

## Protein Tyrosine Phosphatase-Prospective Target against Cancer: A Mini Review

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### Abstract

Contemporary quantum leap on functional characterization of Protein Tyrosine Phosphatase (PTP) superfamily provides an incipient perspective on regulating signal transduction. PTPs are required in the regulation of several cellular processes; especially under stressed and pathogenic conditions leading to sundry human diseases. Concrete inhibition of PTP by oxyanions and active-site directed inhibitors (alkylating agents) may provide implements for human disease treatment involving them. The physiological paramountcy for the advancement of Protein Tyrosine Phosphatase, Non-receptor Type 1 (PTP1B) -predicated therapeutics is a prominent target for diabetes and inordinate corpulence treatment. PTPs are exhilarating quarry for active-site-mediated inhibitors generation. There, proneness to oxidation often create problem on high throughput screens, further the propensity for highly charged potent inhibitors, like non-hydrolysable pTyr mimetics, test with reverence to bioavailability. Subsequent preliminary concerns about specificity and quandaries with deference to hydrophilicity of phosphor-mimetics, promising successes attained by structure-predicated drug design, mainly the one exploit identical surface topology circumventing the catalytic pocket of each PTP. In PTP1B, it was found that a particular pTyr binding site could be habituated to succeed highly concrete bidentate inhibitors that bind both sites. This conventional approach can avail us to target highly categorical and efficacious inhibitors. Tyrosine phosphorylation increases 1-2% of total protein phosphorylation in tumorigenic transformation or magnification factor simulation essential for a controlled cellular event. This event is controlled by two molecular switches of enzymes protein tyrosine kinase and protein tyrosine phosphatase. Eccentric tyrosine phosphorylation is considered as one of the hallmarks of cancer. PTP has been recommended as next generation drug targets and a sum of PTP have been embroiled in sundry human disease, like cancer. The catalytic mechanism of PTP was demystified by site-directed mutagenesis then kinetic analyses with structural information. They have loss/ gain of function in cancer signaling events leading to dearth of inhibitors to control gain of function including modification of loss of function of PTP cognate genes. This review is about the consequentiality of tyrosine phosphatase enzyme and its role in the mundane cellular event and how it modifies the active site to agonise substrate and alter its action ultimately leading to tumorigenesis.

**Keywords:** Protein tyrosine phosphatase; Site-directed mutagenesis; Cancer signalling; Tumorigenesis; Protein phosphorylation

### Introduction

The modification of proteins via integration and abstraction of the phosphate group is a consequential concept in eukaryotic signal transduction systems [1]. The development of protein phosphorylation by Eddy Fischer, Ed Krebs [2,3] in glycogen metabolism was the substructure of signal transduction arena. There is an immensely colossal enzyme superfamily, i.e., protein kinases catalyse the add-on of a phosphate, i.e., hydroxyl residue phosphorylation on the amino acid side chain viz; tyrosine, serine or threonine [4]. Protein Tyrosine Phosphatases (PTPs) [E.C-3.1.3.48] are concrete to remove phosphate from phosphotyrosyl residues. The proteins which are phosphorylated at tyrosine residues present in the cell have precise balance between the kinases and phosphatases enzymes. Thus, it is well established that PTPs and PTKs are involved in the regulation of a sizably voluminous various cellular processes like signal transduction and developmental processes in plants as well as animals [5,6].

Roughly 30% of phosphoproteins are present in cells and utmost of eukaryotic phosphorylation befalls on ser/thr residues [7]. Tyrosine based is 0.01%-0.05% out of whole protein phosphorylation [8].

Nevertheless, oncogenic transformation or else growth factor stimulation, the rate of tyrosine phosphorylation rises to 1%-2% of cell's overall protein phosphorylation. While tyrosine phosphorylation arises much more minute range, it has become pellucid that tyrosine phosphorylation is vital in regulating mundane cellular magnification signalling for survival and immune replication [9]. This review is all about how the tyrosine phosphatase enzyme proves as an anticipating drug target by its catalytic action and substrate recognition.

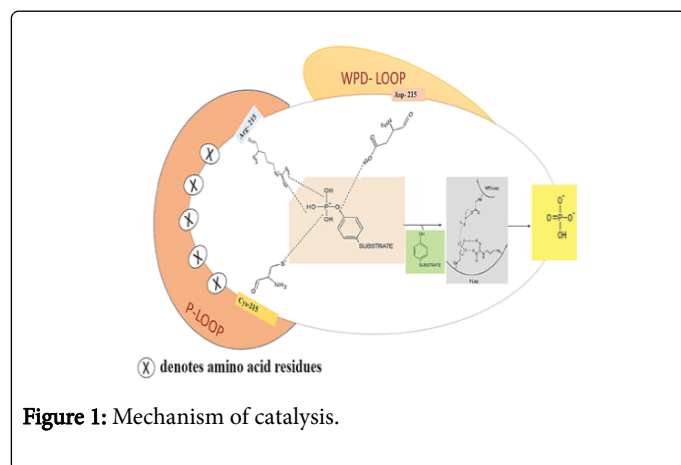
### Anticipation Overdue the Tyrosine Phosphatase as a Target

Till now, protein phosphorylation has been apperceived on His, Asp, Ser, Thr, Tyr, Cys, Lys and Arg residues. A modification in phosphorylation can engender a vicissitude in the activity of enzyme. PTPs employ as positive and negative effects equipollent on signalling pathways [10]. The paramountcy of tyrosine phosphorylation on mundane cell physiology was tainted by the fact that many human diseases occur due to ease of two different states i.e., active state and dormant state. Eccentric tyrosine phosphorylation is cognate to many diseases such as cancers, diabetes, rheumatoid arthritis and hypertension. The involution of PTP cognate genes in sundry diseases

pathways have been suggested as 'controller' of different signalling pathways. So, it was anticipated as a best congruous drug target [11].

### Step Up to Superimpose with PTP

The nature of PTP superfamily is managed by its own signature motif CX<sub>5</sub>R, provide phosphates to bind on active site loop (known as PTP (or) P-loop). In spite of comparison with colossal variation in sequence on X<sub>5</sub> segment of the P-loop is stringently conserved and superimpose from diverse PTP structures, through marginal non-conformities on Ca tracing (<1 Å). These pattern safeguards catalytic Cys and Arg, persist in near proximity and create a fortification to carry phosphate present in substrate intended for the nucleophilic outbreak. The nucleophilic cysteine S<sub>γ</sub>-atom outbreaks phosphate from substrate to form an intermediate (Cys-P reaction intermediate) as depicted in (Figure 1). Arginine helps substrate binding as well as reaction intermediate stabilization [12].



In addition, internal support is provided by P-Loop containing amides and hydrogen bonding to oxygen phosphate. A Ser/Thr residue in the P-loop which is conserved in nature play a paramount role in the maintenance of the thiolate group during transition state availing the phosphoenzyme intermediate breakdown [13]. During PTP reaction a general acid and base requirement was fulfilled by an inimitable aspartic residue present in WPD-loop. During transition state reaction, the catalytic Asp reacts as an acid by donating proton in tyrosine residue. Similarly, the same Asp respond as a base in phosphoenzyme hydrolysis by transmutation of the phospho-Cys to its reposing Cys-SH state reviving the free enzyme [13,14]. Thus, even minuscule variations on active site microenvironment may perturb the efficiency of PTP catalysis.

### Gain/Loss of Function of PTP towards Cancer

Peculiar tyrosine phosphorylation ensuing as of the perturbed protein tyrosine kinase and protein tyrosine phosphatase (PTK-PTP) balance are one of the major root cause of numerous human diseases [15]. Indeed, uncontrolled phosphorylation of tyrosine site is one of the hallmarks of cancer. PTP remain captivating targets of cancer therapeutics development [16,17]. The prevalent damage of Phosphatase and tensin homolog (PTEN) occurs in various malignancies including breast and prostate cancer [18]. Likewise, Src homology region 2 domain-containing phosphatase-1 (PTPN6) is often loss in myelodysplastic syndrome and lymphomas.

Though, PTPs not only lose its function but also has "positive" mechanism in signalling pathways and cell functions, such hyperactive PTPs are Src homology region 2 domain-containing phosphatase-1 (PTPN11) a kened oncogene along with sundry mutants present in several forms of leukemia [19]. CDC25, a rate-limiting enzyme for cyclin-dependent kinase (CDK)-dependent transition from G1/S phase and G2/M phase in cell cycle, those CDK expression level is more in various cancer cells [20]. Protein tyrosine phosphatase 1B (PTPN1), first identified negative regulator in insulin and leptin signalling pathway, recently establish that the same Protein Tyrosine Phosphatase, Non-receptor Type 1 (PTP1B) has positive role in ErbB2 (HER2/neu) tempted signal to root-cause breast tumorigenesis and metastasis.

Tumour suppressor PTP are one of the causative factors in cancer progress that may be focused via downstream signalling actions for therapeutic determinations. Loss of the hematopoietic-categorical Transmembrane PTP CD45 (Protein Tyrosine Phosphatase, Receptor Type C), regulates Src kinases essential for T and B cell activation, has been related to astringent coalesced immunodeficiency disease. Activated via gain-of-function of several PTPs are life-threatening oncogenes in human cancer that can be targeted with tiny chemical inhibitors [21]. In additament, PTP are vital negative regulators of cytokines or immune cells by targeting these negative PTP may ameliorate the efficacy of cytokine therapy and immunotherapy, which are having modest replication rates and inhibited survival benefit. Inhibitors of selective PTP have preclinical antitumor action [22].

Regulation of Phosphatase of Regenerating Liver 1 (PRL-1) PTP occurs with tissue-concrete patterns on epithelial tissues. The mechanism of phosphorylation in tyrosine residues of cellular proteins is of paramount importance in development and differentiation process of cell. Pleiotropic regulatory locus 1 (PRL-1) are immediate-early gene in liver regeneration their presence is linked by development on some tissues but with differentiation in others [23]. Tyrosine phosphorylation has regulatory cellular functions on enzymatic activity, gene expression, cell cycle progression and motility [24,25]. Protein tyrosine phosphatases (PTPs) are essential for tyrosine kinases to regulate consequential pathways especially tyrosine phosphorylation based pathways [26-28].

Experiments designated that some PTPs play consequential roles in vertebrate development. Several PTP receptors show great effect on fetal encephalon, tempting cell-cell adhesion, neurite magnification, axon guidance and cell recognition target [29-31]. The leucocyte common antigen-related PTP (LAR-PTP2) receptor was highly seen in the fetal lung where maximal tissue differentiation on bronchioles and alveolar sacs are being composed [32]. *In situ* hybridization experiments explain that MAP kinase phosphatase-1 (MKP-1) PTP is more expressed on tissue-restricted and temporal pattern during mouse development. Paramount levels occur preliminary in gut development, accompanied mRNA spotted at 10.5 days, whereas level of expression need to be inhibited to villus enterocytes. PTP1B and T-cell PTP are involved to control Insulin-like growth factor 2 (IGF-2) triggered MCF-7 cell migration levels [33,34], also down-regulate tyrosine kinase receptors, showing anti-oncogenic properties toward PTPs [35]. Recent studies show that PTP1B has oncogenic properties in ERK pathway of breast cancer cells. This outcome strengthens probable role of PTP as a target for treatment of cancer.

Various studies of drug revelation pointing against PTKs are due to congruous cellular tyrosine phosphorylation levels that remain balanced by the synchronized kinases and phosphatases activity.

Therefore, it is asserted that PTPs may arise as next generation drug targets [36,37]. Recent study suggested that terpenoid (agelasine) contain bromine activates insulin signalling pathway via inhibiting PTP1B action [38]. Similarly, the furanosesterterpenes from Indonesian marine sponge's shows better IC<sub>50</sub> value and less cytotoxicity against PTP1B enzyme inhibitor in Huh-7 human cancer cell line and also for the treatment of type 2 diabetes [39]. PTPs have been an attractive topic in biomedical research for the earlier two decades, and many PTPs reported on many human diseases, such as cancer, diabetes, autoimmune, and neurological diseases [40]. These verdicts have further invigorated the credence that targeting PTP could be the next frontier in drug revelation.

## Conclusion

PTP regulate numerous cellular events, especially under stressed and pathogenic conditions leading to various human diseases. In some diseases, PTPs are under-expressed whereas in others they are overexpressed. The molecular characterization of PTP may provide insight into its future application for the treatment of human diseases. The finding of effective, cell permeable and orally bioavailable PTP1B inhibitors is an exciting medicinal chemistry objective. PTP1B inhibitors target should have a potent cellular invasion with in cells, and an orally available drug is anticipated. This is a tough job as of the physical feature of target. Specific inhibition of PTP by various inhibitors viz.; oxyanions and site-directed inhibitors (alkylating agents) may provide tools for the treatment of human diseases involving over expression of PTP (diabetes, obesity, tumours etc.). Therefore, PTP might form a novel attractive target for cancer therapy.

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