Receptor type protein tyrosine phosphatases (RPTPs) – roles in signal transduction and human disease

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Abstract Protein tyrosine phosphorylation is a fundamental regulatory mechanism controlling cell proliferation, differentiation, communication, and adhesion. Disruption of this key regulatory mechanism contributes to a variety of human diseases including cancer, diabetes, and auto-immune diseases. Net protein tyrosine phosphorylation is determined by the dynamic balance of the activity of protein tyrosine kinases (PTKs) and protein tyrosine phosphatases (PTPs). Mammals express many distinct PTKs and PTPs. Both of these families can be sub-divided into non-receptor and receptor subtypes. Receptor protein tyrosine kinases (RPTKs) comprise a large family of cell surface proteins that initiate intracellular tyrosine phosphorylation-dependent signal transduction in response to binding of extracellular ligands, such as growth factors and cytokines. Receptor-type protein tyrosine phosphatases (RPTPs) are enzymatic and functional counterparts of RPTKs. RPTPs are a family of integral cell surface proteins that possess intracellular PTP activity, and extracellular domains that have sequence homology to cell adhesion molecules. In comparison to extensively studied RPTKs, much less is known about RPTPs, especially regarding their substrate specificities, regulatory mechanisms, biological functions, and their roles in human diseases. Based on the structure of their extracellular domains, the RPTP family can be

grouped into eight sub-families. This article will review one representative member from each RPTP sub-family.

Keywords Protein tyrosine phosphorylation · Receptor protein tyrosine phosphatase · Cell surface receptor · Signal Transduction · Cell adhesion · Cell communication

Abbreviations

PTP	Protein tyrosine phosphatase
ECD	Extracellular domain
ICD	Intracellular domains
FN3	Fibronectin type III
MAM	Meprin A5, PTP μ
Ig	Immunoglobulin
CA	Carbonic anhydrase
CAM	Cell adhesion molecule
SFKs	Src family kinases

Introduction

Reversible protein tyrosine phosphorylation is a major mechanism regulating cellular signaling that affects fundamental cellular events including metabolism, proliferation, adhesion, differentiation, migration and development (Hunter 1987). Protein tyrosine phosphorylation determines protein functions, including protein-protein interactions, conformation, stability, enzymatic activity and cellular localization. Net protein tyrosine phosphorylation is governed by the dynamic equilibrium between two counter-acting enzyme families - protein tyrosine kinases (PTKs) and protein tyrosine phosphatases (PTPs) (Hunter 1995; Mustelin and Tasken 2003). Aberrant regulation of the delicate balance between PTKs and PTPs is involved in the pathogenesis of a number of human diseases such as cancer, diabetes, and autoimmune diseases (Ostman et al. 2006; Tonks 2006).

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Similar to PTKs, PTPs constitute a large and structurally diverse family of enzymes (Fischer et al. 1991; Mustelin et al. 2002; Tonks and Neel 1996; Walton and Dixon 1993). Sequencing data indicate that there are 107 PTP genes in the human genome, of which 81 encode active protein phosphatases (Alonso et al. 2004). Among the PTP super family, 38 are classical, tyrosine-specific PTPs, while the other 43 are dual-specificity tyrosine/serine, threonine phosphatases. The classical PTPs possess at least one catalytic domain known as the PTP domain. The 280-amino acid PTP catalytic domain contains an invariable active site signature motif (I/V)HCXAGXXR(S/T)G, which includes an essential cysteine that catalyzes nucleophilic attack on the phosphoryl group of its substrate and subsequent substrate dephosphorylation (Guan and Dixon 1991). The classical PTPs can be further sub-divided into 21 transmembrane receptor-like PTPs (RPTPs) and 17 non-transmembrane PTPs based on their overall structure (Alonso et al. 2004).

The RPTPs, which are the focus of this review, have a single transmembrane domain and variable N-terminal extracellular domains (ECDs) that share homology to cell adhesion molecules (CAMs). Intracellular domains (ICDs) of most of the RPTPs contain two tandem PTP domains. Usually membrane proximal PTP domain (D1) possesses most of the catalytic activity, whereas membrane-distal PTP domain (D2) has weak, if any, catalytic activity. This finding suggests that D2 domains may serve a regulatory rather than a catalytic role (Tonks 2006). The ECDs of RPTPs contain combinations of CAM-like motifs with sequences homologous to fibronectin type III (FN3), meprin, A5, PTP μ (MAM), immunoglobulin (Ig), and carbonic anhydrase (CA). Collectively, the molecular structure of RPTPs enables direct coupling of extracellular adhesion-mediated events to regulation of intracellular signaling pathways (Beltran and Bixby 2003).

Currently, ligands for majority of the RPTPs are not well-defined. The ECDs of RPTPs are highly variable, ranging from very short sequences lacking predictable functions to very long sequences with multiple CAM motifs (Brady-Kalnay and Tonks 1995; Saito 1993). Based on sequence features of their

ECDs, the RPTP family can be sub-divided into eight sub-families: R1/R6; R2A; R2B; R3; R4; R5; R7; and R8 (Andersen et al. 2001; Brady-Kalnay and Tonks 1995). Table 1 illustrates the structural features that define each sub-family. Key feature of a representative member from each subfamily will be described below to illustrate molecular/biochemical structure, proposed mode of regulation, proposed substrate specificity, and biological functions (Table 2).

CD45 and R1/R6 subfamily

Molecular/biochemical structure CD45 (encoded by the gene *Ptpre*) is the first RPTP to be identified based on the sequence homology of its PTP domain (Tonks et al. 1988) and is the only member of R1/R6 subfamily. As the prototypical RPTP, CD45 has served as a model for understanding RPTP function (Charbonneau et al. 1988). Expression of CD45 is restricted to cells of hematopoietic lineage (Thomas and Lefrancois 1988). The ECD of CD45 is heavily glycosylated and contains a single FN3 motif, whereas its ICD consists of a wedge-like structure followed by tandem PTP domains (Fischer et al. 1991). Among the two PTP domains, only the D1 domain is enzymatically active, although there is a report that deletion of a large portion of the D1 domain reveals PTP activity of the D2 domain in vitro (Streuli et al. 1990; Tan et al. 1993). Variable splicing of three exons in the N-terminal region of CD45 is responsible for a number of CD45 isoforms, whose expressions are cell type-specific and dependent on the stage of cellular differentiation and activation.

Proposed regulatory mechanisms Possible regulatory mechanisms of CD45 function include ligand binding, dimerization, cell-specific isoform expression, sub-cellular localization (e.g. lipid raft), and phosphorylation (Hermiston et al. 2003; Holmes 2006). Several putative ligands for CD45 have been identified. One is the lectin CD22, although the interaction does not modulate the PTP activity of CD45 (Hermiston et al. 2003). Walzel and co-workers demonstrated binding of Galectin-1 to CD45 (Walzel et al. 1999) that lowered CD45

Table 1 Structural features of RPTP subfamilies

	Subfamily	Example	# of PTP domain	FN3	Ig	MAM	CA	RDGS
<i>PTP</i> Protein tyrosine phosphatase domain, <i>FN3</i> Fibronectin type III domain, <i>Ig</i> Immunoglobulin domain, <i>MAM</i> Meprin, <i>A5</i> , and <i>PTPμ</i> domain, <i>CA</i> Carbonic anhydrase domain, <i>RDGS</i> Integrin-ligand peptide	R1/R6	CD45	2	+	–	–	–	–
	R2A	LAR	2	+	+	–	–	–
	R2B	RPTP- κ	2	+	+	+	–	–
	R3	DEP-1	1	+	–	–	–	–
	R4	RPTP- α	2	–	–	–	–	–
	R5	RPTP- ζ	2	+	–	–	+	–
	R7	PTPRR	1	–	–	–	–	–
	R8	IA2	1	–	–	–	–	+

Table 2 Functional features of representative RPTPs

Name	Gene	Chromosome location	Major substrates	Major modes of regulation	Related diseases
CD45	Ptpnc	1q	SFKs, JAK	Glycosylation, isoforms, dimerization, ligand binding, phosphorylation, subcellular localization	autoimmune diseases, infection
LAR	Ptprf	1p	β -catenin, p130 ^{cas} , SFKs, EGFR, HGFR, Ret	Isoforms, proteolysis, ligand binding	cancer
RPTP- κ	Ptprk	6q	EGFR, β -catenin	proteolysis, oxidation, ligand binding	cancer
DEP-1	Ptprj	11p	PDGFR, HGFR, SFK, VEGFR2, Ret, PI3K, Erk	dimerization, ligand binding	cancer
RPTP- α	Ptpna	20p	SFKs	phosphorylation, dimerization, oxidation	gastric ulcer, cancer
RPTP- ζ	Ptprz	7q	β -catenin, Git1, Magi1, RhoGAP, SFKs, β -adducin, ALK, TrkA	Isoforms, ligand binding, proteolysis	Parkinson's disease, demyelinating disease, gastric ulcer
PTPRR	Ptprr	12p	Erk	Isoforms, subcellular localization	Cancer, psychological disorders, endometriosis
IA2	Ptpm	2q	Not an active PTP	Proteolysis, glycosylation	diabetes

substrate activity (Nguyen et al. 2001), suggesting that Galectin-1 is a physiological ligand for CD45. Forced dimerization of CD45 inhibits its PTP activity (Desai et al. 1993). For example, PTP activity of chimeric CD45 in which the ECD and transmembrane domains are replaced with epidermal growth factor receptor (EGFR) domains is inhibited by addition of epidermal growth factor, which induces dimerization of the chimeric protein.

Sub-cellular localization of CD45 within detergent-insoluble microdomains (known as rafts) is a proposed mode of regulating substrate access to CD45. In resting T cells, approximately 10 % of CD45 is associated with rafts (Edmonds and Ostergaard 2002; Zhang et al. 2005) which seems to be important for T cell receptor (TCR) signaling (Irles et al. 2003). In T cells, segregation of CD45 from rafts is necessary to achieve sustainable TCR signaling (Zhang et al. 2005). Upon TCR engagement, CD45 is transiently tyrosine phosphorylated, although the functional significance of this event is not clear (Stover et al. 1991). In addition, CD45 is serine phosphorylated on an acidic loop in the D2 domain by casein kinase II in vitro (Wang et al. 1999) in T lymphoblasts and cultured T-cell lines (Autero et al. 1994). Deletion of the acidic loop or mutation of four of the serine residues within the loop suppresses the ability of CD45 to restore TCR signaling in CD45-deficient Jurkat cells (Greer et al. 2001).

Proposed substrates and biologic functions CD45 plays critical roles in immune system development and function and is required for antigen-specific lymphocyte stimulation and proliferation (den Hertog et al. 1999). CD45 mediates T- and B-cell receptor function by regulating tyrosine phosphorylation of the Src family of PTKs (SFKs) like Lyn and Lck. CD45 dephosphorylates the inhibitory C-terminal phosphorylation site in Lyn and Lck, thereby potentiating

the activity of these SFKs (Furukawa et al. 1994; Katagiri et al. 1999; Lee et al. 1996; Spertini et al. 1994). Attenuation of SFK activity by CD45-mediated dephosphorylation of other tyrosines has also been reported (Ashwell and D'Oro 1999; Thomas and Brown 1999). Studies in CD45 knockout mice show that CD45-mediated activation of Fyn and Lck is important in thymocyte development (Byth et al. 1996; Kong et al. 1995; Sato et al. 1999). Upon TCR ligation, activated Fyn and Lck phosphorylate components of the TCR complex like TCR-zeta and CD3-epsilon. These tyrosine-phosphorylated proteins provide docking sites for Src-homology 2 (SH2) domain-containing proteins to transmit down-stream signal. In CD45-null thymocytes, ligation of TCR does not lead to Lyn or Lck activation or to subsequent tyrosine phosphorylation of the TCR complex. Therefore, none of the down-stream signaling events occur; indicating the essential role of CD45 in TCR activation. CD45 has also been identified as a PTP that specifically dephosphorylates Janus kinases (JAKs) and negatively regulates cytokine receptor activation (Irie-Sasaki et al. 2001).

CD45 regulates immune responses by controlling the TCR activation threshold, modulating cytokine responses, and regulating lymphocyte survival. All of these processes are essential in the pathogenesis of autoimmune and infectious diseases. Due to its central role in T- and B-cell antigen receptor signaling, CD45 deficiency results in a severe combined immunodeficiency (SCID) phenotype (Kung et al. 2000; Tchilian et al. 2001) and is implicated as a genetic modifier in autoimmune, infectious, and malignant diseases (Tchilian and Beverley 2006). Furthermore, two CD45 polymorphisms have been described to play important roles in human diseases. The A138G allele is a high frequency polymorphism that causes an amino acid substitution of Thr47→Ala in exon 6 (Stanton et al. 2003). This mutation may affect glycosylation of CD45 and consequent reactivity

with lectin-like ligands. The high frequency of the allele is advantageous in protecting individuals against hepatitis B virus and preventing autoimmune Graves' thyroiditis (Boxall et al. 2004). Another CD45 polymorphism is the low-frequency C77G point mutation in exon 4, which prevents excision of the exon (Lynch and Weiss 2001). As a result, memory/effector lymphocytes of affected individuals express higher molecular weight CD45RA isoform, instead of the common low molecular weight CD45RO isoform, and have higher intensity of TCR signaling (Do et al. 2006). An increased frequency of C77G variant is reported in patients suffering from multiple sclerosis, systemic sclerosis, autoimmune hepatitis, Langerhans cell histiocytosis, and HIV-1 infection (Tchilian and Beverley 2006).

LAR and R2A subfamily

Molecular/biochemical structure The R2A subfamily members of RPTPs are characterized by the presence of Ig and FN3 domains in their ECD, and tandem PTP domains in their ICD. Subfamily members include RPTP- δ , RPTP- σ , and Leukocyte common antigen-related (LAR) protein, which is encoded by *Ptprf* gene (Streuli et al. 1988). Spatially- and temporally-regulated alternative splicing generates a variety of LAR isoforms that differ in the ECD (Chagnon et al. 2004). The extracellular domain of LAR can be proteolytically cleaved into two subunits that remain non-covalently associated at the cell surface (Streuli et al. 1992). Further proteolytic cleavage results in ectodomain shedding (Serra-Pages et al. 1994). The biological consequence of the proteolytic processing is not clear.

Proposed regulatory mechanisms LAR associates with both surface-bound and soluble ligands. Two heparin sulphate proteoglycans, syndecan (Sdc) and Dallylike (Dlp), are high-affinity ligands for LAR in *Drosophila* (Fox and Zinn 2005; Johnson et al. 2006). Sdc is a trans-membrane cell surface protein on muscle cells and interacts with the Ig domains of LAR in trans to increase its PTP activity and promote neuromuscular-junction formation (Fox and Zinn 2005). In contrast, the binding of GPI-anchored Dlp to LAR Ig domains negatively regulates PTP activity and suppresses synaptic morphogenesis. These two ligands compete for binding to LAR, and Dlp is the dominant effector (Johnson et al. 2006). Full-length LAR can also form homophilic interactions with a soluble isoform of its ECD segment. LARFN5C, which consists of a unique N-terminal sequence fused to the C-terminal portion of FN3 domain 5, associates with FN3 domains of LAR in neurons to promote neurite outgrowth (Yang et al. 2003). Moreover, an extracellular matrix complex of laminin and nidogen is reported to be a LAR ligand (O'Grady et al. 1998).

Proposed substrates and biologic functions LAR localizes to focal adhesions, and PTP activity seems to be required for focal adhesion turnover (Serra-Pages et al. 1995). The focal adhesion molecules β -catenin and p130cas are substrates for LAR (Kypta et al. 1996). Dephosphorylation of p130cas by LAR reduces its stability and leads to p130cas degradation, an event that is associated with cell death (Weng et al. 1999). LAR is reported to interact and modulate several PTK signaling pathways such as those involving EGFR (Suarez Pestana et al. 1999), HGFR (Kulas et al. 1996), Ret (Qiao et al. 2001), Lck, and Fyn (Tsujikawa et al. 2002). LAR also co-immunoprecipitates with insulin receptor (IR) and modulates down-stream events by regulating IR substrate phosphorylation (Mooney and LeVea 2003; Tsujikawa et al. 2001; Zabolotny et al. 2001). Transgenic mice over-expressing LAR in skeletal muscle exhibit normal glucose levels but have increased fasting insulin and reduced glucose uptake in skeletal muscle compared to wild-type mice. Both observations are positive indicators of insulin resistance and suggest that LAR may be involved in diabetes pathogenesis (Zabolotny et al. 2001). However, LAR knockout mice show normal insulin sensitivity. Additionally, LAR knockout mice have abnormal mammary gland development due to aberrant terminal differentiation of alveoli during pregnancy (Schaapveld et al. 1997) and display defects in hippocampus organization and forebrain size (Yeo et al. 1997).

LAR may also affect carcinogenesis. LAR gene amplification and mutation have been reported in human cancers such as small-cell lung carcinoma and colon cancer (Andersen et al. 2004; Harder et al. 1995; Wang et al. 2004). In addition, LAR expression is significantly increased in thyroid carcinomas (Konishi et al. 2003) and breast cancer (Yang et al. 1999), especially in breast cancer tissues with metastatic potential, suggesting that LAR may be an attractive prognostic marker (Levea et al. 2000). LAR co-immunoprecipitates with cadherin and β -catenin complex and stimulates tyrosine dephosphorylation of β -catenin in PC12 cells (Kypta et al. 1996). The association of LAR with the cadherin-catenin complex is important for maintenance of epithelial integrity and inhibition of tumor formation in nude mice (Muller et al. 1999).

RPTP- κ and the R2B subfamily

Molecular/biochemical structure The R2B subfamily members of RPTPs display Ig, FN3, and MAM domains in their ECDs. A representative R2B subfamily member is RPTP- κ , which is encoded by the *Ptprk* gene (Jiang et al. 1993). Other subfamily members include RPTP- μ , RPTP- π and RPTP- ρ (encoded by the genes *Ptprm*, *Ptpru* and *Ptprt*, respectively) (Gebbinck et al. 1991). They R2B subfamily members all contain tandem PTP domains in their ICDs.

Proposed regulatory mechanisms RPTP- κ is subjected to multiple steps of proteolytic processing in intact cells. Three proteases (furin, ADAM 10, and γ -secretase) are involved in the intracellular processing of RPTP- κ (Anders et al. 2006). High cell density promotes ADAM 10-mediated cleavage and subsequent shedding of RPTP- κ ectodomain. This event is followed by γ -secretase-dependent cleavage of the remaining transmembrane part of RPTP- κ to release the catalytic phosphatase intracellular (PIC) fragment from the membrane, thereby allowing its nuclear translocation. PIC of RPTP- κ is an active PTP that binds to and dephosphorylates its substrate β -catenin in the nucleus, which enhances transcriptional activity of β -catenin (Anders et al. 2006).

RPTP- κ , like all members of the PTP family, contains a highly conserved, active-site cysteine that is required for catalytic activity. Due to the unique environment in the active site, this cysteine residue has a very low pKa of 5.5 at physiological pH and is therefore susceptible to oxidation. Oxidation of the active site cysteine residue inhibits PTP activity (van Montfort et al. 2003). Ultraviolet (UV) irradiation elevates reactive oxygen species that oxidatively modify the active site cysteine residue causing RPTP- κ inhibition. Inhibition of RPTP- κ activity disrupts the kinase-phosphatase balance and results in UV irradiation-induced EGFR activation (Xu et al. 2006).

No heterologous ligand has been identified for RPTP- κ . However, RPTP- κ can form homophilic interactions in trans on the surface of adjacent cells (Gebink et al. 1993; Sap et al. 1994). Structure-function analysis indicates that the homophilic interaction site resides within the Ig domain, whereas the MAM motif determines binding specificity among closely related RPTPs (Brady-Kalnay and Tonks 1994; Zondag et al. 1995). In addition, a soluble form of RPTP- κ participates in the positive regulation of neurite outgrowth (Drosopoulos et al. 1999).

Proposed substrates and biologic functions RPTP- κ is a key regulator of EGFR tyrosine phosphorylation and function by directly dephosphorylating multiple C-terminal tyrosines (Wang et al. 2005; Xu et al. 2005). Expression of RPTP- κ , a negative regulator of EGFR, is up-regulated when cells reach confluence (Fuchs et al. 1996; Xu et al. 2005), suggesting that RPTP- κ is involved in contact inhibition in cells dependent on EGFR for proliferation. Furthermore, transforming growth factor beta (TGF- β), a potent inhibitor of epithelial cell proliferation (Coffey et al. 1988; Moses et al. 1990), induces RPTP- κ expression and leads to suppression of EGFR activity (Xu et al. 2010). Since EGFR is a major mitogen in many epithelial cells, suppression of EGFR activation via induction of its negative regulator RPTP- κ (Xu et al. 2010) contributes to TGF- β inhibition of cell proliferation. Besides EGFR, β -catenin is a reported substrate for RPTP- κ (Fuchs et al. 1996). RPTP- κ interacts with both β -catenin and γ -catenin

(plakoglobin) in vivo and in vitro. Furthermore, recombinant RPTP- κ can directly dephosphorylate β -catenin in vitro (Fuchs et al. 1996).

RPTP- κ is mapped to a 140 kb deletion that is associated with 18 out of 29 primary central nervous system lymphomas, suggesting that RPTP- κ may have tumor suppressor role (Nakamura et al. 2003). The notion that RPTP- κ may function as a tumor suppressor is further supported by the fact that RPTP- κ expression is reduced or undetectable in more than 20 % of melanoma cell lines and in some melanoma biopsies (Novellino et al. 2003). In addition, the human RPTP- κ gene is localized within a region in chromosome 6 that is frequently deleted in hematological neoplasia, ovary carcinomas, melanomas, and many other types of solid tumors where EGFR may function as an oncogene (Nakamura et al. 2003). Moreover, peptide derived from mutated RPTP- κ has been identified as a HLA-DR10-restricted melanoma CD4⁺ T-cell antigen (Flavell et al. 2008).

DEP-1 and the R3 subfamily

Molecular/biochemical structure The R3 RPTP subfamily members bear various numbers of FN3 domains in their ECDs and contain a single PTP domain in their ICD. A representative R3 subfamily member is DEP-1 (density enhanced phosphatase-1). Other members of the R3 subfamily include RPTP- β (encoded by the *Ptprb* gene), SAP1 (encoded by the *Ptprh* gene), GLEPP (encoded by the *Ptpro* gene) and PTPS31 (encoded by the *Ptprp* gene). DEP-1, encoded by the *Ptprj* gene, is also known as CD148 and PTP-eta. Disruption of the DEP-1 gene in transgenic mice leads to embryonic lethality with severe defects in vascular organization and enlarged vessels due to high endothelial cell proliferation (Takahashi et al. 2003). DEP-1 is associated with contact inhibition of VEGF-induced endothelial cell growth (Grazia Lampugnani et al. 2003).

Proposed regulatory mechanisms The ECD of DEP-1 contains eight FN3 repeats that are critical for its subcellular localization and biological function (Iuliano et al. 2009). Expression of wild-type DEP-1 inhibits HeLa cell proliferation. A deletion in the eighth FN3 domain of DEP-1 impairs its dimerization in the plasma membrane. Although this deletion mutant maintains its catalytic activity, it no longer inhibits HeLa cell proliferation. An unknown component of Matrigel, a preparation of basement membrane extracellular matrix proteins, is reported to interact with ECD of DEP-1 and increase DEP-1 activity (Sorby et al. 2001). This is another example that binding of a ligand to a RPTP stimulates its PTP activity.

Proposed substrates and biologic functions DEP-1 regulates density-dependent inhibition of cell growth (Ostman et al. 1994). Accumulating evidence suggests that DEP-1 may function as a tumor suppressor. DEP1 is located in colon cancer susceptibility locus SCC1, and loss of heterozygosity (LOH) at the DEP-1/PTPRJ locus is frequently found in human cancers (Ruivenkamp et al. 2002). Deletions and mutations of the DEP-1 gene have been reported in human breast, colon and lung cancer (Iuliano et al. 2004; Takahashi et al. 2006). The expression of DEP-1 is down-regulated in many cancer cells, and forced expression of DEP-1 inhibits their malignant phenotype (Balavenkatraman et al. 2006; Keane et al. 1996; Trapasso et al. 2000; Zhang et al. 1997). The anti-proliferative effect of DEP-1 is probably due to its ability to negatively regulate kinases like PDGFR (Kovalenko et al. 2000), HGFR (Palka et al. 2003), Src (Pera et al. 2005), VEGFR2 (Lampugnani et al. 2006), Ret (Iervolino et al. 2006), p85 subunit of PI3 kinase (Tsuboi et al. 2008), and Erk (Sacco et al. 2009) directly.

RPTP- α and the R4 subfamily

Molecular/biochemical structure The R4 subfamily members include RPTP- α (encoded by the *Ptp α* gene) and RPTP- ϵ (encoded by the *Ptp ϵ* gene). They contain short, highly glycosylated segments with no CAM homology domains in their ECDs, and have tandem PTP domains in their ICDs (Kaplan et al. 1990; Krueger et al. 1990). Both D1 and D2 domains of RPTP- α display highly similar three dimension structures (den Hertog 1999) and possess detectable PTP activity (Wang and Pallen 1991). However the PTP activity of the D1 domain is much higher than that of the D2 domain. The physiological function of the D2 domain catalytic activity is not entirely clear. Mutation of two residues (Val536 and Glu671) in the D2 domain increases PTP activity greater than that of the D1 domain (Buist et al. 1999; Lim et al. 1998).

Proposed regulatory mechanisms Analysis of crystal structure of RPTP- α reveals that the D1 domain forms a symmetrical dimer; a helix-turn-helix wedge motif from one monomer is inserted into the catalytic cleft of the other monomer to block substrate access (Bilwes et al. 1996). Furthermore, forced dimerization reduces the biological activity of full-length RPTP- α in a wedge-dependent manner (Jiang et al. 1999). The active-site cysteine residue of the RPTP- α D2 domain is more sensitive to oxidation than the cysteine residue of D1 domain, suggesting that the D2 domain may serve as a redox sensor (Persson et al. 2004). Oxidative stress such as H₂O₂ treatment and UV irradiation induces a conformational change in RPTP- α D2 domain in an active site cysteine-dependent manner, leading to

stabilization of RPTP- α dimer formation and inactivation of PTP activity (Blanchetot et al. 2002). The physiological relevance of the RPTP- α dimer has been suggested by the observation that exogenously expressed RPTP- α exists predominantly as dimers on the cell surface (Jiang et al. 2000).

PTP activity of RPTP- α is regulated by both tyrosine and serine phosphorylation. RPTP- α is constitutively phosphorylated on C-terminal tyrosine 789, which results in enhanced PTP activity toward Src tyrosine 527 (Zheng et al. 2000). Mutation of tyrosine 789 into a non-phosphorylatable amino acid alters functional properties of RPTP- α (Lammers et al. 2000; Su et al. 1996). Tyrosine 789-phosphorylated RPTP- α binds the adaptor protein Grb-2, which blocks binding of Grb-2 to Sos, a guanine nucleotide exchange factor needed for Ras activation, resulting in inhibition of down-stream MAP kinase signaling (den Hertog and Hunter 1996; den Hertog et al. 1994; Su et al. 1994, 1996). Protein kinase C (PKC) activator phorbol ester increases serine phosphorylation of RPTP- α , with concomitant enhancement of PTP activity (den Hertog et al. 1995). Phosphorylation occurs on serine 180 and 204 within the juxtamembrane helix-turn-helix wedge structure of RPTP- α . The negative charge induced by serine phosphorylation in this region may prevent RPTP- α dimer formation and thereby increase PTP activity (Bilwes et al. 1996). Serine 180 and 204 can be phosphorylated by PKC in vitro (Tracy et al. 1995), suggesting that PKC may regulate RPTP- α activity.

No ligand that binds to the ECD of RPTP- α has been identified. However, RPTP- α interacts with other cell surface receptors on the same cell such as contactin and N-CAM (Bodrikov et al. 2005; Zeng et al. 1999). Antibody-mediated clustering of N-CAM induces co-clustering of RPTP- α in lipid rafts where it can dephosphorylate and activate Fyn (Bodrikov et al. 2005; Zeng et al. 1999). This type of regulation illustrates that physical interactions with proteins can promote re-localization of RPTP- α and increase accessibility of its substrate SFKs.

Proposed substrates and biologic functions Similar to CD45, the widely expressed RPTP- α is known to specifically dephosphorylate the negative regulatory tyrosine of c-Src. Over-expression of RPTP- α increases c-Src kinase activity (den Hertog et al. 1993; Zheng et al. 1992). Conversely, RPTP- α knockout mice have reduced Src and Fyn kinase activity (Ponniah et al. 1999; Su et al. 1999). Despite the importance of the SFKs in multiple cellular and biological processes, RPTP- α knockout mice with reduced SFK activity are viable and appear normal (Le et al. 2004). In cell culture, RPTP- α co-localizes with α_v/β_3 -integrins at the leading edge during early cell spreading and co-immunoprecipitates with α_v -integrins during cell spreading on a fibronectin and vitronectin matrix. Furthermore, activation of Fyn by RPTP- α is required for mechanical force-dependent reinforcement of α_v/β_3 -integrin-mediated cell-

matrix connections (von Wichert et al. 2003). High RPTP- α protein levels are reported to significantly correlate with low tumor grade and positive estrogen receptor status in breast cancer. Furthermore, expression of RPTP- α in breast carcinoma cells leads to growth inhibition and delayed tumor growth and metastasis (Ardini et al. 2000). Expression of RPTP- α in susceptible cells has also been implicated in the pathogenesis of gastric ulcers caused by *Helicobacter pylori* (Yahiro et al. 2003). RPTP- α co-immunoprecipitates with VacA, a secreted potent vacuolating cytotoxin produced by *Helicobacter pylori* (De Guzman et al. 2005), which causes gastric ulcers. Binding of VacA to susceptible epithelial cells directly induces progressive vacuolation, mitochondrial damage and apoptosis. Another reported function of RPTP- α is regulation of voltage-gated potassium channel Kv1.2 activity. RPTP- α dephosphorylates Kv1.2 channel to re-activate K⁺ channel activity (Tsai et al. 1999).

RPTP- ζ and the R5 subfamily

Molecular/biochemical structure Members of the R5 subfamily include RPTP- ζ and RPTP- γ . RPTP- ζ , encoded by the gene *Ptprz*, possesses an N-terminal carbonic anhydrase-like (CA) domain and a single FN3 domain in its ECD, and an ICD with tandem PTP domains (Barnea et al. 1993; Krueger and Saito 1992). The atypical CA domain cannot hydrate carbon dioxide due to lack of an active-site histidine residue, but it can serve as a hydrophobic binding pocket for contactin (Peles et al. 1995).

Proposed regulatory mechanisms Binding of recombinant RPTP- ζ CA domain to contactin promotes cell adhesion and neurite outgrowth of primary neurons (Peles et al. 1995). Other heterophilic ligands that can bind to ECD of RPTP- ζ include tenascin, N-CAM, pleiotrophin and midkine (Maeda et al. 1999; Maeda and Noda 1998; Peles et al. 1998). Four isoforms of RPTP- ζ are generated via alternative splicing: the full length form *Ptprz*-A; the short receptor form *Ptprz*-B, with a deletion in the ECD; the secretory variant of the full length form *Ptprz*-S (Maeda et al. 1994; Peles et al. 1998); and the PSI isoform that is expressed only in neurons (Heck et al. 2005). Both the full length receptor form and the secreted form contain the entire ECD and are also known as chondroitin sulfate proteoglycans (Barnea et al. 1993; Maurel et al. 1994). The ECD of the receptor isoforms can be cleaved by metalloproteinases and by presenilin/ γ -secretase complex, causing the release of the intracellular region of RPTP- ζ into the cytoplasm (Chow et al. 2008).

Proposed substrates and biologic functions To date, multiple substrates have been identified for RPTP- ζ . They include

β -catenin (Meng et al. 2000), G protein-coupled receptor kinase interactor 1 (Git1) (Kawachi et al. 2001), p190 Rho-GAP, Magi1 (Fukada et al. 2005), Fyn (Pariser et al. 2005a), β -adducin (Pariser et al. 2005b), anaplastic lymphoma kinase (ALK) (Perez-Pinera et al. 2007), and Tropomyosin-related kinase A (TrkA) (Shintani and Noda 2008).

RPTP- ζ is expressed in neurons and glia within the central nervous system and plays critical roles in oligodendrocyte survival, in recovery from demyelinating disease, and in memory formation (Harroch et al. 2002; Tamura et al. 2006). Several soluble ligands such as pleiotrophin and midkine have been identified as RPTP- ζ ligands that not only bind to RPTP- ζ but also modulate its intrinsic PTP activity (Maeda et al. 1999; Maeda and Noda 1998). Meng et al. demonstrated that pleiotrophin binding to RPTP- ζ increases β -catenin tyrosine phosphorylation by inhibiting RPTP- ζ PTP activity (Meng et al. 2000). Ligand-induced dimerization seems to be the major mechanism of inhibiting intrinsic PTP activity by blocking substrate access to the active site in the D1 domain of RPTP- ζ (Fukada et al. 2006).

Pleiotrophin expression is up-regulated during repair processes in the nervous system (Blondet et al. 2005; Kikuchi-Horie et al. 2004) and is implicated in Parkinson's disease in both rodent models and humans (Herradon and Ezquerra 2009; Marchionini et al. 2007). Functionally, pleiotrophin increases dopaminergic neuron survival and promotes differentiation of neural stem cells to dopaminergic neurons (Hida et al. 2003; Jung et al. 2004). Participation of pleiotrophin in repair processes in the injured nervous system suggests that pleiotrophin may offer protective effects in Parkinson's disease. The inhibitory effect of pleiotrophin on the enzymatic activity of RPTP- ζ increases tyrosine phosphorylation of RPTP- ζ substrates such as β -catenin, Fyn and β -adducin. Increased tyrosine phosphorylation activates these substrates, which are vital for proliferation of dopaminergic progenitors and survival and differentiation of dopaminergic neurons (Herradon and Ezquerra 2009). Therefore, RPTP- ζ specific inhibitor may have therapeutic benefit in Parkinson's disease.

In addition to effects on the nervous system, RPTP- ζ may also affect carcinogenesis. RPTP- ζ is implicated in the pathogenesis of gastric ulcers. Similar to RPTP- α , RPTP- ζ can serve as a cell surface receptor for VacA, the protein toxin produced by the pathogen *Helicobacter pylori* (Padilla et al. 2000; Yahiro et al. 1999). Binding of VacA to RPTP- ζ inhibits its PTP activity and induces gastric epithelial detachment by increased tyrosine phosphorylation of its substrate Git-1 (Kawachi et al. 2001; Manabe et al. 2002). Git-1 regulates cell adhesion and cytoskeleton (Kawachi et al. 2001; Manabe et al. 2002). Tyrosine phosphorylation of Git-1, with concomitant epithelial detachment, leads to gastric ulceration by direct action of gastric acid. Therefore, aberrant RPTP- ζ signaling is a key mechanism of gastric

ulceration caused by *Helicobacter pylori*. Consistent with this conclusion is the finding that RPTP- ζ knockout mice are resistant to gastric ulcer induction by VacA of *Helicobacter pylori* (Fujikawa et al. 2003).

PTPRR and the R7 subfamily

Molecular/biochemical structure and proposed regulatory mechanisms The R7 subfamily is composed of PTPRR and STEP (striatal-enriched protein tyrosine phosphatase). PTPRR, also known as PCPTP-1 and PTPBR7, is encoded by Ptprr gene and is mainly expressed in neuronal cells (Hendriks et al. 2009). PTPRR displays a single PTP domain in its ICD, and its ECD shares no structural similarity to any known molecules. Alternative transcripts of the Ptprr gene give rise to multiple isoforms. These isoforms differ in their N-terminal sequence and thus have different subcellular localization. In mouse, the receptor type isoforms PTPBR7 and PTP-SL are mainly localized to the plasma membrane and vesicular structures/Golgi apparatus, respectively. The non-receptor type isoforms PTPPBS γ -42 and PTPPBS γ -37 are localized in the cytosol (Chirivi et al. 2004).

Proposed substrates and biologic functions All PTPRR isoforms specifically bind to Erk1 and Erk2 via a 16-amino acid kinase-interacting motif (KIM) located just N-terminal of the PTP domain (Chirivi et al. 2007; Pulido et al. 1998). Erk1/2, which belongs to mitogen activated protein kinases (MAPKs) family, are tyrosine and threonine dually phosphorylated on two regulatory residues in the activation motif (pT-E-pY) upon growth factor receptor activation (Schlessinger 2000). The full kinase activity of Erk1/2 requires phosphorylation of both threonine and tyrosine. Therefore, termination of MAPK activity can be achieved by either serine/threonine specific phosphatases, tyrosine specific phosphatases, or dual specific phosphatases. Accumulating evidence supports that tyrosine-phosphorylated Erk1/2/5 are PTPRR substrates (Buschbeck et al. 2002; Munoz et al. 2003; Pulido et al. 1998; Zuniga et al. 1999). PTP-SL-deficient mice show ataxia that is characterized by defects in fine motor coordination and balance skills (Chirivi et al. 2007). PTPRR is speculated to be involved in several human disorders. Increased PTPRR expression is observed in postmortem orbito-frontal cortex tissue from suicide subjects, compared to normal controls (Thalmeier et al. 2008). Consistent with this observation, the prefrontal cortex and hippocampus of suicide subjects shows significantly decreased activation and expression of Erk1/2 (Dwivedi et al. 2001). PTPRR is also implicated as a predisposing factor in endometriosis based on the observation that PTPRR expression is greatly increased during the transition from proliferative phase to secretory phase in the menstrual cycle. Additionally, increased PTPRR expression is detected in the endometrium of

women with endometriosis, when compared with normal controls (Sherwin et al. 2008). Furthermore, PTPBR7 is implicated in acute myelogenous leukemia, where exon 7 of Ptprr gene is fused to exon 4 of TEL gene (Nakamura et al. 2005). However, the resulting TEL-PTPRR fusion protein does not seem to have catalytic activity, and it is thought to be involved in leukemia pathogenesis by interfering with the function of wild-type TEL protein (Nakamura et al. 2005).

IA2 and the R8 subfamily

Molecular/biochemical structure and proposed regulatory mechanisms The R8 subfamily is composed of human islet antigen-2 (IA2 or ICA512) and IA2 β , which share 74 % sequence identity (Lan et al. 1994). IA2, encoded by Prprm gene, consists of an N-terminal cysteine-rich ECD domain, a trans-membrane domain, and an ICD with a single PTP domain. Interestingly, PTP domain of IA2 contains substitutions at two amino acids (Ala911 $\rightarrow$ Asp and Asp877 $\rightarrow$ Ala) that are known to be critical for catalytic activity in other PTPs. Consequently, IA2 fails to show any detectable enzymatic activity with generic PTP substrates. Changing the two amino acids to those present in active site of other PTPs restores IA2 PTP activity.

Proposed biologic functions IA2 is a major auto-antigen in type I diabetes (Notkins 2002). Approximately 70 % of newly diagnosed type I diabetes patients have auto-antibodies to IA2 (Lan et al. 1996). These auto-antibodies appear years before the onset of clinical symptoms. Approximately 50 % of subjects who display auto-antigens to both IA2 and GAD65 (a glutamic acid decarboxylase identified as another major type I diabetes auto-antigen) will develop type I diabetes within 5 years (Hu et al. 2005). Therefore, IA2 auto-antibody screening is now widely used to enrich trial enrollment for clinical studies of type I diabetes interventions.

Endogenous IA2 resides in the membrane of dense core secretory vesicles of various neuroendocrine tissue including the alpha and beta cells of pancreatic islets (Solimena et al. 1996). IA2 is implicated in glucose-induced insulin secretion. Targeted disruption of IA2 in transgenic mice results in mild glucose intolerance due to impaired insulin secretion (Saeki et al. 2002). In contrast, over-expression of IA2 in mouse beta cell lines increases glucose-induced insulin secretion (Harashima et al. 2005). Although IA2 has been independently demonstrated to be a positive modulator of insulin secretion, the precise molecular mechanism remains unclear.

Perspectives

RPTPs are a structurally diverse family of enzymes with characteristics of cell surface receptors. Although tremendous

progress has been made in the field of RPTPs in the past two decades, much detail remains to be learned. Extensive efforts are required to better understand the regulatory mechanisms controlling RPTP function, from transcriptional to post-translational levels. For example, redox regulation of RPTP enzymatic activity has been demonstrated to be an important part of post-translational regulatory mechanisms, so has proteolytic processing of RPTPs. Identification of *bona fide* ligands and how ligand binding affects RPTP function remains a major challenge for RPTP research. Identification of specific RPTP substrates and how specificity is achieved in vivo remains another challenging area for the foreseeable future. Although technical hurdles must first be overcome, the crystal structure of a full-length RPTP, either by itself or in complexes with binding partners will yield key information to guide RPTP research in the future.

Given the critical roles that RPTPs play in a variety of cellular processes and in the pathophysiology of human diseases, RPTPs are well positioned as potential therapeutic targets for pharmaceutical interventions. However, due to the highly conserved nature of their active sites and the desired objective to activate, rather than inhibit, RPTPs are commonly considered as undruggable. However, the discovery of secondary substrate-binding sites in most RPTPs provides potential opportunity for development of highly specific RPTP inhibitors. Alternatively, high affinity small molecules which mimic ligand binding and target ECDs of RPTPs have the potential to up-regulate RPTP activity. Advancement in the understanding of RPTP physiological functions and regulatory mechanisms will help to expand the therapeutic arsenal directed at balancing protein tyrosine phosphorylation.

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