Toxicological Disruption of Signaling Homeostasis: Tyrosine Phosphatases as Targets

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Annu. Rev. Pharmacol. Toxicol. 2010. 50:215–35

First published online as a Review in Advance on November 17, 2009

The *Annual Review of Pharmacology and Toxicology* is online at pharmtox.annualreviews.org

This article's doi: 10.1146/annurev.pharmtox.010909.105841

0362-1642/10/0210-0215$20.00

Annu. Rev. Pharmacol. Toxicol. 2010.50:215-235.

Key Words

protein tyrosine phosphatase, cell signaling, toxicology

Abstract

The protein tyrosine phosphatases (PTPs) consist of a diverse group of enzymes whose activity opposes that of the tyrosine kinases. As such, the PTPs have critical roles in maintaining signaling quiescence in resting cells and in restoring homeostasis by effecting signal termination. Interest in these enzymes has increased in recent years following the discovery that the activity of PTPs is modulated through redox mechanisms during signaling. The molecular features that enable redox regulation of PTPs during physiological signaling also render them highly susceptible to oxidative and electrophilic inactivation by a broad spectrum of structurally disparate xenobiotic compounds. The loss of PTP activity results in a profound disregulation of protein phosphotyrosine metabolism, leading to widespread and persistent activation of signaling cascades in the cell.

INTRODUCTION

The phosphorylation of protein tyrosines is a pivotal regulatory mechanism that controls virtually every aspect of the cell's response to its environment (1–9). Phosphorylation of protein tyrosines is a key event in signaling that leads to cellular responses that range from cellular proliferation, apopotosis, and differentiation to metabolism, adhesion, and migration. The display of phosphotyrosines is recognized by the Src homology 2 (SH2) domain of specific proteins, leading to their recruitment and activation (10–12). Although there are important examples of the phosphorylation of specific tyrosines functioning to maintain homeostasis, tyrosine phosphorylation is regarded generally as representing the activated state of proteins (13, 14). This is based on the observation that resting cells contain very low levels of protein phosphotyrosines, and the positive correlation that exists between the phosphotyrosine content of cells and the magnitude of cellular activity. Levels of protein phosphotyrosines are closely regulated by the opposing action of two groups of enzymes: the tyrosine kinases (TKs), which mediate ATP-dependent tyrosine phosphorylation, and the protein tyrosine phosphatases (PTPs), which catalyze the hydrolysis of phosphate from phosphotyrosines (4, 13).

Two critical features of the function of phosphotyrosine content as an intracellular signal transduction mechanism are its inducibility and reversibility. Appropriate stimuli result in increased TK activity that raises phosphotyrosine levels above baseline concentrations. Dephosphorylation is typically a major component of signal termination and is accomplished by the action of PTPs. The dynamic interplay between TKs and PTPs is not limited to the reversal of signal activation; it is also the basis for the maintenance of signaling quiescence (4).

The activity of inducible TK in unstimulated cells is relatively low and is far exceeded by the constitutive activity of PTP (4). The net result of this gross disparity between TK and PTP activities is that resting cells typically have very low levels of protein phosphotyrosines. Whereas there are notable instances in which PTP-mediated dephosphorylations have a clear positive effect on signaling (15), in general PTP activity represents the primary mechanism for the maintenance of signaling quiescence in the cell. Given their critical importance in normal physiological processes ranging from development to metabolism, disregulation of phosphorylation-dependent signaling pathways is potentially a broad toxicological effect that can lead to pleiotropic effects. This review considers PTPs as critical toxicological targets of a broad range of chemical agents that produce their adverse effects through impairment of signaling homeostasis resulting from toxicant-induced loss of PTP activity.

THE PROTEIN TYROSINE PHOSPHATASES

The earliest reports describe PTP activity in A431 skin carcinoma cell membrane preparations and temperature-sensitive mutants of the Rous sarcoma virus (16–19). Tonks and colleagues (20) carried out the first successful purification of PTP from human placenta. Although the PTP superfamily shows considerable heterogeneity, these enzymes are characterized by strict conservation of the signature motif CX_5R, which comprises the PTP loop that binds the phosphate group on phosphotyrosines [see the excellent review by Tabernero et al. (21)]. The PTP loop contains the catalytic Cys whose S atom initiates the reaction through a nucleophilic attack on the phosphorus atom in the phosphate moiety of the substrate to form a cysteinyl-phosphate bond. The essential Arg assists in the binding and stabilization of this reaction, while surrounding PTP-loop amides provide additional stabilization by interacting with the oxygen atoms on the phosphate. Another important regulatory element in PTP is an Asp residue that is found as part of either a WPD or DPYY loop. This Asp first acts as an acid by providing a proton to the oxygen atom on the tyrosine residue and then acts as a base by accepting a proton from water during the regeneration

Annu. Rev. Pharmacol. Toxicol. 2010.50:215-235.

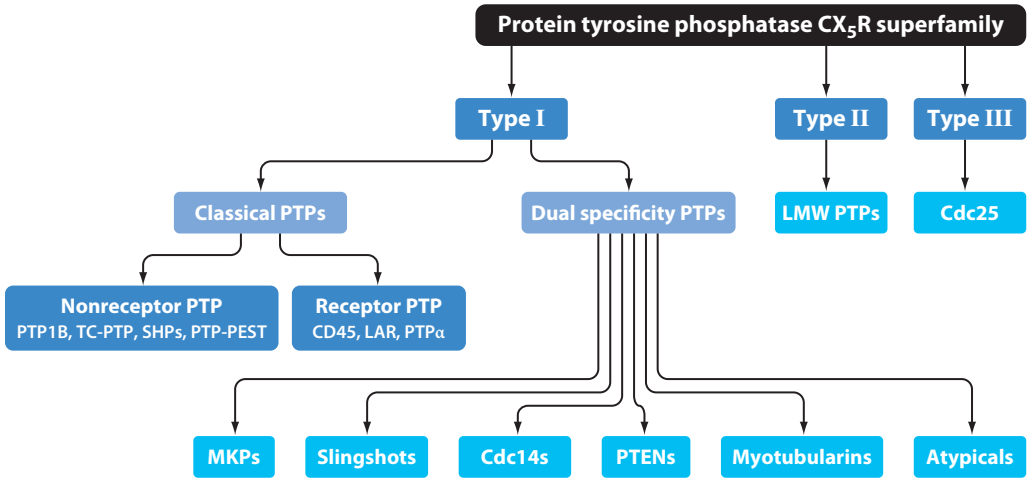

Figure 1

The CX_5R tyrosine phosphatase superfamily.

of sulfhydryl on the catalytic Cys (22). PTP also contains an invariant His residue that lowers the pKa of the catalytic Cys to approximately 4.6. Therefore, the catalytic Cys exists not as a thiol group (R-SH) but as a thiolate anion ($R\text{-}S^-$) at physiological pH (23). The negative charge on the thiolate anion considerably increases its nucleophilic reactivity toward the substrate. However, as discussed below, it also renders PTP highly susceptible to inactivation by oxidative and electrophilic attack.

As recently reviewed by Tonks (24), it is estimated that the human genome codes for over 100 proteins in the PTP superfamily, with additional diversity introduced by alternative promoters, splice sites, and post-translational modifications (24). The PTP superfamily is subdivided into multiple classes based upon their structure and substrate specificities (25) (**Figure 1**). The classical PTPs include the transmembrane receptor-like PTPs (RPTPs) and the nontransmembrane or cytosolic PTPs. RPTPs, such as CD45 and LAR, contain an extracellular ligand-binding domain, a transmembrane domain, and two tandem intracellular PTP domains (D1 and D2). The catalytic activity resides in the proximal D1 domain, whereas the distal D2 PTP domain is inactive in all but one known instance: PTPα (26). The D2 domain is believed to impart enzymatic specificity and stability and to play a role in RPTP dimerization (27). There is greater sequence homology among the catalytically inactive D2 domain of RPTP family members than in the catalytically active D1 segment, suggesting that the inactive domain has an important regulatory function (28).

RPTPs have similarities to adhesion molecules, and the few RPTP ligands identified to date support this notion (21). PTPα is a highly glycosylated surface protein that has been implicated in the dephosphorylation-mediated activation of Src family kinases, and as such, its activity is linked to a myriad of cellular responses ranging from proliferation to differentiation and tumorigenesis (29). CD45 also has a highly glycosylated domain and plays a critical role in T-cell development, recognition, and survival through complex interactions with other proteins (30). The LAR subfamily of RPTP has important functions in the development of the nervous system, including neurite growth and regeneration (31). LAR PTP proproteins are also known to be regulated by proteolytic cleavage. Interestingly, substitution of just two amino acids increases the phosphatase activity of the D2 domain in LAR to that of its D1 domain, suggesting that both domains have physiological roles *in vivo* (21).

Annu. Rev. Pharmacol. Toxicol. 2010.50:215-235.

The cytosolic classical PTP includes well-studied enzymes such as PTP1B, TC-PTP, SHP1, SHP2, and PTP-PEST. These PTPs contain regulatory regions that flank the catalytic site and control enzymatic activity directly—by interactions with the active site or by influencing substrate specificity—and spatially—by directing subcellular localization (24, 32). PTP1B and the closely related TC-PTP have been studied as prototypes of various properties of PTP. They are approximately 50-kDa PTPs that are widely expressed in tissues. PTP1B and TC-PTP have been shown to dephosphorylate growth factor receptors such as the epidermal growth factor receptor (EGFR) and platelet-derived growth factor receptor (PDGFR) (33) and have roles in cancer and tumorigenesis (34). They interact with their substrates in a bidentate mode in which two phosphotyrosine-binding sites within their catalytic domains recognize specific phosphotyrosines (21).

SHP1 expression occurs primarily in hematopoietic cells, whereas expression of SHP2 is ubiquitous (35). SHP1 and SHP2 each contain two Src homology 2 domain (SH2) motifs, at least one of which enables these PTPs to localize with phosphotyrosine-containing substrates and modulate their activity. In addition, the SHPs have two tyrosines in their carboxy termini that are phosphorylated in response to certain stimuli, an event that has also been associated with increased activity of these PTPs. The proline-, glutamic acid-, serine-, and threonine-rich (PEST) PTP family includes lymphoid tyrosine phosphatase (LYP) and PTP-hematopoietic stem cell fraction (PTP-HSCF) (36, 37). They differ considerably in expression, with LYP being restricted to immune cells, whereas PTP-HSCF and PTP-PEST are present in hematopoietic and other tissues. LYP and PTP-HSCF appear to interact with the inhibitory PK C-Src kinase (Csk) and thus could play an important regulatory role in the activation of Src. PTP-PEST also associates with Csk and with cytoskeletal proteins such as Cas, paxillin, FAK, and Pyk2 (36).

The second large class of Type I PTP consists of the heterogeneous cytosolic dual specificity phosphatases (DSPs) (38). DSPs are defined by their ability to dephosphorylate phospho-serine and phospho-threonine residues, in addition to phospho-tyrosine bearing substrates in the same protein. These enzymes have a catalytic pocket that is broader and shallower than that of the classical PTP, which appears to enable them to catalyze the simultaneous dephosphorylation of P-Ser/P-Thr as well as P-Tyr. Currently, seven subgroups of DSP are recognized (**Figure 1**). The three mammalian slingshot phosphatase genes, SSH1L, SSH2L, and SSH3L, are ubiquitously expressed. These PTPs are involved in the regulation of actin polymerization by opposing the action of the kinases TESK1 and LIMK1 (39). The phosphatases of regenerating liver (PRL-1, PRL-2, and PRL-3) are involved in cancer metastasis and appear to have membrane-targeting post-translational modifications (40). Four known PTPs are categorized in the Cdc14 subgroup: KAP, Cdc14A, Cdc14B, and PTP9Q22. Most of what is known about the Cdc14 PTPs is derived from work on yeast cells. However, the mammalian forms appear to serve analogous functions by coupling mitotic processes. These enzymes are similar in function to the class III Cdc25 family of PTPs and are involved in cell cycle control, apparently by regulating elements in the mitotic apparatus (41) and dephosphorylating Cdk2 (38).

The phosphatase and tensin homolog deleted on chromosome 10 (PTEN) PTP group has five members whose substrates include proteins and phosphatidylinositol phospholipids with a phosphate on D3 of the inositol ring, specifically phosphatidylinositol-3,4,5-trisphosphate (PIP3). PIP3 is produced by the phosphorylation of phosphatidylinositol-4,5-bisphosphate (PIP2) by the action of phosphatidylinositol-3-kinase (PI3K) in response to integrin and growth factor receptor stimuli. PIP3 and its congeners activate effector proteins by recruiting them to specific membrane compartments. Thus, PTEN PTPs oppose the activity of PI3K and its growth-promoting and anti-apoptotic effects (42). In addition to roles in embryonic development and cell migration and survival, PTEN is recognized as a tumor-suppressor gene. Deletions or somatic mutations of the

Annu. Rev. Pharmacol. Toxicol. 2010.50:215-235.

human PTEN gene are commonly observed in primary human cancers, tumor cell lines, and familial cancer disorders (43, 44). There are 14 human myotubularin PTPs that dephosphorylate phosphatidylinositol polyphosphates and, therefore, their function overlaps with that of PTEN PTPs (45). Interestingly, about half of the myotubularin genes encode proteins that have substitutions of the Cys and Arg residues of the CX_5R motif, predicting that they are catalytically inactive. These inactive proteins may have regulatory roles that involve binding with active myotubularins to regulate phosphatidylinositol polyphosphate levels. Mutations in several myotubularin genes are associated with myotubular myopathy and peripheral neuropathy (45).

The best-characterized subdivision of DSPs, the MAPK phosphatases, inactivate mitogen-activated protein kinases (MAPKs) by dephosphorylating the signature tyrosine-X-threonine sequence in the MAPK activation loop (46). The 10 mitogen-activated protein kinase phosphatases (MKP) contain an extended catalytic domain, DX26(V/L)X(V/I)HCXAG(I/V)SRSXT(I/V)XXAY(L/I)M, and kinase-interactive motifs in the amino terminus (38, 47). MKPs have relative specificities for different MAPKs and can be phosphorylated by them on specific Ser residues, which increases the half-life of the MKP by inhibiting its proteosomal degradation (48). Additionally, the expression of MKP is inducible as early-response genes whose expression is low in resting cells and dependent on MAPK activity (38). Certain MKPs have been intensively studied for their roles in pancreatic (49) and ovarian (50) cancer (DUSP6), innate immunity (DUSP1) (38), and inflammation (DUSP10) (51).

Widely expressed class II PTPs are referred to as low-molecular-weight PTPs (LMW-PTPs) [reviewed by Raugei et al. (52)]. The LMW-PTPs are a family of 18-kDa enzymes whose primary role is the regulation of cell growth initiated through growth factor receptors. LMW-PTPs have been shown to dephosphorylate the platelet-derived growth factor receptor (53), insulin receptor (54), fibroblast–growth factor receptor (55), and ephrin receptor (56)—in addition to the Rho regulator p190RhoGAP (57), focal adhesion kinase (Fak) (52), and the transcription factor STAT5 (58). The activity of the LMW-PTPs is increased by phosphorylation at specific tyrosine residues by Src kinase family members Src, Fyn, and Lck (52).

The Cdc25 PTPs (Cdc25A, Cdc25B, and Cdc25C) comprise the class III PTPs [reviewed by Rudolph (59)]. Overexpression of Cdc25A and Cdc25B is seen in many primary tumors and has been correlated with adverse clinical prognosis. The Cdc25 PTPs dephosphorylate specific phosphoThr and phosphoTyr residues on cyclin-dependent kinases (Cdk/cyclins), key regulators of eukaryotic cell cycle and cell division, whose activity is suppressed by phosphorylation by Wee1 and Myt1. Cdc25-mediated dephosphorylation causes the activation of Cdk/cyclins. Cdc25A, Cdc25B, and Cdc25C control G2-to-M transitions; Cdc25A is also capable of promoting G1-to-S progression. Cellular levels of Cdc25 PTP are regulated by phosphorylation by the kinases Chk1 and Chk2, which induces their ubiquitin-mediated degradation (32, 60). Cdc25B is also a p38 substrate that participates in the checkpoint response that prevents Cdk/cyclin activation and G2-to-M transition following DNA damage (61). Interestingly, in contrast to other PTPs, the Cdc25 PTPs do not have an Asp near the active site (59).

REGULATION OF PTP ACTIVITY

Once thought to be constitutive, the activity of CX_5R PTP superfamily members is now known to be modulated through a number of regulatory mechanisms (62). As mentioned above, RPTP activity can be increased or decreased by binding of specific ligands (24). PTPζ activity is suppressed by binding to pleiotrophin, permitting higher levels of phosphorylated β-Catenin, β-Adducin, and p-190 Rho GAP, thereby promoting cytoskeletal and adhesion changes. Similarly, the activity of the RPTP LAR is increased by binding to Syndecan but inhibited by Dallylike. Changes in LAR

Annu. Rev. Pharmacol. Toxicol. 2010.50:215-235.

activity modulate levels of phosphorylated Enabled, a protein that has a role in synaptogenesis. Although its relationship to ligand binding is still unclear, dimerization of RPTP appears to be an important regulatory mechanism in its own right. Dimerization has been demonstrated for PTPα and CD45, and it has been suggested to occur for all RPTPs (62). For PTPα, dimerization *in vivo* has been shown to correlate with a loss of phosphatase activity due to a change in the rotational orientation of the PTP (63). Crystallography of PTPα dimers revealed the existence of inhibitory helix-turn-helix wedge motifs with which each member of the dimer blocks the D1 active site of the other. How this mechanism relates to ligand binding is not known at present, but modulation of RPTP activity through intermolecular conformational changes is likely to be a regulatory mechanism for these enzymes (24).

Phosphorylation modification of PTPα has also been shown to regulate its activity, though more specifically, by regulating access to its substrate (62). PTPα is constitutively phosphorylated at a Tyr residue in the D2 active site, which causes it to bind to Grb2 through an SH2 interaction. Ser phosphorylation of PTPα by PKCδ initiates an SH2 exchange wherein Grb2 is released to participate in other interactions that lead to signal transduction activation, whereas the free P-Tyr on PTPα binds to the SH2 domain of Src. The binding of PTPα results in the activation of Src through dephosphorylation of the inhibitory P-Tyr at its C-terminus (29, 64). PTPα and PTPε are also known to be regulated by proteolytic cleavage, a mechanism thought to result in a redistribution of their subcellular localization. Proteolysis of these RPTPs is carried out *in vivo* by Calpain and produces distinct cytoplasmic forms of these enzymes that include the catalytic domains (65). In another example of regulation by differential localization as a regulatory mechanism for PTP, PTPε activity is suppressed by reversible association with microtubules. This microtubule sequestration is induced by EGFR activation and coincides with Tyr phosphorylation of PTPε (66). A number of RPTPs have been shown to be subject to extracellular proteolysis by serine endopeptidases, leading to ectodomain shedding (62).

REDOX REGULATION OF PTP ACTIVITY

The first report of redox regulation of PTP during signaling was a seminal article by Lee et al. that described transient loss of PTP1B activity in A431 cells stimulated with epidermal growth factor (EGF) that correlated with the oxidation of the PTP (67). Since then, studies have extended these findings widely within the CX_5R superfamily, including LMW-PTP (68), PTEN (69), PTPα (70), and cytosolic TC-PTP (71). Reversible oxidation of the catalytic Cys is now recognized as a pivotal mechanism for the modulation of PTP activity during physiological signaling (**Figure 2**) (24, 72). Additionally, detailed mechanistic information exists on the oxidation of the catalytic Cys in the active site of PTP. Whereas a typical Cys pKa is approximately 8.5, owing to the acidic microenvironment in which it resides, the pKa of the CX_5R Cys is unusually low, with values ranging from 4.7 to 5.6 for various PTPs (73–75). As previously noted, this low pKa means that, at normal intracellular pH values, the Cys thiol exists in the ionized state, specifically as a thiolate anion ($-S^-$). Compared with the neutral thiol species, the negative charge on the Cys S atom makes it a considerably better nucleophile toward the substrate P atom. However, it also renders it susceptible to oxidation to the sulfenic acid (-SOH) form or the higher oxidation states, sulfinic (-SOOH) and sulfonic (-SOOOH) acids (76). Unlike the sulfinic and sulfonic derivates, which are mostly irreversible under intracellular conditions, the sulfenic form of the catalytic Cys is readily reduced to the thiolate anion (67, 76).

Multiple mechanisms have been proposed to prevent oxidation of the thiolate anion beyond the sulfenic acid derivative and facilitate reduction of the starting thiolate (77). Reaction between the sulfenic acid S and the main chain N of a neighboring amino acid residue results in the

Annu. Rev. Pharmacol. Toxicol. 2010.50:215-235.

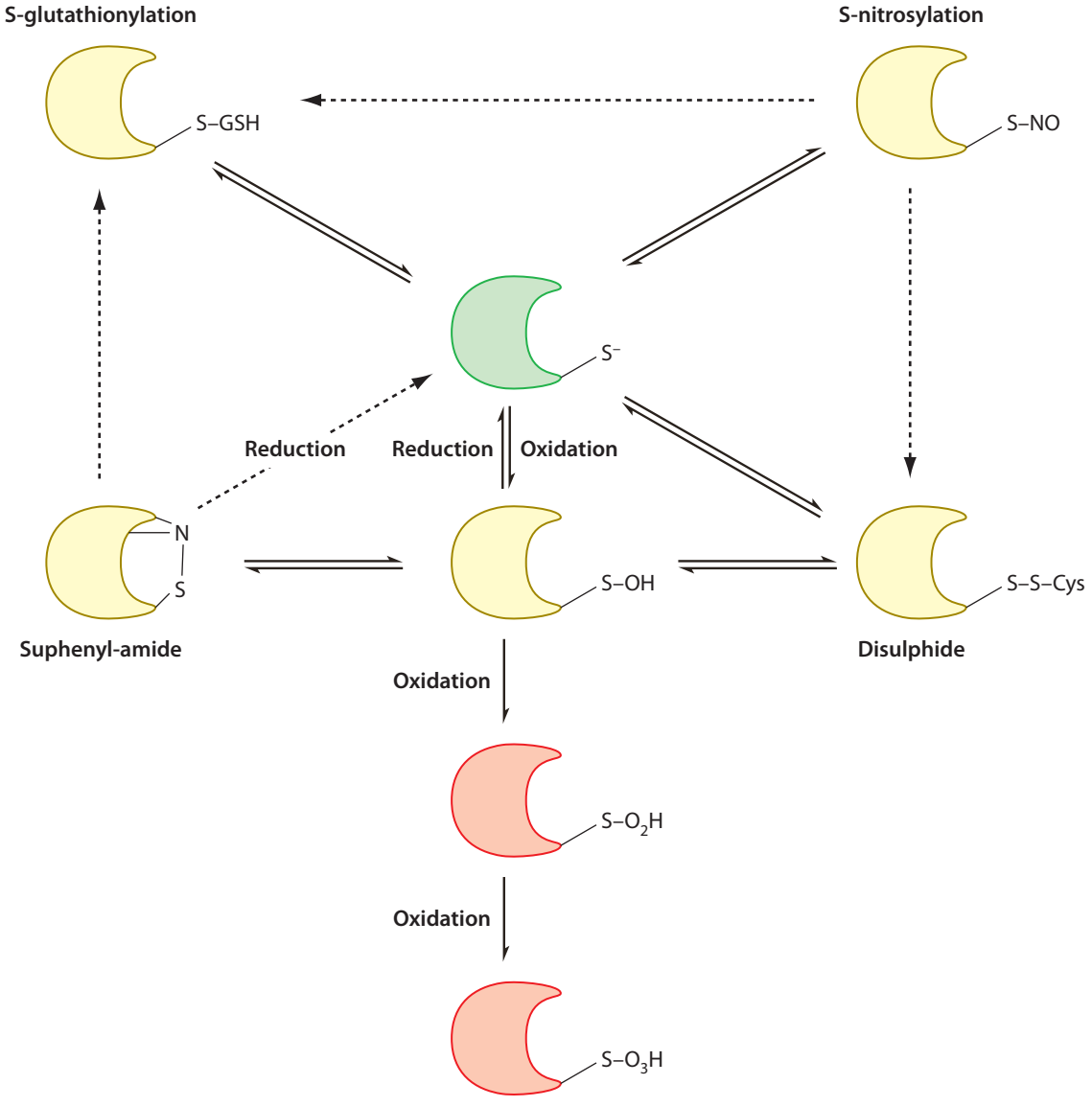

Figure 2

Redox regulation of PTP activity. PTPs are characterized by a signature motif, [I/V]HCXXGXXR[S/T], in which the invariant Cys residue serves as a catalytic nucleophile that attacks the phosphate. The environment of the active site confers an unusually low pKa on this cysteine residue, which therefore is present as a thiolate anion (*green*) at physiological pH. The thiolate is highly susceptible to oxidation to sulfenic, sulfinic, and sulfonic acids, all of which are catalytically inactive. Reversible and irreversible oxidation states are shown in yellow and red, respectively. Reversible S-glutathionylation and S-nitrosylation post-translational modifications have also been reported.

formation of a previously unknown sulfenyl-amide species that is resistant to further oxidation and can be reduced by glutathione back to the thiolate anion (78). S-nitrosylation of the catalytic Cys in PTP1B has been reported and has been suggested as a mechanism that prevents irreversible inactivation of the enzyme (79). Similarly, selective and reversible glutathionylation of PTP1B is induced in macrophages stimulated to undergo an oxidative burst in response to ADP treatment

Annu. Rev. Pharmacol. Toxicol. 2010.50:215-235.

(80). The presence of a Cys vicinal to the catalytic Cys is a unique feature of LMW-PTP, Cdc25C, and PTEN that permits the formation of a disulfide (-S-S-) bond with the sulfenic derivative of the catalytic Cys that protects it from irreversible oxidation but can also be reduced by intracellular thiols (24, 77, 81). The oxidation of RPTP presents additional features with regulatory implications (72). The thiolate residue in the highly conserved but catalytically inactive D2 domain of RPTP has been shown to be even more susceptible to oxidation than the thiolate in the active D1 domains (82). In addition, the RPTP D2 domains can form reversible and inactive intermolecular -S-S- links upon oxidation (83, 84). It has been suggested that D2 domains are intracellular redox sensors whose oxidation can be transmitted to the extracellular domain of RPTP (24).

The structure of the catalytic Cys during oxidative inhibition of PTP has been unequivocally shown using proteomic and biochemical approaches (69, 85, 86). Strong evidence implicates H_2O_2 as the reactive oxygen species involved (67, 69). Similarly, there is a growing consensus that thioredoxin is the intracellular reductant that reverses the oxidative inactivation of PTP by regenerating the catalytic thiolate (67, 69, 87). However, their fleeting nature and limitations of conventional methods used for their detection have prevented absolute identification of the oxidants that participate in the redox regulation of PTP during physiological signaling. It is not surprising then that the mechanisms that lead to the generation of the oxidant species responsible and the regulatory events surrounding the oxidation of PTP are incompletely understood (24).

Inhibition of specific PTP activity has been linked with the physiological activation of a number of growth factor receptors with their natural ligands (24). The initial report of redox regulation of PTP involved activation of EGFR in A431 cells treated with EGF (67). Studies have also shown reversible inactivation of various PTPs in conjunction with the activation of receptors in cells responding to PDGF (81) and insulin (71). Other examples include the activation of T-cell receptors (88), endothelin-1 signaling (89, 90), adhesion-mediated activation of lymphocyte function-associated antigen-1 (91), and B-cell receptor signal modulation (92).

Redox regulation of PTP has also been linked to the activation of nonreceptor kinases. In a study of oxidant-induced MAPK activation, H_2O_2 was shown to induce JNK phosphorylation through a mechanism that involves inhibition of SHP-1, whereas the activation of p38 occurred through HePTP suppression, and the mechanism of activation of extracellular-signal regulated kinase (ERK) included the inhibition of both SHP-1 and HePTP (93). Similarly, it has been reported that LMW-PTP inactivation by exogenous oxidants potentiates ERK activation (94) and that impairment of JAK2 dephosphorylation leads to sustained activation of this kinase (95).

Another mechanism for the physiological regulation of PTP has been proposed by Haase & Maret (96). This pathway also involves intracellular redox changes; however, it posits that the divalent metal cation Zn^{2+} is the effector of PTP inhibition. In this pathway, stimulation of the cell results in the production of reactive oxygen species that oxidize proteins that serve as Zn^{2+} storage sites, such as metallothionein to produce thionein and free Zn^{2+}. The free Zn^{2+} then interacts with thiolate and other conserved active site residues on PTP via electrostatic interactions, thereby inactivating the enzyme. Return to homeostasis is accomplished by the reduction of thiol groups on thionein, which restores its affinity for Zn^{2+}, effectively removing the Zn^{2+} from PTP (97). Haase & Maret have also suggested a hybrid version of this mechanism and classical redox regulation of PTP. In this scenario, PTPs exist in a partially inhibited state by normal intracellular levels of Zn^{2+}, with fluctuating Zn^{2+} concentrations (Zn transients) that are modulated by redox-sensitive zinc-buffering systems such as metallothionein and thionein (98, 99).

Annu. Rev. Pharmacol. Toxicol. 2010.50:215-235.

CONCEPTUALIZING THE ROLE OF PTP REGULATION IN SIGNALING HOMEOSTASIS

The functional role of PTP inhibition during physiological activation of signaling is generally interpreted to be supportive, with the temporary suppression of PTP activity serving to increase the magnitude and duration of the phosphorylation action of TKs. Thus, in this conceptual model, the activation of TK activity and the inhibition of PTPs are temporally coincident events coordinated to maximize the amplitude of the signal. From an efficiency standpoint, this regulatory system works best if the basal activity of PTP exceeds that of the basal TK activity that it opposes. Such an arrangement enables a quiet signaling environment in cells at rest because it effectively imposes a threshold kinase activity below which protein phosphorylation does not accumulate over time. A useful analogy to a resting cell is that of a kitchen sink, where the volume of water in the sink represents the intracellular level of protein phosphotyrosines, the TKs are the equivalent of a dripping faucet, and PTPs function as a drain. As long as the rate of drainage is greater than that of the input from the dripping faucet, no net accumulation can occur. In the scenario of a stimulated cell, there is a frank activation of TK activity that is equivalent to a full opening of the faucet, whereas the oxidant-mediated inhibition of PTP is akin to restricting the drain.

As with a filling sink, the combination of these events raises the concentration of protein phosphotyrosines in the cell. The return to the basal signaling state is also a two-pronged event, involving the inactivation of TKs and the resumption of PTP activity. A variety of mechanisms exist for the inactivation of TKs, such as receptor internalization and degradation, ligand dissociation, and dephosphorylation. As discussed above, the reversal of PTP inactivation through the reduction of the catalytic Cys sulfenyl is mediated by intracellular antioxidants such as thioredoxin. In the kitchen sink analogy, reversal events are represented as restricting the flow of water from the faucet back to a drip and reopening the drain.

A critical premise of the conceptual model described here is that TK activity in resting cells is not zero; that is, the faucet is never turned off completely. Indeed, ample experimental evidence supports the notion that basal TK activity exists in unstimulated cells and that it is a vital part of normal cellular physiology. Baseline activity can be readily measured for many TKs in a variety of unstimulated cells (100–106). Moreover, inhibition of basal TK activity with inhibitors of broad or targeted specificity has demonstrable effects on signaling activity and a host of cellular processes that it controls (107–109). The presence of a basal tone of TK activity in resting cells is of critical importance because it has the effect of placing the burden of cellular homeostasis on the PTP. As discussed above, the excess of PTP over TK activity ensures that protein phosphotyrosines in unstimulated cells do not accumulate above a threshold required to transition to an activated state. A shift in this dynamic equilibrium toward an increase in protein phosphotyrosine levels can be achieved by an elevation in TK activity alone or, more efficiently, in conjunction with a decrease in PTP activity.

A third possibility in the conceptual model, one that is especially pertinent to toxicological effects on signaling, is the decrease of PTP activity without an alteration of basal TK tone. Any loss of PTP activity would be expected to shift the balance toward increased levels of protein phosphotyrosines as the opposition to basal TK activity is diminished. To return to the kitchen sink analogy, a partial restriction of the drain would increase the amount of water that accumulates in the sink from the dripping faucet. A sufficiently large inhibition of PTP activity leads to an excess of the threshold phosphotyrosine level, causing activation of signaling. The magnitude of the signaling initiated in this manner may not be distinguishable from signaling involving physiological TK activation accompanied by redox PTP inhibition. Kinetically, signaling activation

Annu. Rev. Pharmacol. Toxicol. 2010.50:215-235.

induced by loss of PTP activity would be expected to show a relatively slow onset, as the rate of phosphorylation is entirely determined by the basal TK activity. Given that dephosphorylation is not possible in the absence of PTP activity, the most striking features of signaling induced by loss of PTP activity are that it is cumulative and irreversible. Experimental evidence supports the predictions of the conceptual model: Treatment of cells with known inhibitors of PTP activity such as orthovanadate (110) induces time-dependent accumulation of protein phosphotyrosines (111), as well as a pan-activation of multiple signaling pathways (112–121). These studies show that diminished dephosphorylation capacity leads to loss of homeostasis and passive activation of signaling.

TOXICOLOGICAL DISREGULATION OF PTP ACTIVITY

Although notable examples of xenobiotic exposure leading to gain of function exist, loss of function is the dominant mechanistic paradigm in toxicology. Stated another way, it is far more common for a chemical agent to interfere with the function of a macromolecule than it is for a toxicant to induce the thermodynamically unfavorable transition of a macromolecule from its basal state to its activated form. A significant body of evidence shows that this basic toxicological principle extends to signaling transduction effects as well. One of the earliest signal transduction toxicology studies to make this observation was a paper by Knebel et al. (122). In trying to understand the mechanism for UV-induced activation of multiple growth factor receptors, these researchers identified inhibition of dephosphorylation as the initiating lesion common to UV, oxidant stressors, and alkylating agents. Moreover, they showed that the loss of dephosphorylation activity involved the modification of the thiol group in PTP, in effect pointing to PTP as toxicological targets. Broadly, the mechanisms through which toxicants inhibit PTP can be categorized into two types: direct inhibition by metals and organic nucleophiles and indirect inhibition through the generation of an oxidative redox environment in the cell.

DIRECT PTP INHIBITION

A growing body of literature supports the notion that both metallic and organic components associated with ambient particulate matter (PM) components can directly impair PTP activity by forming inhibitory electrostatic interactions with the catalytic Cys or by covalent modification of catalytic and regulatory residues, respectively. Zn^{2+} is a ubiquitous PM constituent that has been implicated in the toxicity associated with PM inhalation (123–127). Mechanistically, Zn^{2+} is of interest as a transition metal ion that lacks an adjacent valence state and is therefore unable to support redox cycling reactions. Zn^{2+} is also a potent inhibitor of PTP (96, 98, 128), including a broad spectrum of PTP present in airway epithelial cells (129).

Toxicological exposure to Zn^{2+} has pleiotropic effects on signaling that are attributable to PTP inhibition. In cultured human airway epithelial cells (HAEC), Zn^{2+} exposure induces phosphorylation of EGFR at tyrosine residues known to be trans- and auto-phosphorylation sites through a mechanism that requires EGFR kinase activity (126). The same study showed that Zn^{2+}-induced phosphorylation of EGFR is unaffected by blocking antibodies directed against the external ligand-binding domain of the EGFR, demonstrating ligand-independent receptor activation. Consistent with these observations, phosphorylation of the receptor is not accompanied by dimerization of EGFR in A431 cells treated with Zn^{2+} (124). Experiments in intact cells or using recombinant EGFR added exogenously to cell lysates revealed that the rate of dephosphorylation of P-EGFR

Annu. Rev. Pharmacol. Toxicol. 2010.50:215-235.

is significantly reduced in HAEC treated with Zn^{2+} (126). In an earlier study of EGFR activation by various alkylating and redox-cycling quinones, Abdelmohsen et al. showed that exposure to menadione impairs EGFR dephosphorylation in rat liver epithelial cells (130). Using the same experimental approach, a recent study reported that exposure to diesel exhaust particles of varying organic content induces EGFR phosphorylation through an inhibition of EGFR-directed phosphatase activity (131). Evidence of direct toxicological targeting of PTP and its effect on signaling is not limited to receptor TK. Kim et al. showed that proinflammatory signaling through the MAPKs ERK and JNK is linked to a marked inhibition of P-ERK and P-JNK dephosphorylation in HAEC treated with Zn^{2+} (132).

A mechanism of direct inhibition has been proposed wherein Zn^{2+} blocks PTP activity by binding to the catalytic cysteine and to neighboring histidine or aspartate residues present in the highly conserved active site (96). More recently, these investigators suggested that Zn^{2+}-coordinated thiolates can also participate in redox cycling, generating disulfide and irreversibly oxidized sulfur moieties (133, 134). However, treatment of Zn^{2+}-exposed HAEC with either the specific Zn^{2+} chelator TPEN or the strong reductant/weak Zn^{2+} chelator dithiothreitol, but not other structurally unrelated antioxidants, reverses Zn^{2+}-mediated inhibition of EGFR-directed PTP activity (T. L. Tal, unpublished observations). This suggests that Zn^{2+}-mediated PTP inhibition may occur through direct attack on the PTP catalytic site, rather than indirectly inhibiting PTP by oxidation. Interestingly, exposure to nucleophilic aldehydes (commonly associated with ambient PM) was reported to mobilize cellular Zn^{2+} from metallothionein and thionein at levels sufficient to reduce PTP activity in HepG2 cells (135).

A second mechanism by which toxicological agents directly impair PTP activity is through covalent modification of the catalytic thiolate. Certain reactive organic compounds present in ambient PM, such as quinones and aldehydes, can directly inactivate PTP1B activity by a covalent modification of reactive cysteines (136, 137). Seiner et al. reported that the reactive α-β-unsaturated aldehyde acrolein inhibited PTP1B activity through conjugate addition to the catalytic Cys in vitro (137). Notably, treatment of A431 cells with 1,2-napthoquinone was shown to arylate two reactive cysteinyl residues in PTP1B, thereby inhibiting its activity and leading to a prolonged and irreversible activation of EGFR (136). Taken together, these studies are in keeping with the concept that PM-associated oxy-organics can inhibit PTP activity and thereby directly contribute to proinflammatory phosphorylation-dependent signaling. In support of this notion, activation of vanilloid receptor 1 leading to contraction of tracheal smooth muscle in guinea pigs exposed to 1,2-napthoquinone was blocked when tracheal tissue was pretreated with the EGFR kinase inhibitor PD153035 (138).

Although the catalytic cysteine is often hypothesized to be susceptible to post-translational modification (139), it is likely that other regulatory residues are targets of direct and indirect inhibition by Zn^{2+} and diesel exhaust particles (DEP). A recent report examining the effects of 1,2-napthoquinone on PTP1B activity demonstrated that nucleophilic His (His^{25}) and Cys (Cys^{121}) residues, in addition to the catalytic cysteine (Cys^{215}), are susceptible to covalent modification by 1,2-napthoquinone (136). The authors speculate that although Cys^{121} is noncatalytic, it may act as a site of allosteric inhibition (136). In the case of Zn^{2+}, the metal cation is hypothesized to form inhibitory electrostatic interactions with multiple Cys and His residues located near the catalytic groove (96). In addition to the evidence that specific electrophilic aldehydes and quinones such as acrolein and 1,2-napthoquinone can covalently modify critical cysteine and histidine residues (136, 137), a recent study demonstrated that DEP exposure reduces the rate of EGFR-directed PTP activity, leading to sustained EGFR phosphorylation in HAEC (131).

Annu. Rev. Pharmacol. Toxicol. 2010.50:215-235.

TOXICOLOGICAL INHIBITION OF PTP THROUGH OXIDATIVE MECHANISMS

Numerous studies have sought to identify the mechanism by which particle inhalation induces local and systemic inflammation. Particle mass, size, and surface area, metallic and organic contents, acids, sulfates, nitrates, elemental carbon, and copollutants have been investigated, and oxidative stress has emerged as a leading mechanism by which PM elicits pulmonary toxicity (140–143). Oxidative stress, induced by the imbalance of oxidant generation and elimination, is tightly regulated by both enzymatic (e.g., superoxide dismutase, catalase, and glutathione peroxidase) and nonenzymatic (e.g., α-tocopherol and glutathione) defenses. One characteristic of oxidative stress is the depletion of reduced glutathione with an accompanying accumulation of the oxidized form diglutathione. Glutathione depletion induced by glutamate has been shown to drive neuronal toxicity through a mechanism that involves inhibition of ERK-directed PTP activity (144). The same study also showed that overexpression of MKP3 confers neuroprotection against an oxidant insult in primary neuron cultures. An interesting effect of oxidative stress induced by peroxynitrite, by the redox reagent dithiopyridine, or by the biocide methylisothiazolinone is the release of Zn^{2+} from metallothionein stores. The liberated Zn^{2+} then acts negatively on MKP to initiate or potentiate the phosphorylation-dependent activation of ERK1/2 in neurons (145).

Oxidative changes can also activate redox-sensitive signaling pathways that culminate in the expression of genes encoding cytoprotective and inflammatory proteins (146). However, generation of reactive oxygen and nitrogen species is not limited to pathological outcomes. It is also a critical physiological contributor to immunological host defense (147) and a proposed mediator of phospho-dependent signaling (148). Interestingly, the formation of reactive oxygen or nitrogen species has been described in response to growth factor-mediated activation of transmembrane receptors (67, 149) and has been implicated in PM-related signaling aberrations (126, 132).

PM is thought to exert oxidative stress on the lung by presenting or stimulating cells to produce reactive species via its metals, organics (semiquinones and hydrocarbons), lipopolysaccharides, and reactive carbon surfaces (150) (**Figure 3**). Studies using residual oil fly ash, essentially an inorganic metallic ash, have demonstrated that pulmonary inflammation is attributable to water-soluble metal constituents (151–153). Common soluble metallic components associated with PM include Fe^{3+}, Cu^{2+}, Zn^{2+}, $V^{3+/5+}$, and $Cr^{3+/6+}$ (151). Mechanistically, redox-cycling metals, such as Fe^{3+}, Cu^{2+}, $V^{3+/5+}$, and $Cr^{3+/6+}$, can generate reactive oxygen species (ROS) by Fenton-type chemistry and act as catalysts by Haber-Weiss reactions (154). Fe^{3+} in particular is reported to be a primary contributor to DEP-induced H_2O_2 generation (155).

In addition to metals, bioavailable organic compounds have been reported to contribute to oxidative effects induced by PM exposure (156). Two main families of compounds, polycyclic aromatic hydrocarbons (PAHs) and quinones, are adsorbed on diesel particles (157) and are thereby delivered to the airway epithelium following inhalation. Both reactive PAH metabolites and redox-cycling quinones generate reactive oxygen species. In particular, NADPH-cytochrome P450 reductase reduces quinones to semiquinone radicals that in turn reduce oxygen to O_2^- and become reoxidized to the original quinone. PM-associated PAHs are metabolized by cytochrome P450s and peroxidases to oxidized derivatives such as epoxides, diols, and redox-cycling quinones (reviewed in 158). A body of work supports the notion that the organic fraction of DEP, via reactive oxygen species generation, is the primary mediator of PM-associated inflammation and toxicity (158, 159). Recent work has added organic hydroperoxides such as peracetic acid and aromatic peracids (160) to the list of compounds that react with PTP as extremely potent inhibitors of PTP1B in vitro. Similarly, amino acid, peptide, and protein hydroperoxides, products of protein oxidation, have also been shown to be potent thiol reactive inhibitors of PTP, thus expanding the

Annu. Rev. Pharmacol. Toxicol. 2010.50:215-235.

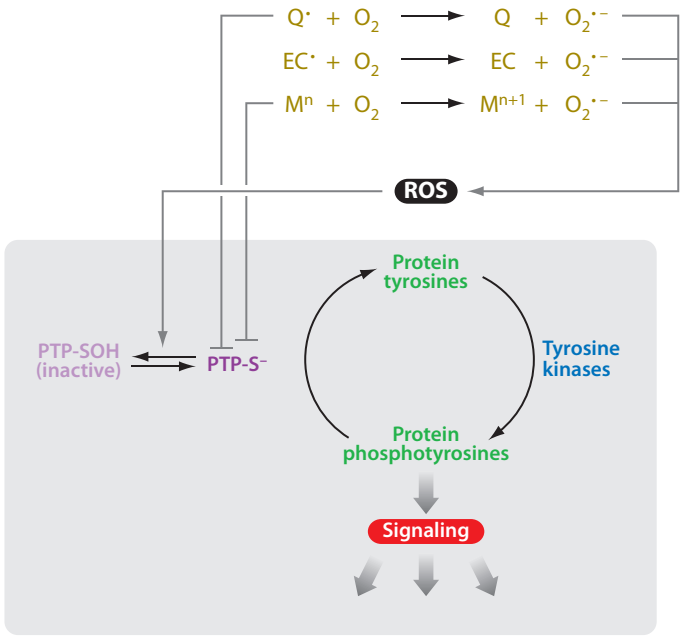

Figure 3

Toxicological disruption of signaling homeostasis through PTP inhibition. Electrophilic agents such as quinones and certain soluble metal cations such as Zn^{2+} can attack the catalytic Cys thiolate anion in PTP directly. Alternatively redox active organic species and Elemental Carbon (EC) and mineral particle surfaces, or Fenton-active transition metal ions, can generate reactive oxygen species (ROS) that inactivate PTP by promoting the conversion of the catalytic Cys to the inactive sulfenyl derivative. Loss of PTP activity allows basal kinase activity to work unopposed, leading to the accumulation of protein phosphotyrosines and the initiation of signaling cascades.

mechanisms through which oxidative stress can lead to loss of PTP activity and the disregulation of signaling (161).

SUMMARY POINTS

1. PTPs maintain signaling quiescence in resting cells and have a pivotal role in the termination of signaling.
2. Although there is great diversity among the PTPs, they all share an invariable catalytic Cys that is physiologically regulated through reversible redox modification.
3. The same catalytic Cys in PTP is also highly susceptible to inhibition by direct or oxidative electrophilic attack by a broad spectrum of compounds.
4. The loss of PTP activity disregulates phosphotyrosine metabolism, leading to persistent ligand-independent activation of multiple signaling cascades in the cell.
5. Inhibition of PTP represents a fundamental toxicological mechanism through which exposure to structurally disparate xenobiotic compounds leads to adverse cellular responses.

Annu. Rev. Pharmacol. Toxicol. 2010.50:215-235.

FUTURE ISSUES

1. Much remains to be known about the generation of the oxidant species that modify PTPs during physiological stimulation of the cell.
2. It is likely that toxicological inhibition of PTP activity occurs through a disregulation of physiological mechanisms for oxidant production in the cell.
3. Studies are needed to examine the involvement of PTP inhibition in response to xenobiotics under real-world exposure conditions.
4. More work is needed to test the link between toxicological PTP inhibition and specific adverse outcomes.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

The research described herein has been reviewed by the National Health and Environmental Effects Research Laboratory and has been approved for publication. Approval does not signify that the contents necessarily reflect the views and policies of the U.S. EPA, nor does mention of trade names constitute endorsement of recommendation for use.

ACKNOWLEDGMENTS

The authors are grateful to Dr. Philip Bromberg, Dr. Lee Graves, and Mr. Robert Silbajoris for their critical review of this manuscript.

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Annu. Rev. Pharmacol. Toxicol. 2010.50:215-235.

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Annu. Rev. Pharmacol. Toxicol. 2010.50:215-235.

Annual Review of Pharmacology and Toxicology

Volume 50, 2010

Contents

Annu. Rev. Pharmacol. Toxicol. 2010.50:215-235.

Indexes

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Annu. Rev. Pharmacol. Toxicol. 2010.50:215-235.