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MINIREVIEW

Protein tyrosine phosphatases: functional inferences from mouse models and human diseases

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Some 40-odd genes in mammals encode phosphotyrosine-specific, 'classical' protein tyrosine phosphatases. The generation of animal model systems and the study of various human disease states have begun to elucidate the important and diverse roles of protein tyrosine phosphatases in cellular signalling pathways, development and disease. Here, we provide an overview of those findings from mice and men, and indicate several novel approaches that are now being exploited to further our knowledge of this fascinating enzyme family.

Reversible tyrosine phosphorylation

Research on how oncoviruses transform mammalian cells has led to the firm establishment of the tyrosine-specific phosphorylation of cellular proteins as a key signalling mechanism to evoke essential cell decisions, for example proliferation and differentiation. Many viral oncogenes have, in fact, been found to represent hyperactive mutants of protein tyrosine kinases found in the genome and thus distort the delicate phosphotyrosine balance within cells. Protein tyrosine phosphatases (PTPs), by virtue of their ability to counteract the activity of kinases, were therefore expected to have tumour-suppressive powers. Several years after the identification and isolation of PTPs, their catalytic activities were found to exceed those of kinases by log orders of magnitude. This led to the view that PTP enzymes represent housekeeping 'kinase counteractors' that, in isolation, display limited substrate selectivity. Since then, many specific defects have been found to be attributable to mutations in distinct PTP genes, highlighting that catalytic behaviour in the test tube cannot easily be extrapolated to PTP functioning within the live cell. Nowadays, protein tyrosine kinases and PTPs are regarded as corporate enzymes that coordinate the regulation of signalling responses, sometimes even by

Abbreviations
Me, motheaten; PTP, protein tyrosine phosphatase; RPTP, receptor-type PTP.

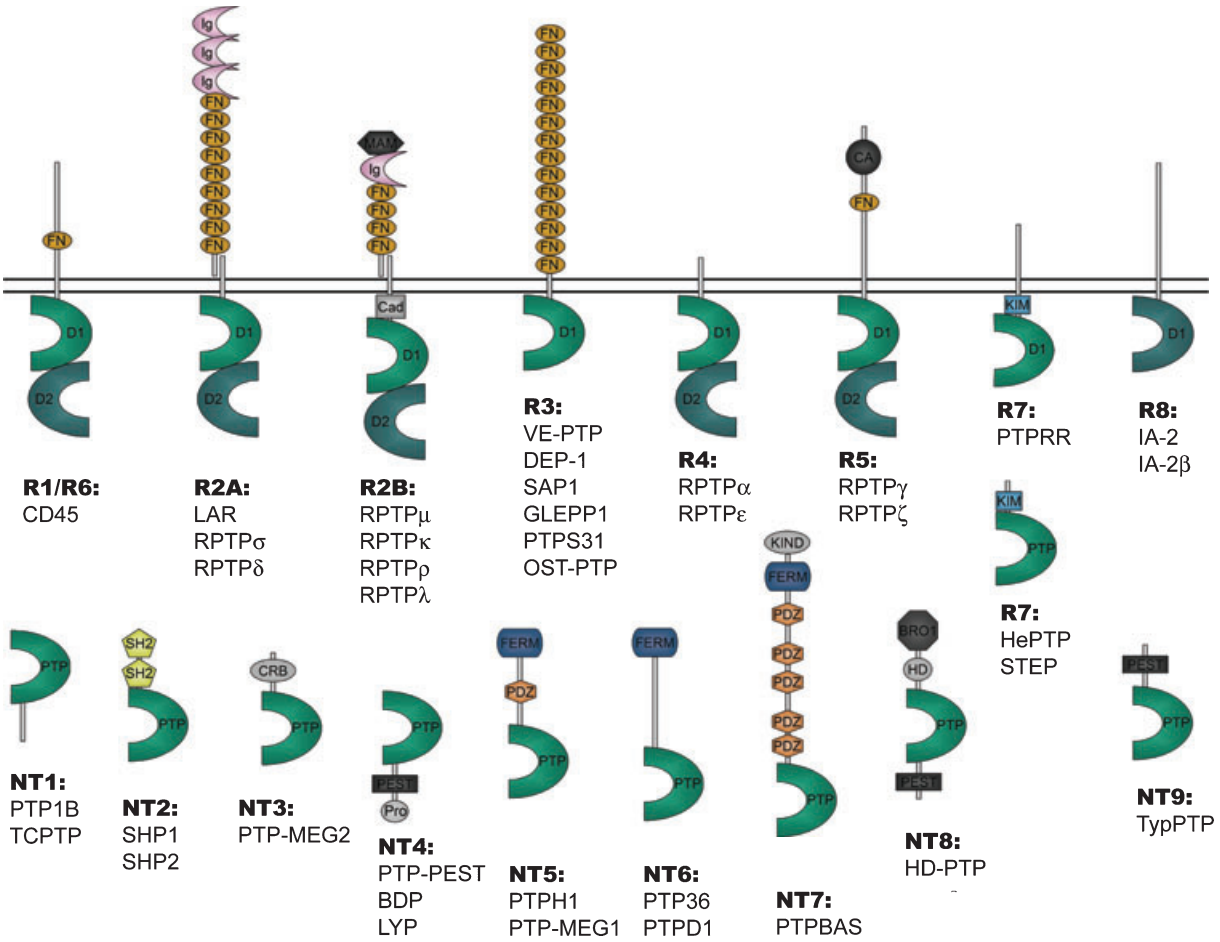

Fig. 1. Schematic depiction of the domain composition for all subfamilies of classical phosphotyrosine-specific PTPs. Each of the 38 classical mammalian PTP genes is represented by a single protein isoform. PTP subtypes, according to Andersen *et al.* [11], are listed. Please note that because of, for example alternative splicing, a single PTP gene may encode multiple isoforms, sometimes including receptor-like and non-transmembrane enzymes (hence the R7 subtype classification for cytosolic KIM-containing PTPs). In addition, specific isoforms within subtype families may contain additional protein domains and/or targeting sequences (e.g. the ER anchoring tail in PTP1B and the nuclear localization signal in TCPTP) [6,96]. Domain abbreviations: BRO1, baculovirus BRO homology 1; CA, carbonic anhydrase-like; Cad, cadherin-like; CRB, cellular retinaldehyde-binding protein-like; D1 and D2, membrane-proximal and membrane distal PTP domains, respectively (enzymatically active domains are in green, PTP domains with reduced or even no activity are in bluish green); FERM, band 4.1/ezrin/radixin/moesin homology (in blue); FN, fibronectin type-III repeat-like (orange ovals); HD, His domain; Ig, immunoglobulin-like; KIM, kinase interaction motif (light blue); KIND, kinase N-lobe-like domain; MAM, meprin/A2/RPTPμ homology; PDZ, postsynaptic density-95/discs large/ZO1 homology; Pro, proline-rich sequence; SH2, src homology 2 (in yellow). Adapted from Alonso *et al.* [9] and Andersen *et al.* [10].

acting in concert. Here, we review current knowledge on the physiological roles of the classical, phosphotyrosine-specific PTPs (Fig. 1) as derived from studies of mammalian pathologies or the use of animal models. In particular, we discuss the novel roads taken to deepen our understanding of this enzyme family, as well as their growing involvement in human pathologies, strengthening their nomination as desirable drug targets. We refer to other minireviews in this series [1–3] for a discussion of the regulatory principles and structure–function relationships displayed by classical and dual-specificity tyrosine phosphatases.

PTP function: animal models lead the way

Because of their high enzymatic activity and usually very low endogenous expression levels, many researchers have found that ectopic expression of PTPs in cell models can lead to off-target effects. Quite a number of PTPs, for example, were able to dephosphorylate the activated insulin receptor when tested in overexpression systems [4]. By contrast, *in vivo* studies have pointed to PTP1B, and to a lesser extend TCPTP and SHP1, as being responsible for

down-tuning the insulin-induced signals at the receptor level [5,6]. Not infrequently, PTP overexpression appeared incompatible with cell survival, frustrating attempts to generate stably transfected cell lines [7] and leading to faulty implications in apoptosis. Because it is still unclear which residues within a catalytic PTP domain structure actually contribute to substrate-specificity profiles [8], predicting PTP involvement in signalling networks on the basis of sequence information is currently not an option. Therefore, given the scarce knowledge on relevant ligands and substrates and the experimental drawbacks of overexpression in cell models, insight into the physiological role of individual phosphatases has come mostly from loss-of-function animal studies.

In Table 1 functional data based on transgenic (knockout) mouse models and/or mutations as identified in human pathologies are listed for all classical PTP genes. For some PTPs, such information has not yet been obtained, and occasionally functional clues that come from other types of studies are included (in parentheses). Please note that both the mammalian PTP gene nomenclature [9] and the PTP subtype indication [10,11] suggest a clear subdivision between receptor-type and non-receptor-type encoding ones. Such a distinction, however, is somewhat artificial because several PTP genes, e.g. *PTPN5* [12], *PTPRE* [13], *PTPRQ* [14] and *PTPRR* [15], give rise to both receptor-type and non-transmembrane PTP isoforms by means of an alternative use of promoters, splice sites and AUG start codons, or due to proteolytic processing. Table 1 illustrates that the construction of knockout mouse models, via homologous recombination in embryonic stem cells, for the different PTP genes is rapidly nearing completion. The phenotypes obtained all advocate the importance of PTP signalling. PTP loss has lethal consequences during early embryonic development or results in no or only mild effects, presumably reflecting redundancy as a safeguard for the organism.

For the mouse gene *Ptprj* it may seem that conflicting reports are listed in Table 1, but this reflects the two different ways in which the mouse models were created. Mice carrying a DEP-1 null mutation, caused by replacing of exons 3–5 within the *Ptprj* locus with a β-galactosidase–neomycin phosphotransferase fusion cassette, have not revealed any phenotypic consequences [16]. However, transgenic mice in which the intracellular catalytic domain of DEP-1 was replaced by the enhanced green fluorescent protein displayed an embryonic lethal phenotype because of vascularization failure, disorganized vascular structures and cardiac defects [17]. Apparently, the remaining extracellular portion of the DEP-1 molecule in the latter model acts as a functional ligand that blocks the pathways responsible for the correct assembly of endothelial cells during angiogenesis. Indeed, the relevance of DEP-1 extracellular segment-derived signals for endothelial-cell growth and angiogenesis was recently corroborated in wild-type mice by administration of a bivalent mAb against the DEP-1 ectodomain that resulted in clustering and activation of the phosphatase [18]. Mapping of a colon-cancer-susceptibility locus in mice and investigations into human tumour types pointed to potential tumour-suppressor activity for DEP-1 [19–24]. However, no spontaneous tumour development has been observed in DEP-1-deficient mice [16], indicating that additional genetic alterations may be required for tumours to arise and urging for studies on the susceptibility to experimentally induced cancers in this mouse model.

Knockout intercrosses: less is more

To overcome the hurdle of redundancy within the PTP family, cross-breeding of different PTP mutant mouse strains, especially within the respective subfamilies (Fig. 1), has recently been taken up. The receptor-type 8 (R8; nomenclature according to Andersen *et al.* [11]) PTPs IA-2 and IA-2β, for example, are enzymatically inactive transmembrane proteins that localize in dense core vesicles of neuroendocrine cells, including pancreatic insulin-producing beta cells. Single knockout mice revealed subtle defects in insulin secretion and, consequently, in the regulation of blood glucose levels [25,26]. Double knockouts, completely devoid of R8 PTPs, appeared normal and healthy but showed clear glucose intolerance and an absent first-phase insulin-release curve compared with wild-type mice [27]. In addition, female double-knockout mice were essentially infertile due to impaired luteinizing hormone secretion from dense core vesicles in pituitary cells [28]. These findings, and comparable observations in *Caenorhabditis elegans* [29], show that IA-2 and IA-2β cooperate in the first-phase release of hormones from neuroendocrine cells. Because R8 PTPs are enzymatically inactive, their mode of action may reflect phosphotyrosine-dependent protein binding, much like the SH2 and PTB protein domains [30], rather than dephosphorylation. Elegant work in cell models provided an intriguing two-way mode of action in which a 'substrate-binding' PTP combines phosphorylation-dependent and -independent protein interactions to regulate the secretory activity of exocrine cells in response to metabolic demands [31]. Secretory stimuli were found to induce the release of dense core vesicles

Table 1. Phosphotyrosine-specific class I PTP-related phenotypes in mouse and human.

Gene symbol	Protein name	PTP type[a]	Mouse model	Human/mouse/rat phenotype description (functional evidence from other sources)	Ref
PTPN1	PTP1B	NT1	Yes	M: NOP[b] – Increased insulin sensitivity, obesity resistance	[6,96]
PTPN2	TCPTP	NT1	Yes	M: Die 3–5 weeks postpartum; defective haematopoiesis and immune function	[6,96]
PTPN3	PTPH1	NT5	Yes	M: Enhanced growth due to augmented GH signalling, normal haematopoietic functions	[97,98]
PTPN4	PTP-MEG1	NT5	–	M: Involved in motor learning and cerebellar synaptic plasticity	[99]
PTPN5	STEP	R7	–	(duration of ERK signalling in the brain, neuronal plasticity)	[94,100,101]
PTPN6	SHP1	NT2	Yes	M: Die within first month; haematopoietic defects, splenomegaly, autoimmune disease, osteoporosis, increased insulin sensitivity H: Candidate tumour suppressor in lymphomas	[5,46,48,102] [103]
PTPN7	HePTP	R7	Yes	M: NOP (suppresses ERK activation)	[104]
PTPN9	PTP-MEG2	NT3	Yes	M: Embryonic lethal; defective secretory vesicle function	[105]
PTPN11	SHP2	NT2	Yes	M: Lethal at preimplantation stage; defective cell survival signalling H: Mutated in Noonan syndrome and Leopard syndrome	[51,106] [107]
PTPN12	PTP-PEST	NT4	Yes	M: Embryonic lethal; regulator of cell motility H: CD2BP1, a PTP-PEST binding protein, is mutated in PAPA syndrome	[108] [83]
PTPN13	PTPBAS	NT7	Yes	M: NOP – Impaired regenerative neurite outgrowth, negative regulator of STAT signalling (control of oocyte meiotic maturation)	[109–111]
PTPN14	PTP36	NT6	Yes	M: Androgenization of female mice (US Patent 20020152493) (negative regulator of cell motility)	[112]
PTPN18	BDP	NT4	–	(involved in HER2 signal attenuation)	[113]
PTPN20	TypPTP	NT9	–	(regulator of actin cytoskeleton dynamics)	[114]
PTPN21	PTPD1	NT6	–	(modulator of Tec family kinases and Stat3 activity)	[115]
PTPN22	LYP	NT4	Yes	M: Enhanced immune functions, splenomegaly, lymphadenopathy. H: Gain of function mutant causes autoimmune diseases	[81] [82]
PTPN23	HD-PTP	NT8	–	(candidate tumour suppressor on 3p21.3; regulates endothelial migration via FAK)	[116] [117]
PTPRA	RPTPα	R4	Yes	M: NOP – affected neuronal migration and synaptic plasticity, learning deficit, decreased anxiety, impaired NCAM-mediated neurite elongation	[34,35,118–120]
PTPRB	VE-PTP	R3	Yes	M: Embryonic lethal, reduced vascular development, heterozygotes are normal	[121,122]
PTPRC	CD45	R1	Yes	M: No T cells, immature B cells, impaired differentiation of oligodendrocyte precursor cells, dysmyelination	[123,124]
PTPRD	RPTPδ	R2A	Yes	M: Impaired learning and memory, retarded growth, early mortality, posture and motor defects	[39]
PTPRE	RPTPε	R4	Yes	M: NOP – Hypomyelination, defective osteoclast functioning, reduced src activity, aberrant macrophage function	[36,74,125,126]
PTPRF	LAR	R2A	Yes	M: NOP – Mammary gland defect, altered neuronal circuitry, learning deficits, enhanced IGF-1 signaling	[44,127–129]
PTPRG	RPTPγ	R5	Yes	M: NOP (tumor suppressor candidate on 3p14)	[33] [130,131]
PTPRH	SAP1	R3	–	(negatively regulates cell motility)	[132]

Table 1. (Continued).

Gene symbol	Protein name	PTP type[a]	Mouse model	Human/mouse/rat phenotype description (functional evidence from other sources)	Ref
PTPRJ	DEP-1	R3	Yes[c]	M: NOP / Die at mid gestation with severe defects in vascular organization H: frequently deleted in human cancers	[16,17] [19–24]
PTPRK	RPTPκ	R2B	Yes	M: NOP R: defective thymocyte development (tumor suppressor candidate on 6q22-23)	[42] [133] [134]
PTPRM	RPTPμ	R2B	Yes	M: NOP – Reduced dilatation in mesenteric arteries	[135,136]
PTPRN	IA-2	R8	Yes	M: NOP- Glucose intolerance, defective insulin secretion	[26]
PTPRN2	IA-2β	R8	Yes	M: NOP – Glucose intolerance, impaired insulin secretion	[25]
PTPRO	GLEPP1	R3	Yes	M: Reduced renal filtration surface area (tumour suppressor candidate in lung and hepatocellular carcinomas and CLL)	[137] [138]
PTPRQ	PTPS31	R3	Yes	M: Impaired development of cochlear hair bundles (inositol lipid phosphatase activity)	[139] [63]
PTPRR	PTPRR	R7	Yes	M: Hyperphosphorylated ERK in brain, locomotive impairment	[140]
PTPRS	RPTPσ	R2A	Yes	M: Decreased brain size, pituitary dysplasia, defects in olfactory lobes, enhanced nerve regeneration, ulcerative colitis of the gut	[141–148]
PTPRT	RPTPρ	R2B	–	H: Mutated in colon cancer specimen (associates with cadherin complexes, dephosphorylates STAT3)	[64,65] [149,150]
PTPRU	RPTPλ	R2B	–	(associates with cadherin complexes, dephosphorylates β-catenin)	[151]
PTPRV	OST-PTP	R3	Yes	M: Increased susceptibility to chemically induced tumours, increased perinatal lethality, hypoglycaemia, beta cell hyperproliferation (mediator of p53-induced cell cycle arrest)	[152,153] [154]
PTPRZ	RPTPζ	R5	Yes	M: NOP – Remyelination defects, impaired learning, resistant to Helicobacter pylori-induced gastric ulcers	[32,155,156]

[a] PTP types according to Andersen *et al.* [11]. Phenotypic consequences of mutations in human (H), mouse (M) or rat (R) are given. In absence of such information, the functional data derived from cell models are mentioned between brackets and aligned to the right. [b] NOP (no obvious phenotype): normal and healthy appearance, normal breeding and behaviour. [c] The apparently conflicting phenotypes reflect different mouse mutants. See text for explanation.

and their subsequent exocytosis via calpain-mediated cleavage of IA-2, which immobilizes these granules onto the submembranous cytoskeleton. The resulting IA-2 cytoplasmic tail subsequently moves into the nucleus and enhances secretory granule gene expression by binding and protecting STAT5 phosphotyrosines.

For the R4 (RPTPα and RPTPε) and R5 (RPTPγ and RPTPζ) receptor-type PTPs the individual knockout strains lack obvious phenotypes [32–36]. Perhaps RPTPα/RPTPε and RPTPγ/RPTPζ double-knockout mice will shed more light on the role of these enzymes. To date, studies on RPTPα/RPTPε double-knockout mice have revealed that the R4 PTPs display significant differences in their regulation of Kv channels and the tyrosine kinase Src [37] and, thus, that sequence similarity does not necessarily imply functional redundancy *in vivo*. By contrast, intercrossing of RPTPδ and RPTPσ knockout mice yielded double-knockout animals that were paralysed, did not breathe and died shortly after birth by caesarean section [38]. These mice exhibited extensive muscle dysgenesis and spinal cord motoneuron loss, demonstrating that these R2A-type PTPs are functionally redundant with respect to appropriate motoneuron survival and axon targeting in mammals [38]. This predicts that the generation and study of mice that lack all three R2A PTPs (LAR, RPTPδ and RPTPσ) are rather daunting tasks with a likely 'embryonic lethal' outcome. Crossing of LAR mutant mice with either RPTPδ- or RPTPσ-deficient mice may prove informative. The phenotype of mice with a combined deficiency for LAR and RPTPσ

phosphatase activity is currently under study (N. Uetani and M. Tremblay, personal communication). Investigating the joint functions of LAR and PTPδ would be of interest in the synaptic field, given that each has been shown to play a role in synaptic plasticity and memory [39,40]. Other RPTPs may also play roles in synapse dynamics [35,41]. Unfortunately, the genes encoding LAR and RPTPδ (*Ptprf* and *Ptprd*) both map on mouse chromosome 4, some 20 cM apart. Thus, to obtain alleles that harbour mutations in these two R2A-type genes, an extensive breeding programme of double-heterozygous animals or a laborious double knockout at the ES cell stage would be required. It should be noted that current LAR mutant mouse models, lines ST534 [42] and LARΔP [43], do not represent full null alleles [44] and may express trace amounts of wild-type [45] or truncated [43] protein, respectively.

Customizing PTP expression

Multiple mutant mouse models are available for the two cytosolic SH2 domain-containing PTPs, SHP1 and SHP2 (Table 1). SHP1-deficient mice, provided by a naturally occurring point mutation in the so-called motheaten (me) strain, die within the first month after birth [46–48]. Motheaten viable (me^v) mice contain a more limited inactivation of the gene and have a less severe phenotype. Likewise, both the first generation of SHP2 knockout animals [49,50], which resulted in the expression of N-terminally truncated SHP2 mutants, and the recent full null mouse model [51] were incompatible with life. SHP1 is expressed mainly in haematopoietic cells and SHP2 displays a rather ubiquitous profile [52]. The lethal phenotypes of SHP-deficient animals encouraged the use of novel *in vivo* approaches to study their physiological function; in recent years several conditionally defective SHP alleles have been developed [51,53–56] through the use of tissue- or developmental-stage-specific recombination strategies [57]. Also, the strategy of overexpressing a dominant-negative SHP2 mutant in specific tissues has been exploited [58]. In conjunction with work on cell models, these studies demonstrated that SHP2 is required for optimal activation of Ras-Erk growth factor signalling cascades; however, key substrates of this PTP remain to be discovered [52,59]. The identification of inherited dominant autosomal mutations in the SHP2-encoding gene *PTPN11* as a major cause of Noonan syndrome, a disease manifested by short stature, congenital heart defects and facial abnormalities, pointed for the first time to the detrimental effect of SHP2 hyperactivity [60]. Noonan syndrome is associated with an increased risk for developing leukaemia, and somatic mutations of *PTPN11* that result in hyperactivation of SHP2 have been identified in sporadic cases of juvenile myelomonocytic leukaemia and childhood acute lymphoblastic leukaemia [59,60]. Such mutations have also been detected, albeit at low frequency, in solid tumours. Thus, SHP2 should, in fact, be viewed as the product of a genuine proto-oncogene. Intriguingly, SHP2 hypoactivity leads to a disease as well: Leopard syndrome [60]. The clinical features of Noonan and Leopard syndromes largely overlap, thus providing a mechanistic conundrum. Recent studies on SHP2 function and the identification of other genes involved in developmental syndromes related to Noonan and Leopard begin to provide a picture in which developmental processes depend heavily on a very narrow bandwidth of MAPK signal strength; MAPK activities that are either below or above this range would result in comparable phenotypes [61].

Oncogenic as well as tumour-suppressive PTPs

Led by the original belief that as counteractors of oncogenic protein tyrosine kinases the PTPs would function as tumour suppressors, the search for mutations in PTP genes was taken up rapidly following their initial discovery. However, despite the mapping of several PTP genes in genomic regions that are frequently deleted in human tumours, such an anti-cancer link never progressed beyond the 'association' to the 'causal' level. By contrast, a major tumour suppressor has been successfully identified among the dual-specific phosphatases: PTEN (see the accompanying minireview by Pulido and Hooft van Huijsduijnen [2]). PTEN's tumour-suppressive action, however, is primarily attributable to its lipid phosphatase activity [62]. Interestingly, one of the classical PTP genes, *PTPRQ*, encodes an inositol lipid phosphatase [63]; undoubtedly research groups are searching for altered PTPRQ function in tumour specimens. In an impressive mutational analysis of 83 different tyrosine phosphatase genes in human cancer specimens [64], the *PTPRQ* gene did not emerge as a hot spot for mutations. Rather, 26% of the colon cancer cases and a smaller fraction of lung, breast and gastric cancers were found to have mutations in one of no fewer than six, classic phosphotyrosine-specific genes: *PTPRF*, *PTPRG*, *PTPRT*, *PTPN3*, *PTPN13* and *PTPN14*. The most commonly mutated PTP gene was *PTPRT* and reintroduction of *PTPRT* in human cancer cells inhibited cell growth [64]. It therefore came as a surprise that in another cohort study, hardly any mutations in

PTPRT were encountered [65], weakening a possible critical role for *PTPRT* mutations in cancer development. Additional studies of this subject are clearly warranted.

As mentioned previously, various lines of evidence point to the DEP-1-encoding gene *PTPRJ* as a tumour-suppressor gene, especially in colon cancer [19–24]. DEP-1 mutations were not identified in the tyrosine phosphatome study [64] mentioned above, but because the common DEP-1 lesions in cancer specimens reflect allelic loss rather than point mutations or small insertions/deletions this may well be due to the experimental design. Irrespective, DEP-1-deficient mice did not show an increase in tumour incidence [16]. This may well reflect the accepted paradigm that tumorigenesis depends on multiple genetic alterations acting in concert; the tumour-suppressive powers of PTPs may require the context of additional specific genetic defects, possibly in other PTP genes, to become noticeable. For example, RPTPδ has been highlighted recently as a potential target for microdeletions in lung cancer, cutaneous squamous cell carcinomas and neuroblastomas [66–68].

A recent experiment that underscores the need for further genetic lesions, involved the crossing of PTP1B deficiency onto a p53 null background in mice [69]. PTP1B/p53 double-knockouts displayed decreased survival rates compared with mice lacking p53 alone, due to an increased development of B-cell lymphomas. This is in line with the observation that PTP1B null mice have increased numbers of B cells in bone marrow and lymph nodes. Thus, in a p53-null background, PTP1B determines the latency and type of tumour development via its role in B-cell development. Bearing in mind this 'anti-oncogenic effect' of PTP1B, one might have expected a similar outcome from the crossing of PTP1B null mice with transgenic mice prone to develop breast cancer due to mutations in ErbB2. By contrast, two groups found that the absence of PTP1B actually delays ErbB2-induced tumour formation considerably and significantly reduces the incidence of lung metastases in these animal models [70,71]. Thus, although the mechanism is unclear [72], PTP1B supports ErbB2 signalling in these mouse tumour models, thereby joining SHP2 in the dubious honour of being an 'oncogenic' PTP. Several lines of evidence also indicate that RPTPε harbours tumour-promoting activity. Expression of RPTPε is upregulated in mouse mammary tumours induced by ErbB2 or Ras, and transgenic mice that overexpress this PTP in their mammary epithelium developed mammary hyperplasia and often solitary mammary tumours [73]. Cells derived from ErbB2-induced mammary tumours in RPTPε-deficient mice were less transformed than cells expressing PTPε [73,74]. RPTPε exerts is effect by activating Src in ErbB2-induced mammary tumours [74,75] and provides a necessary, but insufficient, signal for oncogenesis. For further discussions on the potential oncogenic role of PTPs, including RPTPα, SAP1, LAR, SHP1 and HePTP, see Östman *et al.* [76].

PTPs in the immune system

Because immunological processes intrinsically require the cooperative action of many different cells, tissues and even organs, it is not surprising that the use of animal models has been crucial in elucidating PTP involvement in these matters [77–79]. The motheaten mouse strains, which carry mutations in SHP1, provided a first example of an autoimmune disease caused by defective PTP signalling [47,48]. Autoimmune diseases were subsequently reported for mice that express a CD45 gain-of-function mutant [80] or lack LYP expression [81]. These latter two PTPs have also been found to be associated with human diseases. CD45 abnormalities have been detected in some severe combined immunodeficiency patients and in T cells from patients with systemic lupus erythematosus [77]. More recently, a polymorphism in the LYP-encoding gene *PTPN22* was linked to a range of human autoimmune disorders including type 1 diabetes, rheumatoid arthritis, Graves' disease, generalized vitiligo and systemic lupus erythematosus [82]. The polymorphism markedly affects the binding of LYP to its partner-in-crime CSK, resulting in impaired downregulation of T-cell receptor signals and thus an increased risk of hyperreactive T cells mounting a destructive immune response against autoantigens. A similar situation is encountered in the autoinflammatory disorder PAPA syndrome (pyogenic sterile arthritis, Pyoderma gangrenosum and acne) where mutations in CD2BP1 severely reduce its binding to PTP-PEST [83]. Consequently, the suppressive effect normally exerted by the CD2BP1/PTP-PEST complex on CD2-mediated T-cell activation is impaired and inflammation cannot be properly controlled.

Attractive new ways to address PTP function

Molecular and mechanistic information on the position of PTPs within cellular signalling pathways has also been obtained through exploitation of cell lines derived from knockout animals. For example, the use of mouse embryonic fibroblasts derived from various PTP-deficient strains enabled a 'physiological search'

for negative regulators of PDGF beta receptor signalling [84]. The study underscored that '*in cellulo*' PTPs do display extensive site selectivity in their action on tyrosine kinase receptors, a characteristic that is often lost when studied in the test tube. The increasing use of RNAi technology [85] to effectively reduce PTP protein levels is a powerful alternative, especially if functional redundancy needs to be taken into account.

Novel ways to interfere with PTP action at the protein level are also being explored. Synthesis of small molecule PTP inhibitors has gained significant priority given the exciting discoveries on PTP1B biology. However, thus far, it has proved quite difficult to achieve proper PTP specificity for such molecules, preferably combined with good cell penetrability and biodistribution. Intriguingly, the application of interfering peptides to study PTP function has also gained momentum. As discussed in the accompanying review by den Hertog *et al.* [1], several RPTPs contain a wedge-shaped helix–loop–helix region just N-terminal of their first, catalytically active PTP domain that, upon RPTP dimerization, can inhibit enzyme function by blocking entrance to the catalytic site of the opposing RPTP subunit [86,87]. Taking this knowledge one step further, Longo and co-workers recently demonstrated that the administration of cell-penetrable wedge-domain peptides does affect cellular signalling processes in a PTP-specific way, providing an alternative strategy to inhibit PTPs [88]. A subset of RPTPs dimerize via interactions mediated by their single-pass transmembrane segment [89] which may potentially influence their activity [90]. Therefore, reminiscent of the wedge peptide strategy, the design of peptides that target transmembrane helices [91] may well provide complementary peptide tools to manipulate RPTP signalling. Importantly, since transcellular signalling via dimerization-dependent ligand binding to the RPTP ectodomains may be at stake [92] such peptides may influence both intracellular and extracellular signalling pathways. Reasoning along these lines, the future identification of RPTP ligands and the mapping of their binding sites on RPTP ectodomains may yield additional peptide tools to fine-tune RPTP signalling, much like the *in vivo* exploitation of an antibody recognizing the extracellular domain of DEP-1 [18]. Further support for this approach has come from studies of a small homophilic peptide derived from LAR ectodomain, which appears to activate the enzyme [93]. In addition, short peptides screened for affinity to PTPσ ectodomains can block ligand interactions and alter neurite outgrowth in culture (Stoker and Hawadle, unpublished). Furthermore, for some applications, one may even envisage turning to the *in situ* application of complete PTP mutant domains [94,95].

These novel approaches to modulate PTP signalling in live cells leave untouched the daunting task of identifying the actual partner proteins and substrates with which PTPs interact. Rapid progress in isolation of native protein complexes, for example, by exploiting tandem affinity purification protocols and the selective enrichment of phosphoprotein-containing proteins, and in their subsequent identification by dedicated mass spectrometric means should therefore be exploited to provide a wealth of information on the signalling nodes involving PTPs within the coming years. Furthermore, the power of modern proteomics should also help uncover PTP targets after analysis of changes in total cellular tyrosine phosphoprotein profiles in various knockout animals and cell lines.

Conclusion

We have come a long way in recognizing the impact of reversible tyrosine phosphorylation on cell fate, tissue development and health, and the contribution of protein tyrosine phosphatases to these matters, not in the least by exploiting animal models with PTP-specific deficiencies. To date, the data underscore the importance of investigating PTP action under close-to-physiological conditions. By and large, the mouse data correlate well with observations from human disease states, corroborating the value of these animal models in uncovering the aetiology of human diseases. The advent of novel approaches to manipulate PTP activity now enables careful design of functional studies in cell models. Most notably, boosted by PTP1B's modulatory effect in diabetes, obesity and cancer, and LYP's involvement in multiple autoimmune diseases, we are bound to expect major advances regarding the development of specific, cell-penetrable small molecule inhibitors or agonists in the upcoming years, serving both the research community and public health.

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