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Protein tyrosine phosphatases in pathological process

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1. ABSTRACT

Protein tyrosine phosphatases (PTPs) modulate the cellular level of tyrosine phosphorylation under normal and pathological conditions, and thus exert either stimulatory or inhibitory effect on signal transduction. Hence, PTPs are potential pharmacological targets for novel drugs being developed in order to treat numerous pathologies including cancer. For example, PTPs have been found to play a key role in pathogenesis of autoimmune disorders, allergic response, cardiovascular or neurodegenerative diseases, among others Alzheimer's disease. Moreover, since many PTPs fine-tune subtle regulation of microbial biochemistry controlling the viability and virulence, they can be candidates for new therapies of infection diseases. In this review, authors summarize the current knowledge on PTPs implication in etiopathogenesis of most common human diseases focusing on PTPs as potential therapeutical targets.

2. INTRODUCTION

Protein tyrosine phospahatases (PTPs) are a large family of enzymes present in diverse organisms including bacteria, yeast, insects and vertebrates (1). They remove hydrolytically phosphate groups from phosphotyrosine residues (dephosphorylation) on various proteins.

The human genome comprises over a hundred genes for different PTPs (analogously to protein tyrosine kinase family) encoding approximately five hundred phosphatases. Such a large number of PTPs is a consequence of the alternative splicing, and posttranslational modifications (2). A critical role in pathogenesis of various disorders, and physiological significance of PTPs were one of the main reasons for human genome sequencing studies as well as mice gene knockout projects (3,4). PTP genes are involved in many human diseases, the most frequently in immunological disorders (>50%) and metabolic ones (~14%). It is worth noting that the human PTP genes are often associated with more than one pathology, e.g. PTPN11 encoding SHP2 phosphatase is implicated in pathogenesis of 14 diseases (including cancer, cardiovascular, developmental or immune disorders). A PTP gene that has been, up to date, associated with the largest number (~50) of

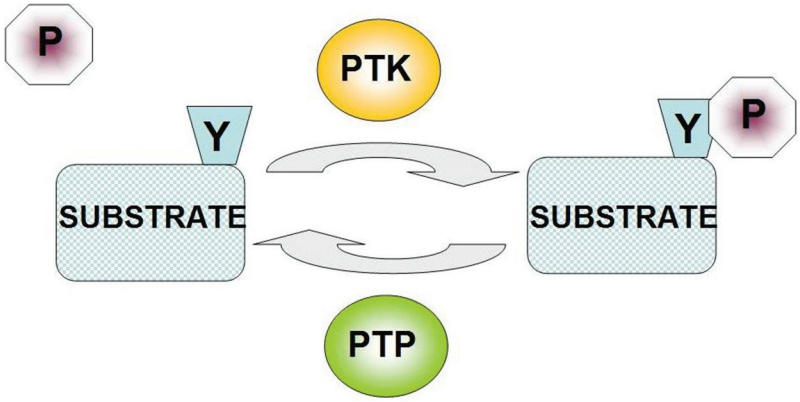

Figure 1. The reversible phosphorylation - opposing activity of PTPs and PTKs.

pathological processes is PTPN22 (encoding LYP phospahtase) (5).

3. IMPORTANCE OF REVERSIBLE PHOSPHORYLATION

The protein tyrosine phosphorylation and dephosphorylation processes are evolutionarily conserved mechanisms of signal transduction in eukaryotic cells, that are of fundamental importance for controlling cellular physiology, e.g. cell proliferation, differentiation, migration and oncogenic transformation (6). The phosphorylation process modifies target proteins causing conformational changes, inducing relocation within a cell or exposing new binding sites for ligands (7). The reversible phosphorylation of proteins at specific tyrosine residues is regulated by delicate balance between the antagonistic activities of protein tyrosine phosphatases and protein tyrosine kinases (8). Protein tyrosine kinases (PTKs) are responsible for tyrosine phosphorylation as opposed to protein phosphatases which remove the phosphate group (Figure 1). This kind of balance between opposing activities is fundamental for maintaining homeostasis, and any disturbance may contribute to disease development (9). In the recent decades, PTPs have been believed to play mostly a housekeeping role in the cell, together with PTKs regulating tyrosine phosphorylation. Now, several studies have changed this perception and put PTPs in a new perspective as partner enzymes equally contributing to the regulation of reversible protein phosphorylation (10). Protein tyrosine phosphatases regulate signaling pathways involved in numerous processes including cell-substrate adhesion, cell-cell adhesion, and insulin signaling (7).

3.1. Classification of PTPs

According to the primary structure of the catalytic domain, protein tyrosine phosphatases fall into four categories. Class I of PTPs, based on their substrate specificity, is comprised of 38 classical tyrosine phosphatases (strictly tyrosine specific) and 61 phosphatases of dual specificity (tyrosine and serine/threonine or tyrosine and threonine specific) (3). Class II is represented in human genome by a single gene encoding a relatively small (18 kDa) tyrosine-specific low molecular weight phosphatase (LMWPTP). Three tyrosine/threonine phosphatases, which play a role of the cell cycle regulator, belong to Class III (2). Class IV comprises four tyrosine and serine/tyrosine phosphatases, which differ from the other ones with respect to catalytically active amino acid residue of aspartic acid rather than the most common cysteine residue typical for PTPs of Class I, II and III (11).

Based on the cellular localization, classical PTPs are categorized as transmembrane (receptor-like PTPs) and intracellular (cytosolic) phosphatases (non-receptor PTPs) (Figure 2). Cytosolic PTPs are localized in a variety of intracellular compartments, such as cytosol, plasma membrane or endoplasmic reticulum, while receptor-like PTPs are predominantly found in the plasma membrane (12). Every non-receptor tyrosine phosphatase contains a single catalytic domain connected to variable sequences modulating the activity and intracellular localization of the enzyme (13). The structure of receptor PTPs is perfectly designed to transduce a signal across the plasma membrane. The majority of receptor protein tyrosine phosphatases have an extracellular region, a single transmembrane domain and two conserved intracellular PTP domains (D1 and D2) (14). The

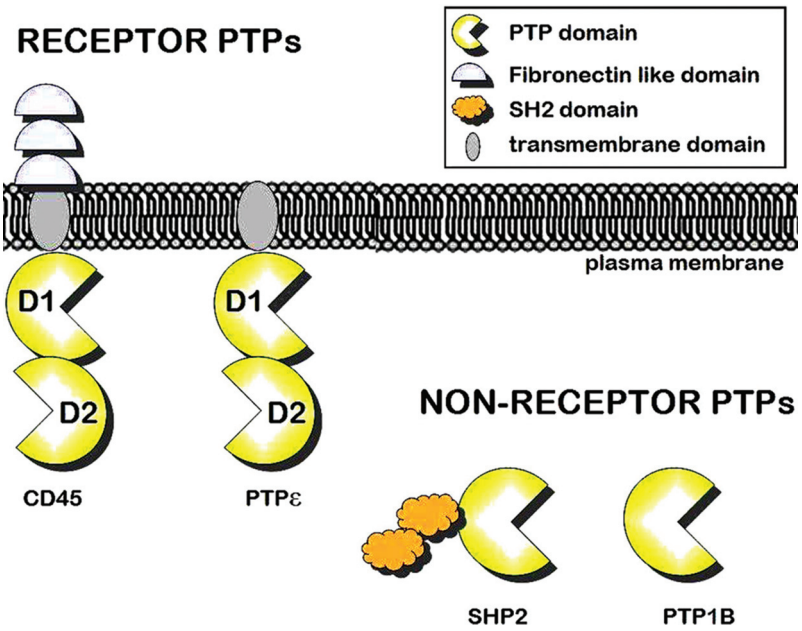

Figure 2. Schematic illustration of representative receptor and none-receptor PTPs.

PTP	Tumor suppressive function
LAR	mutations identified in colon cancer
DEP1	overexpression reverts the transformed phenotype of i.a. colon cancer cell
SHP1	is inactivated in leukaemias, lymphomas and multiple myeloma
GLEPP1	is inactivated in lung and colorectal cancer; re-expression is associated with tumour suppression

Figure 3. Tumor suppression activity of selected PTPs.

catalytic activity has been reported only in D1 domain being the one closest to the membrane domain. The other PTP domain, i.e. D2 has been proposed to play a regulatory role. Although D2 domain manifests no catalytic activity, it is still necessary for maintaining specificity and stability of the enzyme (7, 15).

4. TUMORIGENESIS

An impairment of tyrosine phosphorylation process may lead to abnormal replication, growth or metastasis, as observed in cancer. The aberrant tyrosine phosphorylation is one of the primary initiators of human cancer, or is required to maintain the oncogenic status, and among others resistance to growth inhibition (6). Multiple protein tyrosine kinases were identified as proto-oncogenes; their enzymatic counterparts - phosphatases - are believed to be tumor suppressors (16). Nowadays there is evidence that some PTPs can function as tumor suppressors (17) (Figure 3), but PTPs upregulating certain growth-factor receptors can exert also tumor promoting effects (18). The cytosolic tyroisne phospahatase Shp2 is a positive regulator of growth factor signaling and its mutation related enhanced activity has pro-oncogenic character. Phosphatase

PTP1B can display both tumor suppressing and oncogenic potential depending on the cellular context (19). The most frequently mutating human tumor suppressor is PTEN phosphatase, being recognized in the brain, breast and prostate cancers, which emphasizes the role of PTPs in cancer development (20).

It was estimated that 6.5% of all the pathological processes associated with PTP genes is assigned to cancerogenesis (5). The role of PTP enzyme family members in development and progression of tumors was presented in many studies. PTPs proved implicated in gliomagenesis are receptor-type (e.g., RPTPdelta, DEP1, RPTPmicro, RPTPzeta), intracellular (e.g., PTP1B, TCPTP, SHP2, PTPN13) classical PTPs and dual-specific (e.g., MKP-1, VHP, PRL-3, KAP, PTEN) PTPs (21). Phosphatases SHP2 and PTP1B are potentially important targets for the treatment of breast cancer (22).

A mutational analysis identified 83 somatic mutations in tyrosine phosphatase genes encoding LAR, rPTPgamma, rPTPrho, PTPH1, PTPBL and PTP36, affecting 26% of colorectal cancers and a smaller fraction of lung, breast, and gastric cancers (23). PTP CD45 plays a crucial role in determining signaling and proliferation of myeloma cells (24, 25).

The studies focusing on indetification of anti-apoptotic PTP genes in Hela cells show that products of 28 PTP genes positively regulate cell survival and only 4 PTPs were identified as cell death promoting. The number of PTP genes contributing to human cancer is likely to be higher as Hela cells express only a portion of the human PTP genome (26).

Due to many implications in cancer biology, PTPs may be promising targets for the development of novel diagnostic and therapeutic strategies in the treatment of cancer.

The tumor suppressor function as well as tumor promoting function of some tyrosine phosphatases raises concerns about potential cross-inhibition of these PTPs by insufficiently selective inhibitors. However, the tumor suppressors are likely to be defective or absent in cancer cells, thus the cross-inhibition of tumor suppressor PTP under this condition will have no functional significance (27).

4.1. Oxidative stress related regulation of PTPs

The involvement of PTPs in tumorigenesis might be partly explained by the increased generation of reactive oxygen species (ROS) in cancer cells as compared to normal cells, which can lead to pathologically enhanced oxidation of PTPs (28, 29). Elevated ROS formation enhances mutagenesis, thereby contributing to tumor promoting lesions. An increased level of ROS observed in cancer cells has led to therapeutic considerations of ROS as agents that induce toxic effects on cancer cells (30). Such a strategy was tested during studies on parthenolide, the compound that shows anticancer activities in a variety of cell lines. Parthenolide not only inhibits the nuclear factor NF-κB activity, but also decreases the level of reduced glutathione, leading to ROS accumulation and apoptosis of cancer cells (31).

Reactive oxygen species control the function of cellular proteins via post-translational modifications. According to the location within the cell, ROS are generated extracellularly or in various intracellular compartments. Many enzymes, including those of the mitochondrial electron transport chain, oxidases, oxygenases, peroxidases, produce reactive oxygen species (Figure 4). There are many studies on oxidative stress and the impact on pathogenesis. Oxidative stress is associated with numerous pathologies such as cancer, neurodegeneration and Alzheimer's disease. The overexpression of the Nox1 ROS-producing protein can cause cellular transformation and tumor formation (32).

Oxidative stress, defined as excessive reactive oxygen species formation, may induce inactivation of protein tyrosine phosphatases. Inactivation via oxidation was suggested as a mechanism of protein tyrosine phosphatase regulation (15).

A unique biochemical and structural characteristic of the PTPs catalytic cysteine engendered a hypothesis that these enzymes might be direct targets of ROS chemistry. Many PTPs have been shown to be oxidized transiently in response to various cellular stimuli. Reactive oxygen species, such as hydrogen peroxide, function as second messengers in response to extracellular stimuli and can regulate tyrosine phosphorylation-mediated signaling pathways (33) (Figure 4).

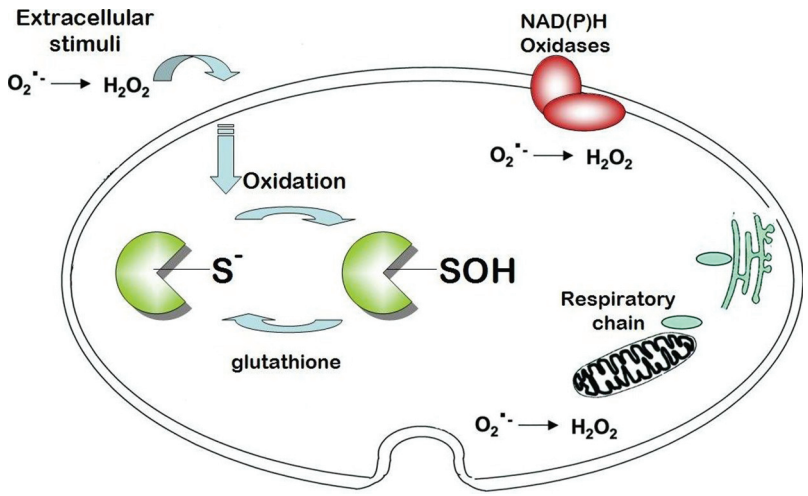

Figure 4. Hydrogen peroxide may oxidize the catalytic cysteine residues in PTPs.

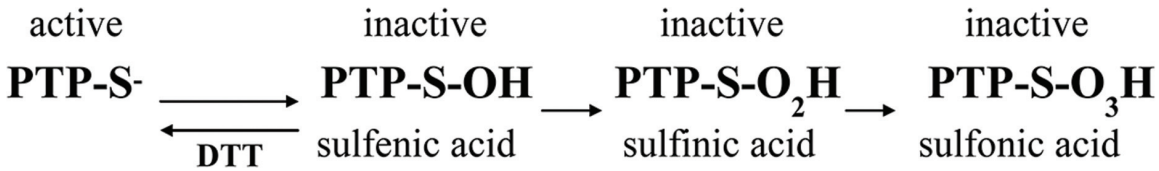

Figure 5. Reversible and irreversible oxidation of PTPs catalytic cysteine.

Hydrogen peroxide may relatively easily cross the cell membrane in response to insulin or epidermal growth factor, and control the cellular activity of protein tyrosine phosphatases therein (34). Hydrogen peroxide may oxidize catalytic cysteine residue to sulfenic acid derivative, which can be then reversibly reduced to cysteine by various cellular reducing agents (35).

The essential cysteine residue, namely the sulfhydryl group, in the catalytic center of PTPs exists in the form of a thiolate anion at physiological pH, and thanks to the specific amino acid microenvironment, has a relatively low pKa. These properties allow the cysteine residue to function as a nucleophile in catalytic process, but at the same time make it highly vulnerable to oxidation (36). Depending on the degree of oxidation, the catalytic cysteine residue can be converted to either sulfenic (SOH), sufhinic (SO_2H) or sulfonic (SO_3H) acid residue (Figure 5) (37).

Oxidation of the cysteine residue to sulfenic acid is reversible, unlike further oxidation to sulfinic and sulfonic acid residues, which are considered irreversible. The sulfenic acid group can undergo reduction to cysteine residue via formation of a sulfenylamide intermediate (8). Sulfenylamide generation induces major conformational changes in the catalytic center of the enzyme. It protects the cysteine residue from irreversible oxidation to sulfinic or sulfonic acid, and facilitates enzyme reactivation. Sulfenylamide can be converted in the cell by thioredoxins and glutathione into the active form of thiolate anion (38).

Nowadays, it has been proposed, that in some cases, conversion to sulfinic acid may be reversible. Sulfiredoxin from Saccharomyces cerevisiae has been reported to reduce sulfinic acid residue of peroxyredoxin Tsa1 in the presence of magnesium and ATP (39). Both peroxyredoxin and protein tyrosine phosphatases contain a reactive cysteine residue in the catalytic center (40).

A reversible oxidation is considered as a novel mechanism of PTPs regulation, also observed in other proteins with the active-site cysteine, e.g. caspases, kinases, phosphatases or proteases. Reversible chemical modifications of the active site cysteine residue play a role in various physiological

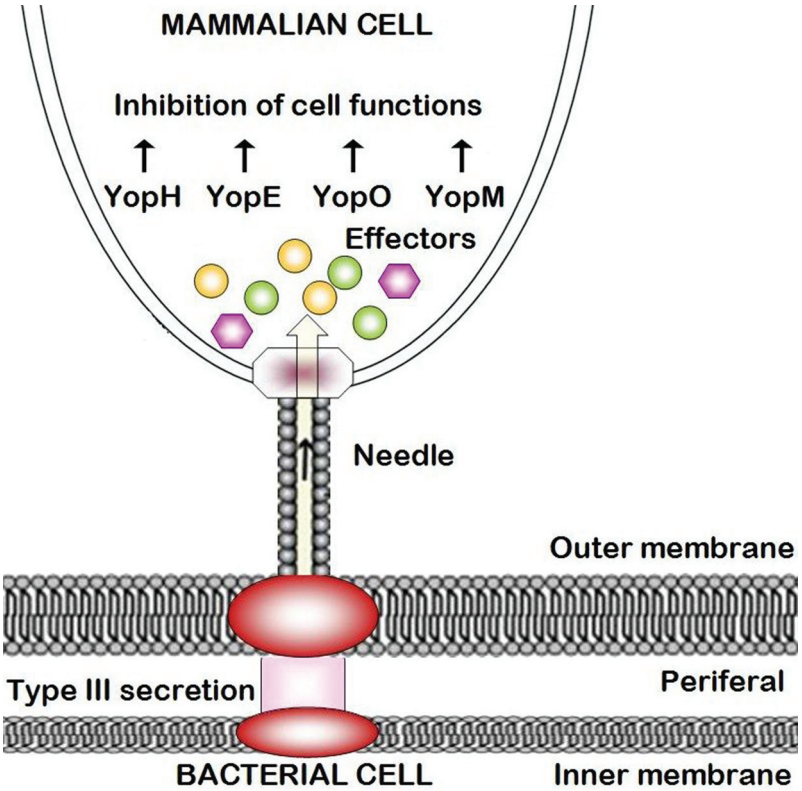

Figure 6. Yops are translocated into the host cells via a type III secretion system.

processes, like apoptosis, angiogenesis, cell proliferation, and receptor-mediated signaling. The reactive thiols are oxidized to either sulfenic acid residues or disulfides. Thiols are essential components of the redox chemistry in biological systems, and the reversible oxidation-reduction reactions provide a sort of an "on-off" switch in the process of metabolism regulation (41).

5. PROTEIN TYROSINE PHOSPHATASES AND PATHOGENIC MICROORGANISMS

Many PTPs have been found to play important roles in controlling physiology and pathogenicity of various microorganisms. The PTPs are often exploited by pathogenic viruses and bacteria to cause infection, or proliferate in the host cell. A bacterial infection process involves the modification of the host signaling pathways by certain effectors, some of which are protein tyrosine phosphatases (42).

A few structures of viral PTPs have been successfully determined in *Vaccinia virus*, *Baculovirus* and *Variola virus*. Protein tyrosine phosphatase from *Variola virus* seems to act as a causative agent in smallpox being essential for the virus viability (43).

Numerous PTPs have been reported in bacteria, and except for differences in the primary structure and electrostatic surface charge, protein folding pattern resembles that of mammalian phosphatases. The bacterial enzymes are mainly virulence effectors causing deregulation of cellular functions (*Yersinia pestis*, *Yersinia enterocolitica*) or cytoskeletal rearrangements in the host cell (*Salmonella enterica*) (44). *Yersinia* species utilize type III secretion system for translocation being essential for virulence effects on the host cell, like inhibiting the innate immune response and inducing infection (Figure 6). PTP YopH, which is one of the effectors, plays a role of a bacterial agency, controlling signaling pathways required for phagocytosis (45). It causes disruption of focal complex structures and blockage of the phagocytic process (46). The YopH phosphatase is one of the most active PTPs characterized to date, and it is

PTPs involved	Diseases
CD45	SCID, multiple sclerosis, Alzheimer's disease
PTP1B	diabetes, obesity
LAR	neurological diseases, diabetes
SHP1	immune, neurological disease
SHP2	neurological, infectious diseases
GLEPP1	osteoporosis
PTPε	osteoporosis, immune diseases
PTP MEG2	autism

Figure 7. Involvment of selected PTPs in human diseases.

speculated that YopH gene might have a eukaryotic origin (47).

PTPs can act as effectors, but it has been evidenced that PTPs may also be targets of bacterial virulence factors, leading to the modification of host signaling pathways. PTP SHP-2 is a key target of *Helicobacter Pylori* CagA protein, which after infecting the host cell forms a physical complex with Shp2, resuling in the catalytic activation (48, 49).

6. IMPLICATION OF PTPs IN OTHER HUMAN DISEASES

Dysfunctions of PTPs contribute to the development of a number of other human diseases, including autoimmunity disorders, diabetes mellitus, cardiovascular and neurological pathology (50) (Figure 7).

Current research on pathophysiological roles of protein tyrosine phosphatases has focused on transgenic or knockout mice studies, best highlighted by the discovery of the role of protein tyrosine phosphatase 1B in type II diabetes, and obesity. It was found that mice lacking PTP1B phosphatase are healthy, and have enhanced sensitivity to insulin. Moreover, mice with PTP1B deletion are lean and protected against diet-induced obesity (51). Other studies demonstrated that PTP1B-deficient mice are protected from fat accumulation, peripheral insulin resistance and inflammation in white adipose tissue during age-associated obesity (52).

PTPs are crucial for immune functions and a perturbation of their activity may lead to the development of immune system disorders including multiple sclerosis (53). Mutations in PTPs encoding genes may be the main cause of severe combined immunodeficiency, Noonan syndrome, autosomal dominant congenital disorders, and juvenile acute myeloid leukemia, to mention just a few(54, 55). The key role of PTPs in the immune response is underscored by the fact that there is a higher level of PTPs genes expressed in the immune system cell than in any other cell (56).

7. PTPs AS THERAPEUTICAL TARGETS

A number of studies have been conducted to discover the involvement of PTPs in various pathological disorders. However, PTPs should also be seen as potential pharmacological targets for drug development (57). Disturbances of PTPs activity drew attention of pharmacists and scientists due to association with the development of human diseases(58). Such treatment has been already applied to alleviate osteoporosis symptoms via inhibition of PTP-ε. Phosphatase PTP-ε controls development of osteoclasts implicated in bone resorption (59). PTP CD45 is a key pharmacological target in allergic reactions, neurodegenerative disorders and may be a new approach to cure

Alzheimer's disease (60). Because of PTP1B implication in diabetes mellitus and obesity, PTP1B has become a major target for pharmacological modulation in the therapy of these pathologies. Moreover, because of the role of PTPs in the viability and pathogenic virulence, they can be new candidates in treatment of infections diseases, and prevention of bioterrorism (*Yersinia pestis*) (44).

7.1. Inhibitors of PTPs

Based on essential roles of PTPS in numerous signal transduction pathways and their implication in pathology, there is increasing interest in the identification of novel PTPs inhibitors. In general, tyrosine phosphatase inhibitors are mainly inorganic compounds, like sodium orthovanadate, nitric oxide and phenylarsine oxide. The main disadvantage of these compounds is that they are not selective enough, and effective at relatively high concentrations. There have been many studies on novel PTPs inhibitors, that would be more potent and selective, but a major problem here, is the high sequence homology of the catalytic center shared by different PTPs (58).

In the literature there are many reports on natural compounds that inhibit different types of enzymes, including PTPs. Natural PTPs inhibitors are extracted form plants, algae or some microorganisms. For example, the natural compound dephostatin being a competitive PTPs inhibitor at micromolar concentration was isolated from *Streptomyces sp* (50). Another inhibitor, 4-isoavenaciolide, was isolated from a fungal strain. There are numerous compounds derived from fruits presenting inhibitory properties against PTPs, such as nornuciferine from *Annona muricata* or karanjin from *Pongamia pinnata*. However, the therapeutic usefulness of natural compounds is limited, because of their low stability and selectivity, but again it might be a good starting point for development of more effective synthetic analogs (57). Many studies, involving NMR-based screening or molecular modeling, have been focused on development of compounds that inactivate protein tyrosine phosphatases by structurally mimicking phosphotyrosine as the natural substrate. The posphotyrosyl group was replaced by the mimetic structures like sulfotyrosyl, thiophosphotyrosyl or phosphonomethylphenylalanine (60). The phosphotyrosine mimicing PTPs inhibitors display a high inhibitory activity, but their permeability through the cell membrane is much limited. The identification of a novel binding site of PTPs located about 20 angstroms away from the catalytic center, which is less conserved among phosphatases, constitutes a new paradigm for a potential inhibitor design. Such compounds may bind to both the primary catalytic center, and the secondary binding site inducing allosteric inhibition (61).

The vast majority of described PTP inhibitors do not display drug-like properties, with low cell permeability, selectivity and pharmacological activity (62).

It is worth underlining that the use of therapeutic agents causing PTPs inhibition may be limited by a few major concerns. The main problem is that a single phosphatase may regulate several signal transduction pathways, and thus inhibiting its activity may result in multiple side effects (57). There is a chance, that in the nearestfuture, the studies oriented on deepening our understanding of PTPs regulation and their roles in human pathology, will help to design PTPs inhibitors of potential clinical importance (2).

8. CONCLUSIONS

A number of studies with various experimental models, including transgenic mice, indicated that PTPs are involved in many pathologies. Here, we have briefly reviewed the association of PTPs with a variety of pathological processes. Based on the essential roles of PTPs in numerous signal transduction pathways and their implication in pathophysiology, there is increasing interest in the identification of novel PTPs inhibitors. PTPs are considered potential pharmacological targets for drug development, based on the critical roles that they play in the development of human disease. PTPs are also promising candidates for novel therapies of infections diseases because of the fact that they control microbial physiology and pathogenicity.

9. ACKNOWLEDGMENTS

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