Protein tyrosine phosphatases: characterization of extracellular and intracellular domains

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Protein tyrosine phosphatases (PTPs) play an important role in the regulation of cell growth and differentiation. With over 30 PTPs identified, the specific functions of these enzymes are now being addressed. The identification of extracellular domain receptor-like PTP interactions and the characterization of intracellular PTP 'targeting' domains represent recent efforts in this pursuit.

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Introduction

The importance of protein tyrosine phosphorylation in growth, differentiation and cytoskeletal integrity has been well established over the past decade. Protein tyrosine phosphatases (PTPs), enzymes that hydrolyze phosphotyrosyl groups, were initially considered to play 'housekeeping' roles by returning the tyrosine phosphorylation state of target substrates back to basal levels. This overly simplistic view now seems to be incorrect, since a number of PTPs have been shown to regulate integral components of signal transduction pathways (for recent reviews, see [1••,2•,3••]). PTPs have been implicated in tumor suppression [4,5,6•,7–9], cytoskeletal reorganization [10••,11•], development and differentiation [12••,13,14••], mitotic induction [15•,16,17•], T-cell activation [18•], and in growth factor [19•–21•,22–24], somatostatin [25] and interferon [26••,27•] signaling pathways. This review will focus on recent advances in understanding the function of receptor-like PTP extracellular domains, as well as the role of specific 'zip code' domains that govern intracellular PTP subcellular localization.

Protein tyrosine phosphatase structural domains

PTPs can be separated into two major groups: transmembrane receptor-like PTPs (Fig. 1), and intracellular PTPs (Fig. 2). All PTPs possess at least one catalytic domain of approximately 250 amino acids which contains the 'active site' signature motif (I/V)HCXAGXXR(S/T)G (in the one-letter amino acid code, where X can be any amino acid) [3••,28••]. Studies using chemical modification and site-directed mutagenesis have established that the cysteinyl residue within this consensus motif is essential for phosphatase activity, forming a thiophosphate enzyme intermediate necessary for catalysis [29]. This catalytic domain is unique to PTPs, bearing little resemblance to the catalytic domains of serine/threonine protein phospahatases, alkaline protein phosphatases, or acid protein phosphatases.

The receptor-like PTPs (Fig. 1) possess an extracellular domain, a single transmembrane domain, and usually two intracellular PTP catalytic domains. The first intracellular PTP domain generally accounts for the majority of catalytic activity, while the second domain is inactive or (in some cases) weakly active [30•]. The only transmembrane PTPs containing a single catalytic domain are human (H) PTPβ and *Drosophila* (D) PTP10D [31–33]. Receptor-like PTPs can be further subdivided into five types on the basis of common features found in the extracellular domain [1••]. Type I is represented by the CD45 family, exhibiting multiple isoforms arising from differential splicing of sequences at the amino terminus [34]. Type II members (e.g. LAR, HPTPκ, and HPTPμ) contain tandem repeats of immunoglobulin-like and fibronectin type III-like domains resembling neural cell adhesion molecules [35,36,37•]. Type III members bear multiple fibronectin type III-like repeats (e.g. DPTP10 and DPTP99A) [32,33,38]. HPTPα and HPTPε represent type IV isoforms, possessing small glycosylated segments [31,39]. Type V constituents include HPTPζ and RPTPγ, which exhibit amino-terminal carbonic anhydrase-like domains [40,41•]. Although the structural features of the receptor-like PTPs suggest that they may bind ligands, no 'ligand' interaction has yet been identified. However, the extracellular domain of a receptor-like PTP has recently been shown to mediate cell–cell aggregation via homophilic binding [42••,43••].

Abbreviations

CA—carbonic anhydrase; **CAM**—cellular adhesion molecule; **EGF**—epidermal growth factor; **D**—*Drosophila*; **GFR**—growth factor receptor; **H**—human; **LAR**—leukocyte common antigen related molecule; **MAP kinase**—mitogen-activated protein kinase; **PEST**—proline-, glutamic acid-, serine- and threonine-rich; **PTK**—protein tyrosine kinase; **PTP**—protein tyrosine phosphatase; **SH2**—Src homology 2; **TCR**—T-cell receptor.

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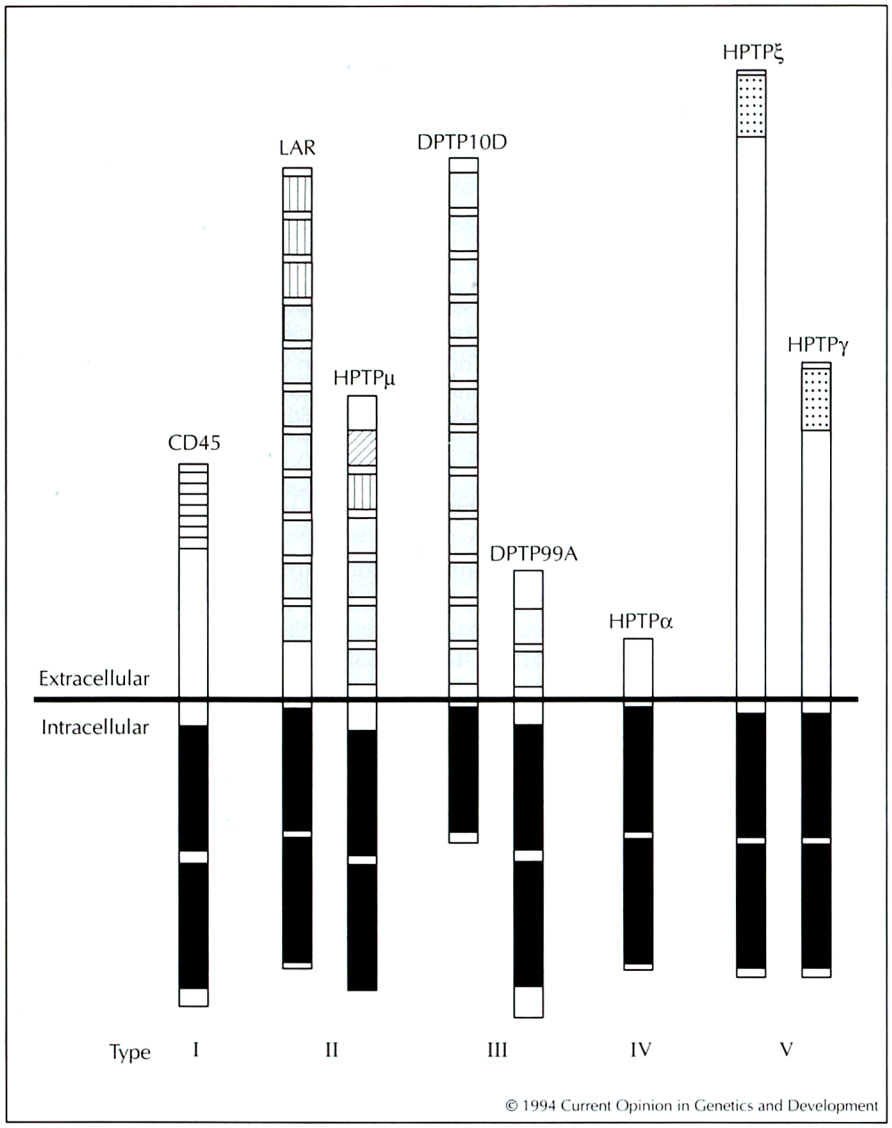

Fig. 1. Transmembrane receptor-like PTPs. The members of this family of PTPs possess a single transmembrane domain, and one or two intracellular PTP catalytic domains (black bar). They can be subdivided into five types on the basis of their extracellular domain structures: I, for example CD45; II, for example LAR and HPTPμ; III, for example DPTP10D and DPTP99A; IV, for example HPTPα; and V, for example HPTPζ and HPTPγ [1••]. The extracellular domain structures are shown: amino terminus isoforms (horizontal lines) resulting from differential splicing; immunoglobulin-like (vertical lines); fibronectin type III-like (shaded bar); MAM adhesive protein homology-like (diagonal lines); and carbonic anhydrase-like (stippled).

Intracellular PTPs (Fig. 2) possess a single catalytic domain with flanking regions that often contain amino acid sequences which direct the enzyme to specific intracellular locations. These zip code sequences can target PTPs to the endoplasmic reticulum (e.g. PTP1B) [44,45•], to the nucleus (e.g. DPTP61F) [46••], or perhaps result in their rapid degradation (e.g. PTP-PEST) [47•]. Several amino-terminal structural motifs have been identified that may direct intracellular PTPs to interact with cytoskeletal proteins (e.g. HPTPMeg1, HPTPH1) [48,49] or with phosphotyrosine-containing proteins via Src homology 2 (SH2) domains (e.g. PTP1C, SH-PTP2) [50,51•].

Transmembrane protein tyrosine phosphatases and extracellular domain interactions

CD45

The receptor-like structure of transmembrane PTPs suggests that they may interact with ligands. CD45, the first transmembrane PTP to be identified [34], has served as a model for understanding the function of the receptor-like PTPs. CD45 plays a role in T-cell receptor (TCR) mediated signal transduction and has been shown to reconstitute TCR signaling in CD45-deficient T cells [18•,52]. In an effort to determine whether the extracellular domain of CD45 influences its function in TCR signal transduction, Desai *et al.* [53••] constructed a chimera of the epidermal growth factor (EGF) receptor extracellular domain and the CD45 intracellular domain. The expression of this chimera in CD45-deficient T-cells restored TCR signal transduction (measured as intracellular calcium flux), indicating that the extracellular domain of CD45 is not absolutely required for TCR signaling. When EGF was added, TCR signaling was inhibited. The coexpression of a truncated EGF receptor (missing its cytoplasmic domain) with the EGF receptor/CD45 chimera restored TCR signaling. This suggests that the chimera may dimerize on addition of EGF, resulting in inactivation of intracellular PTP activity. Expression of sufficient truncated EGF receptor would presumably prevent chimera self-as-

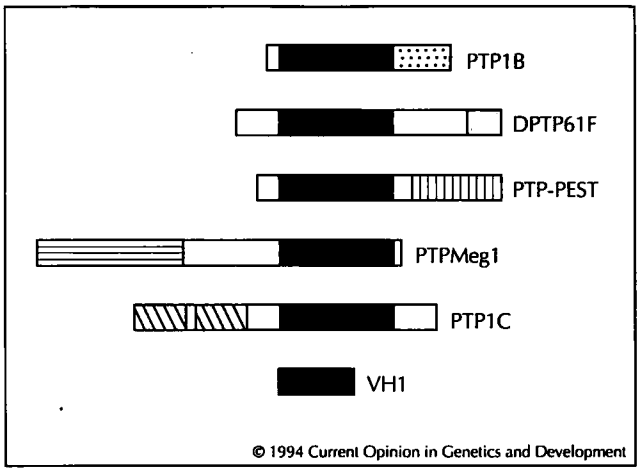

Fig. 2. Intracellular PTPs. The members of this family of PTPs possess a single catalytic domain (black bar) with flanking regions that often contain intracellular 'targeting' domains. Carboxy-terminal domains can target PTPs to the endoplasmic reticulum (stippled) for PTP 1B, to the nucleus (shaded box) for DPTP6IF, or result in their rapid degradation (vertical lines) for PTP-PEST. Amino-terminal domains may direct PTPs to interact with cytoskeletal proteins (horizontal lines) for PTPMeg1, or with phosphotyrosine via SH2 domains (diagonal lines) for PTP1C.

sociation. Data have also been published suggesting that CD45 is tyrosine-phosphorylated following TCR activation [54]. The specific effects of phosphorylation are unknown. It has been proposed that endogenous ligand-induced dimerization of CD45 may lead to trans-dephosphorylation and functional inactivation, analogous to the dimerization, transphosphorylation and activation of receptor protein tyrosine kinases (PTKs) [55].

Cell adhesion molecule-like protein tyrosine phosphatases

Type II receptor-like PTPs share extracellular domain similarities to cell adhesion molecules (CAMs). PTPμ and PTPκ contain one immunoglobulin-like domain and four fibronectin type III repeats [36,37•]. In addition, they both contain an 'MAM' (meprin, A5, μ) motif amino-terminal to the immunoglobulin-like domain. MAM motifs span approximately 170 amino acids and contain four conserved cysteines that may form disulfide bridges [56•]. The function of this domain is unknown. However, the MAM motif occurs in several diverse transmembrane adhesion proteins (e.g. A5 and meprin) and may therefore contribute 'adhesive' properties to PTPμ and PTPκ.

The sequence similarity of type II PTPs to CAMs has led researchers to suggest that these PTPs also promote homophilic binding. Expression of full-length PTPμ in SF9 insect cells results in cell aggregation, suggesting that PTPμ may mediate this process [42••,43••]. The expression of cytoplasmic domain-deleted constructs indicates that PTP catalytic activity is not required for the observed adhesion; only the extracellular domain is essential for cell–cell interactions. This was further substantiated by the observation that purified extracellular domain conjugated to resin beads can mediate bead–bead adhesion. Work from Schlessinger's laboratory, reported in a 'research news' article in *Science* [57••], indicates that the closely related molecule PTPκ also displays homophilic adhesive properties [57••]. When cells expressing PTPμ are mixed with cells expressing PTPκ, the cells segregate and adhere in a homophilic fashion. This shows that although PTPμ and PTPκ are structurally very similar, they display a high degree of specificity in their cell–cell adhesion. In addition, structurally similar LAR is not known to undergo homophilic interactions.

Carbonic anhydrase-like protein tyrosine phosphatases

Type V transmembrane PTPs contain a carbonic anhydrase (CA)-like domain in the amino-terminal 300 amino acids of their extracellular domain. These PTPs include the neural-specific human PTPζ [40], mouse RPTPβ [58•], rat PTP18 ([59]; RJ Mourey, KL Guan, unpublished data), and RPTPγ [41•], which is expressed in kidney, brain and lung. The CA domains of these PTPs are 25–40% identical to the seven isotypes of CA. It is unlikely that this domain functions as a carbonic anhydrase, since two of the three essential histidyl residues required for catalysis are missing. Rather, the overall structure of the CA domain may be utilized for ligand binding. Indeed, computer modeling of this domain and comparison with the crystal structure of CA indicates that 11 of the 19 residues that form the active site of CA are conserved [41•]. Interestingly, the type V PTPs show the same degree of identity to CA as does the vaccinia virus transmembrane protein D8 over almost its entire external domain, lacking two of the three catalytically required histidines [60]. Evidence suggests that the function of D8 is adsorption of the vaccinia virus to cell surfaces [61]. The shared homology between vaccinia D8 and this subclass of PTPs suggests that the D8 binding site may be a potential ligand for these PTPs.

Targeting of intracellular protein tyrosine phosphatases to specific subcellular locations

SH2 domains

The Src homology 2 (SH2) domain is a conserved sequence motif of approximately 100 amino acids that promotes interactions between cytoplasmic signaling molecules and specific phosphotyrosyl residues on activated (i.e. autophosphorylated) growth factor receptors or other signaling molecules. These interactions bring the appropriate signaling components of mitogenic pathways together [62••,63•,64]. Over the past two years, several new PTPs that contain two SH2 domains in their amino-terminal regions have been identified. These include PTP1C [50] and its homologs (SH-PTP1 [65], HCP [66] and SHP [67]), which are expressed predominantly in hematopoietic cells. More ubiquitously expressed SH2-containing PTPs include

SH-PTP2 [51•] and its homologs (Syp [68•], PTP1D [69••], PTP2C [70], and SH-PTP3 [71]).

Evidence that these SH2-PTPs may play a role in signal transduction comes from the characterization of two developmental genes, *Hcph* [14••,72] and *corkscrew* (*csw*) [73••]. Mice homozygous for the recessive allelic mutation *motheaten* display severe hematopoietic abnormalities [14••,72]. These mutations were recently localized to the *Hcph* gene, which encodes the SH2-containing PTP hematopoietic cell protein phosphatase [66]. Abnormalities in this protein may lead to defective signaling in hematopoiesis. Further evidence for the role of SH2-PTPs in signal transduction is provided by the *Drosophila* gene *csw*. This gene encodes an SH2-PTP that functions in the terminal class signal transduction pathway essential for normal development of anterior and posterior segments of the *Drosophila* embryo [73••]. Genetic experiments suggest that *csw* interacts with *polehole* (the *Drosophila* homolog of c-*raf*) [74] to transduce signals generated from the receptor PTK *torso* (a PDGF receptor homolog) [75]. The *csw* protein has high sequence identity with SH-PTP2 and may share functional similarities as well [76•].

The exact nature of the interaction of SH2-containing PTPs with PTKs to positively transduce signals is unclear, although several possible models have been suggested [76•]. One possibility is that the amino-terminal SH2 domain of the PTP binds an activated growth factor receptor (GFR), allowing the second SH2 domain to bind other phosphotyrosyl proteins. In this way, the PTP is acting to bring proteins to the GFR for further phosphorylation, or to participate in other protein–protein interactions. In an alternative model, SH2-binding of PTPs to GFRs may allow the PTP to dephosphorylate nearby phosphotyrosyl-regulated proteins. For example, activation of the insulin receptor results in the association of Syp with tyrosine-phosphorylated insulin receptor substrate 1, a protein participating in the insulin receptor signaling pathway [77•]. In addition, the proximal PTP may dephosphorylate and inactivate GFRs, thus terminating signal transduction. It is important to realize, however, that these two models may not be mutually exclusive

A third mechanism of SH2-PTP-mediated GFR signal transduction has been suggested by more recent results. In this model, the SH2 domains facilitate PTP–GFR interaction, whereupon the PTP is subsequently tyrosine-phosphorylated. The phosphorylated PTP could then interact with other SH2-containing proteins in signal transduction. In addition, tyrosine phosphorylation may increase PTP catalytic activity, potentially increasing the dephosphorylation of downstream effector molecules. Both Syp and PTP1D were shown to associate *in vivo* with activated PDGF and EGF receptors [68•,69••]. Both PTPs failed to dephosphorylate the GFR, but were themselves tyrosine-phosphorylated. Phosphorylation of SH2-PTPs may be required for interaction with receptor tyrosine kinases and other signaling molecules [68•,69••,76•,78•]. In the case of PTP1D, phosphorylation is correlated with a small increase in PTP catalytic activity *in vitro* [69••]. These findings indicate that SH2-PTPs may interact with PTKs, not simply to inactivate the GFR, but rather to work in concert with the GFR to regulate the phosphorylation state of signal transduction effector molecules.

Nuclear-targeting domains

Recently, several PTPs were shown to localize to the nucleus [46••,79•], which is intriguing given the suggested functional role of PTPs in cell cycle regulation and gene transcription [15•,16,26••,27•]. In the case of the *Drosophila* PTP DPTP61F, alternative splicing can produce two different carboxy-terminal zip codes directing the PTP to alternative locations [79•]. Expression of each alternatively spliced form in COS-1 cells indicated that the form possessing a highly basic 11 amino acid carboxyl terminus was directed to the nucleus. The other DPTP61F species, containing a carboxy-terminal splice of 24 hydrophobic amino acids, was localized to a 'reticular' network and mitochondria-like organelles within the cell. The substrate specificities of the nuclear and membrane PTPs were indistinguishable, as expected, since they share the identical catalytic domain. This underlines the fact that subcellular location can define and restrict the substrate specificity of PTPases within the cell.

Endoplasmic reticulum-targeting domains

PTP1B was originally purified from placental tissue as a soluble 39 kDa protein [80]. However, the molecular cloning of rat and human PTP1B predicted a 50 kDa protein containing a hydrophobic carboxyl terminus [81,82]. Frangioni *et al.* [44] and Woodford-Thomas and co-workers [45•] showed that full length PTP1B is normally localized to the endoplasmic reticulum in cells and that this localization is dictated by the carboxy-terminal 35 amino acids. Expression of carboxy-terminal truncated PTP1B results in a soluble enzyme. PTP1B can be released from the endoplasmic reticulum particulate fraction by trypsinization. The targeting of PTPs to the endoplasmic reticulum via their hydrophobic carboxyl terminus may result in limited substrate availability and act to keep PTPs in reserve until a cellular stimulus induces translocation of the PTP to the cytoplasm by carboxy-terminal proteolysis. Such an agonist-mediated stimulation of proteolysis and subsequent release of soluble PTP is observed in platelets [83•]. Activation of platelets by mixing, thrombin, or antibody engagement of the fibrinogen receptor gpIIb-IIIa, results in the activation of calpain, a calcium-dependent neutral protease. Activated calpain then cleaves PTP1B between its catalytic domain and its membrane-anchoring carboxyl terminus, resulting in a soluble PTP. The cleavage of PTP1B correlates with irreversible platelet aggregation [83•]. In addition, cleavage and subcellular relocation of PTP1B results in a twofold stimulation of its enzymatic activity and an altered pattern of phosphotyrosyl-substrate dephosphorylation [83•].

Dual specificity tyrosine/serine protein phosphatases

The first member of the class of dual specificity PTPs was identified in vaccinia virus [84]. This phosphatase, VH1, is a small (20 kDa) soluble phosphatase (Fig. 2) that dephosphorylates both phosphotyrosine- and phosphoserine-containing substrates. VH1-like phosphatases have also been identified in smallpox variola virus, several orthopoxviruses and baculovirus [85]. In mammals, several VH1-like phosphatases have been cloned and shown to be induced as immediate-early genes. The synthesis of human T-cell PAC-1 [79•], human CL100 [86] and the mouse homolog 3CH134 [20•] is induced by serum growth factors and oxidative or heat stress. In addition, a yeast VH1-like phosphatase has been shown to be induced upon nitrogen starvation [87].

Serum growth factors activate transmembrane protein tyrosine kinases [88]. Mitogen-activated protein kinase (MAP kinase) has been shown to be a major component of the signaling pathway involved in transducing the signal from activated PTKs to downstream effector molecules [89]. MAP kinase (p42) is activated by phosphorylation on Thr183 and Tyr185 by MAP kinase kinase [90]. The dual specificity phosphatases appear to dephosphorylate activated MAP kinase. Transcription of 3CH134 VH1-like phosphatase is rapidly induced by mitogenic stimulation, and synthesis occurs within the first hour [20•]. 3CH134 dephosphorylates Thr183 and Tyr185 on activated MAP kinase both *in vitro* and *in vivo* [91••]. In serum-stimulated fibroblasts, the inactivation of MAP kinase coincides with the new synthesis of 3CH134 [91••]. Expression of 3CH134 in COS cells blocks serum-stimulation of MAP kinase, while the expression of a catalytically inactive 3CH134 augments MAP kinase phosphorylation. In addition, inactive 3CH134 can be immunoprecipitated with phosphorylated MAP kinase demonstrating a physical interaction [91••]. These findings suggest that 3CH134 may be the physiological MAP kinase phosphate.

Conclusions

With the recent characterization of receptor-like PTP homophilic interactions, investigators can begin to approach the problem of understanding how these catalysts regulate signal processing during cell–cell contact. In addition, the characterization of intracellular PTP targeting domains will allow researchers to begin to determine how the substrate specificity of these enzymes is controlled. Characterization of targeting domains will also provide clues about PTP localization and function in the cellular landscape.

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