REVIEW

Protein tyrosine phosphatases and signalling

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Abstract

A cornerstone of many cell-signalling events rests on reversible phosphorylation of tyrosine residues on proteins. The reversibility relies on the co-ordinated actions of protein tyrosine kinases and protein tyrosine phosphatases (PTPs), both of which exist as large protein families. This review focuses on the rapidly evolving field of the PTPs. We now know that rather than simply scavenging phosphotyrosine, the PTPs specifically regulate a wide range of signalling pathways. To illustrate this and to highlight current areas of agreement and contention in the

field, this review will present our understanding of PTP action in selected areas and will present current knowledge surrounding the regulatory mechanisms that control PTP enzymes themselves. It will be seen that PTPs control diverse processes such as focal adhesion dynamics, cell-cell adhesion and insulin signalling, and their own actions are in turn regulated by dimerisation, phosphorylation and reversible oxidation.

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Introduction

The development and physiology of multicellular organisms rely heavily on dynamic interactions between hundreds of cell types in the body. Cell-cell communication through biochemical signalling underpins this multicellularity and we are learning an ever-increasing amount about the molecules and processes involved. One cornerstone of intracellular signalling rests on the ability of proteins to be reversibly phosphorylated by protein kinases and protein phosphatases. Such phosphorylation alters target proteins by inducing conformational changes, creating docking sites for other proteins and causing intracellular relocation. Phosphotyrosine, which makes up around 0.1% of the total cellular phosphoamino acid content, plays a disproportionate part in cell signalling. Protein tyrosine phosphorylation is regulated by protein tyrosine kinases (PTKs) and protein tyrosine phosphatases (PTPs) and this review will concentrate on the latter. The function of PTPs is not simply to scavenge phosphotyrosine and to 'reset the clock'. Instead, the past decade has uncovered a wide range of signalling pathways that are regulated by PTPs as will be illustrated and discussed below.

The PTP family

PTPs fall into four classes: the classical receptor PTPs (RPTPs), the classical non-receptor PTP (nrPTPs), the

dual specificity PTP (dsPTPs) and the low M_r PTPs (Alonso *et al.* 2004). Only RPTPs and nrPTPs will be discussed here and readers are encouraged to refer to additional, recent reviews on the enzyme family (Fauman & Saper 1996, Ramponi & Stefani 1997, Beltran & Bixby 2003, Johnson & Van Vactor 2003, Paul & Lombroso 2003). RPTPs and nrPTPs fall into several subtypes based on their non-catalytic domain structures (examples in Fig. 1) (Paul & Lombroso 2003). RPTPs are predominantly found in the plasma membrane, whereas nrPTPs are localised to a variety of intracellular compartments, including the cytosol, plasma membrane and endoplasmic reticulum. The catalytic targets of most PTPs were largely unclear until recently, as were the extracellular ligands of most RPTPs. Nevertheless, this has gradually been changing and recent years have seen important advances in our knowledge surrounding PTP regulation and signalling.

Roles in signalling

To illustrate our current state of understanding, as well as its deficiencies, this review will examine three topical areas of PTP function, (a) cell-substrate adhesion, (b) cell-cell adhesion and (c) insulin signalling. Interested readers are encouraged to read other excellent reviews that cover additional areas of PTP signalling as well as their cellular and developmental functions (Espanel *et al.* 2001, Stoker 2001, Beltran & Bixby 2003, Johnson & Van Vactor 2003,

Figure 1 Schematic of the PTP family. The structures of RPTPs discussed in this review are shown: LAR, PTP σ , PTP δ (type IIa); PTP μ , PTP κ , PTP $\lambda/\psi/O$ (type IIb); PTP ϕ , DEP-1 (type III); PTP α , PTP ϵ (type IV); PTP ζ/β , PTP γ (type V). All but class III have duplicated catalytic domains D1 and D2. Each subclass has unique extracellular domain structures depicted by coloured symbols as indicated. The cytoplasmic PTPs only have single PTP catalytic domains, and their additional domain structures are discussed elsewhere. For further references, see 'The PTP family' in the text. IG, immunoglobulin-like domain; FNIII, fibronectin type III domain; MAM, meprin/A5-protein/PTPmu.

Paul & Lombroso 2003, Ensslen-Craig & Brady-Kalnay 2004).

Substrate adhesion and motility

Interactions between cells and the extracellular matrix are essential for the maintenance of cell differentiation, survival and motility. These interactions are governed largely by integrins, heterodimeric transmembrane protein complexes that can bind multiple extracellular molecules and can nucleate adhesive structures known as focal adhesions (FAs) (Schwartz 2001, Zamir & Geiger 2001, Miranti & Brugge 2002, Parsons 2003). Integrin binding leads to autophosphorylation of focal adhesion kinase (FAK), activation of the pp60^{src} PTK and then a cascade of downstream tyrosine phosphorylations (Fig. 2A) (Schaller *et al.* 1994). For a cell to de-attach and migrate, the phosphorylation of focal adhesion components must be revers-

ible (Schwarzbauer 1997) and this is the job of the PTPs. Several of these enzymes have now been implicated in the regulation of cell adhesion and FA dynamics (Angers-Loustau *et al.* 1999a, Beltran & Bixby 2003, Larsen *et al.* 2003) (Fig. 2A).

PTP-PEST PTP-PEST is a widely expressed nrPTP with interaction domains rich in proline, glutamic acid, serine and threonine (Garton & Tonks 1994). PTP-PEST binds directly to p130^{cas} (Garton *et al.* 1997), Grb2 (Charest *et al.* 1997), Csk (Davidson *et al.* 1997), Shc (Davidson & Veillette 2001) and paxillin (Shen *et al.* 1998). The roles of these interactions are largely unclear, but the dephosphorylation of p130^{cas} may be central to PTP-PEST's actions. Overexpression of PTP-PEST in fibroblasts induces p130^{cas} hypophosphorylation, hindering the translocation of p130^{cas} to membrane ruffles, and reducing cell migration (Garton & Tonks 1999).

PTP-PEST-deficient fibroblasts also exhibit increased numbers of focal adhesions, increased phosphorylation of p130^{cas}, paxillin and FAK, and defects in cell motility (Angers-Loustau *et al.* 1999b). PTP-PEST therefore appears to regulate FA turnover, such that either over- or underexpression of PTP-PEST can cause an imbalance resulting in impaired motility.

PTP1B Evidence for the involvement of PTP1B in integrin signalling, FA formation and cell motility provides a complex, contradictory picture. Knock-down of PTP1B expression using antisense oligonucleotides (Hassid *et al.* 1999) or overexpression of wild-type PTP1B (Liu *et al.* 1998) both suggest correlations between PTP1B activity and decreased adhesion, motility and FA formation. PTP1B may negatively regulate adhesion-based signalling by directly dephosphorylating p130^{cas} (Fig. 2A). However, other studies using dominant-negative PTP1B (Arregui *et al.* 1998) and PTP1B-deficient fibroblasts (Cheng *et al.* 2001) both support the opposite view that PTP1B activates pp60^{src} (or fyn) directly or indirectly, thereby stimulating FAK and p130^{cas} phosphorylation and FA formation. Until we can clarify whether, in different cell types and under different conditions, PTP1B does indeed have divergent effects, the contradictions in these data will remain.

RPTP α pp60^{src}-like PTKs heavily influence FA dynamics (Parsons 2003). pp60^{src} is regulated by a carboxy-terminal, inhibitory tyrosine (Schwartzberg 1998), the phosphorylation of which is reciprocally controlled by the Csk PTK and PTPs such as RPTP α (Harder *et al.* 1998). PTP α overexpression in A431 cells causes increased pp60^{src} activity and pp60^{src}/FAK association (Harder *et al.* 1998). The opposite seems to occur in RPTP α -deficient cells (Su *et al.* 1999, Zeng *et al.* 2003). By acting as a pp60^{src} activator, RPTP α is thus uniquely situated to act upstream of FAK in integrin signalling. PTP α can also target p130^{cas} as a direct substrate in cultured cells (Buist *et al.* 2000). One puzzle with RPTP α is how, or indeed if, it is regulated by external cues, upstream of any effects on FAs. This must await the identification of an extracellular ligand.

SHP-2 SHP-2 is an ubiquitous enzyme implicated in both growth factor receptor signalling and integrin signalling (Feng 1999, Neel *et al.* 2003). The mechanism of SHP-2 action remains controversial, though, and the critical downstream targets are largely unclear (Neel *et al.* 2003). SHP-2 is an nrPTP with two integral SH2 domains that bind to phosphotyrosine residues in receptors and docking proteins (see also 'Regulation of PTP action' below) (Neel *et al.* 2003). Several studies point to SHP-2 being either a positive or a negative regulator of cell adhesion and motility. One model suggests that integrin engagement causes pp60^{src}-dependent phosphorylation of

membrane-bound SHPS-1 (SHP substrate 1), which in turn recruits SHP-2. SHP-2 may then further activate pp60^{src}, possibly via inhibition of Csk (Zhang *et al.* 2004), leading to increased FAK phosphorylation (Fig. 2A). To support this, SHP-2-deficient fibroblasts exhibit FAK and pp60^{src} hypophosphorylation (Oh *et al.* 1999). Other studies, however, show that SHP-2 either triggers FAK hypophosphorylation or has little effect (Tsuda *et al.* 1998, Yu *et al.* 1998, Manes *et al.* 1999, Inagaki *et al.* 2000). SHP-2 is also implicated in the repulsive guidance of cell migration triggered by Eph receptor tyrosine kinases (RTKs), which bind to FAK constitutively. This repulsion is regulated in part by preventing integrin-mediated adhesion (Miao *et al.* 2000, Poliakov *et al.* 2004). Upon EphA2 activation by ephrins, SHP-2 binds to EphA2, leading to a loss of FAK and paxillin phosphorylation; EphA2-FAK complexes also break down. Here again, SHP-2 may be a negative regulator of FAK phosphorylation and integrin signalling. Therefore, although the precise mode of action of SHP-2 remains to be clarified, and indeed it may vary between cell types, there is no doubt that SHP-2 can influence FAK activity, cell adhesion and motility.

PTEN PTEN is a tumour suppressor and an unusual enzyme in being able to dephosphorylate both the lipid phosphatidylinositol 3,4,5-triphosphate and phosphotyrosine (Yamada & Araki 2001). PTEN is implicated in many cellular processes, including cell adhesion, migration, invasion and anoikis (Yamada & Araki 2001), the latter being apoptosis of cells after loss of matrix contact (Grossmann 2002). Overexpression of PTEN in cells causes hypophosphorylation of FAK and p130^{cas} and reduces cell motility (Tamura *et al.* 1998, 1999a,c). Furthermore, dominant-negative PTEN causes FAK hyperphosphorylation and can co-purify FAK (Tamura *et al.* 1998, 1999c). PTEN also targets the adaptor Shc, which binds to integrin complexes and in turn affects Erk MAP kinase signalling (Gu *et al.* 1998). There are still doubts over PTEN's level of influence over FAK *in vivo*, however, since PTEN^{-/-} cells show no alteration in FAK phosphorylation even though motility is increased (Sun *et al.* 1999, Liliental *et al.* 2000). Perhaps PTP-PEST and SHP-2 share the majority of control over FAK and p130^{cas} phosphorylation, while PTEN has a minor, or a very context-specific role. PTEN also appears to promote cell death through anoikis, by hydrolysing phosphatidylinositol 3,4,5-triphosphate (PIP₃) and inactivating the AKT/PKB pathway. By also dampening FAK and phosphatidylinositol 3-kinase (PI3)-kinase activities, PTEN may therefore accelerate this apoptosis pathway (Tamura *et al.* 1999b, Yamada & Araki 2001).

LAR LAR is an adhesion molecule-like RPTP that localises to FAs (Streuli *et al.* 1988, Serra Pages *et al.* 1995). LAR binds to liprins, which are enriched at these sites of

adhesion (Serra-Pages *et al.* 1998), and to Trio, a large Rac/Rho GTPase that influences the actin cytoskeleton (Debant *et al.* 1996). An important role for LAR in FAs may revolve around p130^{cas}. Overexpression of LAR in U2OS cells causes apoptosis and p130^{cas} degradation (Weng *et al.* 1998, 1999). Anoikis can be triggered by proteolytic fragments of p130^{cas} (O'Neill *et al.* 2000, Wei *et al.* 2004) and proteolysis of p130^{cas} can be initiated by hypophosphorylation, induced either by tyrosine kinase inhibition (Wei *et al.* 2002) or, in all likelihood, by increased PTP activity. Indeed, LAR specifically targets p130^{cas} for dephosphorylation, which may in turn lead directly to its degradation (Weng *et al.* 1999). Re-introduction of excess p130^{cas} into LAR-expressing cells can partially rescue apoptosis. Interestingly, LAR-induced apoptosis is relatively direct and does not require prior loss of substrate adhesion (Weng *et al.* 1998). One isoform of LAR is known to bind to laminin (O'Grady *et al.* 1998) and this PTP may therefore respond directly to the ECM at FAs. The effect of laminin binding on the biochemical activity of LAR remains unclear.

PTP ϕ PTP ϕ is a type III RPTP, also known as GLEPP1 (Pixley *et al.* 1995). Studies in macrophages show that paxillin is a PTP ϕ substrate, and PTP ϕ co-localises with paxillin in membrane ruffles. Overexpression of PTP ϕ in BAC1.2F5 macrophages causes enhanced motility, possibly by reducing the quantity of phosphorylated paxillin available for focal adhesions and increasing FA turnover (Pixley *et al.* 2001).

While we probably know most of the central PTP players in integrin and FA signalling, there remain many interesting questions. For example, which PTPs are the most influential for focal adhesion dynamics and do different PTPs act in strict concert or are their actions more cell type specific? Put another way, do the conflicting experimental data with individual PTPs reflect genuine, cell-specific differences in enzyme action, or confusion arising from the wide range of under- and overexpression systems and cell types used? Either way, it is clear that a range of cytoplasmic and receptor-type PTPs are involved at several key levels in integrin signalling.

Cell-cell adhesion

Cell-cell adhesion within epithelia is largely controlled by the cadherin family of homophilic, calcium-dependent

adhesion molecules (Daniel & Reynolds 1997). Their regulated adhesive properties are critical for many morphogenic events including epithelial to mesenchymal transitions (Nakagawa & Takeichi 1998, Lilien *et al.* 2002), while defects in cadherin function are also linked to cancer progression (Hirohashi 1998). Understanding how cadherin-based adhesion is regulated is therefore of great importance in the fields of development and disease.

Cadherins are linked to the actin cytoskeleton by α -catenin, β -catenin and p120^{ctn} (Daniel & Reynolds 1997) (Fig. 2B). The adhesive functions of cadherins are particularly sensitive to tyrosine phosphorylation of β -catenin. Phosphorylation of β -catenin causes its dissociation from cadherin and loss of cell-cell adhesion complexes (Balsamo *et al.* 1996, 1998, Roura *et al.* 1999). p120^{ctn} may stabilise cadherins at the plasma membrane (Peifer & Yap 2003, Kowalczyk & Reynolds 2004) and its tyrosine phosphorylation causes loss of cadherin function (Ozawa & Ohkubo 2001). Since tyrosine phosphorylation is central to cadherin/catenin function, it is not surprising that PTPs are again found in the arena (Beltran & Bixby 2003) (Fig. 2B). PTP μ interacts with cadherin and may be able to dephosphorylate it directly (Brady Kalnay *et al.* 1995, Brady-Kalnay *et al.* 1998), although this remains a little controversial (Zondag *et al.* 1996). PTP1B binds directly to cadherin, but in this case its target is β -catenin (Fig. 2B). A dominant-negative form of PTP1B causes hyperphosphorylation of β -catenin and loss of cadherin function, possibly by displacing the wild-type enzyme (Balsamo *et al.* 1996, 1998, Pathre *et al.* 2001). PTP1B itself is activated by tyrosine phosphorylation on tyrosine residue 152, catalysed by the PTK Fer (Xu *et al.* 2004); Fer binds p120^{ctn}, thereby holding it near to PTP1B. The p120^{ctn} protein can be dephosphorylated by PTP μ and this has been proposed to be a route by which this RPTP controls N-cadherin function in axons (Zondag *et al.* 2000). DEP-1, a type III RPTP, and the nrPTP SHP-1 can also target p120^{ctn} as a potential substrate (Keilhack *et al.* 2000, Holsinger *et al.* 2002).

β -Catenin interacts directly with several RPTPs, including LAR (Kypta *et al.* 1996), PTP ζ / β (Meng *et al.* 2000), PTP κ (Fuchs *et al.* 1996) and PTP λ (Cheng *et al.* 1997). All of these PTPs (except PTP λ) can dephosphorylate β -catenin and have been proposed to regulate cadherin/ β -catenin interactions. It is not clear, though, how most of these biochemical events are actually regulated in the cell. In the case of PTP ζ / β , its ligand

Figure 2 PTP involvement with integrin and cadherin signalling. This schematic shows some of the documented binding partners and substrates of PTPs, at (A) sites of focal adhesions and (B) sites of cadherin binding. Dephosphorylation steps are depicted by red lines and tyrosine kinase reactions are shown by green arrows. Black lines indicate pathways that are stimulated. Grey arrows indicate the binding of extracellular ligands where known. All PTPs are shown in purple. In (B), cadherin and PTP μ / λ / κ each have homophilic binding partners, binding in *trans* from another cell. Note that all of the above interactions have been documented in at least one study, but their relative physiological importance is not yet known in every case. Some of these interactions may be competitive or cell specific and may not occur concurrently. See text for further details. SFKs, src family kinases; ECM, extracellular matrix.

Figure 3 PTPs and insulin signalling. This diagram depicts the documented interactions between PTPs and components of the insulin signalling pathway. On the left of the diagram are some of the major pathways stimulated by the insulin receptor (IR) tyrosine kinase, leading to activation of glycogen synthase (GS) and movement of the glucose transporter Glut4 to the plasma membrane. PTP enzymes are shown in purple and dephosphorylation events are shown by red lines. Phosphorylation by tyrosine kinases is shown by green arrows; black lines indicate further pathways that are stimulated. Inactivation of PTPs by peroxide, which is produced following IR stimulation, is shown in blue. Note that all of the above interactions have been documented in at least one study, but their relative physiological importance is not yet known in every case. Some of these interactions may be competitive or cell specific and may not occur concurrently. See text for further details.

pleiotrophin can inactivate the RPTP and this results in increased β -catenin phosphorylation (Meng *et al.* 2000). Although it is evident that PTPs can strongly influence the dynamics of cell-cell adhesion, we have much yet to learn. For example, if cadherin/ β -catenin interactions are regulated by the PTPs describe above, then why do we see so little perturbation of epithelial tissues in animals lacking their genes? The lack of such phenotypes may indicate a high level of biochemical redundancy in the control of β -catenin phosphorylation. Whether several PTPs must actively co-operate to regulate β -catenin phosphorylation, or whether there are key PTPs in specific cell types, remains to be determined.

In cultured tumour cells, overexpression of LAR causes reduced β -catenin phosphorylation, stabilisation of adherens junctions and loss of tumour formation, indicating that this RPTP could have a powerful controlling effect over epithelial integrity *in vivo* (Müller *et al.* 1999). In this context, it will be most interesting to see if LAR

or any other PTPs are developmentally controlled in order to influence events such as epithelial–mesenchymal transitions.

Insulin signalling

One field in which PTP action has been well studied is that of insulin signalling (Cheng *et al.* 2002a, Asante-Appiah & Kennedy 2003) (Fig. 3). Given the increasing concern surrounding diabetes and obesity, particularly with insulin-resistant forms, it is not surprising that the molecular regulation of the insulin receptor (IR; an RTK), has come under scrutiny. There is particularly keen interest in understanding how PTPs might impinge on the signalling of the IR and whether PTPs are relevant therapeutic targets. Here, a number of PTPs have been implicated in recent years (Fig. 3), although their status as IR regulators is still controversial in most cases.

LAR LAR expression is increased in fat tissue of clinically obese humans (Ahmad *et al.* 1995) and increased co-immunoprecipitation of LAR with the IR occurs after insulin treatment (Ahmad & Goldstein 1997). Furthermore, overexpression of LAR suppresses insulin action (Li *et al.* 1996, Zhang *et al.* 1996) and antisense knock-down of LAR enhances and prolongs insulin signalling in McA-RH7777 hepatoma cells (Kulas *et al.* 1995, 1996, Mooney *et al.* 1997). These data are consistent with LAR being a direct, negative regulator of the IR. Engineered overexpression of LAR in mouse skeletal muscle suppresses IR signalling, causing insulin resistance possibly through deactivation of the insulin receptor substrate IRS-2 (Zabolotny *et al.* 2001). In LAR-deficient mice, although there is increased insulin sensitivity at the resting state, there are also unexpected defects in glucose homeostasis after insulin treatment that are more consistent with insulin resistance (Ren *et al.* 1998). The case for LAR being a significant regulator of the IR therefore remains unresolved.

PTP α and PTP ϵ Overexpression of PTP α in BHK-IR cells causes dephosphorylation of the IR and suppresses IR-mediated cell rounding (Lammers *et al.* 1997). The highly related PTP ϵ enzyme has also been implicated as a potential IR phosphatase in one overexpression study in BHK cells (Andersen *et al.* 2001). Furthermore, in adipocytes, rat PTP α can decrease the transport of the insulin-responsive glucose transporter Glut4 after insulin stimulation (Cong *et al.* 1999). However, a case against PTP α being a physiological regulator of the IR comes from studies of 3T3-L1 cells, where antisense PTP α does not affect insulin-induced MAP kinase activation or DNA synthesis (Arnott *et al.* 1999), and from mice deficient for PTP α , where there are no defects in glucose homeostasis yet reported (Ponniah *et al.* 1999, Su *et al.* 1999).

SHP-2 SHP-2 binds to the IR and to IRS-1 in yeast two-hybrid assays (Rocchi *et al.* 1996) and in transfected cells (Kharitonov *et al.* 1995), and IRS-1 is also likely to be a direct substrate (Hayashi *et al.* 2004). In another study, wild-type SHP-2 did not interact with the IR in yeast two-hybrids, whereas a phosphatase-dead mutant did (via tyrosine 1146 on the IR). This suggests that the IR is also a direct substrate (Rocchi *et al.* 1996). However, a further study suggests that IR is not a substrate, but instead indicates that SHP-2 may bind to the IR in order to recruit IRS-1 (Kharitonov *et al.* 1995).

Several studies conclude that SHP-2 does affect the insulin signalling process itself, but again there is a lack of consensus. Interference with SHP-2 activity can block insulin-stimulated mitosis in 3T3 cells (Milarski & Saltiel 1994) and block downstream activation of Ras (Noguchi *et al.* 1994). In contrast, mutated forms of IRS-1 that do not bind SHP-2 can facilitate effective insulin signalling in

32D cells and these IRS-1 forms are even hyperphosphorylated (Myers *et al.* 1998). SHP-2 also binds to IRS-3 (Ross *et al.* 1998) and IRS-4 (Escribano *et al.* 2003), so perhaps there is further degeneracy in the system. Another pathway through which SHP-2 may act in concert with the IR involves SHPS-1 (see also Fig. 2) (Takada *et al.* 1998). SHPS-1 is phosphorylated in response to IR stimulation, and recruits SHP-2. Overexpression of wild-type SHPS-1 in CHO cells enhances MAP kinase activation downstream of insulin stimulation, whereas mutated forms of SHPS-1 that cannot recruit SHP-2 show no enhancement (Takada *et al.* 1998). How SHPS-1/SHP-2 interactions stimulate MAP kinase in this system remains to be determined.

Transgenic analyses of SHP-2 function have also proved equivocal. Homozygous null mice do not survive, whereas heterozygotes appear normal with respect to glucose homeostasis, and IR and IRS-1 phosphorylation (Arrandale *et al.* 1996). Nevertheless, ubiquitous expression of a dominant-negative form of SHP-2 causes significant insulin resistance and reduced IRS-1 phosphorylation (Maegawa *et al.* 1999). This latter study again supports the idea that SHP-2 plays a positive role in insulin signalling.

PTP1B PTP1B has drawn much recent attention as being a negative regulator of insulin action (Cheng *et al.* 2002a, Asante-Appiah & Kennedy 2003). PTP1B associates with the IR after insulin treatment and several critical tyrosine residues in PTP1B become phosphorylated (Seely *et al.* 1996, Bandyopadhyay *et al.* 1997). Importantly, the IR is a substrate for PTP1B (Bandyopadhyay *et al.* 1997, Dadke *et al.* 2000, Salmeen *et al.* 2000) and there is evidence that IRS-1 is also (Goldstein *et al.* 2000). Homozygous loss of PTP1B has no gross effect on mouse development or viability. However, the mice have defects in glucose and insulin tolerance, they also remain sensitive to insulin (when on high fat diets) and they show increases in IR phosphorylation after insulin treatment (Elchebly *et al.* 1999, Klamann *et al.* 2000). However, most of these effects only occur in muscle and liver, suggesting that further PTPs might control insulin signalling in fat cells.

PTP1B is widely expressed and localises predominantly in the endoplasmic reticulum (Frangioni *et al.* 1992), although it does have a cleavable carboxy-terminal domain that allows release into the cytosol (Frangioni *et al.* 1993). It is not exactly clear, therefore, how PTP1B is getting access to the IR. Like some other RPTKs, the IR may become endocytosed and thereby gain access to endoplasmic reticulum-associated PTP1B (Cheng *et al.* 2002a, Haj *et al.* 2002). Lastly, it is worth noting that PTP1B has also been implicated in controlling obesity, through the regulation of leptin action (Cheng A. *et al.* 2002b, Zabolotny *et al.* 2002). Interested readers are encouraged to read further details reviewed by Asante-Appiah & Kennedy (2003).

Other PTPs The PTPs that act upon the IR may not be limited to those above. A study employing substrate-trapping PTPs suggested that PTP γ , Sap-1 and TC-PTP could bind specifically to phosphorylated IR 'baits' (Walchli *et al.* 2000). However, further tests showed that a wider range of wild-type PTPs could dephosphorylate an IR-derived target peptide (containing the principal PTP target tyrosines; PTPGMTRDIYETDYYRKGGKG). It is not clear, therefore, how these *in vitro* assays will relate to the substrate specificity or accessibility of these PTPs towards the IR *in vivo*.

It is clear that PTPs significantly influence the level of insulin signalling and these enzymes do represent potential, pharmacological targets in insulin-resistant diabetes. This field remains controversial, however, with strong evidence pointing to PTP1B being the major player, but with several other PTPs hovering in the wings. The field currently suffers from numerous apparently contradictory findings and the loss-of-function mouse strains have added to the uncertainty by sometimes failing to corroborate cell culture data. Tissue-specific action of certain PTPs, or the concerted actions of multiple PTPs, may both therefore serve to control IR phosphorylation levels *in vivo*. Developing any diabetes therapies based on PTP inhibition therefore remains a worthy goal, and a considerable challenge.

Regulation of PTP action

It is evident from the discussion above that molecular control of the PTPs themselves is still relatively poorly understood. Recent research, however, is beginning to provide much-needed insight and some key findings are discussed below.

Phosphorylation and SH2 domains

PTP enzymes can be phosphorylated on tyrosines, providing binding sites for SH2-containing proteins. SH2 domains are protein adaptor modules with specific affinity for phosphorylated tyrosine residues on proteins (Pawson *et al.* 2001, Pawson 2004). These domains act as docking devices, facilitating the formation of supramolecular signalling complexes (Pawson *et al.* 2001, Neel *et al.* 2003, Pawson 2004). One RPTP that attracts such SH2 domains is PTP α . The tyrosine residue 789 in D2 of PTP α is constitutively phosphorylated and associates with the SH2 domain of Grb2 (Fig. 4) (Den Hertog & Hunter 1996, Su *et al.* 1996). Upon PKC δ phosphorylation of PTP α , Grb2 is exchanged for pp60^{src}, whose own SH2 domain now associates with tyr789 (Zheng *et al.* 2002, Brandt *et al.* 2003). Through a 'phosphotyrosine displacement' mechanism, the inhibitory C-terminal tyr527 of pp60^{src} is thus released and is then dephosphorylated by PTP α , activating pp60^{src} (Zheng *et al.* 2000, 2002). Concurrently, Grb2 is

released from PTP α and becomes free to associate, via its SH3 domain, with SOS, leading to downstream signalling (Fig. 4) (Den Hertog & Hunter 1996).

Cleavage and differential localisation

Many proteins are subject to post-translational proteolytic cleavage and PTPs are no exception. A number of RPTPs are cleaved by subtilisin-like proteases (Streuli *et al.* 1992, Jiang *et al.* 1993, SerraPages *et al.* 1994, Gebbink *et al.* 1995, Campan *et al.* 1996, Aicher *et al.* 1997) and this can ultimately result in ectodomain 'shedding', at least in cell culture. A role for shedding *in vivo* is currently conjectural, but it may be a mechanism to either terminate RPTP signalling, facilitate internalisation of catalytic domains, or to release ectodomains to compete for ligands. Intracellular cleavage also occurs. PTP ϵ , PTP α and PTP1B can be cleaved in a calpain-dependent manner, releasing their catalytic domains into the cytoplasm (Frangioni *et al.* 1993, Gil-Henn *et al.* 2001). This may prevent access of the PTPs to membrane-associated substrates, or provide access to novel substrates.

Ligands for RPTPs

Upon the discovery of receptor-like RPTPs with their highly conserved ectodomains, there was great interest in their potential to be regulated by extracellular ligands. Since that time there have been great difficulties in identifying the ligands for many RPTPs and, even more so, understanding their effects on RPTP activity. A number of RPTPs have homophilic binding properties, including the type IIb enzymes, as well as PTP δ and isoforms of LAR (Yang *et al.* 2003, for reviews see Beltran & Bixby 2003, Johnson & van Vactor 2003). Of those RPTPs with heterophilic binding properties, PTP ζ / β binds pleiotrophin and adhesion molecules (Beltran & Bixby 2003), PTP σ binds to heparan sulphate proteoglycans (Aricescu *et al.* 2002) and LAR binds the laminin/nidogen complex (O'Grady *et al.* 1998). Of these RPTP interactions, only the interaction between pleiotrophin and PTP ζ / β has so far been shown to have a clear effect on enzyme activity: pleiotrophin binding inhibits PTP ζ / β and causes an increase in β -catenin phosphorylation (Meng *et al.* 2000).

Several major areas must therefore be clarified with respect to RPTP ligands. Why has it been so hard to identify heterotypic ligands for many RPTPs? Does this mean that some RPTPs do not have ligands? For example, work with CD45 suggests that the activity of this enzyme can be modulated through changes in protein isoform expression and the consequent changes in ectodomain glycosylation and dimerisation (Xu & Weiss 2002). Understanding whether the *trans* interactions of RPTP ectodomains generally activate or inactivate the catalytic activity of RPTPs also remains a challenge for the field.

Figure 4 The regulation of PTP activity. This diagram shows three different ways in which RPTPs are regulated (A) by cleavage, (B) by oxidation and dimerisation and (C) by phosphorylation. The precise role of these events is still uncertain for many RPTPs. (A) Cleavage and extracellular shedding of ectodomains has been reported for several RPTPs (shown here for LAR). (B) Some RPTPs, including PTP α and CD45 are present as dimers in the membrane. Inactivation of dimers can occur through oxidation of D1/D2 catalytic sites and conformational changes. Oxidation is caused by peroxide that is released following growth factor receptor activation; this oxidation is reversible in the cell. (C) Phosphorylation of PTP α by PKC δ causes detachment of Grb2 followed by attachment of pp60^{src}, effectively through SH2 domain exchange. Binding of the SH2 domain of pp60^{src} to PTP α exposes phosphotyrosine 527 in pp60^{src} (yellow star), which is then dephosphorylated by PTP α .

There remains the possibility that RPTPs require *cis* rather than *trans* interactions to promote intramembrane compartmentalisation into, for example, lipid rafts. Finally, *cis* interactions between ectodomains themselves may not necessarily require a ligand, but could still be essential in enforcing dimerisation and regulating enzyme activity.

PTP dimerisation

A well-known prerequisite for the activation of receptor PTKs is their dimerisation and autophosphorylation (Heldin 1995). In 1998, It was found that the catalytic domains of PTP α formed dimer-like structures when crystallised (Majeti *et al.* 1998, Wallace *et al.* 1998), and it was subsequently shown that the full-length protein dimerises in live cells (Jiang *et al.* 1999, 2000). Dimerisation *in cis* has also been demonstrated for CD45 (Takeda *et al.* 1992) and it could well be a common phenomenon for RPTPs in general. Suggestions as to how dimers might regulate RPTP signalling have been given. As with RPTKs (Heldin 1995), the rotational orientation of dimerised receptor PTP α has been shown to be critical for its full

activation (Jiang *et al.* 1999). It was also found that an inhibitory peptide 'wedge' caused reciprocal blockade of the catalytic sites of the dimerised D1 domains, revealing a potential inactivation mechanism (Majeti *et al.* 1998, Wallace *et al.* 1998). However, although 'wedge' inhibition may occur with PTP α and CD45, it appears less feasible with LAR and PTP μ (Hoffmann *et al.* 1997, Nam *et al.* 1999), and therefore may not be a universal inhibitory mechanism. It is still likely, however, that RPTPs can have a dimerised, rotational state that engenders catalytic inactivity with or without involvement of a wedge. One further, outstanding question is whether the dimerisation process itself is generally constitutive, or whether it requires the presence of a ligand.

PTP oxidation

The catalytic site cysteines of PTPs have an ionisation constant (PK_a) of between 5 and 6. They are therefore usually deprotonated and susceptible to oxidative attack, which inactivates the catalytic site at least temporarily (Fig. 4) (Xu *et al.* 2002). Oxidation of PTPs could be an elegant

mechanism by which RPTKs briefly impede local PTP activity and thereby prolong PTK signals (Xu *et al.* 2002). Indeed, the activation of growth factor receptors does produce a local burst of peroxide capable of oxidising PTPs (Bae *et al.* 1997, Lee *et al.* 1998, Meng *et al.* 2002, 2004). In the case of the IR, PTP1B may inhibit insulin signalling, but the IR itself may in turn inhibit (albeit temporarily) PTP1B through local oxidant production (Mahadev *et al.* 2001). For most RPTPs, the obvious candidate for oxidative attack is the catalytically active D1 domain. However, studies of PTP α show that D2 is the initial, selective target, and its oxidation causes conformational shifts in the catalytic domains that result in prolonged enzyme inactivation (Blanchetot *et al.* 2002, Persson *et al.* 2004) (Fig. 4). Finally, a recent study suggests that PTP α can briefly form disulphide-linked dimers when treated with peroxide and that the D2 active site cysteines are again critical for this event (van der Wijk *et al.* 2004). The relevance of this event to other native RPTPs remains to be addressed.

There is therefore justifiable excitement that a universal regulatory mechanism may now have been uncovered for PTPs, although many key questions remain. For example, how precisely do PTKs stimulate peroxide production and how localised is it in the cell? In addition, the percentage of a given PTP that is inactivated varies widely between studies. Although much of this may arise from the varied experimental protocols, we have yet to define the necessary levels of PTP inactivation that would be required for the sustained activation of RPTK signalling. This is not a trivial undertaking, but it has far-reaching consequences for our understanding of PTP regulation.

Conclusions and future prospects

The road to discovery with the PTP family has been long and arduous, but its box of secrets is finally being prised open, revealing true surprises. We see that PTPs are closely involved in many levels of cell biological control. Furthermore, the enzymes can be controlled and modulated in diverse and novel ways, including through oxidation, dimerisation, cleavage, differential localisation, use of differential mRNA splicing, or combinations of these. There also appears to be cellular and developmental tolerance to their individual loss of function in many cases, suggesting that highly conserved redundancy or degeneracy is in place in order to maintain control of PTK signalling pathways. The discovery of oxidative regulation in particular has profound implications and may trigger novel pharmacological approaches for PTP inhibition or activation. Other exciting challenges include understanding the structure and function of RPTP ectodomains, defining more precisely the substrate specificities of PTPs, and finally discovering how these extremely active enzymes are harnessed by cells to act with apparent

specificity in so many signalling pathways. As our knowledge thus increases, the ultimate goal of applying it to a therapeutic setting, tackling human diseases with underlying dysregulation of phosphotyrosine signalling, will come closer to fruition.

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