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Review article

Recent advances in understanding the role of protein-tyrosine phosphatases in development and disease

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ABSTRACT

Protein-tyrosine phosphatases (PTPs) remove phosphate groups from tyrosine residues, and thereby propagate or inhibit signal transduction, and hence influence cellular processes such as cell proliferation and differentiation. The importance of tightly controlled PTP activity is reflected by the numerous mechanisms employed by the cell to control PTP activity, including a variety of post-translational modifications, and restricted subcellular localization. This review highlights the strides made in the last decade and discusses the important role of PTPs in key aspects of embryonic development: the regulation of stem cell self-renewal and differentiation, gastrulation and somitogenesis during early embryonic development, osteogenesis, and angiogenesis. The tentative importance of PTPs in these processes is highlighted by the diseases that present upon aberrant activity.

1. Introduction

The Hubrecht Institute has a long history of signal transduction research and how signalling affects developmental biology and stem cells. More than a quarter of a century ago, den Hertog cloned genes encoding PTPs and ever since, the function of PTPs in development and disease has been studied at the Hubrecht Institute. Recent progress in our understanding of PTP function resulting from research at the Hubrecht and elsewhere will be discussed here.

The phosphorylation and de-phosphorylation of proteins is an essential mechanism by which cellular signalling is regulated. Proteins are phosphorylated on tyrosine residues by protein-tyrosine kinases (PTKs) and de-phosphorylated by protein-tyrosine phosphatases (PTPs). PTPs have demonstrated to be important regulators of fundamental cellular processes, including proliferation, differentiation, and cell-cell adhesion.

Since the purification of the first PTP, PTP1B, in 1988 (Tonks et al., 1988), 125 PTPs have been identified in the human genome, constituting an enzyme superfamily divided into three groups: the classical PTPs, dual-specificity PTPs, and the low molecular weight PTPs (Alonso and Pulido, 2016; Tonks, 2013). The classical PTPs are further subdivided into receptor and non-receptor PTPs (Table 1 and Fig. 1). Each PTP holds one or two catalytic domains with a conserved signature motif (I/V)H**C**XAGXXR(S/T)G containing the catalytic cysteine (in **bold**) essential for catalysing the removal of a phosphate group from a phospho-tyrosine residue. The domains associated with the catalytic domains of PTPs are diverse and contribute to their specificity, regulation, and activity (Tonks, 2013). PTPs are often regulated by post-translational modifications, including phosphorylation and oxidation. For example, RPTPα and SHP2 are activated by phosphorylation of two serine residues and a tyrosine residue respectively (den Hertog et al., 2008). Most classical PTPs are inhibited by reversible oxidation of the cysteine residue in the catalytic site, and the unique micro-environment of the catalytic site determines the sensitivity of each PTP to oxidation-mediated inhibition (Östman et al., 2011). The activity of RPTPs is also regulated by dimerization, where activation or inactivation is determined by the exact orientation of the dimer. In addition, post-translational modifications alter the status of the RPTP dimer, and thereby influence catalytic activity (den Hertog et al., 2008).

In the last decades, research has revealed an important role for PTPs in development. Moreover, mutations in PTPs, which lead to aberrant PTP activity, result in disease or contribute to disease progression. This review will focus on the recent advances in understanding the role of PTPs in stem cell self-renewal and differentiation, gastrulation and somitogenesis during early embryonic development, osteogenesis, and angiogenesis. Finally, disease phenotypes correlated with mutations in PTPs will be discussed.

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Table 1
Family of classical PTPs divided into receptor PTPs and non-receptor, cytoplasmic PTPs.

	Human		Mouse		Zebrafish	
	GENE	PROTEIN	*Gene*	PROTEIN	*gene*	Protein
Cytoplasmic	*PTPN1*	PTP1B	*Ptpn1*	PTP1B	*ptpn1*	Ptp1b
	PTPN2	TC-PTP	*Ptpn2*	TC-PTP	*ptpn2a*	Tc-ptpa
					ptpn2b	Tc-ptpb
	PTPN3	PTPH1	*Ptpn3*	PTPH1	*ptpn3*	Ptp-h1
	PTPN4	PTP-MEG1	*Ptpn4*	PTP-MEG1	*ptpn4a*	Meg1a
					ptpn4b	Meg1b
	PTPN5	STEP	*Ptpn5*	STEP	*ptpn5*	Step
	PTPN6	SHP1	*Ptpn6*	SHP1	*ptpn6*	Shp1
	PTPN7	HE-PTP	*Ptpn7*	HE-PTP	*ptpn7*	He-ptp
	PTPN9	PTP-MEG2	*Ptpn9*	PTP-MEG2	*ptpn9a*	Meg2a
					ptpn9b	Meg2b
	PTPN11	SHP2	*Ptpn11*	SHP2	*ptpn11a*	Shp2a
					ptpn11b	Shp2b
	PTPN12	PTP-PEST	*Ptpn12*	PTP-PEST	*ptpn12*	Pest
	PTPN13	PTP-BAS	*Ptpn13*	PTP-BAS	*ptpn13*	Ptp-bas
	PTPN14	PTPD2/PEZ	*Ptpn14*	PTPD2/PEZ	*ptpn14*	Pez
	PTPN18	PTP-HSCF	*Ptpn18*	PTP-HSCF	*ptpn18*	Ptp-hscf
	PTPN20	PTPN20	*Ptpn20*	PTPN20	*ptpn20*	Ptpn20
	PTPN21	PTP-D1	*Ptpn21*	PTP-D1	*ptpn21*	Ptp-d1
	PTPN22	LYP	*Ptpn22*	LYP	*ptpn22*	Lyp
	PTPN23	HD-PTP	*Ptpn23*	HD-PTP	*ptpn23a*	Hd-ptpa
					ptpn23b	Hd-ptpb
Receptor	*PTPRC*	CD45	*Ptprc*	CD45	*ptprc*	Cd45
	PTPRM	RPTPμ	*Ptprm*	RPTPμ	*ptprm*	Rptpμ
	PTPRK	RPTPκ	*Ptprk*	RPTPκ	*ptprk*	Rptpκ
	PTPRT	RPTPρ	*Ptprt*	RPTPρ	*ptprt*	Rptpρ
	PTPRU	RPTPʎ	*Ptpru*	RPTPʎ	*ptprua*	Rptpʎa
					ptprub	Rptpʎb
	PTPRF	LAR	*Ptprf*	LAR	*ptprfa*	LARa
					ptprfb	LARb
	PTPRS	RPTPσ	*Ptprs*	RPTPσ	*ptprsa*	Rptpσa
					ptprsb	Rptpσb
	PTPRD	RPTPδ	*Ptprd*	RPTPδ	*ptprda*	Rptpδa
					ptprdb	Rptpδb
	PTPRB	RPTPβ	*Ptprb*	RPTPβ	*ptprb*	Rptpβ
	PTPRJ	DEP-1	*Ptprj*	DEP-1	*ptprja*	Dep-1a
					ptprjb	Dep-1b
	PTPRH	SAP1	*Ptprh*	SAP1	*ptprh*	Sap1
	PTPRO	RPTPO	*Ptpro*	RPTPO	*ptpro*	Rptpo
	PTPRQ	RPTPQ/PTPS31	*Ptpro*	RPTPQ/PTPS31	*ptprq*	Rptpq
	PTPRA	RPTPα	*Ptpra*	RPTPα	*ptpra*	Rptpα
	PTPRE	RPTPε	*Ptpre*	RPTPε	*ptprea*	Rptpεa
					ptpreb	Rptpεb
	PTPRZ	RPTPζ	*Ptprz*	RPTPζ	*ptprza*	Rptpζa
					ptprzb	Rptpζb
	PTPRG	RPTPγ	*Ptprg*	RPTPγ	*ptprga*	Rptpγa
					ptprgb	Rptpγb
	PTPRR	PC-PTP	*Ptprr*	PC-PTP	*ptprr*	Rptpr
	PTPRN	IA2	*Ptprn*	IA2	*ptprna*	Rptpna
					ptprnb	Rptpnb
	PTPRN2	IA2β	*Ptprn2*	IA2β	*ptprn2*	Rptpn2

PTP types are listed with gene and protein names for the vertebrate species covered in this review. Zebrafish experienced a genome duplication early in evolution, and duplicated PTPs are conventionally named “a” and “b”. Conventional nomenclature for each species is used and, unless referring to species specific studies, the text adheres to human nomenclature.

2. PTPs in the regulation of stem cell self-renewal and differentiation

Stem cells are able to proliferate and maintain their pluripotent capacity by self-renewal, and are at the origin of all cell types. In response to key stimuli, stem cells forfeit their pluripotency and differentiate into tissue specific cell lineages. PTPs are involved in the regulation of stem cell fate via various signalling pathways (reviewed in van Eekelen et al. (2010)). Here, we will discuss the importance of PTP regulation in stem cell fate and differentiation during development.

2.1. Embryonic stem cells

Several PTPs have been found to be important in determining embryonic stem cell (ESC) fate. SHP2, a cytoplasmic PTP encoded by the *PTPN11* gene and containing two SRC homology 2 (SH2) domains, is required in the initial stages of mouse and human embryonic development for the differentiation of ESCs into the three germ layers (Wu et al., 2009; Chan et al., 2003). In mice, it has been reported that SHP2 promotes ESC differentiation into hemangioblasts, multipotent precursor cells that differentiate into cells of the hematopoietic cell lineage and endothelial cells (Chan et al., 2003). SHP2 has a crucial role in adipogenesis, as SHP2 deficiency suppresses differentiation of ESCs to adipocytes (He et al., 2013), and of pre-adipocytes to adipocytes (Tao et al., 2016).

Phosphatase and Tensin Homolog (PTEN) belongs to the PTP superfamily and is a dual specificity phosphatase with roles in cell motility, metabolism, and polarity (Song et al., 2012). PTEN negatively

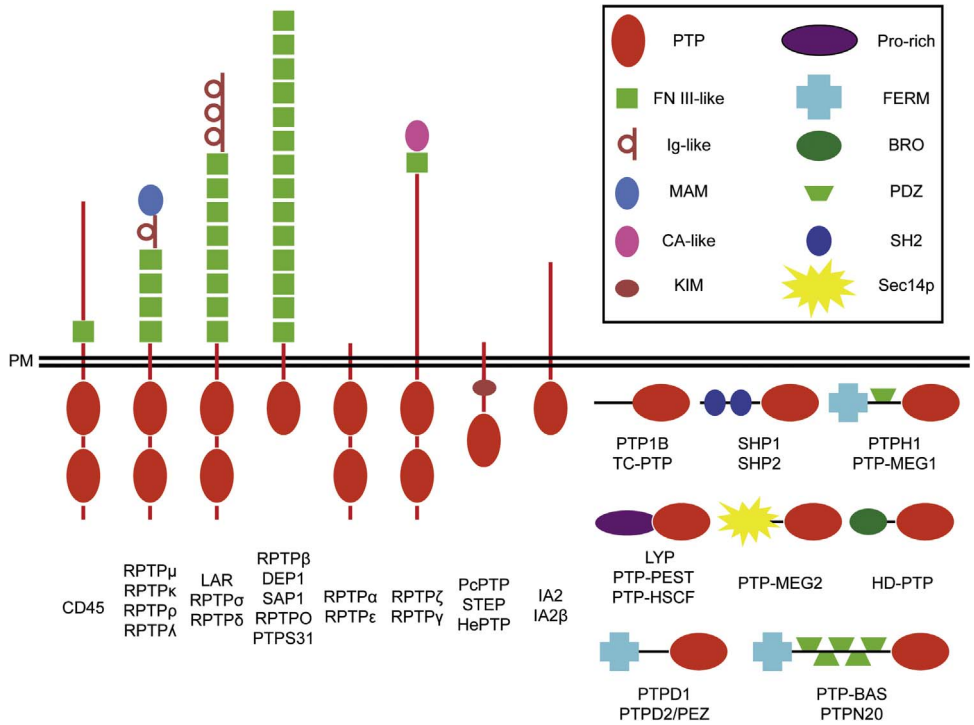

Fig. 1. Family of classical protein-tyrosine phosphatases divided into receptor PTPs and non-receptor, cytoplasmic, PTPs. PTPs are clustered based on their functional domains, indicated in the boxed legend (top right).

regulates AKT, a major instigator of cellular processes such as proliferation, migration, and cell survival. PTEN de-phosphorylation of phosphatidylinositol 3,4,5-triphosphate (PIP3) to phosphatidylinositol 4,5-bisphosphate (PIP2) inhibits the phosphorylation cascade that activates AKT. Knockdown of PTEN in human ESCs results in increased proliferation, survival, and self-renewal. In addition, ESC differentiation into neuro-ectoderm, rather than cells of the other germ layers, increases (Alva et al., 2012). This indicates that PTEN is not solely important for ESC growth, but is also required for proper differentiation of ESCs into all three lineages.

Protein-tyrosine phosphatase 1B (PTP1B), encoded by the *PTPN1* gene, has an important role in determining the mesendodermal fate of ESCs. Overexpression of PTP1B results in ESC differentiation towards a mesendodermal fate, whilst PTP1B knockdown leads to differentiation towards a neuro-ectodermal fate (Matulka et al., 2013).

2.2. Hematopoietic stem cells

PTPs are important for the regulation of hematopoietic stem cells (HSCs). SHP2 is essential for the maintenance of the HSC pool and differentiation into lineages of the hematopoietic system. Loss of *Ptpn11* in the HSCs of mice leads to loss of almost all HSCs and progenitors of hematopoietic cell lineages, and mortality within 6–8 weeks post birth (Chan et al., 2011). Whilst knockdown of SHP2 in human $CD34^+$ cells results in reduced proliferation and differentiation into hematopoietic cell lineages in vivo, gain-of-function mutations in SHP2 result in aberrant differentiation and proliferation profiles of HSCs (Chan et al., 2009; Dong et al., 2016; Li et al., 2012; Xu et al., 2010).

In contrast, T-cell PTP (TC-PTP), encoded by *PTPN2* and so named because it was originally cloned from T-cells and is highly expressed in cells of the hematopoietic system, negatively regulates HSC self-renewal and differentiation. Knockout of *Ptpn2* or pharmacological inhibition of TC-PTP increases the number of stem and progenitor cells in mice (Bourdeau et al., 2013). RPTPσ, encoded by *PTPRS*, also negatively regulates HSC self-renewal because transplanting $Ptprs^{-/-}$ bone marrow cells in mice increases HSC regeneration (Quarmyne et al., 2015).

2.3. Neuronal stem cells

In addition to ESCs and HSCs, SHP2 is vital to the proliferation and self-renewal of neuronal stem cells (NSCs), neuronal migration, and neurite outgrowth. SHP2 deficient NSCs have severely decreased neuron and oligodendrocyte differentiation, and mice suffer postnatal lethality (Ke et al., 2007; Huang et al., 2012). In contrast, neurite outgrowth is negatively suppressed by RPTPσ, since neurite outgrowth is enhanced in RPTPσ deficient neurons (Kirkham et al., 2006).

2.4. Mesenchymal stem cells

Leukocyte common antigen-related RPTP (LAR), RPTPQ, and SHP1, encoded by *PTPRF*, *PTPRQ*, and *PTPN6* respectively, are all involved in differentiation of mesenchymal stem cells (MSCs) into adipocytes. Knockdown of LAR increases adipogenesis, whereas overexpression of LAR decreases adipogenic differentiation (Kim et al., 2009). Similarly, RPTPQ overexpression decreases MSC differentiation into adipocytes (Jung et al., 2009).

Like LAR and RPTPQ, SHP1 negatively regulates MSC differentiation into adipocytes. SHP1 modulates Wnt/β-catenin signalling to express transcription factors needed for differentiation of MSCs into osteoblasts, shifting the balance between adipogenesis and osteogenesis in favour of MSC differentiation to an osteoblast fate (Jiang et al., 2016). SHP1 deficient mice therefore have increased adipogenic markers and decreased osteogenic markers, accompanied by an increase in adipose tissue and a reduction in bone mass.

3. Role of PTPs in gastrulation and somitogenesis during early embryonic development

During early embryonic development, gastrulation is the process where the single-layered blastula is reorganized to form the three primary germ layers: endoderm, ectoderm, and mesoderm, that will eventually give rise to all organs. Gastrulation starts with emboly, the

process where a layer of cells migrates and converges into the interior of the embryo forming an underlying layer. Following emboly, cells extend along one axis and converge (narrow) along a perpendicular axis in convergence and extension (C & E) movements. Epiboly, the thinning and spreading of cell layers, mostly of ectoderm, that will finally cover the whole embryo, occurs in parallel (Solnica-Krezel and Sepich, 2012). After gastrulation, the ectoderm will form the epidermis and nervous system, and the endoderm the epithelium of the digestive system, organs associated with this system, and the respiratory system. The mesodermal layer will give rise to somites on either side of the neural tube, which will eventually give rise to blood and blood vessels, the skeletomuscular system, connective tissue, and internal organs (Kiecker et al., 2016). A substantial number of PTPs have been identified as important regulators of development. The exact timing when each PTP acts, and on which signalling pathways, for normal development to occur still needs to be mapped. Here, we provide an overview of the recent research investigating the role of PTPs in early embryonic development.

3.1. Cytoplasmic PTPs

PTEN is undoubtedly important to normal development as *Pten* knockout mice suffer early embryonic lethality (Cristofano et al., 1998; Suzuki et al., 1998; Stambolic et al., 1998). Zebrafish contain two *pten* genes, *ptena* and *ptenb*, that are both highly homologous to human *PTEN*. Zebrafish deficient for both Ptena and Ptenb are embryonic lethal by 5–7 days post fertilization. Pten deficient zebrafish are characterized by smaller eyes that are set wider apart, a shortened body axis, an enlarged head, and heart oedema (Faucherre et al., 2008). Increased Akt phosphorylation, which enhances proliferation and cell survival, in Pten deficient zebrafish is the underlying cause of their phenotype, as treatment with a PI3K inhibitor can rescue the abnormalities. Further studies in mice demonstrated that PTEN is important for the formation of the anterior-posterior axis, by regulating migration of anterior visceral endoderm. Mouse embryos lacking PTEN in the epiblast demonstrate defects in migration of the embryonic layers, suggesting an important role for PTEN in migration of endoderm and mesoderm after gastrulation (Bloomekatz et al., 2012).

Overexpression of Ptp1b in zebrafish induces lethal defects in gastrulation and somitogenesis (Van Der Sar et al., 1999). Later studies in *Drosophila* emphasized the importance of correct tyrosine phosphorylation of proteins in early embryonic development. Lack of PTP61F, the *Drosophila* gene that encodes both the PTP1B and TC-PTP orthologues, results in reduced fecundity and life span. Reducing PTP61F expression by RNAi results in eye overgrowth and thickened and deformed veins in the wings, and overexpression of PTP61F impairs growth (Buszard et al., 2013). PTP1B and TC-PTP regulate insulin receptor (IR) signalling in non-redundant and distinct ways. Importantly, whereas loss of PTP1B results in enhanced MAPK signal transduction, loss of TC-PTP does not affect insulin stimulated MAPK signalling in mouse embryonic fibroblasts (Galic et al., 2005; van Vliet et al., 2005; Blanquart et al., 2010). Of note is that MAPK signal transduction induced by other ligands, such as tumour necrosis factor (TNF), is enhanced by loss of TC-PTP. In *Drosophila*, PTP61F acts as a negative regulator of MAPK signal transduction (Tchankouo-Nguetcheu et al., 2014), suggesting a similar role as PTP1B. However, further research is needed to determine if the observed phenotype in *Drosophila* is due to aberrations in MAPK signalling, and hence that the defects can be ascribed to the orthologue of PTP1B, TC-PTP or both.

PTP-PEST, encoded by the *PTPN12* gene, is a phosphatase containing PEST-sequences, and is mostly expressed by cells of the hematopoietic system. Gastrulation occurs normally in PTP-PEST deficient mouse embryos, however after E9.5 several developmental defects such as growth retardation, a smaller cardiac region, caudal development arrest, and disrupted somite formation are observed. These mice also lack the formation of a fetal liver and reach embryonic lethality between E9.5 – E10.5. The precise role of PTP-PEST in embryonic development needs to be elucidated, but these results imply that PTP-PEST is more important in later embryonic development (Sirois et al., 2006). As PTP1B appears to affect early embryonic development, and that PTP-PEST appears to affect later stages, there is evidence that specific PTPs may regulate distinct stages of embryonic development.

In early mouse development, SHP2 deficiency leads to embryonic lethality due to aberrant ERK signalling causing increased apoptosis in trophoblast stem cells (Yang et al., 2006). Similarly, Shp2 deficient zebrafish are embryonic lethal at 6–7 days post fertilization and display a reduced body axis, heart and eye oedema, and craniofacial defects (Bonetti et al., 2014).

3.2. Receptor PTPs

The *C. elegans* orthologue of the mammalian RPTP, LAR, has two isoforms, PTP-3A and PTP-3B, and loss-of-function results in mild, but lethal, gastrulation defects (Harrington et al., 2002; Hartin et al., 2015). Mutations in Syndecan-1 (SDN-1), a heparin sulphate proteoglycan with which members of the LAR family interact, lead to movement and egg-laying defects, and low levels of lethality. As mutations in both PTP-3B and SDN-1 result in severe defects during gastrulation and arrested embryogenesis during epiboly, PTP-3B and SDN-1 may have overlapping functions during early embryonic development (Hartin et al., 2015). PTP-3B likely acts in Wnt signalling during embryonic development as knockdown of the Wnt ligand LIN-44 in PTP-3B mutants did not result in synergistic phenotypes. Ongoing research aims to explore the mechanism by which SDN-1, PTP-3B, and LIN-44 affect gastrulation.

In early mouse embryogenesis, knockout of *Ptprs* and *Ptprf* leads to urogenital and craniofacial defects, such as smaller lower jaws, cleft palates, and no nasal capsules, resulting in a phenotype similar to Pierre-Robin Sequence (Uetani et al., 2009; Stewart et al., 2013). This phenotype in RPTPσ and LAR deficient mice is thought to be due to decreased proliferation of mandibular cells and defective patterning of mandibular bone and cartilage, as a result of altered regulation of the BMP and Wnt signalling pathways (Stewart et al., 2013).

In *Drosophila* a potential orthologue of the human stomach-associated SAP1 PTP, PTP52F, has an essential role in the transition from larva to pupa, as mutations lead to mortality at the post pupal stage (Santhanam et al., 2013).

In Zebrafish, Rptpα, Rptpε, Ptp-bas, and Ptpn20 are all essential for gastrulation. Knockdown of these four PTPs in zebrafish embryos induces phenotypes that correlate with defects in C & E movements and epiboly cell migration, formation of oedemas around the yolk and heart upon Rptpα knockdown, and a shortened body axis upon both Rptpα and Rptpε knockdown (van Eekelen et al., 2010, 2012). Rptpα and Rptpε, encoded by *ptpra* and *ptpre* respectively, act upstream of kinases Fyn and Yes, activating RhoA, which in turn activates Rock, ultimately resulting in cell polarization. In contrast, Ptpn20 and Ptp-bas, encoded by *ptpn20* and *ptpn13* respectively, signal to reduce RhoA activity. This balance of positive and negative regulation of RhoA is essential for cell polarization, which in turn determines proper C & E movements and epiboly cell migration.

4. PTPs in bone formation

Osteoblasts and osteoclasts are important cells in the maintenance of bone matrix, and have opposing activities to constantly remodel bone. Osteoblasts form a specialized unit of connected cells, called the osteon, which synthesize essential cross-linked collagen and a calcium- and phosphate-based mineral, called hydroxyapatite, for the formation and mineralization of bone in a process known as osteogenesis (Fratzl and Weinkamer, 2007). Osteoclasts, multi-nucleated cells formed through the fusion of monocyte-macrophage precursor cells, digest

bone in the process known as bone resorption. Differentiation of precursor cells into osteoclasts is regulated by receptor activator of nuclear factor kappa-B ligand (RANKL) and macrophage colony-stimulating factor (M-CSF) (Mellis et al., 2011). When attached to bone, osteoclasts form adhesion structures called podosomes, which are densely packed into a ring referred to as the sealing zone. Osteoclasts then release acid and collagenase to demineralise and degrade the bone matrix. The podosome core is composed of filamentous actin and its formation is regulated by a multi-protein branching machinery that consists of cortactin, Wiskott-Aldrich syndrome protein (WASP), WASP interacting protein (WIP), and the Arp2/3 complex. When integrins from osteoclasts bind to ligands in the bone, they recruit proteins involved in podosome dynamics and organization, such as PYK2 and SRC (Mellis et al., 2011; Georgess et al., 2014). Knockout of *Csk* in mice leads to osteopetrosis, i.e. increased bone density, due to reduced bone resorption (Marzia et al., 2000), underpinning the importance of well regulated SRC activity during bone formation.

4.1. Cytoplasmic PTPs

In 1995, Ari Elson discovered a cytoplasmic form of PTPε encoded by the *PTPRE* gene (Elson and Leder, 1995), which is referred to as cyt-PTPε and plays an important role in osteogenesis. Lack of cyt-PTPε increases the trabecular bone mass of young adult female mice, as a consequence of reduced bone resorption. cyt-PTPε deficient mice show reduced numbers of osteoclasts in contact with bone, but no reduction in total osteoclast number, suggesting impaired functioning of osteoclasts (Finkelshtein et al., 2014; Chiusaroli et al., 2004). In addition, podosomes have a perturbed internal structure, cellular organization, and reduced stability, presumably because of dysregulated SRC, PYK2, RHO, and RAC activity, which are involved in integrin signalling pathways required for podosome formation. cyt-PTPε is activated by SRC following integrin signalling and maintains SRC activity via a positive feedback loop (Granot-Attas et al., 2009; Levy-Apter et al., 2014). Since RPTPα is closely related tot PTPε, it has been suggested that RPTPα performs a similar role in osteoclast function. However, mice lacking RPTPα do not show any changes in bone mass, function of osteoclasts, or podosome organization and function (Finkelshtein et al., 2014).

PTP-PEST is associated with SRC, PYK2, proline-serine-threonine phosphatase-interacting protein (PSTPIP), and WASP in podosomes. PTP-PEST dephosphorylates SRC at Y527, allowing SRC-mediated phosphorylation and activation of WASP and Cortactin, ultimately resulting in formation of the sealing zone (Chellaiah et al., 2007; Chellaiah and Schaller, 2009). PTP-PEST also regulates osteoclast function through dephosphorylation of PYK2, leading to PYK2 inactivation and reduced osteoclast activity, followed by re-organization of the sealing zone (Eleniste et al., 2012). Furthermore, monocyte-macrophage fusion, required for osteoclast formation, is dependent on delicate PTP-PEST controlled PYK2 phosphorylation; both PYK2 hyperphosphorylation, as a result of PTP-PEST deficiency, and PYK2 inhibition lead to a fusion defect (Rhee et al., 2013). PTP-PEST also has an important role in osteoblasts because PTP-PEST increases differentiation of pre-osteoblasts to osteoblasts and has been shown to decrease osteoblast migration in vitro, by inactivating the GTPase Dynamin (Eleniste et al., 2014).

SHP2 deficient mice suffer such severe impairment of osteogenesis that they develop osteopetrotic bones and develop cartilage abnormalities (Bauler et al., 2011; Zhou et al., 2015). However, how SHP2 regulates osteogenesis in mice is under debate. Bauler *et al.* suggest that osteogenesis is impaired in SHP2 deficient mice as a result of a lack of AKT activation required for the proliferation and survival of osteoclast precursor cells (Bauler et al., 2011). In contrast, Zhou *et al.* demonstrate that SHP2 deletion has little effect on the proliferation and survival of osteoclast precursor cells in the presence of M-CSF and RANKL, and instead propose that SHP2 is important in pre-osteoclast fusion by responding to RANKL signalling (Zhou et al., 2015). Whichever pathway SHP2 acts on, it is likely in response to, or in an effort to regulate, SRC activity.

4.2. Receptor PTPs

RPTPO, encoded by the *PTPRO* gene, is an osteoclast transmembrane PTP and mainly expressed in hematopoietic cells, such as B-lymphocytes, osteoclasts, and their precursor cells. RPTPO has been demonstrated to be important for the differentiation and activity of osteoclast-like cells derived from a lymphoblast cell line (Amoui et al., 2004), and likely regulates osteoclast activity, migration, and survival through a SRC-dependent manner (Lau et al., 2006; Amoui et al., 2007). Overexpression of RPTPO maintains increased osteoclast activity as a result of reduced apoptosis, whereas knockdown, or overexpression of inactive RPTPO leads to increased apoptosis and reduced osteoclast activity (Amoui et al., 2007). Furthermore, overexpression of RPTPO in osteoclast-like cells decreases bone density and mass in young adult male mice due to increased bone resorption (Sheng et al., 2009). This is in stark contrast to the effect of knocking-out the aforementioned cyt-*Ptpε* in female mice. Since overexpression of RPTPO or knockout of cyt-*Ptpε* results in the same phenotype in male or female mice respectively, it could be that sex-dependent hormone signalling in osteoclasts is affected by the activity of each PTP and that both converge on the same pathway. In parallel to activation of SRC, RPTPO also increases the bone resorption activity of osteoclasts independently of SRC by inactivating EPHA4, a negative regulator of osteoclast activity (Lau et al., 2015).

5. PTPs in angiogenesis

Blood vessel formation is regulated by VEGF mediated signalling through the VEGF tyrosine kinase receptor family, consisting of VEGF receptor (VEGFR) 1, 2 and 3, of which VEGFR2 mediates the major actions. Stimulation with VEGF activates VEGFR2 signalling that induces VE-Cadherin tyrosine phosphorylation (Esser et al., 1998). Hence, it comes as no surprise that PTPs have a critical role in angiogenesis. New blood vessels are formed by sprouting of endothelial tip cells from pre-existing blood vessels towards an angiogenic stimulus, such as VEGF. Tip cells contain filopodia that have many VEGFR2 receptors to 'sense' the VEGF gradient and migrate towards the source of this gradient. The stalk cells that are positioned next to tip cells proliferate upon tip cell movement, causing the blood vessel to elongate. This vessel-branching model of tip cell migration and stalk cell proliferation is under the control of NOTCH signalling. The permeability and stability of blood vessels is regulated by intercellular junctions, and vascular endothelial (VE)-Cadherin is the major determinant of blood vessel wall integrity, changing the activity or presence of VE-Cadherin at cell-cell contacts will affect the permeability and stability of the blood vessel walls. Loss of VE-Cadherin, therefore, does not lead to inhibition of angiogenesis, but to defects in vessel remodelling and cell-cell junction integrity (Carmeliet and Jain, 2011).

5.1. Cytoplasmic PTPs

PTP1B overexpression in endothelial cells inhibits VEGF mediated phosphorylation of VEGFR2 and reduces VE-Cadherin tyrosine phosphorylation, resulting in reduced proliferation and migration, stabilized cell-cell contacts between endothelial cells, and disrupted angiogenesis (Nakamura et al., 2008; Lanahan et al., 2014). PTP1B knockout primary mouse endothelial cells display enhanced VEGF induced MAPK and VEGFR2 phosphorylation, and PTP1B deficient mice and leptin deficient obese mice (ob/ob mice), in which PTP1B is inhibited, demonstrate enhanced angiogenesis (Lanahan et al., 2014; Zhang et al., 2015). Hence, PTP1B negatively regulates angiogenesis, and recent research implicates PTP1B in a Calpain-dependent negative

feedback mechanism of VEGF induced angiogenesis (Zhang et al., 2017). Yet, it remains to be determined if PTP1B acts on VEGFR2 directly.

In contrast to PTP1B, PTP-PEST positively regulates angiogenesis by stimulating endothelial cell migration and vascular development. Loss of *Ptpn12* in mice leads to a reduced number of endothelial cells in the aorta and yolk sac, fewer, but larger vessels, and mortality between E9.5 and E10.5 (Sirois et al., 2006). Moreover, when PTP-PEST deficiency is limited exclusively to endothelial cells, these cells show a decreased adhesion to collagen and fibronectin, and reduced migration, with the resulting perturbation in angiogenesis leading to embryonic lethality (Souza et al., 2012). PTP-PEST has been shown in vitro to contribute to integrin-mediated adhesion and migration of endothelial cells, through the dephosphorylation of CAS, Paxillin, and PYK2.

Zebrafish deficient for Ptena and Ptenb, alongside elevated phospho-Akt levels, have upregulated levels of Vegfaa, and subsequently demonstrate hyper-vascularization (Choorapoikayil et al., 2013). It is the lipid phosphatase activity of Pten, rather than the protein phosphatase activity, and proper spatial expression of Pten that are essential for regulation of angiogenesis and the development of blood vessels in zebrafish. Pten mutated at lysine 13 to an arginine has enhanced plasma membrane localization in mammalian and zebrafish cells, and rescues the hyper-vascularization phenotype (Stumpf et al., 2016; Stumpf and Den Hertog, 2016). However, stalled intersegmental vessels are observed during development when this Pten mutant is expressed in wild-type zebrafish embryos, suggesting that sufficient, and not excess, membrane localized Pten is required for proper angiogenesis. In mice, PTEN is important for the regulation of stalk cell proliferation, and NOTCH induced PTEN expression results in cell cycle arrest, and hence proper formation of blood vessels (Phng and Gerhardt, 2009). Overexpression of PTEN reduces endothelial cell proliferation and vascular density, and aberrant angiogenesis is observed when PTEN activity is reduced (Serra et al., 2015), suggesting a fine balance of PTEN activity is required for proper blood vessel formation. One of the limitations to understanding the exact role of PTEN in angiogenesis during normal embryonic development is that knowledge pertaining to angiogenesis has mostly been inferred from tumour angiogenesis. Tumours often exhibit enhanced angiogenesis but, also, PTEN is a tumour suppressor gene that is often mutated in tumours (Fang et al., 2007; Ma et al., 2009; Tian et al., 2010). It is therefore difficult to appreciate the role of PTEN in angiogenesis. Nevertheless, it is evident from studies to date that PTEN has a crucial role in angiogenesis and is a factor that ensures proper blood vessel development.

5.2. Receptor PTPs

Mice deficient for RPTPβ, also known as vascular endothelial PTP (VE-PTP) because it is exclusively expressed in endothelial cells, display severe vascular remodelling defects, and reach mortality by E10. The mice are not able to form a hierarchical branched vascular network, indicating that RPTPβ is not necessary at the initial stages of blood vessel formation, but for the maintenance of blood vessels. In addition, RPTPβ deficient mice have defects in heart formation (Bäumer et al., 2006; Dominguez et al., 2007). RPTPβ, encoded by the *PTPRB* gene, maintains blood vessels by binding VE-Cadherin and ensuring optimal VE-Cadherin function, and thereby endothelial cell-cell adhesion. Furthermore, RPTPβ cooperates with integrins and RAS to induce endothelial cell spreading and migration. In the presence of fibronectin, RPTPβ promotes the formation of filopodia and lamellipodia, and induces cell migration. These effects are abolished when SRC family kinases are inhibited, suggesting that integrin-induced activation of SRC family kinase signalling is important for RPTPβ induced endothelial cell spreading and migration (Mori et al., 2010). VEGF stimulation induces dissociation of RPTPβ from VE-Cadherin, and, due to the loss of endothelial cell-cell adhesion, results in increased cell layer permeability and diapedesis of leukocytes (Nottebaum et al., 2008; Broermann et al., 2011). Although proximity ligation assays suggested a direct association of RPTPβ with VEGFR2 (Mellberg et al., 2009), the mechanism is proposed to be mediated by PYK2 activation of RPTPβ substrates. Substrate binding to RPTPβ would then induce a conformational change resulting in detachment of the extracellular domain of RPTPβ from VE-Cadherin (Vockel and Vestweber, 2013). RPTPβ is also implicated in orchestrating vessel remodelling independent of VE-Cadherin via TIE-2, a receptor tyrosine kinase that functions downstream of vascular growth factor Angiopoietin. When RPTPβ is inhibited, TIE-2 dissociates and is activated, driving endothelial cell proliferation, and stabilizing endothelial cell-cell junctions (Winderlich et al., 2009; Frye et al., 2015). Since TIE-2 also determines blood vessel size, its activity is restricted by RPTPβ to ensure proper blood vessel formation and size (Winderlich et al., 2009). Interestingly, the stimulation of VE-Cadherin by active RPTPβ and the activation of TIE-2 upon RPTPβ inhibition, is a feedback mechanism that ensures endothelial cell-cell integrity: active RPTPβ inhibits TIE-2 and stimulates endothelial cell-cell adhesion via VE-Cadherin, whereas inactive RPTPβ cannot activate VE-Cadherin, but endothelial cell-cell adhesions are still stabilised by the now active TIE-2 (Frye et al., 2015).

Density Enhanced PTP (DEP-1), also known as CD148, is a glycoprotein encoded by *PTPRJ*, and found at the cell surface. It is closely related to RPTPO, RPTPQ and RPTPβ, and consists of a single PTP domain and an extracellular domain consisting of fibronectin III repeats (Fig. 1). DEP-1 deficient mice have impaired VEGF induced formation of functional capillaries, and the capillaries that do form are shorter and less dense (Fournier et al., 2016). This results in a phenotype, similar to PTP-PEST deficient mice, characterized by impaired angiogenesis, enlarged vessel formation, disruption of branching and vascular remodelling, and embryonic lethality by E11.5 (Takahashi et al., 2003). DEP-1, encoded by the *PTPRJ* gene, functions to maintain endothelial cell permeability by activating SRC in response to VEGF, and SRC subsequently phosphorylates Cortactin and VE-Cadherin (Fournier et al., 2016; Spring et al., 2014, 2012). Depletion of DEP-1 leads to a reduction of VEGF induced phosphorylation of VE-Cadherin, thus maintaining cell-cell junction integrity, and to decreased Cortactin phosphorylation, resulting in impaired vascular branching and invasion of endothelial cells. Interestingly, increasing DEP-1 activity, using a bivalent antibody, also impairs endothelial cell proliferation and angiogenesis (Takahashi et al., 2006). And consistent with this, overexpression of DEP-1 inhibits proliferation, migration, and formation of capillary-like structures of primary endothelial cells (Brunner et al., 2011). In addition, DEP-1 overexpression promotes VEGF induced cell layer permeability in cultured human umbilical vein endothelial cells (HUVECs) (Spring et al., 2012). Taken together, these studies confirm the importance of regulating DEP-1 activity for angiogenesis.

6. PTPs in disease

Recent and ongoing research continues to highlight the importance of PTPs in development, and it is therefore not surprising that PTPs contribute to a plethora of human diseases and disorders (Hendriks WJAJ et al., 2013; WJAJ and Pulido, 2013). For some PTPs it is still unclear what their role is in disease. *PTPN22*, for example, has been implicated in type 1 diabetes (T1DM) and breast cancer, but little follow up work has been done and mutations in *PTPN22* are even predicted to be over-represented in breast cancer (Qu et al., 2005; Sharp et al., 2015; Cerosaletti and Buckner, 2012; Muzny et al., 2012). PTPs are often considered the guardians of kinase driven phosphorylation cascades, and loss-of-function is fittingly associated with enhanced signal transduction, as observed in many cancers (Östman et al., 2006). However, there are numerous examples where PTP activity is not

inhibiting, and is required to stimulate signal transduction and promote cellular responses. Of 21 RPTPs, 20 are mutated in multiple cancers and RPTPs more often experience a gene amplification rather than a gene loss (Du and Grandis, 2015). However, as the most common mechanism of genetic modification of RPTPs is mutation, further research will have to be done to determine if these are activating or silencing mutations, or rather neutral mutations acquired during the tumorigenic process. Both too little or too much PTP activity may lead to disease, and the role of each PTP, whether it is limiting signalling or promoting signalling, may very well be context (i.e. cell type) dependent. For example, a gain-of-function mutation in SHP2 is found in juvenile myelomonocytic leukemia (JMML) patients (Loh et al., 2003), but in hepatocellular carcinogenesis SHP2 acts as a tumour suppressor (Bard-Chapeau et al., 2011).

6.1. *SHP2 (*PTPN11*)*

A large number of mutations, activating and inactivating, have been identified in SHP2 in association with human disease (Tajan et al., 2015). Mutations in SHP2 that increase or decrease its catalytic activity are associated with Noonan syndrome (NS) and Noonan syndrome with multiple lentigines (NS-ML, formerly LEOPARD syndrome), respectively. Individuals with NS and NS-ML have characteristic cranio-facial abnormalities, heart defects, short stature, and an increased risk of developing JMML. Interestingly, NS is caused by mutations in SHP2 that activate SHP2 catalytic activity (e.g. D61G), whereas NS-ML is caused by mutations in SHP2 that strongly reduce catalytic activity (e.g. A461T). Recently, it was demonstrated that the NS-ML SHP2 mutants Y279C, A461T, G464A, T468M, R498L, Q506P, and Q510E do indeed have impaired catalytic activity but also display structural properties typical of activating mutations, which could explain the similar symptoms presented by individuals with NS and NS-ML (Yu et al., 2014, 2013). The SHP2 mutant proteins from NS and NS-ML patients appear to have an increased tendency to adopt an open conformation and interact longer with scaffolding adaptors, prolonging substrate turnover, and thereby compensate for the reduced phosphatase activity (Yu et al., 2014, 2013). The exact mechanism by which mutated SHP2 induces NS and NS-ML is poorly understood, but aberrant ERK phosphorylation and signalling is a likely consequence of unbalanced SHP2 activity. Enhanced SHP2 activity is associated with systemic lupus erythematosus and, recently, Wang et al. (2016) demonstrated that inhibition of SHP2 reduced the autoimmune response thought to underlie the disease. SHP2 inhibition normalized ERK/MAPK signalling and reduced proliferation of cultured human lupus T cells. In contrast, mutations in SHP2 that lead to a loss-of-function result in a myeloproliferative disorder, because of enhanced proliferation and decreased apoptosis of hematopoietic stem cells (Xu et al., 2010). This may be because of pro-inflammatory cytokines, secreted by monocytes recruited to the stem cell micro-environment of SHP2 deficient hematopoietic stem cells, having detrimental effects on the homeostasis of the hematopoietic stem cell population (Dong et al., 2016).

6.2. *PTP1B (*PTPN1*) and RPTPσ (*PTPRS*)*

Type 2 diabetes (T2DM) is associated with mutations in *PTPN1* and *PTPRS*. Negative regulation of insulin receptor (IR) signalling by PTP1B is well established (reviewed by Bakke and Haj (2015)), and *Ptpn1* knockout mice fed a high fat diet are resistant to weight gain compared to control mice (Elchebly et al., 1999). PTP1B deficiency also increases insulin sensitivity and glucose uptake in insulin receptor substrate-2 (IRS-2) deficient mice, suggesting PTP1B inhibits IR signalling by acting on or downstream of IRS-2 (Xue et al., 2007). Indeed, PTP1B depletion improves insulin sensitivity and glucose tolerance, as well as decreasing the occurrence of diabetes development, in mice deficient for IR and IRS-1 (González-Rodríguez et al., 2010). However, mice lacking PTP1B also display an accentuated pro-inflammatory response and compromised macrophage viability (Través et al., 2014), indicating care should be taken in ongoing clinical trials. Variations in the *PTPRS* gene are associated with T2DM development (Långberg et al., 2007), and, similar to PTP1B, RPTPσ deficient mice have a reduced body mass and increased insulin sensitivity (Chagnon et al., 2006).

6.3. *TC-PTP (*PTPN2*)*

Development of T1DM is associated with mutations in *PTPN2*, which negatively regulates IR signalling in concurrence with PTP1B. Lack of TC-PTP leads to multiple cellular defects related to T1DM, including increased β-cell apoptosis, altered β-cell function, and decreased self-antigen tolerance due to increased T-cell receptor signalling and dysregulation of FOXP3 T-regulatory cells (Sharp et al., 2015; Cerosaletti and Buckner, 2012). Mutations in *PTPN2* also influence susceptibility to Crohn's disease (CD) (Franke et al., 2010; Glas et al., 2012; Marcil et al., 2013). CD development is driven by epithelial barrier defects and a dysfunctional immune response, and TC-PTP plays a role in preserving the epithelial barrier function by regulating the inflammatory response (Scharl et al., 2009; McCole, 2012). In addition, TC-PTP deficiency leads to impaired autophagosome formation, resulting in defective bacterial clearance of intestinal cells and increased apoptosis in intestinal epithelial cells (Scharl et al., 2012). Moreover, mutations in *PTPN2* lead to aberrant T-cell dysfunction, and consequently increased intestinal inflammation and dysbiosis (microbial imbalance) (Spalinger et al., 2015). Both autophagy and T-cell dysfunctions are also found in CD patients, implicating TC-PTP.

6.4. *PTEN (*PTEN*)*

Mutations in *PTEN* cause PTEN hamartoma tumour syndromes (PHTS), rare inherited syndromes characterized by hamartomas in tissues originating from all three germ layers. PHTS encompasses four distinct syndromes: Proteus syndrome, Proteus-like syndrome, Cowden syndrome, and Bannayan-Riley-Ruvalcaba syndrome, of which Cowden syndrome is the most prevalent (Blumenthal and Dennis, 2008). PHTS are consistent with mutant zebrafish lacking three of four pten alleles, that develop hemangiosarcomas (Choorapoikayil et al., 2012). Not only the lipid phosphatase activity of PTEN, which suppresses Akt activity, but also the protein phosphatase activity of PTEN, important in cell cycle arrest and inhibition of cell invasion, has been shown to have a tumour suppressive function (Hollander et al., 2011). Loss-of-function mutations in *PTEN*, which lead to increased AKT activation, IR signalling, and thus insulin sensitivity, are also associated with an increase in adiposity and obesity (Pal et al., 2012). Constitutive AKT activation also corresponds with the development of autism spectrum disorders (ASDs), extensively reviewed in other publications (Zhou and Parada, 2012; Lv et al., 2013; Tilot et al., 2015). ASDs are neurodevelopmental disorders characterized by communication deficits, impaired social interactions, and restricted and repetitive behaviour. PTEN is involved by influencing different cellular processes, for example deletion of *Pten* in the hippocampal adult neural stem cells of mice results in an increased proliferation and differentiation of these stem cells, leading to depletion of the stem cell pool, and development of hypertrophied neurons. These mice display seizure activity, macrocephaly, and impairments in social interactions (Amiri et al., 2012).

7. Conclusion and future perspectives

In conclusion, PTPs have diverse roles in various biological processes, as represented schematically in Fig. 2. This schematic is not comprehensive and future research on the role of PTPs in development will undoubtedly lead to the inclusion of more PTPs

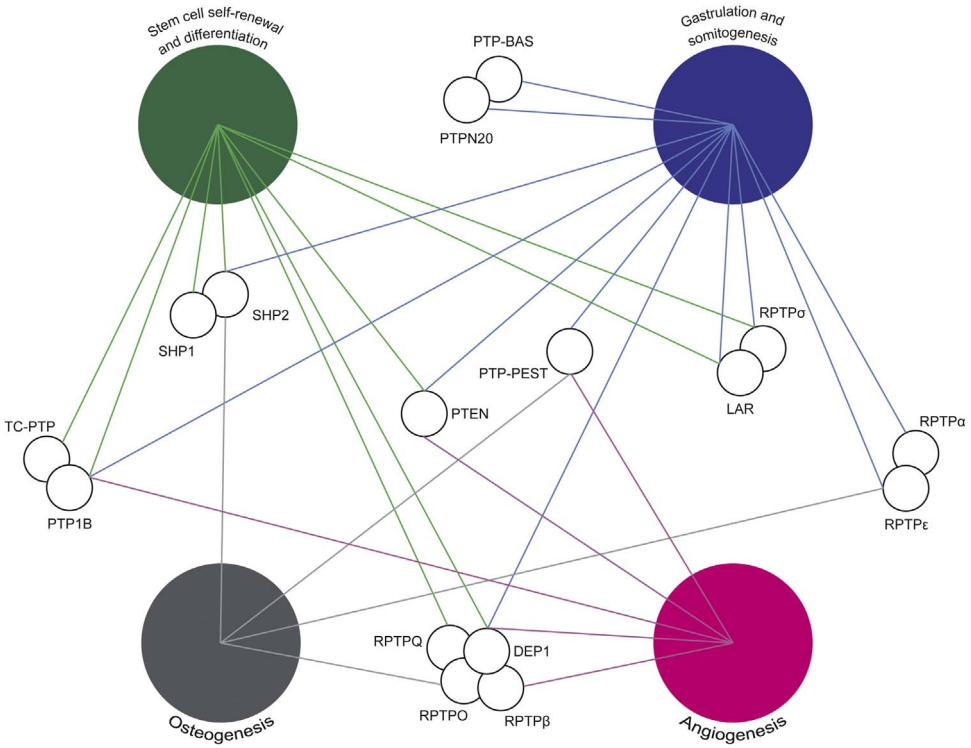

Fig. 2. Protein-tyrosine phosphatases are involved in key aspects of development. Big circles represent developmental processes and small circles are individual PTPs. Lines indicate involvement of the PTP in particular developmental processes. PTPs are clustered based on similar overall architecture.

and more developmental processes. Nevertheless, it is evident that PTPs have crucial roles in various developmental processes and, as a result, also in disease. Because PTPs have a pivotal role in disease and because they regulate protein-tyrosine phosphorylation enzymatically, PTPs are now being considered as drug targets. The major concern regarding the development of PTP inhibitors is selectivity because the PTP catalytic site is highly conserved and it is therefore challenging to develop inhibitors that target the catalytic site of just one specific PTP. In addition, the catalytic site is positively charged, and heavily charged molecules that may target such a site do not easily cross the cell membrane. For this reason, and in the hope to gain specificity, attempts are being made to develop inhibitors that do not target the conserved catalytic site directly, but instead less conserved allosteric sites.

Various non-specific PTP1B inhibitors have been developed (Tamrakar et al., 2014; Barr, 2010), and one of the latest, anti-sense oligonucleotide ISIS-113715, looks promising as it increases insulin sensitivity and adiponectin concentrations in monkeys (Swarbrick et al., 2009). In 2014 the lab of Nick Tonks tested a novel allosteric inhibitor of PTP1B, MSI-1436, which does not target the catalytic site but instead the C-terminus of PTP1B (Krishnan et al., 2014). MSI-1436 traps PTP1B in an inactive state, and its effectiveness was demonstrated in a mouse model of HER2 driven breast tumourigenesis, where it inhibited HER2 signalling and abrogated metastasis.

In contrast to the large number of PTP1B inhibitors, there are only a few SHP2 inhibitors. In recent years, SHP2 inhibitors have been developed that block proliferation of patient derived hematopoietic progenitor cells expressing the E67K or the D61Y mutation, and leukemic cells and mouse myeloid progenitor cells that carry the E76K mutation (Yu et al., 2013; Zhang et al., 2010; Liu et al., 2013). Since D61G is the most common mutation in NS, it should be determined whether these compounds also work for NS patients with the D61G, and other SHP2 mutations. Recently, a highly potent and selective allosteric inhibitor for SHP2 (SHP099) has been developed which inhibits proliferation and differentiation in mouse tumours, and in human cancer cells in vitro driven by mutated receptor tyrosine kinases (Chen et al., 2016).

Taken together, the great strides made in the last decade in fundamental and translational research to understand the function and importance of PTPs, and to target them in an attempt to cure disease, have left a bright future for research and the well-being of patients alike. With more research to elucidate the function and regulation of PTPs, and development of drugs that target PTPs, PTP inhibitors may soon appear in the clinic.

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