-type protein tyrosine phosphatases (NRPTPs), depending on whether they are transmembrane or cytosolic proteins. These are also segregated into several subtypes on the basis of sequences or functional domains outside their catalytic domain. The DUSPs and LMW-PTPs have been reviewed in detail for their involvement in neoplastic disease and potential for pharmacological intervention (6,7). Although the classical PTPs are receiving increased attention for their role in cancer, there is a lack of critical analysis of each PTP subtype and each individual PTP therein, comparison of the similarities and differences between the action of closely related PTPs, and how such information can be applied to the development of novel therapeutics. This chapter will discuss the implications of genetic and epigenetic alterations of the classical PTPs in cancer and their potential as novel molecular targets in cancer therapy.

II. Genetic and Epigenetic Alterations of *PTP* Genes

Tumor suppressor genes are characterized by loss of gene function, which can occur as a result of deletions, inactivating mutations, and epigenetic alterations. Knudson's two-hit hypothesis coined in the early 70s called for two genetic hits that would inactivate both alleles of a gene. However, it is found that inactivation of a single allele (haploinsufficiency) can result in cellular phenotype leading to tumorigenesis. On the contrary, oncogenes are characterized by gain of gene function as a result of gene amplification, activating mutations, and translocations leading to aberrant expression. The next sections discuss the alterations in expression of *PTP* genes and their functional involvement in growth and apoptosis, the processes that are deregulated in cancer.

A. PTPs Localized to Regions of Loss/Gain in Human Cancers

A review on the genetic variations of PTPs in human diseases has implicated locations of 19 genes (of the 38 classical PTP-encoding genes) as regions frequently deleted in different human cancers (8). This assignment is, however, based essentially on reports of loss of heterozygosity (LOH) within the particular cytogenetic band. Such a large region could harbor many genes, which could potentially include the *PTP*. Demonstration of the loss of a single or both copies of a specific PTP associated with a particular or several different types of cancers will prove its involvement in carcinogenesis. To date, there are reports of specific loss of *RPTPs PTPRG*, *PTPRJ*, *PTPRD*, and *PTPRK* in several solid tumors (refer to Table I for additional information). In most cases, loss of these genes is associated with reduced expression (9–11). Further, *PTPRG* and *PTPRJ* also exhibit growth suppressive potential in

cancer cell lines (11,12) and are the commonly accepted tumor suppressive genes amongst the classical tyrosine phosphatase family. Additionally, using specific sequence-tagged site (STS) markers, deletions observed in some human cancers have been narrowed to specific smaller areas of minimal losses, thus, facilitating the identification of candidate tumor suppressors associated with cancer. Such analysis has implicated *PTPRF* in neuroectodermal cancer (13), *PTPN6* in acute lymphoblastic leukemia (14), *PTPN12* and *PTPN23* in many different cancers (15,16). These genes can, therefore, be considered candidate tumor suppressors. Besides gene loss there is report of amplification of the gene encoding an intracellular tyrosine phosphatase PTPN1 in several different solid tumors, including gastric, cancer, Barrett's adenocarcinoma, ovarian cancer, hepatocellular carcinoma (HCC), and breast cancer (17–23). Consistent with gene amplification, the PTPN1 transcript was upregulated in ovarian cancer (17,22). Amplification of the *PTPN1* gene in solid tumors of different origins suggests that it has oncogenic potential.

B. PTPs Mutated in Cancers

Activating mutations are the most common mechanism resulting in deregulation of *PTKs* (24) that function as oncogenes. If a majority of *PTPs* are considered potential tumor suppressors, it is anticipated that at least some of these genes would carry inactivating mutations. It is, however, surprising that a detailed analysis for mutations within the coding regions of the tyrosine phosphatase superfamily was only recently performed in colorectal cancers (25). This analysis identified a total of 83 nonsynonymous, somatic mutations in 3 RPTPs (PTPRF, PTPRG, and PTPRT) and 3 nonreceptor-type tyrosine phosphatases (PTPN3, PTPN13, and PTPN14). At least 15 of these mutations were predicted to result in loss of gene function as a result of nonsense, frame shift or splice-site alterations. Based on the evidence discussed in the study it appears that these mutations are functional, exerting growth advantage to the tumors (25). In this respect, it is possible that other missense mutations resulting in amino acid substitution could alter protein structure and thereby its function. Further analysis of these six PTPs in other solid tumors identified some mutations in lung, gastric, and breast cancers but not in medulloblastomas, glioblastomas, pancreatic, and ovarian cancers (refer to Table II for additional information on mutation of PTPs in cancer). Among these PTPs, PTPRG exhibits growth suppressive potential and has been implicated as a tumor suppressor in breast and ovarian cancer (12). Overexpression of PTPRT also resulted in growth suppression of colon cancer cell lines suggesting a role in tumorigenesis. On the contrary, increased expression of PTPRF correlates with metastatic potential in breast and prostate cancer (26,27), suggesting a positive role in transformation. However, a study investigating the relationship between PTPRF/LAR and E-cadherin demonstrated cell density dependent parallel increase of both LAR and E-cadherin and requirement of E-cadherin mediated cell—cell contact for upregulation of LAR (28). This suggests that the increased expression of PTPRF observed in metastatic breast cancer and prostate cancer cell lines could be a consequence rather than the cause of uncontrolled cell proliferation. While the roles of other PTPs mutated in colon cancer have not been fully explored, preliminary studies have shown alteration in growth phenotype upon overexpression of PTPN3 and PTPN14 in NIH/3T3 and HeLa cells, respectively (29,30). It is noteworthy that additional PTPs could be mutated in other cancers. In fact PTPRJ, a tyrosine phosphatase with tumor suppressor properties, was mutated in colon, lung, and breast cancer (31). Additionally, PTPN23 and PTPN12 are also mutated in small cell lung cancer cell line and colon cancer cell line, respectively (15,16). To date, there is report of the contribution of an activating mutation in only one NRPTP, PTPN11 to leukemogenesis (32–34). Functional analysis to investigate the role of this leukemia-associated mutation demonstrated that its overexpression induced aberrant growth in multiple hematopoietic compartments. This study thus confirmed the involvement of hyperactive PTPN11, a positive regulator of Ras, in the pathogenesis of juvenile myelomonocytic leukemia (35).

C. Epigenetic Regulation of PTPs

Epigenetic alterations are inheritable changes affecting gene expression that are mediated by effects on chromatin structure and not on DNA sequence. These alterations include DNA methylation, histone modifications (acetylation, methylation, and phosphorylation), and chromatin remodeling and are emerging as factors contributing to loss of gene expression specifically affecting the wild-type allele. Among these processes, DNA methylation is the most common modification in cancer occurring on the 5′ position of cytosines of CpG dinucleotides. PTPN6 (SHP-1) was the first classical PTP demonstrated to be methylated in cutaneous T-cell lymphoma (36). Subsequently, methylation of the gene encoding this hematopoietic PTP was found in a small subset of leukemia and lymphoma cases, including anaplastic large cell lymphoma (ALCL), multiple myeloma, and acute myeloid leukemia (AML) (37–41) (refer to Table III for effect of methylation on PTPs). Our laboratory was the first to demonstrate methylation-mediated suppression of an RPTP, protein tyrosine phosphatase receptor-type O (PTPRO), in rat HCCs (42). The *PTPRO* gene encodes six different transcript variants that produce two major protein isoforms: (i) full-length (PTPRO-FL, GLEPP1, and PTP-U2) and (ii) truncated (PTPROt) (42). The full-length form is expressed in epithelial cells of tissues like the brain, kidney, lung, and breast while the truncated variant is of hematopoietic origin with high-level expression in B-lymphoid cells (43). Our studies demonstrated that methylation of the CpG island located in the promoter region affects expression of the full-length isoform in solid tumors (lung, HCC, breast) [(42,44) and unpublished data] as well as the truncated isoform in leukemia, specifically chronic lymphocytic leukemia (CLL) (T. Motiwala, S. Majumder, J. Byrd, M. Grever, D. Lucas, and S. Jacob, unpublished data). These results are consistent with an observation that found increased methylation of PTPRO in right-sided MSI+ primary colon tumors (45). Global epigenetic profiling of CLL using restriction landmark genomic scanning (RLGS) identified PTPRN2 and PTPRZ2 as candidate methylation targets in 30% CLL cases tested relative to neutrophils from same individuals and $CD19^{+}$ selected B lymphocytes from normal individuals (46). Similarly, epigenetic screening of cutaneous T-cell lymphomas using differential hybridization on CpG island microarray identified increased methylation of PTPRG relative to benign T cells, which correlated with its transcriptional suppression (47). It is noteworthy that except for PTPN6/SHP-1, methylation of other PTPs was identified during genome-wide search for epigenetic alterations in different types of cancers. It is conceivable that differential methylation of other PTP-coding genes was not identified in cancer due to technical limitations of screening techniques and screening of only a single specific type of cancer. In this context, it is of interest that genomic sequence analysis showed presence of CpG island in the proximal promoters of all PTPs except PTPN22, PTPRC, PTPN7, PTPRR, PTPRQ, and PTPRA (48). Methylation status of the CpG island could, thus, be involved in regulating the expression of these PTPs in normal cells, and its alteration may lead to disease conditions particularly cancer.

Gene expression can also be altered by epigenetic mechanisms that involve changes in posttranslational modification of histones associated with the gene (49–53) as well as differential association of chromatin remodeling complexes (54,55). These factors structurally modify the promoter in chromatin context, making it either accessible or inaccessible to the normal transcriptional machinery. Such epigenetic alterations could also be responsible for the alteration in the expression of *PTP* genes in cancer. Exploration of this possibility could reveal a novel mechanism for the regulation of this class of enzymes in disease states and its application to promising epigenetic therapy (discussed later).

III. Transformation-Related Phenotypes Attributable to PTPs

The first PTP was identified and cloned in the late 1980s (56,57). The identification of any new proteins or class of proteins calls for the study of their function in a specific cell or

tissue type. Because PTPs appear to play a role in several diseases, the most common being cancer and diabetes, their involvement in cellular processes related to these and other diseases have been explored either by overexpression or knockdown studies. Although knockout animal models have facilitated identification of tumor suppressor or oncogenic function of a gene, most studies have been performed using cells in culture. There are several drawbacks in relying completely on animal models. First, in some cases knockout animals may be embryonic lethal in which case an inducible knockout may be appropriate. Second, whole animal knockouts may not be as beneficial as tissue-specific knockout to study the role of a gene product. Third, several *PTP* genes express multiple transcripts, which could functionally compensate for the loss of another isoform. Alternatively, the function of one PTP may be compensated by another closely related PTP. Fourth, cancer is a complex disease with multiple players involved in its etiology. These factors may be intrinsic (genetic alterations, which in turn could be hereditary or acquired) or extrinsic (environmental). It is, therefore, highly unlikely that knocking out a particular gene would result in spontaneous effect on tumor formation in a complex whole animal system. In this respect, although 22 of the 38 class I cysteine-based classical PTPs have exhibited either positive or negative effects and in a few cases both manifestations on growth and apoptosis, these alterations were not always demonstrated using animal models (refer to Table IV for details on the growth and apoptosis related phenotypes attributable to PTPs). Loss of gene function associated with particular types of cancer prompted investigators to study specific contribution of these genes to cancer. This was accomplished by ectopically expressing them in cancer cell lines of different origins and studying the alterations in phenotypic properties (e.g., proliferation, cell cycle, anchorage independence, contact inhibition, motility, and apoptosis), some or all of which are deregulated in a cancer cell. In this context, overexpression of PTPN6 and PTPRT inhibited growth of hematopoietic and colorectal cells, respectively (25,41). Similarly, overexpression of PTPRJ suppressed the malignant phenotype of transformed rat thyroid cells (11) and inhibited growth of breast cancer cell lines (58). Overexpression of PTPRH altered the morphology, reduced growth rate and migratory activity of a HCC cell line (59), and induced apoptosis in NIH3T3 fibroblasts (60). PTPRH mediated impediment of the migratory activity of the cell suggests its role in influencing the metastatic/invasive potential of a cancer cell. In addition to PTPRH, overexpression of PTPN12 inhibited cell migration in Ratl fibroblast-derived stable cell lines (61) and rat aortic smooth muscle cells (62). More direct evidence of the role of PTPs in determining the metastatic potential of a cell stems from the observation that injection of PTPRA overexpressing mammary tumor cells transgenic for HER2/neu into mice causes reduced tumor growth and delayed lung metastasis (63).

In recent years RNA interference (RNAi) and small interfering RNA (siRNA) technologies to knockdown expression of genes have emerged as alternate and perhaps the most reliable tools to study their functions. Knocking down the expression of a gene that is normally expressed in a particular cell is more physiologically relevant over the artifacts that may be induced particularly on expression of a gene at a much higher level than its normal expression. Studies to demonstrate tumor suppressive properties of *PTPRG*, a gene whose function is lost in cancers as a result of LOH, mutation, or methylation, have used both overexpression and antisense-mediated knockdown approaches. Both techniques showed that PTPRG can inhibit anchorage dependent and independent growth of MCF-7 cells (12). Many studies are now recognizing phosphatases as an important family of enzymes involved in regulation of phosphorylation in practically every cellular process. The complex nature of this regulation by protein phosphatases (i.e., both positive and negative effects on signal transduction) is overriding the importance of kinases, which participate as partners of phosphatases in the same process. A study has, thus, employed RNAi screening for protein phosphatases to determine their role in cancer. Since loss of balance between cell death and survival can result in development of cancer, this study used apoptosis and chemoresistance

as a means to measure the effect of systematic knockdown of each individual PTP in HeLa cells (64). Phosphatases whose knockdown resulted in resistance to the drugs cisplatin, taxol, and etoposide were classified as “cell death phosphatases” that include three classical PTPs: PTPRD, PTPRJ, and PTPRS. On the contrary, knockdown of certain phosphatases increased spontaneous apoptosis in HeLa cells. Such phosphatases designated as “survival phosphatases” consist of several classical PTPs. Considering a twofold increase in apoptosis as significant, a few PTPs with tumor suppressor characteristics (e.g., PTPRK, PTPRO, PTPRG, and PTPRA) were categorized as survival phosphatases. Although this may be a true phenotype in HeLa cells, these PTPs tend to lean towards the tumor suppressor group for the following reasons. First, loss of PTPRK function is implicated in several liquid and solid tumors (65,66). Further, suppression of PTPRK in primary central nervous system lymphomas (PCNSL) as a result of LOH appears to be relevant to its pathogenesis and unfavorable prognosis (9). Second, since our initial observation of extensive *PTPRO* methylation in a large number of primary lung tumors (relative to their normal adjacent tissue) (44), we have demonstrated reduced proliferation and anchorage-independent growth, delayed reentry into cell cycle, and increased susceptibility to apoptosis inducing agent of a nonexpressing human lung cancer cell line ectopically expressing *PTPRO* (compared to the vector transfected cells) (44). We subsequently extended this observation to PTPROt that is predominantly expressed in hematopoietic cells and demonstrated methylation and suppression of PTPROt in primary CLL cells as well as leukemia cell lines of different origins. The gene was, however, essentially unmethylated and functional in control lymphocytes (T. Motiwala, S. Majumder, J. Byrd, M. Grever, D. Lucas, and S. Jacob, unpublished data). Further, expression of *PTPROt* in the nonexpressing cells increased their susceptibility to fludarabine, a drug commonly used in the treatment of CLL. The results are in agreement with earlier findings of the involvement of PTPROt in cell cycle arrest (43) and of PTPU2L/PTPRO in apoptosis subsequent to TPA induced differentiation (67). Third, while PTPRA can transform NIH/3T3 cells by dephosphorylating and activating oncogenic c-Src (68), its overexpression in breast cancer cells suppressed proliferation in both *in vitro* and *in vivo* assays (63). This disparity in the function of PTPRA can be reconciled in several different ways, which could also be extrapolated to some other PTPs showing conflicting phenotypes. First, although PTPRA can activate c-Src and transform fibroblasts, its action in breast cancer may be mediated by some as yet unknown substrate (63,69). Second, the association of increased PTPRA expression with low tumor grade (63) may suggest an involvement in tumor initiation with eventual loss in aggressive disease. Alternatively, increased cell density as a result of uncontrolled proliferation could induce PTPRA consistent with density-dependent upregulation of other PTPs (70). Additionally, while some of the “survival” protein phosphatases may facilitate cell survival by reducing spontaneous apoptosis [as observed by MacKeigan (64)], their effect on growth inhibition may predominate over the cell survival function. PTPN2/TCPTP, a nonreceptor PTP, is an example of the differential effects of a PTP on growth and apoptosis based on a series of detailed studies using overexpression and knockdown approaches. To investigate the role of this PTP, which is upregulated upon mitogenic stimulation of several cell lines, it was overexpressed in HeLa cells. Proliferation and cell cycle assays demonstrated lower serum requirement, formation of larger colonies in soft agar, growth in multiple layers, altered morphology, rapid progress through GI and S phases, and increased rate of cell division for PTPN2 overexpressing cells relative to the control cells (71,72). An independent study demonstrated reduced proliferation rate for TCPTP(−/−) lymphocytes compared to TCPTP(+/+) lymphocytes (73). Although cell cycle and apoptosis are discrete processes, these could be mediated by common regulators. A typical example being *c-myc*, a mitogenic oncogene that can also induce apoptosis (74). Similarly, overexpression of PTPN2 induces apoptosis in the p53+ A549 and MCF-7 cells but not in p53- HeLa cells (75). Unfortunately, this study did not assess the effect of PTPN2 overexpression on proliferation of A549 and MCF-7 cells to rule out the possibility of cell-type specific effect on proliferation and

apoptosis. Another study showed that restoration of TCPTP, which is downregulated in imatinib mesylate resistant human chronic myeloid leukemia (CML) cell line, could revive sensitivity by increasing apoptosis (76). A few classical "survival PTPs", like PTPN5, PTPN9, PTPN7, and PTPRZ1, demonstrate greater than threefold increase in apoptosis upon knockdown (64). Other independent studies have revealed oncogenic potential of these PTPs for the following reasons. First, overexpression of PTPN7 in cell culture resulted in altered cell morphology, anchorage independent and disorganized growth (77). Second, overexpression of the catalytically inactive *C→S* and *D→A* mutants of PTPN9 but not wild-type PTPN9 in erythroid cells suppressed growth in semisolid media (78). Third, siRNA mediated knockdown of PTPRZ1 in glioblastoma cells decreased the migration capacity of the cells indicating that PTPRZ1 is involved in the invasiveness of glioblastomas (79). Similar to the effect of PTPRA on cell growth and proliferation (63,68), the function of certain PTPs in apoptosis also depends on cellular context as well as the pathway involved in mediating this effect. One such effect is observed with PTPN13/FAP-1, which is referred as "antiapoptotic" tyrosine phosphatase. Its increased expression in ovarian cancer, HCC, and pancreatic cancer has been associated with resistance to Fas-mediated apoptosis (80–83). On the contrary, its expression is upregulated by the antiestrogen 4-hydroxy-tamoxifen in breast cancer cells and this expression was necessary for the Fas-independent apoptotic action of tamoxifen (84). PTPN13 is thus considered "proapoptotic" in breast cancer. Apart from the observed phenotypic effects of PTPs on growth and apoptosis, a few PTPs are involved in signaling via adherens junction proteins and are thus implicated in cell—cell contacts, cell shape, and motility (85,86). The extracellular domains of RPTPs, although diverse, are characteristic of cell adhesion molecules. This coupled with the lack of known ligands for the majority of RPTPs reinforces their role in contact inhibition (87). Any disruption in the normal functioning of such PTPs could thus result in uncontrolled growth and metastatic invasion of cancer cells.

IV. PTPs as Drug Targets

PTPs control protein tyrosine phosphorylation status in concert with tyrosine kinases, which comprise 80% of oncoproteins. Oncogenic tyrosine kinases are either overexpressed in wild-type form or expressed as mutated constitutively active enzymes in cancer. It is, therefore, tempting to postulate a tumor suppressive role for the PTPs. Many PTPs are underexpressed in cancers as a result of LOH, inactivating mutations or epigenetic alterations. It is, however, also becoming increasingly clear that PTPs are not simply negative regulators reversing the action of tyrosine kinases. Instead they may also act in synergy with tyrosine kinases to enhance protein phosphorylation. In fact, certain PTPs are upregulated in cancers and function by activating the oncogenic src kinase (88,89). Consistent with this complex regulation of protein phosphorylation by PTPs, these can act as either negative or positive regulators of cell signaling. Additionally, the same PTPs can act in both ways depending on the cellular context (90). Thus, while it is simple to use kinases as targets for anticancer drugs, the application of PTPs as drug targets is a rather complex strategy. In the following paragraphs we will review options for targeting PTPs in anticancer therapy.

A. Gene Therapy

Gene therapy is a means of restoring the function of an inactivated gene either by gene repair (in case of mutated genes) or by introduction of a functional copy of the gene (gene augmentation in case of mutated as well as lost genes). Although gene repair has several advantages over gene augmentation (e.g., it is applicable to both dominant and recessive mutations and the gene expression is regulated by its natural elements), gene therapy has conventionally focused on gene augmentation (91). Such gene transfers into human cells are accomplished by means of a viral vector, which is capable of infecting human cells and introducing the viral DNA (manipulated to carry the gene of interest) into these cells. Other

approaches include direct introduction of the DNA into human cells, liposome-mediated transfer, and receptor-mediated internalization of ligand-linked DNA. Nonviral approaches, however, are less efficient and their lack of integration does not allow for stable long-term expression of the gene of interest. Viral vectors are, therefore, preferred as the gene delivery system. Among the commonly used viral vectors are retrovirus, adenovirus, adeno-associated virus, and herpes simplex virus. Because all viruses except adeno-associated virus can cause human diseases, these viral vectors are genetically engineered to remove any disease-causing genes and introduce the "therapeutic gene". Despite such measures to manipulate the viral genome it is possible that they regain their disease potential. Further, it can generate fatal immune response and such a response if not fatal prevents repetitive gene transfers, which may be necessary for long-lived effect of gene therapy. Additionally, in most cases of gene therapy the introduced genes cannot be directed for integration at specific sites. Their aberrant insertion at random sites can cause secondary damage such as initiation of cancer upon insertion at an oncogenic locus. Since diseases such as cancer are caused by multiple genetic and epigenetic variations, gene therapy can pose serious problems. Despite such challenges more than half of the over 400 gene therapy clinical trials worldwide are related to cancer (92).

Although loss of PTP function may not be the sole cause of a particular cancer, numerous studies have demonstrated that their overexpression can revert the transformed phenotype of cells and in some cases also limit their metastatic potential. Use of gene therapy to restore the function of a PTP that is lost in cancer, therefore, appears to be promising. Several *in vitro* and *in vivo* analyses have demonstrated tumor suppressor functions for DEP-1 or its rat homologue rPTPη (11,31) in thyroid, colorectal, breast, and lung carcinomas. A subsequent study has proposed the use of gene therapy for thyroid cancers specifically in undifferentiated anaplastic thyroid carcinomas that are refractory to radiotherapy and chemotherapy. This study has successfully used a replication deficient adenoviral vector (ONYX-015) to transfer the *rPTPr*η gene into thyroid cancer cell lines. Adenovirus-mediated expression of rPTPη inhibited proliferation of the cells and their growth when engrafted into nude mice (93). A few studies have, however, reported difficulty in obtaining cells stably expressing PTPs (94,95) probably because of its enzymatic involvement in a cascading pathway. To overcome this problem a transposon based "Sleeping Beauty" system was adapted to overexpress an osteoclastic PTP (PTP-oc/PTPROt) in osteoclast cells. This technology enabled to retain stable expression of the protein for over a year without having to maintain selection pressure (95). Transposable elements are natural, relatively safe, nonviral alternatives as gene delivery vehicles and result in stable gene expression. These approaches had been used widely for invertebrate systems (96) but were not available for vertebrate systems until recently. The reconstruction of the vertebrate transposon element Sleeping Beauty from the fossils of the fish genome (97) thus revived interest in using such elements as efficient gene transfer technologies (98). The concerted efforts of different laboratories has made it possible to use this technology in gene therapy as demonstrated by its ability to treat human diseases modeled in mice (99–102) and its applicability to transfer genes into human tissues (103). Unlike viruses that exhibit the tendency to integrate into genes rather than nongenomic sites transposon-mediated integration tends to occur at intergenic sites and repeat elements (104,105) rather than transcribed genes or their regulatory elements (106). They are, therefore, potentially devoid of secondary deleterious effects and considered safer than viral vectors (107,108). A transposable system, which has been proven to be efficient in long-term expression of a *PTP* gene (95), thus, appears to be a promising tool for PTP gene therapy.

Apart from PTPs that are suppressed in cancer, a few PTPs are upregulated or carry activating mutations and demonstrate oncogenic potential. Such PTPs can be targeted using inhibitors as described in the following section. Alternatively, gene repair approach (for *PTP*

genes carrying activating mutations) or antisense oligonucleotide (ASO) therapy can be used for targets that are resistant to small molecule inhibitors. ASOs primarily function by forming a complex with the target mRNA, thus, leading to RNaseH-mediated degradation. Alternatively, they may alter mRNA transport, splicing, or even inhibit transcription by forming a triple helix complex with double-stranded DNA. There are several clinical trials testing this strategy to fight cancer. Antiapoptotic proteins appear to be the most popular targets for such therapy [reviewed in (109)]. Since PTPs are involved in regulating apoptosis and some are implicated in protecting cells from apoptosis, these could emerge as potential targets for ASO therapy.

B. Small Molecule Inhibitors

The large family of tyrosine phosphatases with a common CX_5R catalytic motif is involved in a variety of physiological processes by positively or negatively regulating signal transduction pathways. While this family of enzymes may include promising drug targets, they may also include“antitargets” (5). Inhibition of these PTPs may be detrimental to normal functioning of cells. It, therefore, becomes very critical to test the specificity of any inhibitor designed for a particular PTP. These protein phosphatases are inhibited by several mechanisms, including oxidative inactivation of catalytic site cysteine (110,111), covalent modification of the conserved active site arginine side chain (112), or by noncompetitive inhibitors, which act outside the catalytic site but impair phosphatase activity (113). Competitive inhibitors for PTPs rely on the pTyr-binding site. In some PTPs with two pTyr-binding sites, the use of two pTyr mimetics joined by a linker imparts better specificity (5,114). It is noteworthy that several PTPs have been implicated in diabetes because of their role as negative regulators of insulin receptor signaling. Among these PTPs, PTP1B/PTPN1, TCPTP/PTPN2, and LAR/PTPRF appear to be the most promising drug targets for Type II diabetes and obesity, and PTP1B has been the most widely studied protein tyrosine phosphatase for this purpose. To avoid any unwarranted effects on other PTPs, screens for testing the specificity of inhibitors developed for PTP1B include several other PTPs. Inhibitors of several other PTPs were discovered in such screens. *PTP1B* gene is known to be amplified and upregulated in several different cancers (17–23), which also makes it a promising target for treatment with small molecule inhibitors developed for diabetes and obesity. On the contrary, inhibition of TCPTP and LAR could result in increased proliferation (73,115) making them less attractive as therapeutic targets. Further, several PTPs namely CD45/PTPRC, SHP-I/PTPN6, and SHP-2/PTPN11 are targets for immune-related diseases, for example, transplant rejection and infectious diseases (5). It is important to explore these interesting targets for inhibitor development. Activating mutations of PTPN11 have been implicated in hematopoietic malignancies (32–34). This observation provides an impetus to use SHP-2 inhibitors for treatment of leukemia associated with SHP-2 mutation. Thus far, efforts have been expended to develop inhibitors for these few PTPs. The involvement of certain other PTPs in oncogenic transformation and metastatic potential offers the rationale for further development of specific inhibitors that could be used as anticancer drugs.

C. Epigenetic Therapy

Reactivation of genes silenced by epigenetic modifications, particularly DNA methylation, is usually referred to as epigenetic therapy. A classical agent used for this purpose is 5-azacytidine (5-azaC) or its congener 5-aza-deoxycytidine (5-aza-CdR or decitabine). Both are potent DNA hypomethylating agents used in cancer clinical trials (116–121). Unlike most anticancer drugs available to date, epigenetic therapy is reversible and can target reactions that are unique to cancer. Despite the importance and distinct advantage of this therapeutic concept, this mode of therapy has not been explored extensively.

Unlike 5-azaC that is incorporated into RNA and DNA, decitabine is incorporated only into DNA and is, therefore, much more selective in its action and less toxic than 5-azaC. These drugs can also be deaminated into the respective undines and their triphosphates, which interfere with *de novo* thymidylate synthesis. A noteworthy mechanism is based on studies that showed the inability of DNA methyltransferases (DNMTs) to methylate DNA following the incorporation of decitabine into DNA. Animal cells contain three functional DNMTs. Among these enzymes, DNMT3a and DNMT3b exhibit predominantly *de novo* methyltransferase activity whereas DNMT1 (the predominant enzyme) is exclusively involved in the methylation of hemimethylated DNA. Previous study in our laboratory (122) suggested that 5-azaC or decitabine may have differential effects on DNMTs. A recent study substantiated this notion by demonstrating that DNMT1 is rapidly and selectively degraded. We elucidated the molecular mechanism of this selective action of decitabine by demonstrating that DNMT1 is degraded by a proteasomal pathway that requires the KEN box, a signature motif missing in DNMT3a and 3b. Further, the degradation occurred rapidly and independent of its catalytic function, which did not require incorporation of decitabine into DNA (123). These DNA hypomethylating agents were used to reactivate PTPRO in human lung cancer cells (44). Our laboratory has also shown reexpression of (PTPROt) that is predominantly expressed in hematopoietic cells (T. Motiwala, S. Majumder, J. Byrd, M. Grever, D. Lucas, and S. Jacob, unpublished data) from an independent downstream promoter (124) but appears to be regulated by methylation at the CpG island located upstream. The expression of PTPN6/SHP-1 and PTPRG could also be revived upon treatment with the hypomethylating agent 5-aza-CdR (36,47).

Unmethylated genes can also be suppressed as a result of the association of specific posttranslationally modified histones such as hypoaeetylated histones H3 or H4 with their promoters. In this case, the gene can be reexpressed by treatment of cells with inhibitors of histone deacetylases (HDACs) (125). Several such inhibitors, including suberoyl anilide hydroxamic acid (SAHA), LAQ-824, PXD-101, depsipeptide, valproic acid, phenylbutyrate, MS-275, and CI-994, have been or are being tested for HDAC inhibition in clinical trials (126). Since HDACs can alter cell growth, death, and differentiation, they can play important roles in cancer. HDACs belonging to Class I appear to be involved in regulating the proliferation of cancer cells (127). Class I HDACs could, thus, be promising targets for development of specific inhibitors. Many studies have also shown that combined treatment with inhibitors of DNMTs and HDACs could impede tumor growth (122,128,129). This mode of therapy can cause synergistic activation of some genes (122,130), specifically those that are suppressed by DNA methylation. This combination therapy with inhibitors against DNMTs and HDACs can result in increased potency at lower doses and is being tested in anticancer trials [See (131,132) for reviews].

V. Concluding Remarks

Unlike PTKs that have been the subject of intense investigations for many years because of their oncogenic potential, PTPs have not received much attention until recently. Several observations strongly suggest an important role for PTPs in cancer. First, half of the classical *PTP* genes are located in regions frequently deleted in different human cancers. Second, at least 10 *PTP* genes are mutated in some cancers including activating mutation in one of them. It is conceivable that many other PTPs could also be mutated in cancers and some mutations could be cancer type specific. Third, genes encoding some PTPs are silenced by promoter methylation, a hallmark of many established tumor suppressor genes. To this date, only five *PTP* genes are shown to be methylated of which some are also suppressed upon methylation. In addition to the loss/gain of function by genetic or epigenetic mechanisms, some PTPs also exhibit growth suppressor or oncogenic characteristics (refer to Table V for concise information on all the classical PTPs). Only a

few of them have, however, been extensively studied with respect to their role in cancer (11,12,63,71,72,77,133). One of these PTPs, PTPRO, has been extensively studied by our laboratory with respect to its tumor suppressor potential and ability to induce apoptosis (44). Identification and characterization of additional PTPs with tumor suppressor characteristics will be an important challenge, particularly, if a relationship exists between reduced expression of PTPs and specific cancer types. The role of other factors in the epigenetic machinery, namely posttranslational modifications of histones (histone code) and chromatin remodeling, in the regulation of PTP expression should also be studied in order to elucidate the exact molecular mechanism underlying the altered expression of PTPs in cancer.

Unlike most known tumor suppressors, PTPs are emerging as a unique class of tumor suppressors with inherent enzymatic activities that utilize proteins as substrates. This characteristic provides another level of regulation by these proteins namely modification of the phosphorylation status of their specific substrates. PTPs could themselves promote signaling (positive effect) by dephosphorylation and activation of PTKs, thus, coordinating rather than antagonizing the functions of PTKs (134). The physiological functions of PTPs could depend on the phosphorylated state of a specific PTP substrate(s) that could be critical to the tumor initiation and/or progression. It is, therefore, essential that the substrates of PTPs with suspected tumor suppressor function are identified, and the potential role of the phosphorylated status of these substrates in tumorigenesis is explored.

Most studies addressing the involvement of PTPs in cancer focused on a specific PTP rather than the PTP family or at least PTPs belonging to the same subtype. It is possible that the loss or gain of the function of one PTP is counterbalanced by the gain or loss of another PTP, particularly, if the two PTPs share critical substrates. To address this issue, it is important to develop highly sensitive techniques, like gene arrays, that will help to determine the expression levels of all PTPs simultaneously in specific cancer types. An exhaustive analysis of the levels of these enzymes in different cell types could reveal a specific profile of expressing and nonexpressing PTPs in specific cancers. Further, such comparisons will also assist in explaining the differential phenotypes observed between two different cell types that either express or do not express a particular PTP. Finally, reexpression of the wild-type PTPs in cells where a specific PTP is lost or mutated and reactivation of the PTPs silenced by promoter methylation pose exciting challenges and offer novel molecular targets in cancer therapy. Although not extensively studied, small molecule inhibitors can also be used to compensate for the loss of a gene. In fact, one study has identified inhibitors capable of reversing the consequences of the loss of PTEN by targeting its downstream effector (135). Development of such inhibitors, however, requires a detailed understanding of the cellular functions of the protein. Loss of function of several PTPs in cancer coupled with the ease of developing, screening, and applying small molecule inhibitors to therapy further reinforces the necessity for identifying the critical substrates and ensuing pathways mediating the function of PTPs.

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TABLE I

PTPs Localized to Regions of Loss/Gain in Human Cancers

Gene	PTP	Chr location	Aberration	Type of cancer	Gene/Region[a]	References
PTPRF	hLAR	1p34.2	LOH	Neuroectodermal cancer	Region	(13)
PTPRG	hPTPγ	3p14.2	Homozygous deletion	Benign proliferative breast disease	Gene	(136)
			LOH	Primary lung carcinomas, clear cell renal carcinoma, and renal cell carcinoma cell lines	Gene	(137–139)
PTPN23	hHDPTP	3p21.31	LOH	Lung adenocarcinoma and other soild tumors	Region	(16,140)
PTPRK	hPTPκ	6q22.33	LOH	Primary central nervous system lymphomas (PCNSL)	Gene	(9)
			Deletion	Hematological neoplasms, melanomas, ovary carcinomas, and other soild tumors	Region	(65)
PTPN12	hPEST	7q11.23	Chromosomal rearrangement	Malignant melanoma	Region	(15)
			Chromosomal break	Hematopoietic disorders	Region	(15)
PTPRD	hPTPδ	9p24.1	Homozygous deletion	Small cell and non-small cell lung cancer	Gene	(141)
PTPRJ	hDEP1	11p11.2	LOH	Colon, lung, breast, and thyroid cancer	Gene	(31,93)
PTPN6	hSHP-1	12p13.31	LOH	Acute lymphoblastic leukemia	Gene	(14)
PTPN1	hPTP1B	20q13.13	Amplification	Barrett's adenocarcinoma, HCC, gastric, ovarian, and breast cancer	Gene	(17–23)

[a]Gene/region indicates whether the gene itself or the chromosomal location of the gene is implicated in the cancer.

TABLE II

PTPS Mutated in Cancer

Gene	PTP	Type of cancer	References
PTPRF	hLAR	Colon, breast, and lung cancer	(25)
PTPN14	hPTPD2	Colon cancer	(25)
PTPRG	hPTPγ	Colon	(25)
PTPN23	hHDPTP	Small cell lung cancer cell line	(16)
PTPN13	hPTPBAS	Colon cancer	(25)
PTPN12	hPEST	Colon cancer cell line	(15)
PTPN3	hPTPH1	Colon cancer	(25)
PTPRJ	hDEP1	Colon, lung, and breast cancer	(31)
PTPN11	hSHP-2	Leukemia	(32–34)
PTPRT	hPTPρ	Colon, lung, and gastric cancer	(25)

TABLE III

PTPs Methylated in Cancer

Gene	PTP	Type of cancer	Gene expression	References
PTPRG	hPTPγ	Cutaneous T-cell lymphoma	Suppressed	(47)
PTPRZ1	hPTPζ	CLL	Not tested	(46)
PTPRN2	hPTPIA2β	CLL	Not tested	(46)
PTPN6	hSHP-1	ALCL, multiple myeloma, acute myeloid leukemia, cutaneous T-cell lymphoma	Suppressed	(36–41)
PTPRO	hGLEPP1	Rat hepatocellular carcinoma, lung and colon cancer, CLL	Suppressed	(42,44,45)

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TABLE IV

Phenotypic Characteristics Attributable to the Function of PTPs

Gene	PTP	Technique	Observation	TS/Oncogene	References
PTPN7	hHePTP	Knockdown	Increased apoptosis	Oncogene	(64)
		Overexpression	Altered cell morphology, anchorage-independent, and disorganized growth	Oncogene	(77,133)
PTPN14	hPTPD2	Overexpression	Diminished cell adherence and slow growth	TS[a]	(29)
PTPRG	hPTPγ	Overexpression	Reduced proliferation and anchorage-independent growth	TS	(12)
		Knockdown	Increased proliferation and anchorage-independent growth		
PTPN13	hPTPBAS	Endogenous upregulation	Resistance to Fas-mediated apoptosis	Oncogene	(80–83,142)
		Knockdown	Loss of 4-hydroxy-tamoxifen induced apoptosis (Fas independent)	TS	(84)
PTPRK	hPTPκ	Knockdown	Increased apoptosis	Oncogene	(64)
PTPN12	hPEST	Overexpression	Inhibition of cell migration	TS	(61,62)
PTPRZ1	hPTPζ	Knockdown	Increased apoptosis	Oncogene	(64)
		Knockdown	Reduced cell motility	Oncogene	(79)
PTPRD	hPTPδ	Knockdown	Resistance to apoptosis-inducing agents	TS	(64)
PTPN3	hPTPH1	Overexpression	Inhibition of cell growth by altering reentry into cell cycle and not induction of apoptosis	TS	(30)
PTPRE	hPTPε	Knockout	Larger and flatter cells with slow proliferation	Oncogene	(89,143)
		Transgenic mice	Hyperplastic mammary tissue resulting in increased incidence of mammary tumors	Oncogene	(144)
PTPRJ	hDEP1	Overexpression	Cells are more adherent, arrested in G1 phase, unable to grow in soft agar, and form tumors when injected into nude mice	TS	(11)
		Overexpression	Growth inhibition	TS	(58)
		Knockdown	Resistance to apoptosis-inducing agents	TS	(64)
PTPN5	hSTEP	Knockdown	Increased apoptosis	Oncogene	(64)
PTPN6	hSHP-1	Overexpression	Growth inhibition	TS	(41,145)
PTPRO	hGLEPP1	Overexpression	Reduced proliferation and growth in soft agar, delayed reentry into cell cycle, increased sensitivity to apoptosis-inducing agent	TS	(43,44)
		Overexpression	Increased adherence, differentiated phenotype, and subsequent apoptosis in the presence of TPA	TS	(67)
PTPRQ/PTPGMC1	hPTPS31	Overexpression	PIPase activity (and not PTPase activity) resulted in reduced proliferation and increased apoptosis in low serum environment	TS	(94)
PTPN11	hSHP-2	Overexpression (gain-of-function mutant)	Aberrant growth in multiple hematopoietic compartments	Oncogene	(35)
PTPN9	hMEG2	Overexpression (*CS* and *DA* mutants)	Suppressed growth in semisolid media	Oncogene	(78)
		Knockdown	Increased apoptosis	Oncogene	(64)

Gene	PTP	Technique	Observation	TS/Oncogene	References
PTPN2	hTCPTP	Overexpression	Increased rate of cell division, lower serum requirement, larger colonies in soft agar, loss of contact inhibition, and altered morphology	Oncogene	(71,72)
		Knockout	Lower proliferation rate	Oncogene	(73)
		Overexpression	Increased p53-dependent apoptosis	TS	(75)
		Overexpression	Restoration of imatinib mesylate (Gleevec) sensitivity in resistant chronic myeloid leukemia (CML) cells	TS	(76)
PTPRS	hPTPσ	Knockdown	Resistance to apoptosis-inducing agents	TS	(64)
PTPRH	hSAPI	Overexpression	Altered morphology, contact inhibition, reduced growth rate and migratory activity, increased apoptosis	TS	(59,60,146)
PTPRA	hPTPα	Overexpression	Reduced growth as a result of G0/G1 arrest and not apoptosis, reduced tumor growth and delayed lung metastasis in nude mice	TS	(63)
PTPRT	hPTPρ	Overexpression	Growth suppression	TS	(25)

[a]TS, tumor suppressor.

TABLE V

Summary of the Tumor Suppressor and Oncogenic Properties of the Classical PTPs Grouped by Subtypes

Subtype	Gene	PTP	Genetic/Epigenetic evidence	Expression evidence[a]	phenotypic evidence
R1/R6	*PTPRC*	hCD45	ND[b]		ND
R2A	*PTPRF*	hLAR	TS[b]	Oncogene (147)	Oncogene
	PTPRD	hPTPδ	TS	TS (148)	TS
	PTPRS	hPTPσ	ND		TS
R2B	*PTPRU*	hPTPλ	ND		ND
	PTPRK	hPTPκ	TS	TS (9,66)	Oncogene
	PTPRM	hPTPμ	ND		ND
	PTPRT	hPTPρ	TS		TS
R3	*PTPRJ*	hDEP1	TS	TS (11)	TS
	PTPRO	hGLEPP1	TS		TS
	PTRRB	hPTPβ	ND		ND
	PTPRQ/PTPGMC1	hPTPS31	ND		TS
	PTPRH	hSAP1	ND	TS (59)	TS
R4	*PTPRE*	hPTPε	ND	Oncogene (144)	Oncogene
	PTPRA	hPTPα	ND	Oncogene (149,150)	TS
R5	*PTPRG*	hPTPγ	TS	TS (10,151)	TS
	PTPRZ1	hPTPζ	TS	Oncogene (152,153)	Oncogene
R7	*PTPN7*	hHePTP	ND	Oncogene (77,133)	Oncogene
	PTPN5	hsTEP	ND		Oncogene
	PTPRR	hPCPTP1	ND		
R8	*PTPRN*	hPTPIA2	ND		ND
	PTPRN2	hPTPIA2β	TS		ND
NT1	*PTPN2*	hTCPTP	ND	Oncogene (154)	TS/oncogene
	PTPN1	hPTP1B	Oncogene	Oncogene (17,22,155) TS (156)	Oncogene (src activation)
NT2	*PTPN6*	hSHP-1	TS	TS (41) oncogene (157,158)	TS
	PTPN11	hSHP-2	Oncogene	Oncogene (34)	Oncogene
NT3	*PTPN9*	hMEG2	ND	Oncogene (78)	Oncogene
NT4	*PTPN22*	hLyPTP	ND		ND

Subtype	Gene	PTP	Genetic/Epigenetic evidence	Expression evidence[a]	phenotypic evidence
	PTPN18	hBDP1	ND		ND
	PTPN12	hPEST	TS		TS
NT5	*PTPN4*	hMEG1	ND		ND
	PTPN3	hPTPH1	TS	Oncogene (156)	TS
NT6	*PTPN14*	hPTPD2	TS		TS
	PTPN21	hPTPD1	ND		ND
NT7	*PTPN13*	hPTPBAS	TS	Oncogene (80,81,83,159,160) TS (161)	TS/oncogene
NT8	*PTPN20*	hPTPTyp	ND		ND
NT9	*PTPN23*	hHDPTP	TS		ND

[a]The gene is denoted as TS or oncogene based on observed, reduced, or increased expression, respectively, in cancer. It is, however, not known whether altered expression is a cause or consequence of transformation. References for expression of the PTP are provided in parentheses.

[b]ND, not determined; TS, tumor suppressor.