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MINIREVIEW

Protein tyrosine phosphatases: regulatory mechanisms

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Protein-tyrosine phosphatases are tightly controlled by various mechanisms, ranging from differential expression in specific cell types to restricted subcellular localization, limited proteolysis, post-translational modifications affecting intrinsic catalytic activity, ligand binding and dimerization. Here, we review the regulatory mechanisms found to control the classical protein-tyrosine phosphatases.

Protein phosphorylation on tyrosine residues is an important cell-signaling mechanism, controlled by the combined actions of protein-tyrosine kinases (PTKs) and protein-tyrosine phosphatases (PTPs). PTKs are tightly regulated by various mechanisms. Whereas PTPs were initially regarded as household enzymes with constitutive activity, dephosphorylating all the substrates they encountered, evidence is now accumulating that PTPs are tightly regulated. As described elsewhere in this minireview series, the human genome encodes around 100 enzymes that have the capacity to dephosphorylate phosphotyrosine (pTyr) in proteins [1,2]. We focus on the regulatory mechanisms of classical PTPs, a cysteine-based subclass of the PTP superfamily that exclusively dephosphorylates pTyr in proteins. Classical PTPs comprise cytoplasmic and transmembrane proteins that are tentatively called receptor (R)PTPs. Characterization of the catalytic activities of PTPs indicated that their enzymatic activity is extremely high with a k_{cat} value up to three orders of magnitude higher than that of the PTKs, the enzymatic counterpart of the PTPs. All cells express multiple PTKs and PTPs, therefore, tyrosine phosphorylation can occur in cells only if PTPs are tightly regulated. Different levels of regulation can be discerned from the organismal through the cellular to the molecular level as indicated in Fig. 1. Here, we discuss the different regulatory mechanisms that have evolved.

Expression

Differential expression of PTPs is an obvious regulator of PTP function. Among the PTPs are ubiquitously expressed family members such as SHP2 or PTP1B,

Abbreviations
EGF, epidermal growth factor; ER, endoplasmic reticulum; PDGF, platelet-derived growth factor; PrxII, peroxiredoxin II; PTK, protein-tyrosine kinase; PTP, protein-tyrosine phosphatase; pTyr, phosphotyrosine; ROS, reactive oxygen species; TGF, transforming growth factor.

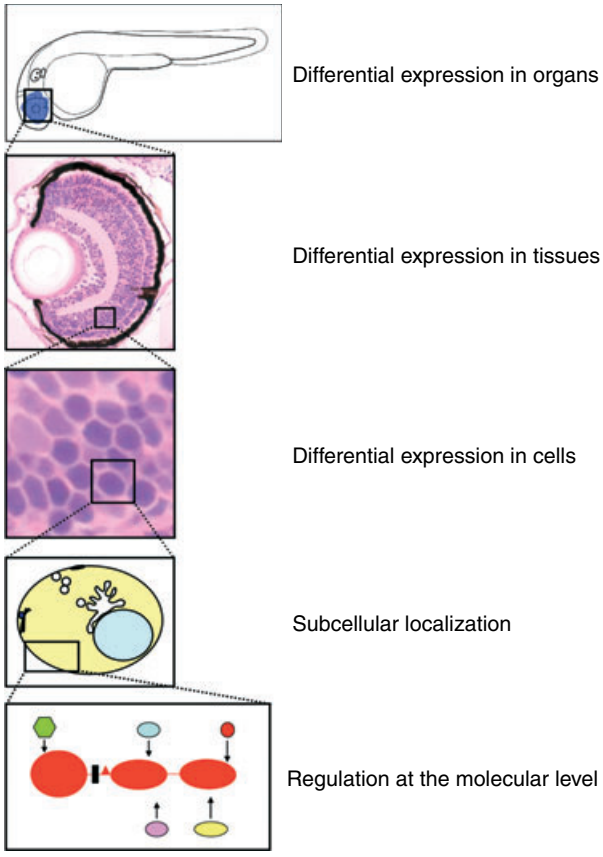

Fig. 1. Regulation of PTPs at different levels. (top to bottom) PTPs are differentially expressed in specific organs, tissues or cells. Within cells, PTPs are directed to specific subcellular locations. At the molecular level, PTPs are regulated by post-translational modifications.

and more selectively expressed members that are abundant in neuronal or hematopoietic compartments [3–5]. However, in a given cell type, such as endothelial cells, many of the 38 classical PTP genes appear to be expressed, at least as represented by low mRNA levels [6] (see http://expression.gnf.org/cgi-bin/index.cgi). PTP mRNA expression is regulated by different mechanisms. Induction of the expression of several PTP genes has, for example, been reported upon neuronal or hematopoietic differentiation [7–11] and a number of PTPs are upregulated in cells reaching high densities, including DEP-1 [12], PTP-LAR [8], RPTPμ [13], RPTPk [14], and PTPβ/VE-PTP [15]. A highly dynamic expression pattern for PTPs has been seen during the onset and termination of smooth muscle cell proliferation in restenosis [16]. In cancer cells, mRNA expression of some PTPs is downregulated by promoter methylation [17].

Relatively few studies have addressed the detailed mechanisms involved in the transcriptional regulation of specific PTP mRNAs. An example is analysis of the PTP1B promoter, which identified a region involved in the induction of PTP1B expression by p210 BCR-Abl activity. This region was designated PRS and interacts with Egr-1 and SP-family transcription factors [18]. Y box-binding protein-1 (YB-1) is another transcriptional inducer of PTP1B and acts by binding to an enhancer element between -152 and -132 of the PTP1B promoter [19]. In a recent search for novel Smad targets in transforming growth factor (TGF)β-stimulated mammary epithelial cells, the PTPκ-encoding gene *PTPRK* was identified [20]. Although details of transcriptional regulation are still unknown, upregulation of PTPκ through the Smad pathway seems to mediate several of the TGFβ responses in these cells, including inhibition of cell proliferation and enhanced cell motility.

Alternate use of promoters within PTP genes is another mechanism that can lead to tissue-specific PTP mRNA expression, as in the case of SHP1 [21], or to the expression of different PTP isoforms, as for RPTPε. In the latter case, alternate promoter use leads to the expression of either a transmembrane RPTPε molecule or a soluble, cytoplasmic version of PTPε with presumably important consequences for the access to substrates [22]. Similarly, three distinct promoters can direct the generation of several isoforms of PTPRR proteins in neuronal cells, of which some are cytoplasmic [23].

Regulation of mRNA stability may be another important level of control in PTP expression. In their analysis of PTP genes, Andersen *et al.* [2] observed that PTP genes often encode long 3′-UTRs, which may be important in this respect. Very few studies have addressed this issue. For example, increased stability of TC-PTP, but not PTP1B, mRNA has been observed in mitogen-stimulated T lymphocytes [24].

Although largely unexplored, PTP levels are likely to also be controlled at the levels of translation and protein stability. Several PTP proteins exhibit rather long half-lives, for example, SHP2 [25], whereas short half-lives have been shown for different isoforms of PTPRR [26]. A cell-density-dependent increase in the expression level of RPTPμ has been attributed to a reduced rate of degradation when this PTP becomes engaged in homophilic interactions upon cell–cell contacts [27].

Subcellular localization

Like protein phosphorylation, dephosphorylation by PTPs is required in a cell-compartment-specific manner. Protein–protein interaction domains and compartment-specific targeting domains in PTPs serve to

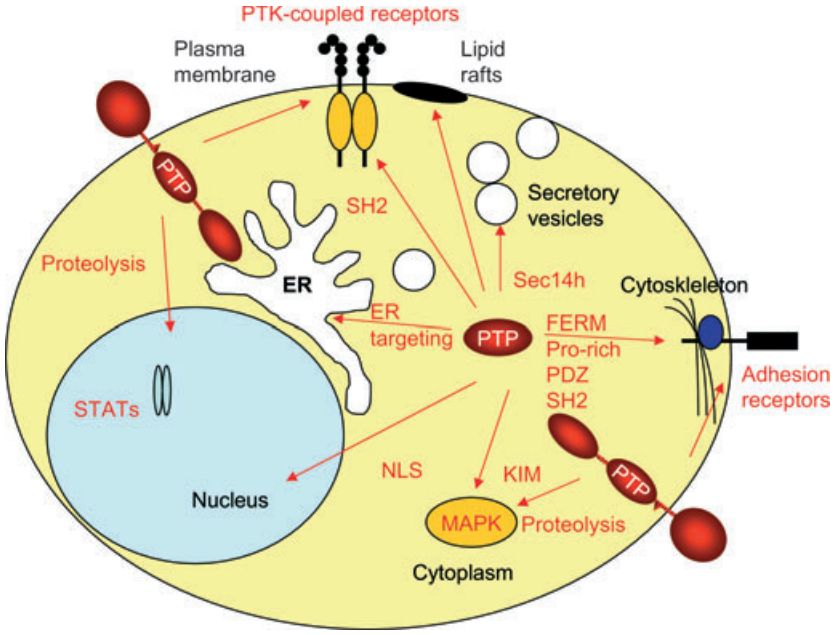

Fig. 2. Subcellular localization of PTPs. Cytoplasmic PTPs are recruited to activated cell-surface receptors by SH2, proline-rich FERM (band 4.1, ezrin, radixin, moesin homology) and PDZ (postsynaptic density protein 95, discs large, Zonula occludens) domains. RPTPs are also engaged in these complexes. Nuclear localization signals (NLS) and ER targeting domains direct PTPs to these compartments. A Sec14-homology domain (Sec14h) mediates functional association with secretory versicles. Cytoplasmic PTPs are recruited into lipid rafts by different domains. The kinase-interacting motif (KIM) in PTPs mediates binding to MAPK. Proteolysis releases the catalytic domain of (R)PTPs into the cytoplasm and possibly also into the nucleus.

achieve the required PTP localization [28,29] from the cell surface to the nucleus (Fig. 2).

At the plasma membrane, RPTPs regulate tyrosine phosphorylation as it occurs in response to cell stimulation of PTK-coupled receptors [30] or in the context of cell–cell or cell–matrix adhesion [31,32]. Complex formation of RPTPs with substrates is important in these cases and has been shown, for example, with several RTKs [33,34]. RPTP domains which mediate such interactions remain to be identified. In addition, cytoplasmic PTPs are recruited to the sites of cell-surface tyrosine phosphorylation. Paradigms are SHP1 and SHP2, which are recruited to tyrosine-phosphorylated cell-surface receptors and adaptor proteins through their SH2 domains [3,4], whose recognition specificities have recently been elucidated in great detail [35]. Interestingly, the C-terminus of SHP1 seems to be involved in targeting this PTP to the plasma membrane. It has previously been shown, that the SHP1 C-terminus harbors a high-affinity binding site for acidic phospholipids [36]. Recent studies revealed that this site is important for targeting SHP1 to lipid rafts in T lymphocytes, where it regulates T-cell receptor signaling [37]. Similarly, HePTP is targeted to lipid rafts. In this case, targeting depends on prior phosphorylation by a PKC isoform [38]. Another non-transmembrane PTP that regulates the tyrosine phosphorylation of surface receptors is PTP1B [39]. Very efficient substrate recognition by this PTP occurs by its catalytic domain [40,41]. However, non-catalytic interactions with substrates may also be important for PTP1B recruitment. A recently published crystal structure revealed binding of PTP1B in a phosphotyrosine-independent manner to the 'backside' of the insulin receptor, an interaction that may facilitate the rapid engagement of substrate residues upon insulin–receptor activation [42]. Interestingly, PTP1B can also be recruited to substrates via adaptor molecules. Phospholipase Cγ1 serves as a scaffold downstream of the activated growth hormone receptor and recruits PTP1B by an as yet unknown mechanism into a ternary complex with JAK2, leading to JAK2 dephosphorylation [43]. It will be interesting to see if phospholipase Cγ1, which binds to many cell-surface receptors, mediates the interaction of PTP1B with other targets as well. Recruitment of non-transmembrane PTPs to cell–cell adhesion complexes and cell–matrix adhesion complexes occurs, for example, via FERM and PDZ domains as in PTP-BAS and via proline-rich domains as in PTP-PEST [28,29,31,32].

Some PTPs reside in the endoplasmic reticulum (ER). The best investigated in this respect is PTP1B whose C-terminus contains an ER-anchoring hydrophobic sequence [39]. Spatial distribution of PTP1B activity over the cell has recently been shown using sophisticated FRET analyses. Most cellular PTP1B activity resides in a perinuclear compartment, whereas the more peripheral PTP1B population has lower activity [44]. How PTP1B can access sites of tyrosine phosphorylation at the cell surface is the topic of intense investigation. In the case of activated epidermal growth factor receptor (EGFR) and platelet-derived growth factor receptor (PDGFR), interaction with

PTP1B takes place in conjunction with endocytosis at the surface of ER membranes, which extend far into the cell periphery [45]. PTP1B, which remains bound to the ER, can also access cell–matrix adhesions and this process involves microtubule activity [46]. Is there a function of PTP1B (and possibly other PTPs) in the ER itself? One function seems to be the regulation of ER stress [47]. Furthermore, it was observed early on that PTP1B can effectively dephosphorylate precursor molecules of cell-surface receptors, such as the insulin receptor or the EGF receptor in the ER, during biogenesis [48,49]. Recently, dephosphorylation of ER-bound immature forms of different RTKs of the PDGFR family, notably of FLT3, has been shown to enhance their maturation to complex glycosylated surface receptors [50]. Similar observations have been made for FGFR3 [51,52]. Spontaneous basal activity of RTKs appears to present an obstacle for efficient processing and an important function of ER-bound PTPs may be suppression of this activity. It should be noted that RPTPs share localization in the ER with maturing RTKs and may also participate in suppression of detrimental RTK basal activity. PTPs may also affect further aspects of RTK trafficking. For example, recycling of internalized PDGFβ-receptor is enhanced in cells lacking T-cell PTP [53].

An interesting, recently explored example of cellular targeting is the localization of PTP-MEG2 to secretory vesicles, where it dephosphorylates *N*-ethylmaleimide-sensitive factor and thereby regulates vesicle fusion [54]. A Sec14-homology domain at the N-terminus of PTP-MEG2 ensures this localization by mediating interactions with resident proteins, such as TIP47 [55].

In the cytoplasm, the specificity of the interaction of PTPs with soluble substrates is enhanced by targeting domains, as exemplified by the kinase-interaction motif which directs HePTP, STEP and PTPRR isoforms to members of the mitogen-activated protein kinase family and facilitates effective dephosphorylation [56,57].

Finally, PTP activity is also needed in the nucleus. Dephosphorylation of tyrosine phosphorylated members of the STAT family is important for terminating STAT signaling, and for recycling of dephosphorylated STAT molecules into the cytoplasm [58]. An important PTP in this context is TC-PTP. An ER-bound 48-kDa version and a 45-kDa version that can shuttle into the nucleus are generated by alternative splicing [49,59]. Nuclear localization of the 45-kDa TC-PTP is accomplished by a nuclear localization signal that is not functional in the 48-kDa isoform. The 45-kDa TC-PTP can effectively suppress STAT1 signaling [60] and may also dephosphorylate STAT3 [61]. SHP1 can localize to the nucleus in some cell types and in response to certain cell stimuli, based on a nuclear localization signal in its C-terminus, however, the functional role of nuclear SHP1 remains to be clarified [62]. SHP2 has been shown to dephosphorylate STAT5, however, in this case dephosphorylation occurs in the cytosol [63] and is unlikely to function in signal termination. Tyrosine-phosphorylated STAT3 has been identified as a possible substrate of RPTPρ/RPTPT [64]. This may occur proximal to the receptor or an as yet unidentified proteolytic fragment of RPTPρ may have access to nuclear pSTAT3.

Alternative splicing and limited proteolysis

Alternative splicing and limited proteolysis may lead to specific changes in the domain structure of PTPs, resulting in functionally different PTP splice variants. Among the receptor-like PTPs, alternative splicing frequently gives rise to structural variants of the extracellular domains [9,65–68], which results in a different profile of ligand interaction [69,70] or in the generation of secreted molecules which engage in alternate ligand/receptor interactions [68,71,72].

Alternative splicing may also result in changes in the regulatory domains. For example, the C-terminus of SHP1 is extended and altered in its amino acid sequence in SHP1-L, a long form of SHP1 generated by exon skipping [73], leading to loss of the raft-targeting sequence and an essential part of the nuclear localization sequence. In PTP-BAS, alternative splicing affects the ligand specificity of one of the PDZ domains [74]. Further, altered PTP activity may be caused by alternative splicing, as shown for SHP2 [75] and recently for RPTPα [76]. Splicing events are regulated, and occur upon acquisition of certain differentiation stages or in response to growth factor stimulation [68,77].

At the post-translational level, many PTPs are regulated in activity and function by limited proteolysis. RPTPs of the R2A family (LAR, RPTPσ and RPTPδ) and the R2B-MAM family (RPTPμ, RPTPκ, RPTPρ and RPTPλ) undergo proteolytic cleavage in the extracellular domain by furin-like proteinases/convertases during their biogenesis, and the mature PTPs are composed of non-covalently associated extracellular (E) and transmembrane–intracellular (P) domains [78,79]. Additional proteolysis occurs when cells are stimulated with phorbol esters or Ca^{2+}-ionophores [80,81] or, in case of MAM-domain PTPs, when cells reach high densities [13,82]. The latter leads to shedding of the extracellular domains and internalization and redistri-

bution of the remaining PTPs [80]. Recent studies have identified further mechanistic details and suggest putative functions for the shedding process in case of MAM-domain PTPs. Secondary cleavage of mature RPTPκ at high cell density occurs by ADAM10, followed by a third, intra-membrane cleavage through the action of γ-secretase. Interestingly, the phosphatase intracellular portion generated in this process was localized to the nucleus [82]. Recent elucidation of the crystal structure of the extracellular domain of RPTPμ (see below) suggests that RPTPμ is acting as a sensor for cell–cell contacts and is locked in cell–cell adherence junctions by a 'spacer–clamp' mechanism to regulate the tyrosine phosphorylation of other junction components. Shedding of the extracellular domain is predicted to allow truncated RPTPμ to leave the junctions [83].

Limited proteolysis is also common in non-transmembrane PTPs. For example, caspase-mediated limited proteolysis of PTP-PEST has recently been linked to the regulation of apoptosis [84]. Fragmentation of PTP-PEST by caspase 3 leads to elevated PTP activity, resulting in an altered interaction between PTP-PEST and adaptor molecules such as Paxillin and facilitating detachment of the cell from the substratum. Notably, degradation of PTP-PEST upon apoptosis was relatively specific and could not be seen with a range of other PTPs. Several PTPs, including PTP1B, PTP-MEG, and SHP1 can undergo limited cleavage by calpain in response to an elevation in intracellular Ca^{2+} levels in platelets [85–88], leading initially to enzyme activation by removing domains that exert negative regulation. Upon platelet aggregation, calpain, however, eventually degrades completely and inactivates PTP1B, a process that is critical for efficient thrombus formation *in vivo* [89]. Another inactivating calpain-dependent cleavage of PTP1B has been seen in epithelial cells upon UVA/B irradiation and requires reversible oxidation (see below) of the PTP [90]. It is important to further elucidate the function of calpain for regulation of PTP activity and PTP localization in more cell types and signaling pathways.

Post-translational modification: phosphorylation

Many PTPs are regulated by covalent post-translational modifications (Fig. 3). In general, phosphorylation modulates the catalytic activity of enzymes directly by allosteric mechanisms or by providing binding sites for other proteins. Phosphorylation was recognized as a potential regulatory mechanism for PTPs early on [91] and several classical PTPs, including

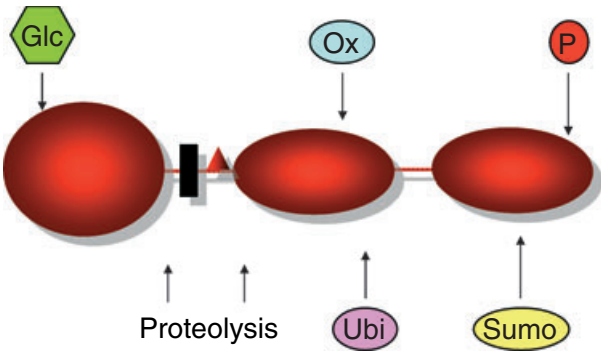

Fig. 3. Post-translational modification of PTPs. Most RPTPs are glycosylated in their extracellular domain (Glc). PTPs are tightly regulated by oxidation of their catalytic-site cysteine, which inhibits catalytic activity. Phosphorylation of serine, threonine and even tyrosine residues is recognized as an important regulatory mechanism of PTPs. Proteolysis in the extracellular domain of RPTPs may lead to shedding of the ectodomain and intracellularly to release of the catalytically active PTP domain. Sumoylation and ubiquitination may be important regulators of PTP stability and/or subcellular localization and thus of their function.

CD45, PTP1B and PTP-PEST, were identified as being phosphorylated on serine residues [92–95]. However, relatively little is known about how phosphorylation regulates PTPs. RPTPα is phosphorylated on two serine residues in the juxtamembrane domain, Ser180 and Ser204 [96], and phosphorylation of these sites stimulates catalytic activity [97]. These two phosphorylation sites are located close to the wedge-like helix–loop–helix structure that is essential for inactivation of the dimeric conformation [98] suggesting that phosphorylation of these sites may lead to disruption of the inactive dimer conformation, thus resulting in catalytic activity. RPTPα is the major activator of Src in mitosis [99,100] and mutation of the two serine phosphorylation sites eliminates the ability of RPTPα to activate Src in mitosis [101]. Whether serine phosphorylation affects the catalytic activity of PTP1B remains to be determined definitively [92,102]. SHP1 and SHP2 are phosphorylated on serine residues in response to PKC activation. SHP2 activity is not affected by serine phosphorylation [103]. Substitution of SHP1 Ser591 by Asp results in reduced catalytic activity, which led Liu *et al.* [104] to suggest that phosphorylation of this site inhibits SHP1 catalytic activity.

PTPs have also been found to be phosphorylated on tyrosine. Tyrosine phosphorylation of PTPs immediately suggests autoregulatory or feedback mechanisms, making it an intriguing regulatory mechanism for PTPs. CD45 was found to be phosphorylated transiently on tyrosine [105,106]. Moreover, the SH2-containing PTP, SHP2, is phosphorylated on tyrosine

[107,108]. Tyrosine phosphorylation of SHP2 generates a binding site for the SH2 domain of the adaptor protein GRB2 and SHP2 thus acts as an adaptor protein, linking GRB2-SOS to activated receptor tyrosine kinases [109,110]. Tyrosine phosphorylation of SHP1 and SHP2 may activate catalytic activity because substitution of the tyrosine-phosphorylation sites by phosphomimetic residues led to enhanced catalytic activity [111,112]. The transmembrane PTP, RPTPα is phosphorylated on a C-terminal tyrosine [113]. This phosphorylation site is a consensus GRB2-binding site and GRB2 binds readily to phosphorylated RPTPα [113,114]. The stoichiometry of Tyr789 phosphorylation is ~20%, which is similar to the percentage of RPTPα bound to GRB2 [113]. This suggests that all tyrosine-phosphorylated RPTPα is bound to GRB2 which is not surprising in light of the autodephosphorylation activity of RPTPα. Zheng *et al.* [99,100] developed a model in which pTyr789 binds the SH2 domain of Src, resulting in activation of Src by RPTPα-mediated dephosphorylation of the inhibitory pTyr527 in Src. CD45 can dephosphorylate RPTPα pTyr789 *in vitro* and RPTPα pTyr789 is not detected in T cells that express CD45, suggesting that RPTPα is a direct substrate of CD45 [115]. The data indicate that there is cross-talk between RPTPs at the level of direct interactions, warranting further investigation into the role of PTPs in the regulation of each other and suggesting the possibility of PTP cascades, much like the kinase cascades identified previously.

Post-translational modification: oxidation

It is now well established that PTPs are negatively regulated through reversible oxidation of the catalytic-site cysteine [116,117]. Inhibitory oxidation caused by elevated levels of reactive oxygen species (ROS) has been shown for various PTPs following activation of different classes of cell-surface receptors, including receptor PTKs, integrins and G-protein-coupled receptors (Table 1). Cell adherence and density, UV-radiation and cell migration also affect levels of PTP oxidation (Table 1). In most cases, NADPH oxidases or mitochondria have been implied as the sources of ROS.

The biochemical mechanisms of PTP oxidation have been elucidated in some detail. The 3D structure of reversibly oxidized PTP1B and RPTPα shows a sulfenyl-amide at the catalytic site, formed by a covalent bond between the sulfur of the catalytic cysteine and the backbone nitrogen of the neighboring serine [118–120]. Glutathionylated and nitrosylated versions of the active site cysteine of oxidized PTPs have also been found, in addition to intermolecular Cys–Cys disulfides [121–123].

Table 1. Oxidation of protein-tyrosine phosphatases (PTPs).

ROS modulator	Target PTP	References
Cell-surface receptors/signaling molecules		
Receptor tyrosine kinases		
EGFR	PTP1B	[164]
InsulinR	PTP1B, TC-PTP	[165,166]
PDGFR	SHP2	[167]
T-cell receptor	SHP2	[127]
B-cell receptor	'BCR-associated PTP'	[168]
Integrins	'FAK-targeting PTP'	[169]
GPCRs		
Lipoxin A4 receptor	SHP2	[170]
Endothelin 1	SHP2	[171]
ROS-scavengers/reductases		
PrxII	'membrane-associated PTPs'	[129]
Other		
UV irradiation	RPTPα, RPTPκ, SHP1, DEP1, PTP1B	[90,124,172,173]
Cell density	SHP2	[174]
Endothelial cell migration	PTP-PEST	[128]

Therefore, intriguing and previously unrecognized cross-talk exists between PTKs and ROS signaling with PTPs as mediators. Some key aspects of this cross-talk now being explored are the specificity of the signaling, the possibility that enzymes involved in ROS metabolism control tyrosine kinase signaling and the *in vivo* significance of PTP oxidation.

Protein-tyrosine phosphatase domains of different PTPs display intrinsic differences with regard to susceptibility to oxidation. This was first demonstrated in analyses of RPTPα, which revealed that the second PTP domain is much more readily oxidized than the catalytically more active membrane proximal PTP domain [124]. A large *in vitro* screen indicates large differences in oxidizability between PTPs that correlates with the conformation of the conserved active-site arginine residue [125]. Similarly, the catalytic activity of a panel of PTPs is differentially sensitive to oxidation [126]. T cells stimulated with increasing concentrations of H_2O_2 show oxidation of SHP2, but not SHP1 [127]. Interestingly, one study also introduced the possibility of localized ROS signals as a mechanism for specificity by demonstring specific oxidation of PTP-PEST caused by co-localization in focal contacts with an activated NADPH oxidase [128].

The overall concept of PTPs as targets of ROS stimulates studies on PTP and RTK activities in cells

where levels of reductases or ROS scavengers are manipulated. Deletion of peroxiredoxin II (PrxII), a peroxidase that eliminates H_2O_2, decreases PTP activity and stimulates PDGF receptor signaling [129]. Independent evidence for cell-context-dependent differences in PTP oxidation comes from a study showing that SHP2 oxidation, following H_2O_2 stimulation, varies dramatically between different cell lines [130].

Recent studies support the notion that PTP oxidation is relevant in tissue settings. Restenosis, involving PDGF receptor-dependent vascular smooth muscle proliferation, is enhanced in $PrxII^{-/-}$ mice [129]. Furthermore, systemic treatment with antioxidants in a rabbit model of restenois attenuates lesion formation in a way that involves increased vessel-wall PTP activity and reduced PDGF receptor phosphorylation [131].

Concerning PTP regulation by oxidation, it should be noted that Sdp1, a yeast PTP, was recently shown to be activated by oxidation [132]. Whether this mode of regulation is also relevant for classical PTPs is likely to be explored. However, it should be noted that the activating oxidation-induced disulfide involves a cysteine residue that is not conserved in classical PTPs, indicating that this mode of regulation might be restricted to other subsets of PTPs.

Ligands

The highly variable extracellular domains of receptor-like PTPs imply regulatory functions. As indicated in Table 2, efforts over the last 15 years have led to the identification of a number of PTP ligands. Type IIB receptor PTPs, including RPTPμ, RPTPκ and RPTPλ, as well as type IIA RPTPδ, all display homophilic interactions that are important in cell adhesion. RPTPβ/ζ has multiple heterologous interaction partners (Table 2) [66]. However, among these, only pleiotrophin directly modulates the activity of this enzyme, acting as an antagonist of RPTPβ/ζ, thus increasing the phosphorylation of a number of RPTPβ/ζ substrates including β-catenin, β-adducin, p190Rho-GAP and ALK [133–136].

RPTPσ also has multiple binding partners, which have been identified in the nervous system and skeletal muscles, including nucleolin, alpha-latrotoxin and the heparan-sulfate proteoglycans agrin and collagen XVIII [137–139]. Characterization of the RPTPσ interactions with these proteins demonstrates that they display a dependency of the dimerization state of RPTPσ and that splice variants of RPTPσ differ with regard to their binding specificities [69,70,139]. The effects of these interactions on the activity of RPTPσ remain to be elucidated.

Some of the most exciting findings showing biologically significant PTP–ligand interactions come from recent studies of the role of PTP-LAR during synaptic development in *Drosophila*. A combination of genetic studies, tissue culture analyses and biochemical experiments led to a model where RPTP-LAR-mediated development of the neuromuscular junction is controlled by two heparan-sulfate proteoglycans; syndecan and dallylike [140,141]. At the neuromuscular junction, RPTP-LAR is expressed in the pre-synaptic neuronal part, whereas the ligands are expressed on the muscle cells. A key substrate for RPTP-LAR in this process is the phospho-protein Enabled (Ena). Syndecan and dallylike both bind RPTP-LAR with high affinity but exert agonistic and antagonistic effects, respectively, on the process of synaptic development. Dallylike controls the activity of RPTP-LAR because downregulation of dallylike increases Ena phosphorylation.

The crystal structure of the homophilic dimer of two RPTPμ ectodomains provides new insight into the structural and mechanistic basis for earlier observations on the cell-adhesive homophilic RPTPμ interactions [83]. In the dimer, the two subunits occur as two antiparallel rigid structures. The dimer structure is maintained through interactions between the MAM and Ig domains of one molecule and the FN1 and FN2 domains of the other. Interestingly, the length of the dimeric complex (~330 Å) is very similar to the width of the extracellular space in the adherens junction. This finding suggests that homophilic interactions between RPTPμ molecules of juxtaposed cells will preferentially occur at adherens junction, and thereby restrict localization of this enzyme to its substrates in cadherin complexes. Furthermore, changes in the width of the intracellular space following expression of different RPTPμ deletion mutants indicate that this rigid interaction has the capacity to directly control the distance between cells. Finally, this structure suggests that many of the previously reported colon-cancer-associated mutations in the related RPTPρ [142] led to proteins that are either misfolded or defective in homophilic interactions.

Dimerization

Dimerization is a well-known regulatory mechanism of transmembrane proteins, including type I transmembrane proteins with a single transmembrane domain [143]. The first evidence that RPTPs are regulated by dimerization was provided by chimeric proteins consisting of the cytoplasmic domain of the RPTP, CD45, and the extracellular domain of the EGFR [144]. This chimera rescues the T-cell response in cells lacking

Table 2. Ligands of receptor protein-tyrosine phosphatases (RPTPs).

Common name	RPTP class	Ligand(s)	Effect on activity	Comments	References
CD45	R1	Galectin-1	Inhibition	Interaction based on recognition of CD45 carbohydrates	[175,176]
RPTPδ	R2A	Homophilic binding	Not reported	Extracellular domain is also a ligand promoting adhesion and neurite outgrowth	[177,178]
LAR	R2A	LARFN5C	Activation	LAR isoform, binds homophilically	[72]
		Laminin-Nidogen	Not reported	Binding is specific for a LAR splice version	[179]
DLAR	R2A	Syndecan (heparan sulfate proteoglycan)	Activation	DLAR ligand	[140,141]
		Dallylike (heparan sulfate proteoglycan)	Inhibition	DLAR ligand; competitive binding with Syndecan	[141]
HmLAR2 (leech)	R2A	Homophilic interaction	Not reported	Interaction induces repulsive responses in comb cells	[180]
RPTPσ	R2A	Heparan sulfate proteoglycans (agrin, collagen XVIII), nucleophilin, α-latrotoxin, unidentified ligand in developing muscle	Not reported	Ligand binding requires PTP dimerization	[69,70,137–139]
RPTPκ	R2B	Homophilic binding	Not reported		[181]
RPTPμ	R2B	Homophilic binding	Not reported	Structure of extracellular domain reveals 'spacer–clamp' mechanism in cell–cell adhesions; homophilic interactions appear to trigger RPTPμ signaling in retial neurites	[83,182–184]
RPTPλ	R2B	Homophilic binding	Not reported		[185]
DEP1	R3	Components in Matrigel	Activation	Molecular identity of ligand(s) not known	[186]
RPTPβ/ζ	R5	Pleiotrophin	Inhibition	May be linked to activation of several pathways; whether inhibition occurs by induction of dimer formation is not known	[133,134,136]
		Tenascin	Not reported		[187]
		Contactin	Not reported		[188]
		TAG-1/Axonin-1	Not reported		[189]

CD45, indicating that the construct is functional. EGF treatment leads to dimerization of the chimera and functionally inactivates the chimera, in that the T-cell response is impaired after EGF treatment. The crystal structure of the membrane-proximal domain of RPTPα provided evidence for dimerization-induced inactivation of RPTPs [98]. Dimers were observed in these crystals with a large buried surface at the interface of the two molecules. A helix–loop–helix, wedge-like structure of one of the molecules inserted into the catalytic cleft of the other and vice versa, thereby occluding access for substrates to the catalytic site and inactivating PTP. Mutation of the wedge in the EGFR–CD45 chimera abolishes EGF-induced functional inactivation of the chimera, indicating that the wedge has an important role in the dimerization-induced inactivation of RPTPs [145]. Introduction of a cysteine residue into the extracellular juxtamembrane domain of RPTPα leads to constitutive dimerization. Depending on the exact location of the cysteine residue, these dimers are active or inactive [146]. Mutation of the wedge in the inactive mutant leads to activation of PTP activity, demonstrating the importance of the wedge in dimerization-induced inactivation of RPTPs. Moreover, peptides encompassing the wedge of LAR or RPTPμ bind these RPTPs in a homophilic manner and administration of these peptides to cells results in specific defects that are consistent with the inhibition of RPTP function [147]. Although the wedge is conserved among RPTPs and functional experiments suggest that it has an important role in dimerization-induced inactivation, the model of wedge-mediated RPTP inactivation is the subject of debate because the crystal structures of full-length LAR and full-length CD45 are not compatible with this role for the wedge [148,149]. The membrane-distal PTP domain causes a steric clash when the wedge of one monomer is modeled into the catalytic site of the other, as observed in

RPTPα. However, if one assumes that there is flexibility between D1 and D2, a wedge–catalytic site interaction is feasible in CD45 and LAR. Flexibility between D1s and D2s may be regulated dynamically, thus controlling the formation of inactive RPTP dimers.

The functional data show that RPTPs can be regulated by dimerization. But do RPTPs dimerize? There is ample evidence that RPTPs dimerize in living cells. Chemical cross-linkers show dimerization of CD45, RPTPα, Sap-1 and RPTPσ [70,150–153]. RPTPα homodimerizes in living cells, as demonstrated by fluorescence resonance energy transfer between chimeras of RPTPα proteins fused to derivatives of green fluorescent protein [154]. Chin *et al.* [155] showed that dimerization of many RPTPs may be driven by their transmembrane domain. PTP domains may also be involved in homo- and heterodimerization [151,156,157]. Co-immunoprecipitation experiments have been used to demonstrate dimerization of full-length RPTPα [150], CD45 [158] and RPTPε [159].

Although dimerization was first shown to inactivate RPTPs, it is now evident that both active and inactive RPTP dimers exist. The exact make-up of the dimers determines the catalytic activity of the RPTPs. RPTPα mutants with disulfide bonds at different positions in the extracellular juxtamembrane domain suggest that subtle changes in the relative orientation of the RPTPs determines whether they are active or inactive and actually provides an appealing model for regulation. Changes in the experimental conditions lead to subtle changes in the quaternary structure of RPTPα, as demonstrated using an epitope tag in the extracellular domain of RPTPα [160]. Rotational coupling within RPTPs may therefore be an important regulatory mechanism (Fig. 4). As described above, Lee *et al.* [70] demonstrated that only dimeric ectodomains of RPTPσ bind ligand and that subtle changes in the rotational coupling of the ectodomains abolished ligand binding. These results provide support for the model that intracellular changes, such as phosphorylation or oxidation, result in changes in the quaternary conformation within RPTP dimers, thus altering the ligand-binding properties. Therefore, RPTPs may not only have the capacity for outside-in signaling, i.e. to bind ligands extracellularly resulting in changes in catalytic activity intracellularly, but also for inside-out signaling, i.e. to alter the ligand binding repertoire in response to intracellular changes.

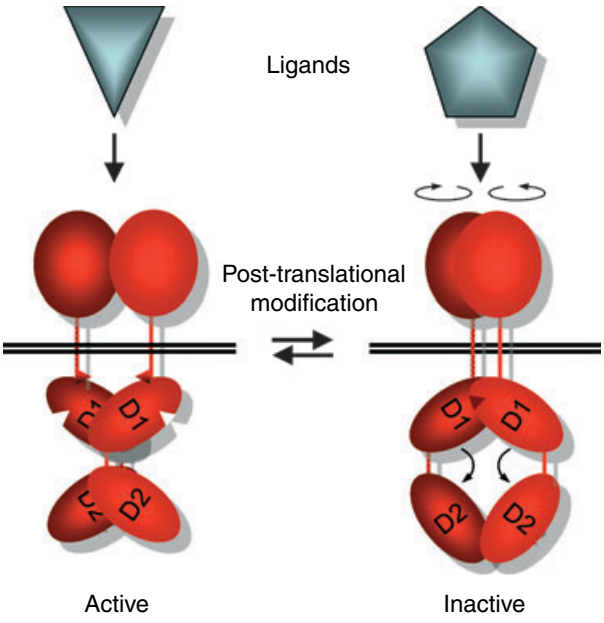

Fig. 4. Rotational coupling regulates RPTP dimers. RPTPs dimerize constitutively. Whether RPTP dimers are active depends on the exact make-up of the dimers. Post-translational modifications, such as oxidation or phosphorylation may shift the dimers from an active to an inactive state or vice versa by inducing subtle changes in rotational coupling. The dimeric states may be stabilized by different ligands binding to either form of the extracellular dimer. Ligand binding may therefore drive the equilibrium of dimers into one of the forms, representing classical outside-in signaling. Alternatively, intracellular post-translational modifications may change the exposed surface of the extracellular domain, resulting in binding of different ligands, which represents inside-out signaling.

Outlook

Control of PTP expression levels remains surprisingly poorly characterized. Improved understanding of transcriptional and translational control is likely to reveal novel processes governed by PTPs. It should also be noted that the involvement of microRNAs in controlling PTP expression remains to be explored.

Recent discoveries of regulatory ligands for *Drosophila* RPTP-LAR should encourage the continued search for additional PTP ligands. It will be interesting to follow-up on the concept of inside-out signaling and to further analyze how oxidation and dimerization affect ligand binding. The structural understanding of the RPTPμ homophilic interactions will assist in studies on whether this type of binding affects the specific activity of RPTPs involved in cell-adhesive interactions.

To date, studies on post-translational PTP modifications have focused on reversible oxidation of the active site and phosphorylation. However, other types of modifications are also involved in controlling PTPs. PTP1B is sumoylated in a manner that inhibits its catalytic activity [161]. It will be interesting to see if other

PTPs are regulated by sumoylation. Likewise, ubiquitination may regulate the stability and activity of PTPs, warranting further investigation.

Further studies on the regulation of PTPs by oxidation will continue to give new insights into fundamental cell processes. One key topic where progress can be expected is the source of ROS involved in PTP regulation. Analyses of whether spatially restricted ROS production is a common mechanism for conferring specificity are also awaited. Furthermore, it is likely that the description of how PrxII modulates RTK signaling by controlling PTP oxidation, will be followed by more studies on how reductases and ROS scavengers control PTP oxidation. Concerning the latter issue, it should be noted that modulation of glutaredoxin has been shown to affect PDGF receptor signaling through effects on the oxidation of LMW-PTP [162].

The refined understanding of PTP regulation suggests novel approaches for the design of PTP agonists and antagonists. Obviously, the identification of extracellular homo- and heterophilic ligands suggests the development of neutralizing ligand-targeted antibodies. The effects of dimerization on RPTP activity suggest the possibility of designing agents that stabilize or disrupt the dimeric state. The recent demonstration of a DEP-1-modulating antibody, which required bivalency to exert its action [163], provides an example of this approach. Finally, it may be possible to exploit the reversible oxidation of PTPs for therapeutic purposes, as indicated by early studies with non-specific antioxidants [131]. It has also been speculated that modifiers that stabilize the inhibited oxidized conformation of the active site could be designed. Hopefully, continued collaborative studies will thus be able to combine the knowledge derived from basic biology studies on PTPs, with analyses of the molecular etiology of human diseases, into novel translational initiatives.

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