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PTP1B: a double agent in metabolism and oncogenesis

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Abstract

PTP1B, a non-transmembrane protein tyrosine phosphatase that has long been studied as a negative regulator of insulin and leptin signaling, has recently received renewed attention as an unexpected positive factor in tumorigenesis. In this review, we highlight how views of this enzyme have evolved from regarding it as a simple metabolic off-switch to a more complex view of PTP1B as an enzyme that can play both negative and positive roles diverse signaling pathways. These dual characteristics make PTP1B a particularly attractive therapeutic target for diabetes, obesity, and perhaps breast cancer.

Keywords

PTP1B; Protein Tyrosine Phosphate; Signal Transduction; Diabetes; Cancer

2 PTP1B: signaling paradigm and paradox

Imagine a pill that could keep you thin, free of diabetes, and protected from breast cancer. This hypothetical medicine would need to have the seemingly magical property of stimulating pathways that signal weight loss and lower blood sugar while simultaneously blocking those that induce cell proliferation and cell survival. In the enzyme protein tyrosine phosphatase 1B (PTP1B), a target for such a hypothetical drug exists. This review is not about how to make such a drug (although many are trying); instead it discusses the unusual combination of properties that render PTP1B such an attractive drug target for a variety of common and serious diseases.

PTP1B was the first enzyme of its class to be purified to homogeneity [1,2] and, with its close cousin TC-PTP, the first to be intentionally cloned [3-5]. Many of the seminal concepts regarding PTP regulation, structure, and function were first discovered in the context of PTP1B. As such, PTP1B can be viewed as a touchstone in phosphatase research, the reference enzyme to which other PTPs are most often compared, much as Src serves as a paradigm for cytoplasmic protein tyrosine kinases. Despite its emblematic role as the prototypical PTP, PTP1B has a number of unique properties that clearly distinguish it from other enzymes in its class, and important new discoveries regarding PTP1B continue to be made with surprising regularity (Table 1).

PTP1B has long been known to play a major role in inhibiting signaling from the insulin and leptin receptors [6]. In the case of insulin signaling, PTP1B dephosphorylates the insulin

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receptor (IR) as well as its primary substrates, the IRS proteins; by contrast, in leptin signaling a downstream element, the tyrosine kinase JAK2 (Janus kinase 2), is the primary target for dephosphorylation. However, hints that PTP1B might also play a positive signaling role in cell proliferation began to emerge a few years ago, with the finding by a number of groups that PTP1B dephosphorylates the inhibitory Y529 site in Src, thereby activating this kinase [7-10]. Other PTP1B substrates might also contribute to pro-growth effects. Indeed, the idea that PTP1B can in some cases serve as a signaling stimulant received key confirmation in two landmark papers that showed that PTP1B plays a positive role in a mouse model of ErbB2-induced breast cancer [11,12]. For these reasons, PTP1B has attracted particular attention as a potential therapeutic target in obesity, diabetes, and now, cancer [13-15].

3 Regulation of PTP1B

PTP1B has an N-terminal catalytic phosphatase domain (residues 1-300) followed by a regulatory region of about 80-100 residues and a membrane localization domain (residues 400-435) that tethers the enzyme to the cytoplasmic face of the endoplasmic reticulum (ER) (Fig. 1) [16,17]. The enzyme is abundantly expressed and has robust catalytic activity that is, under most circumstances, tightly controlled. In addition to its location at the ER surface, which might restrict its access to substrates, four mechanisms, sometimes working in tandem, are known to regulate PTP1B activity: oxidation, phosphorylation, sumoylation, and proteolysis.

Oxidation

PTP1B activity is regulated *in vivo* by reversible oxidation involving Cys 215 residue at its active site, which temporarily abrogates its enzymatic activity [18]. Like the analogous Cys residue in other PTPs, the chemical environment of Cys 215 is unusually acidic (pH 4.5-5.5), and this residue is deprotonated at physiological pH, thereby enhancing its nucleophilic activity in catalysis, but also rendering the enzyme highly susceptible to inactivation by reactive oxygen species (ROS). Crystallographic analysis indicates that hydrogen peroxide-induced oxidation rapidly converts the sulphenic acid (S-OH) form of PTP1B to a cyclic sulphenamide, accompanied by a profound conformational change at the active site, exposing a buried tyrosine residue at the phosphotyrosine binding loop to solvent [19,20]. Whereas oxidation to the sulphenamide state is anticipated to inhibit PTP1B activity in a reversible manner, oxidation to sulphinic (S-O₂H) or sulphonic (S-O₃H) is usually an irreversible process [20].

A transient burst of ROS is generated by many external stimuli, including those that activate receptor protein tyrosine kinases (RPTKs) and integrins, and oxidative inactivation of PTP1B occurs in several cells types in response to epidermal growth factor (EGF) and insulin stimulation [18,21,22]. Such redox modification of reactive cysteine residues is an important mechanism to determine the extent and duration of phosphotyrosine-dependent signaling responses.

Phosphorylation

PTP1B is regulated by both serine and tyrosine phosphorylation at multiple locations, but, in contrast to oxidation, the effects of phosphorylation are either modest or controversial. During metaphase, PTP1B is phosphorylated by protein kinase C (PKC) at S378, and at S352 and S386 by an unknown kinase [23,24] (Fig. 1). These sites are also phosphorylated in response to osmotic stress, but do not markedly change PTP1B activity [24]. Although the significance of these serine phosphorylations remain unclear, phosphorylation of PTP1B at S50 by AKT can decrease PTP1B activity and impair its ability to dephosphorylate the IR

[25], perhaps as part of a positive feedback loop to regulate insulin signaling. However, it should be noted that the dual-specificity kinases CDC-like kinase 1 (CLK1) and CLK2 also have been reported to phosphorylate PTPB1 at S50; in these cases, however, the phosphorylation results in 2-fold stimulation of phosphatase activity [26]. The reasons for these discrepant results are not known.

In addition to serine phosphorylation, insulin stimulates tyrosine phosphorylation of PTP1B at three sites, Y66, Y152 and Y153 [27] (Fig. 1). As with S50 phosphorylation, phosphorylation at these tyrosine sites has been reported to either increase or decrease PTP1B catalytic activity. Rather than directly affecting catalytic activity, it is possible that the phosphorylation of Y152/153 is more important for its effects on protein interaction, as alteration of these residues markedly impairs the association of PTP1B with activated IR [27,28].

Sumoylation

SUMO (Small Ubiquitin-related Modifier) family proteins have recently emerged as important regulators in modulating many cellular functions. Protein modification by SUMO conjugation dynamically regulates protein localization, stability, interactions, and activity [29]. A recent report showed that PTP1B interacts with a SUMO E3 ligase, protein inhibitor of activated STAT-1 (PIAS1); this interaction promotes SUMO modification of PTP1B [30]. PTP1B sumoylation occurs on at least two C-terminal lysine residues and is associated with a reduction in enzymatic activity, rendering it less active towards substrates such as the IR [30]. The subcellular location of PTP1B sumoylation is not firmly established, but sumoylated PTP1B appears to accumulate in punctate structures in the perinuclear region, and the C-terminal, ER-targeting domain of PTP1B is required for its maximal sumoylation [30]. Importantly, insulin stimulates transient modification of PTP1B by SUMO, and exogenous expression of a sumoylation-resistant form of PTP1B is more potent in suppressing v-*crk* induced transformation than is wild-type PTP1B. Collectively, these results suggest that post-translational modification by sumoylation imposes another temporal and spatial layer of regulation on PTP1B.

Proteolysis

Calpain-mediated cleavage of the C-terminal, ER-targeting domain of PTP1B, which occurs in activated platelets, generates an activated, soluble enzyme [31]. Interestingly, disruption of calpain-1 in mice is accompanied with significant defects in platelet aggregation and clot retraction, as well as an overall reduction in protein tyrosine phosphorylation levels [32,33]. Platelets derived from such animals show a two-fold increase in the amount of PTP1B protein without affecting mRNA levels, suggesting that calpain-1, rather than activating PTP1B by cleaving off the C-terminal domain, instead proteolyzes PTP1B into inactive fragments *in vivo*. This notion is supported by the finding that the platelet aggregation and tyrosine phosphorylation defects associated with loss of calpain-1 were rescued in *Capn1*; *Ptp1b* double knockout mice, and the demonstration that calpain-1 can digest PTP1B into small fragments *in vitro* [33]. Interestingly, other groups have reported that reversibly oxidized PTP1B is sensitive to inactivating cleavage by calpain at or near amino acid position 77 in the catalytic domain [34,35]. Thus, it is possible that the fate of PTP1B in platelets – activation by calpain-mediated cleavage of the C-terminus, or inactivation by more complete proteolysis by this protease - is decided by the state of PTP1B oxidation. In other cell types, only the activating cleavage of PTP1B has been reported. For example, in epithelial cells, calpain-2 mediated proteolysis activates PTP1B, an event which plays an important role in c-Src activation during invadopodia (actin rich protrusions of cell membrane often associated with metastatic cells) formation. In this setting, expression of the appropriate proteolytic fragment of PTP1B rescues the defect in invadopodia formation in

calpain-2 deficient breast cancer cells [36]. Other proteases might also influence PTP1B activity. For example, a Leishmania-encoded protease, GP63, cleaves and activates PTP1B in infected macrophages [37]. Interestingly, PTP1B is required for early progression of Leishmania infection in mice.

Identification of PTP1B substrates—How does PTP1B, an ER-tethered enzyme, encounter and dephosphorylate its many substrates, which include cytosolic, plasma-membrane-bound, and adherens-junction proteins? In the case of RPTKs such as the IR, one possibility is that activated receptors are internalized via vesicle-mediated endocytosis, bringing them into close proximity to the ER for dephosphorylation by PTP1B [38,39]. Another possibility, supported by bioluminescence resonance energy transfer (BRET)- and fluorescence resonance energy transfer (FRET)-based live imaging analysis, ER-bound PTP1B might interact with and dephosphorylate the IR during its biosynthesis [39,40]. A third, but not mutually exclusive model, postulates that PTP1B resides in a dynamic or “stretchable” ER membrane that is in constant contact with substrates at the plasma membrane [41]. Finally, PTP1B and substrate interactions are facilitated by adaptor proteins, such as phospholipase C gamma (PLC γ) or N-cadherin, which physically links PTP1B to its substrates in PLC γ –PTP1B–JAK2 and N-cadherin–PTP1B– β -catenin ternary complexes, respectively [42–44].

Although its cellular location imposes certain constraints on PTP1B, several other properties factor into the interaction of this enzyme with its substrates. First, PTP1B possesses binding motifs that direct its interactions with certain tyrosine phosphorylated proteins. For example, one of the two proline-rich domains in the C-terminus mediates association with a number of src-homology 3 (SH3) domain-containing proteins, such as p130^{Cas}, Grb2 (growth factor receptor-bound protein 2), Crk, and Src [45]. Although substitution of key proline residues within this region does not affect the ability of PTP1B to dephosphorylate the IR, it abolishes the ability of PTP1B to bind to and activate Src [8,45,46]. Instead, PTP1B likely targets the IR by a different mechanism. In this case, both biochemical and crystallographic studies suggest that Y152, located in the β 9– β 10 turn of PTP1B within the catalytic domain, mediates interaction of PTP1B with the back face of IR dimers [47]. Interestingly, this same tyrosine residue is phosphorylated by the IR, an event that would disrupt the backside binding interaction, perhaps liberating PTP1B to dephosphorylate phospho-tyrosine residues in the IR activation loop, located on the front side of the dimer. Substitution of this tyrosine residue in PTP1B, or the matching E1022 residue in the IR, disrupts the association of these two proteins and renders PTP1B unable to effectively dephosphorylate the IR [27,48].

In addition to these binding motifs, the catalytic domain of PTP1B, although closely related to those of other PTPs, has intrinsic specificity to certain substrates. This has most clearly been demonstrated in the context of substrate trapping mutants, in which substitution of C215 at the catalytic center of PTP1B or D181 in the highly conserved WPD loop can be used to abolish catalytic activity without affecting binding affinity [49–52]. Such substrate traps indicate that the PTP1B catalytic domain preferentially associates with a limited number of tyrosine phosphorylated proteins, indicating a high degree of selectivity [51]. Recently, a PTP1B substrate trap was used in combination with stable isotope labeling in cultured cells (SILAC) to reduce false positives in screening studies, resulting in the identification of several new potential substrates in mouse embryo fibroblasts (MEFs) [53]. In this study, proteins that were found by SILAC to be hyper-tyrosine phosphorylated in *Ptp1b* knockout MEFs were then tested for binding to a PTP1B substrate trap. This screening method resulted in the identification of several proteins involved in cell motility and adhesion (cortactin, p120^{Ctn}, ZO-1, lipoma-preferred partner) as well as regulators of proliferation (e.g. p62^{Dok}, p120^{RasGap}). This combined methodology holds great promise in sorting out the key substrates of PTP1B that mediate its positive role oncogenic signaling.

In vivo model of PTP1B in metabolism—Although many *in vitro* studies had strongly implicated PTP1B in attenuating IR signaling and glucose metabolism, the generation and analysis of *Ptp1b*-knockout mice provided the most compelling evidence that this enzyme plays such a role in normal physiology. *Ptp1b*-null animals have decreased blood glucose accompanied by decreased circulating insulin, indicating that they are hypersensitive to insulin [54]. Accordingly, tyrosine phosphorylation of the IR β -subunit is greatly enhanced in muscle and liver tissues of such mice. In addition to increased insulin sensitivity, *Ptp1b*^{-/-} animals are also lean and resistant to weight gain when fed a high fat diet [54]. To establish which tissues are responsible for insulin sensitivity and resistance to obesity, mice harboring brain-, liver-, and skeletal muscle-specific deletions of *Ptp1b* have been generated and assessed [55-57]. Despite an elevated leptin level (normally associated with obesity and leptin resistance), neuronal knockout of *Ptp1b* results in reduced body mass and adipose accumulation as a result of decreased food intake and increased energy expenditure [55]. Similar effects are noted when *Ptp1b* deletion is specifically restricted to pro-opiomelanocortin (POMC) neurons within the hypothalamus [58]. Although the exact mechanism(s) for these phenomena remains elusive, deletion of neuronal PTP1B reduces hypothalamic AMPK activity [59]. As AMPK target genes include those that regulate mitochondrial biogenesis, fatty acid oxidation, and energy expenditure, this pathway is likely to be important in explaining the role of PTP1B in weight regulation. Although both liver- and muscle-specific *Ptp1b* knockouts display normal weight gain, both tissue-specific models, as well as the neuronal model, exhibit improved insulin sensitivity and enhanced glucose tolerance, further confirming the regulatory function of PTP1B in insulin signaling and glucose homeostasis [55-57].

By contrast, the resistance of *Ptp1b* knockout mice to obesity when fed a high-fat diet also suggests the involvement of PTP1B in leptin signaling (Fig. 2). Leptin-induced type I cytokine receptor activation requires JAK2 tyrosine phosphorylation and nuclear translocation of phosphorylated signal transducer and activator of transcription 3 (STAT3) to mediate target gene transcription [60]. PTP1B overexpression induces JAK2 dephosphorylation *in vitro* [61], and *Ptp1b* deletion renders mice hypersensitive to leptin treatment and is associated with elevated phosphorylation and activation of JAK2 and its target, STAT3 [62,63]. Interestingly, *ob/ob*; *Ptp1b* double knockout mice weigh less than leptin-deficient *ob/ob* animals, suggesting that PTP1B regulates obesity via a JAK2-mediated leptin-independent signaling pathway [62,63]. Both genetic and biochemical studies indicate that JAK-STAT phosphorylation and the leptin signaling pathway can be attenuated by PTP1B, although a specific correlation between PTP1B and leptin signaling in obesity has not been directly demonstrated [62,63]. In this regard, it is important to note that PTP1B also regulates growth hormone signaling. Growth hormone is a crucial regulator of energy metabolism in animals, and, like leptin, acts through JAK-STAT. In *Ptp1b* knock out mice, increased signaling through this pathway may well contribute to diminished obesity [64,65]. Interestingly, PTP1B expression is itself induced by high-fat feeding, perhaps through the action of obesity-induced inflammatory cytokines, underscoring the complex role of PTP1B in obesity [66].

PTP1B: growth suppressor or oncogene?—Although PTP1B does not appear to be a tumor suppressor in mammals, in that loss of function mutations or gene silencing have not been found in human or in mouse models of cancer, a large body of evidence supports the notion that PTP1B is a negative regulator of cell growth. For example, in addition to its negative effects on the IR, PTP1B can also dephosphorylate other RPTKs, including the EGF and PDGF (platelet-derived growth factor) receptors; consequently, *Ptp1b*^{-/-} MEFs are unusually sensitive to these growth factors [67]. Consistent with these suppressive effects on growth factor signaling, exogenous expression of PTP1B in fibroblasts prevents transformation by ErbB2 (Neu), *v-src*, *v-ras*, *v-crk*, and Bcr-Abl, the driving oncoprotein in

chronic myelogenous leukemia [17,68-70]. In addition, PTP1B has been identified in two independent, unbiased loss-of-function screens for factors that impede Bcr-Abl-mediated transformation *in vitro* [71,72]. At the cellular level, in addition to its direct inhibitory effects on many RPTKs, PTP1B strengthens cell–cell adhesion by inducing N-cadherin– β -catenin complex formation [43,44]. PTP1B also can promote apoptosis by potentiating IRE1-mediated ER stress signaling, or by dephosphorylating STAT3 during TRAIL-induced apoptosis [73-76]. These observations point to a potential tumor suppressive role for PTP1B. Consistent with this idea, in a *Trp53*-null background, loss of *Ptp1b* leads to an increased number of B-cells in bone marrow and lymph nodes, and an increased incidence of B-cell lymphoma in mice [77].

It had long been noted that PTP1B protein levels are elevated in a number of human cancers, most notably, cancer of the breast and ovary [78,79]. Similarly, activation of ErbB2 (Neu) in immortalized human breast epithelial cells, or Bcr-Abl in rat fibroblasts, was noted to be accompanied by increased PTP1B expression [70,80]. Such increases in PTP1B expression might represent a cellular response to rising levels of tyrosine phosphorylation; however, it now seems more likely that, at least in the case of ErbB2 (Neu), PTP1B does not oppose growth and survival signals; rather, it contributes to them. The most powerful evidence for this view derives from two independent studies showing that PTP1B is a positive regulator of the ErbB2 (Neu)-induced mammary tumorigenesis in mice [11,12]. Indeed, because *ERBB2* amplification is common in human breast cancer and is the target of several new therapeutic agents, studies of the signaling requirements for this RPTK are of particular interest. In both studies, *Ptp1b*-deficient mice were crossed with transgenic mice that overexpress activated mutants of the ErbB2 (Neu) oncoprotein in mammary epithelial cells. The onset of ErbB2 (Neu)-driven breast cancer was significantly delayed in the absence of PTP1B, and transgenic *PTP1B* overexpression_[SC1] was sufficient to induce breast tumors in the absence of exogenous *ErbB2* [11]. Moreover, Julien *et al.* demonstrated that a PTP1B inhibitor protected mice against the *ErbB2* oncogene, the first such use for a small PTP1B inhibitor in a mouse cancer model [11]. Importantly, *Ptp1b* deficiency did not offer universal protection against breast cancer, as breast tumors driven by the polyoma middle T antigen were not affected by loss of *Ptp1b* [12]. Thus, PTP1B appears to have a selective, positive role in oncogenic signaling from ErbB2 (Neu). It will be interesting to determine if PTP1B plays a similar role the action of other oncogenes and in other types of tumors. It will also be interesting to determine if these effects are related to decreased insulin levels in *Ptp1b* knock out mice, given the positive relationship between insulin and insulin-like growth factor signaling and breast cancer [81].

At the molecular level, PTP1B exerts a positive effect on activation of small GTPases and their downstream mitogen-activated protein kinase (MAPK) pathways (Fig. 2). In immortalized fibroblasts, loss of *Ptp1b* is accompanied by decreased Ras–GTP and Rac–GTP levels, and diminished extracellular signal-regulated kinase (ERK) activation [8,82]. Similarly, ERK activity is reduced in *Ptp1b*-null mammary cells from *ErbB2* transgenic mice [12]. How does this occur? One PTP1B target that has drawn particular attention is p62^{Dok}, a protein that, when dephosphorylated, inhibits p120^{RasGAP}, thus leading to elevated levels of Ras–GTP [83]. In immortalized MEFs lacking PTP1B function, p62^{Dok} tyrosine phosphorylation is elevated, p120^{RasGAP} is activated, and Ras is inhibited [82]. Consistent with these *in vitro* data, Julien *et al.* also observed enhanced p62^{Dok} phosphorylation in *Ptp1b* deficient tumors, correlating with decreased p120^{RasGAP} phosphorylation in an *ErbB2* transgenic_[SC2] mouse model [11]. However, it should be noted that Betires-Alj *et al.* observed no changes in p62^{Dok} or p120^{RasGAP} phosphorylation levels in *ErbB2*; *Ptp1b*^{-/-} mice [12]. At present, the reasons for these important discrepancies are not known, but might be attributable to the timing of the collected tumor samples, differences in mouse strain background, the specific *ErbB2* transgenic model that was used, or perhaps the quality

of the antisera needed to analyze these signaling proteins. Another plausible PTP1B target is Src, but changes in Src phosphorylation were not reported in either tumor model. However, recent *in vitro* data, carried out in a 3D cell culture setting, indicate that PTP1B-mediated Src activation is a prime target in ErbB2 (Neu)-induced human breast cancer cells [80]. In these studies, activated Src could bypass the requirement of PTP1B for ErbB2-mediated transformation. Furthermore, exogenous expression of PTP1B, but not a catalytically active PTP1B mutant that cannot bind or activate Src, recapitulated the effects of activated ErbB2 on acinar architecture, including loss of luminal apoptosis and maintenance of cell proliferation [80]. These data are consistent with clinical findings showing that increased PTP1B activity correlates with decreased Src Y529 phosphorylation in both colon and breast cancer cells [36,84]. Thus, the issue remains unresolved as to whether p62^{Dok}, Src, or additional proteins are the key substrates of PTP1B that mediate its positive effect in ErbB2 (Neu) signaling *in vivo*. Also unresolved is whether the effects of PTP1B on ErbB2 (Neu) tumorigenesis are cell autonomous or are instead mediated by stromal and/or immune cell effects. This important issue could be resolved via transplantation studies or through specifically deleting *Ptp1b* in either breast epithelial cells or in stromal cells, respectively.

Concluding remarks—PTP1B presents a particularly favorable profile of features as a potential drug target, as its inhibition might be beneficial in common ailments such as adult-onset diabetes, obesity, and perhaps some forms of cancer. Indeed, based on mouse studies, it is tempting to conclude that we would all be better off without this remarkable enzyme. Perhaps PTP1B belongs to a different era of history, when food was less abundant and diseases of old age, such as cancer, had less impact on human health. However, before becoming too sanguine about the prospects of a PTP1B-less world, one must remember that mice, even when raised in a protected environment and with plentiful food, do experience certain problems when *Ptp1b* is disrupted, including an increase in the number of B-cells in bone marrow and lymph nodes, and an increase in the incidence of B-cell lymphoma when *Ptp1b*- and *Trp53* null alleles are combined [77]. Moreover, we have no idea yet if the unexpected positive role of PTP1B in ErbB2 (Neu) signaling is an anomaly or if it will also apply in other oncogenic settings. In this regard, it is interesting to note that signaling from the EGFR (also called ErbB1), which is closely related to ErbB2 (Neu), does not appear to be augmented by PTP1B and in fact, the opposite is more likely to be true. For these reasons, until we know more about the role of this enzyme in malignancy, we will need to worry about the possible cancer-promoting effects of chronic PTP1B inhibition. With those notes of caution in mind, although PTP1B represents a most intriguing opportunity as a drug target, care will be needed in monitoring toxicity as PTP1B inhibitors reach the clinic.

References

1. Tonks NK, et al. Purification of the major protein-tyrosine-phosphatases of human placenta. *J Biol Chem* 1988;263:6722–6730. [PubMed: 2834386]
2. Tonks NK, et al. Characterization of the major protein-tyrosine-phosphatases of human placenta. *J Biol Chem* 1988;263:6731–6737. [PubMed: 2834387]
3. Cool DE, et al. cDNA isolated from a human T-cell library encodes a member of the protein-tyrosine-phosphatase family. *Proc Natl Acad Sci USA* 1989;86:5257–5261. [PubMed: 2546150]
4. Chernoff J, et al. Cloning of a cDNA for a major human protein tyrosine phosphatase. *Proc Natl Acad Sci USA* 1990;87:2735–2739. [PubMed: 2157211]
5. Brown-Shimer S, et al. Molecular cloning and chromosome mapping of the human gene encoding protein phosphotyrosyl phosphatase 1B. *Proc Natl Acad Sci, USA* 1990;87:5148–5152. [PubMed: 2164224]
6. Chernoff J. Protein tyrosine phosphatases as negative regulators of mitogenic signaling. *J Cell Physiol* 1999;180:173–181. [PubMed: 10395287]

7. Bjorge JD, et al. Identification of protein-tyrosine phosphatase 1B as the major tyrosine phosphatase activity capable of dephosphorylating and activating c-Src in several human breast cancer cell lines. *J Biol Chem* 2000;275:41439–41446. [PubMed: 11007774]
8. Dadke S, Chernoff J. Protein-tyrosine phosphatase 1B mediates the effects of insulin on the actin cytoskeleton in immortalized fibroblasts. *J Biol Chem* 2003;278:40607–40611. [PubMed: 12902327]
9. Dadke S, Chernoff J. Interaction of Protein-tyrosine phosphatase (PTP) 1B with its substrates is influenced by two distinct binding domains. *Biochem J* 2002;364:377–383. [PubMed: 12023880]
10. Arias-Salgado EG, et al. PTP-1B is an essential positive regulator of platelet integrin signaling. *J Cell Biol* 2005;837–845. [PubMed: 16115959]
11. Julien SG, et al. Protein tyrosine phosphatase 1B deficiency or inhibition delays ErbB2-induced mammary tumorigenesis and protects from lung metastasis. *Nat Genet* 2007;39:338–346. [PubMed: 17259984]
12. Bentires-Alj M, Neel BG. Protein-tyrosine phosphatase 1B is required for HER2/Neu-induced breast cancer. *Cancer Res* 2007;67:2420–2424. [PubMed: 17347513]
13. Lee S, Wang Q. Recent development of small molecular specific inhibitor of protein tyrosine phosphatase 1B. *Med Res Rev* 2007;553–573. [PubMed: 17039461]
14. Pei Z, et al. Inhibition of protein tyrosine phosphatase 1B as a potential treatment of diabetes and obesity. *Current pharmaceutical design* 2004;10:3481–3504. [PubMed: 15579047]
15. Dadke S, Chernoff J. Protein-Tyrosine Phosphatase 1B as a potential drug target for obesity, *Curr. Drug Targets – Immune. Endocr & Metabol Disord* 2003;3:243–248.
16. Frangioni JV, et al. The nontransmembrane tyrosine phosphatase PTP-1B localizes to the endoplasmic reticulum via its amino acid C-terminal sequence. *Cell* 1992;68:545–560. [PubMed: 1739967]
17. Woodford-Thomas TA, et al. Expression of a protein tyrosine phosphatase in normal and v-src-transformed mouse 3T3 fibroblasts. *J Cell Biol* 1992;117:401–414. [PubMed: 1373143]
18. Lee SR, et al. Reversible inactivation of protein-tyrosine phosphatase 1B in A431 cells stimulated with epidermal growth factor. *J Biol Chem* 1998;273:15366–15372. [PubMed: 9624118]
19. van Montfort RL, et al. Oxidation state of the active-site cysteine in protein tyrosine phosphatase 1B. *Nature* 2003;423:773–777. [PubMed: 12802339]
20. Salmeen A, et al. Redox regulation of protein tyrosine phosphatase 1B involves a sulphenyl-amide intermediate. *Nature* 2003;423:769–773. [PubMed: 12802338]
21. Mahadev K, et al. Insulin-stimulated hydrogen peroxide reversibly inhibits protein-tyrosine phosphatase 1b in vivo and enhances the early insulin action cascade. *J Biol Chem* 2001;276:21938–21942. [PubMed: 11297536]
22. Meng TC, Tonks NK. Analysis of the regulation of protein tyrosine phosphatases in vivo by reversible oxidation. *Methods Enzymol* 2003;366:304–318. [PubMed: 14674257]
23. Flint AJ, et al. Multi-site phosphorylation of the protein tyrosine phosphatase, PTP1B: identification of cell cycle regulated and phorbol ester stimulated sites of phosphorylation. *EMBO J* 1993;12:1937–1946. [PubMed: 8491187]
24. Shifrin VI, et al. Phosphorylation of protein-tyrosine phosphatase PTP-1B on identical sites suggests activation of a common signaling pathway during mitosis and stress response in mammalian cells. *J Biol Chem* 1997;272:2957–2962. [PubMed: 9006942]
25. Ravichandran LV, et al. Phosphorylation of ptp1b at ser(50) by akt impairs its ability to dephosphorylate the insulin receptor. *Mol Endocrinol* 2001;15:1768–1780. [PubMed: 11579209]
26. Moeslein FM, et al. The CLK family kinases, CLK1 and CLK2, phosphorylate and activate the tyrosine phosphatase, PTP-1B. *J Biol Chem* 1999;274:26697–26704. [PubMed: 10480872]
27. Bandyopadhyay D, et al. Protein-tyrosine phosphatase 1B complexes with the insulin receptor in vivo and is tyrosine-phosphorylated in the presence of insulin. *J Biol Chem* 1997;272:1639–1645. [PubMed: 8999839]
28. Dadke S, et al. Phosphorylation and activation of protein tyrosine phosphatase (PTP) 1B by insulin receptor. *Mol Cell Biochem* 2001;221:147–154. [PubMed: 11506178]
29. Hay RT. SUMO: a history of modification. *Mol Cell* 2005;18:1–12. [PubMed: 15808504]

30. Dadke S, et al. Regulation of protein tyrosine phosphatase 1B by sumoylation. *Nat Cell Biol* 2007;9:80–85. [PubMed: 17159996]
31. Frangioni JV, et al. Calpain-catalyzed cleavage and subcellular relocation of protein tyrosine phosphatase 1B (PTP-1B) in human platelets. *EMBO J* 1993;12:4843–4856. [PubMed: 8223493]
32. Azam M, et al. Disruption of the mouse mu-calpain gene reveals an essential role in platelet function. *Mol Cell Biol* 2001;21:2213–2220. [PubMed: 11238954]
33. Kuchay SM, et al. Double knockouts reveal that protein tyrosine phosphatase 1B is a physiological target of calpain-1 in platelets. *Mol Cell Biol* 2007;27:6038–6052. [PubMed: 17576811]
34. Gulati P, et al. UVA inactivates protein tyrosine phosphatases by calpain-mediated degradation. *EMBO Rep* 2004;5:812–817. [PubMed: 15247926]
35. Trumpler A, et al. Calpain-mediated degradation of reversibly oxidized protein-tyrosine phosphatase 1B. *The FEBS journal* 2009;276:5622–5633. [PubMed: 19712109]
36. Cortesio CL, et al. Calpain 2 and PTP1B function in a novel pathway with Src to regulate invadopodia dynamics and breast cancer cell invasion. *J Cell Biol* 2008;180:957–971. [PubMed: 18332219]
37. Gomez MA, et al. Leishmania GP63 alters host signaling through cleavage-activated protein tyrosine phosphatases. *Science signaling* 2009;2:ra58. [PubMed: 19797268]
38. Haj FG, et al. Imaging sites of receptor dephosphorylation by PTP1B on the surface of the endoplasmic reticulum. *Science* 2002;295:1708–1711. [PubMed: 11872838]
39. Romsicki Y, et al. Protein tyrosine phosphatase-1B dephosphorylation of the insulin receptor occurs in a perinuclear endosome compartment in human embryonic kidney 293 cells. *J Biol Chem* 2004;279:12868–12875. [PubMed: 14722096]
40. Boute N, et al. Dynamics of the interaction between the insulin receptor and protein tyrosine-phosphatase 1B in living cells. *EMBO Rep* 2003;4:313–319. [PubMed: 12634852]
41. Anderie I, et al. Direct interaction between ER membrane-bound PTP1B and its plasma membrane-anchored targets. *Cell Signal* 2007;19:582–592. [PubMed: 17092689]
42. Choi JH, et al. Phospholipase C gamma1 negatively regulates growth hormone signalling by forming a ternary complex with Jak2 and protein tyrosine phosphatase-1B. *Nat Cell Biol* 2006;8:1389–1397. [PubMed: 17128263]
43. Balsamo J, et al. Regulated binding of a PTP1B-like phosphatase to N-cadherin: control of cadherin-mediated adhesion by dephosphorylation of b-catenin. *J Cell Biol* 1996;134:801–813. [PubMed: 8707857]
44. Arregui CO, et al. Impaired integrin-mediated adhesion and signaling in fibroblasts expressing a dominant-negative mutant PTP1B. *J Cell Biol* 1998;143:861–873. [PubMed: 9813103]
45. Liu F, et al. Direct binding of the proline rich region of protein tyrosine phosphatase 1B to the src homology 3 domain of p130^{Cas}. *J Biol Chem* 1996;271:31290–31295. [PubMed: 8940134]
46. Liu F, Chernoff J. PTP1B associates with and is tyrosine phosphorylated by epidermal growth factor receptor in cultured cells. *Biochem J* 1997;327:139–145. [PubMed: 9355745]
47. Li S, et al. Crystal structure of a complex between protein tyrosine phosphatase 1B and the insulin receptor tyrosine kinase. *Structure* 2005;13:1643–1651. [PubMed: 16271887]
48. Dadke S, et al. Down-regulation of insulin signaling by protein tyrosine phosphatase (PTP) 1B is mediated by an N-terminal binding region. *J Biol Chem* 2000;275:23642–23647. [PubMed: 10807907]
49. Jia Z, et al. Structural basis for phosphotyrosine peptide recognition by protein tyrosine phosphatase 1B. *Science* 1995;268:1754–1758. [PubMed: 7540771]
50. Kenner KA, et al. Protein-tyrosine phosphatase 1B is a negative regulator of insulin- and insulin-like growth factor-I-stimulated signaling. *J Biol Chem* 1996;271:19810–19816. [PubMed: 8702689]
51. Flint AJ, et al. Development of “substrate-trapping” mutants to identify physiological substrates of protein tyrosine phosphatases. *Proc Natl Acad Sci USA* 1997;94:1680–1685. [PubMed: 9050838]
52. Blanchetot C, et al. Substrate-trapping techniques in the identification of cellular PTP targets. *Methods* 2005;35:44–53. [PubMed: 15588985]

53. Mertins P, et al. Investigation of protein tyrosine phosphatase 1B function by quantitative proteomics. *Mol Cell Proteomics* 2008;1763–77. [PubMed: 18515860]
54. Elchebly M, et al. Increased insulin sensitivity and obesity resistance in mice lacking the protein tyrosine phosphatase-1B gene. *Science* 1999;283:1544–1548. [PubMed: 10066179]
55. Bence KK, et al. Neuronal PTP1B regulates body weight, adiposity and leptin action. *Nature medicine* 2006;12:917–924.
56. Delibegovic M, et al. Improved glucose homeostasis in mice with muscle-specific deletion of protein-tyrosine phosphatase 1B. *Mol Cell Biol* 2007;27:7727–7734. [PubMed: 17724080]
57. Delibegovic M, et al. Liver-specific deletion of protein-tyrosine phosphatase 1B (PTP1B) improves metabolic syndrome and attenuates diet-induced endoplasmic reticulum stress. *Diabetes* 2009;58:590–599. [PubMed: 19074988]
58. Banno R, et al. PTP1B- or SHP2-deficiency in POMC neurons reciprocally regulates energy balance in mice. in press.
59. Xue B, et al. Neuronal protein tyrosine phosphatase 1B deficiency results in inhibition of hypothalamic AMPK and isoform-specific activation of AMPK in peripheral tissues. *Mol Cell Biol* 2009;29:4563–4573. [PubMed: 19528236]
60. Ahima RS, Osei SY. Leptin signaling. *Physiol Behav* 2004;81:223–241. [PubMed: 15159169]
61. Myers MP, et al. TYK2 and JAK2 are substrates of protein-tyrosine phosphatase 1B. *J Biol Chem* 2001;276:47771–47774. [PubMed: 11694501]
62. Zabolotny JM, et al. PTP1B regulates leptin signal transduction in vivo. *Dev Cell* 2002;2:489–495. [PubMed: 11970898]
63. Cheng A, et al. Attenuation of leptin action and regulation of obesity by protein tyrosine phosphatase 1B. *Dev Cell* 2002;2:497–503. [PubMed: 11970899]
64. Pasquali C, et al. Identification of protein tyrosine phosphatases with specificity for the ligand-activated growth hormone receptor. *Mol Endocrinol* 2003;17:2228–2239. [PubMed: 12907755]
65. Gu F, et al. Protein tyrosine phosphatase 1B attenuates growth hormone-mediated JAK2-STAT signaling. *Mol Cell Biol* 2003;23:3753–3762. [PubMed: 12748279]
66. Zabolotny JM, et al. Protein-tyrosine phosphatase 1B expression is induced by inflammation in vivo. *J Biol Chem* 2008;283:14230–14241. [PubMed: 18281274]
67. Haj FG, et al. Regulation of receptor tyrosine kinase signaling by protein tyrosine phosphatase-1B. *J Biol Chem* 2003;278:739–744. [PubMed: 12424235]
68. Brown-Shimer S, et al. Effect of protein tyrosine phosphatase 1B expression on transformation by the human neu oncogene. *Cancer Res* 1992;52:478–482. [PubMed: 1345814]
69. Liu F, Chernoff J. Suppression of oncogene-mediated transformation of rat 3Y1 fibroblasts by protein tyrosine phosphatase 1B requires a functional SH3-ligand. *Mol Cell Biol* 1998;18:250–259. [PubMed: 9418872]
70. LaMontagne KR, et al. Protein tyrosine phosphatase PTP1B suppresses p210 bcr-abl-induced transformation of rat-1 fibroblasts and promotes differentiation of K562 cells. *Proc Natl Acad Sci U S A* 1998;95:14094–14099. [PubMed: 9826659]
71. Luo B, et al. Highly parallel identification of essential genes in cancer cells. *Proc Natl Acad Sci USA* 2008;105:20380–20385. [PubMed: 19091943]
72. Carette JE, et al. Haploid genetic screens in human cells identify host factors used by pathogens. *Science* 2009;326:1231–1235. [PubMed: 19965467]
73. Sangwan V, et al. Protein-tyrosine Phosphatase 1B Deficiency Protects against Fas-induced Hepatic Failure. *J Biol Chem* 2006;281:221–228. [PubMed: 16234234]
74. Gonzalez-Rodriguez A, et al. Developmental switch from prolonged insulin action to increased insulin sensitivity in protein tyrosine phosphatase 1B-deficient hepatocytes. *Endocrinology* 2007;148:594–608. [PubMed: 17068137]
75. Akasaki Y, et al. A peroxisome proliferator-activated receptor-gamma agonist, troglitazone, facilitates caspase-8 and -9 activities by increasing the enzymatic activity of protein-tyrosine phosphatase-1B on human glioma cells. *J Biol Chem* 2006;281:6165–6174. [PubMed: 16319070]
76. Gu F, et al. Protein-tyrosine phosphatase 1B potentiates IRE1 signaling during endoplasmic reticulum stress. *J Biol Chem* 2004;279:49689–49693. [PubMed: 15465829]

77. Dube N, et al. Genetic ablation of protein tyrosine phosphatase 1B accelerates lymphomagenesis of p53-null mice through the regulation of B-cell development. *Cancer Res* 2005;65:10088–10095. [PubMed: 16267035]
78. Wiener JR, et al. Overexpression of the protein tyrosine phosphatase PTP1B in human breast cancer: association with p185c-erbB-2 protein expression. *J Natl Cancer Inst* 1994;86:372–378. [PubMed: 7905928]
79. Wiener JR, et al. Overexpression of the tyrosine phosphatase PTP1B is associated with human ovarian carcinomas. *Am J Obstet Gynecol* 1994;170:1177–1183. [PubMed: 8166206]
80. Arias-Romero LE, et al. Activation of Src by protein tyrosine phosphatase 1B Is required for ErbB2 transformation of human breast epithelial cells. *Cancer Res* 2009;69:4582–4588. [PubMed: 19435911]
81. Jin Q, Esteva FJ. Cross-talk between the ErbB/HER family and the type I insulin-like growth factor receptor signaling pathway in breast cancer. *J Mammary Gland Biol Neoplasia* 2008;13:485–498. [PubMed: 19034632]
82. Dube N, et al. The role of protein tyrosine phosphatase 1B in Ras signaling. *Proc Natl Acad Sci U S A* 2004;101:1834–1839. [PubMed: 14766979]
83. Kashige N, et al. Tyrosine phosphorylation of p62dok by p210bcr-abl inhibits RasGAP activity. *Proc Natl Acad Sci* 2000;97:2093–2098. [PubMed: 10688886]
84. Zhu S, et al. PTP1B contributes to the oncogenic properties of colon cancer cells through Src activation. *Cancer Res* 2007;67:10129–10137. [PubMed: 17974954]
85. He H, et al. Role of Phosphatidylinositol 4,5-Bisphosphate in Ras/Rac-Induced Disruption of the Cortactin-Actomyosin II Complex and Malignant Transformation. *Mol Cell Biol* 1998;18:3829–3837. [PubMed: 9632767]

Figure 1. Structural domains and regulation of PTP1B

Schematic representation of the domain structure of PTP1B. Full-length human PTP1B is composed of an N-terminal catalytic domain (green) and C-terminal ER targeting domain (orange), flanking two proline-rich domains (PRD: 278-401AA; purple), at least one of which is critical for protein–protein interactions. PTP1B is regulated by tyrosine phosphorylation at Y152 and Y153, and serine phosphorylation at the indicated sites, oxidation of Cys215 at its active site, sumoylation at its PRD, and proteolysis by calpain.

Figure 2. metabolic and oncogenic signaling of PTP1B

Whereas PTP1B (dark pink) exerts a negative role in the insulin and leptin signaling pathways in metabolism, it has a positive effect on ErbB2 (Neu)-induced tumorigenesis. Insulin stimulation is followed by autophosphorylation and activation, thereby promoting tyrosine phosphorylation of insulin receptor substrate-1 (IRS-1; aqua), leading to phosphatidylinositol 3 kinase (PI3K; green) and AKT (light green) activation downstream of the IR (brown). PTP1B attenuates insulin signaling following receptor endocytosis, and it also dephosphorylates IRS-1. Activation of the leptin receptor (black) leads to recruitment and tyrosine phosphorylation of JAK2 (green) and subsequent activation of STAT3-mediated transcription. JAK2-STAT3 is also a known target of PTP1B. With respect to the oncogenic role of PTP1B signaling, PTP1B dephosphorylates p62^{Dok} (dark blue), which then inhibits p120^{RasGAP} (blue), thereby augmenting Ras-MAPK-mediated cell proliferation. Similarly, PTP1B-mediated dephosphorylation of Src at Y529 enables subsequent activation of small GTPases such as Ras (brown) and Rac. Phosphorylated tyrosines are noted by red circles.

Table 1

Landmarks in PTP1B research

Year	PTP1B discovery	Refs
1988	• Purification and characterization of PTP1B from human placenta	[1], [2]
1990	• Cloning of hPTP1B cDNA	[4], [5], [86], [85]
	• Microinjection in <i>Xenopus laevis</i> oocytes	
1992	• ER targeting domain identified	[16], [68], [17]
	• The effect of PTP1B on Neu- and V-src transformed fibroblasts	
1993	• Serine phosphorylation of PTP1B	[23], [31]
	• Calpain-induced cleavage of the PTP1B C-term tail	
1994	• Crystal structure of hPTP1B (1–321 at 2.8 Å)	[86], [78], [79].
	• PTP1B over-expression in human breast & ovarian cancers	
1995	• Osmotic loading of neutralizing antibody	[87]
1996	• Characterization of SH3 domain-containing PTP1B binding partners	[45]
1997	• Development of substrate-trapping mutant: PTP1B-D181A	[51]
1998	• Suppression of transformation	[69]
1999	• <i>Ptp1b</i> knockout mice generated	[54]
2000	• Positive role in c-Src activation in cancer cells	[7]
2001	• ROS regulation of PTP1B identified	[21], [61]
	• TYK2 and JAK2 as substrates	
2002	• PTP1B attenuates leptin signaling	[62], [63], [38]
	• FRET imaging of receptor dephosphorylation	
2003	• Structure of oxidized PTP1B	[20]
2004	• Positive role in Ras signaling	[82], [88], [89]
	• Muscle-specific <i>Ptp1b</i> knockout mice generated	
2005	• Crystal structure of non-catalytic binding to IR	[47]
2006	• Brain-specific <i>Ptp1b</i> knockout mice generated	[55]
2007	• SUMO regulation of PTP1B	[30], [11], [12].
	• MMTV- <i>ErbB2</i> ; <i>Ptp1b</i> ^{-/-} mouse models generated	
2008	• Quantitative SILAC proteomics of PTP1B substrates	[53]
2009	• Src activation in ErbB2-mediated transformation in 3D culture	[80], [57].
	• Liver-specific <i>Ptp1b</i> knockout mice generated	