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Mini Review

Vascular PTPs: Current developments and challenges for exploitation in Type 2 diabetes-associated vascular dysfunction

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ABSTRACT

Protein Tyrosine Phosphatases (PTPs) are important contributors to vascular cells normal function, by balancing signaling proteins activation exerted by phosphorylating kinases. Type 2 diabetes related insults, such as hyperglycemia, oxidative stress, and insulin resistance disturb the phosphorylation/dephosphorylation equilibrium towards an abnormal augmented phosphorylation of signaling proteins associated with changes in PTPs expression, enzymatic activity and interaction with cellular substrates. We briefly review here: (i) the new findings on receptor and non-receptor PTPs and their role in vascular cells, (ii) several data on oxidation and phosphorylation of these molecules in endothelial and smooth muscle cells, (iii) vascular PTPs intrinsic activity and dysregulation under the insults of diabetic milieu, and (iv) the potential use of PTPs and their inhibitors as therapeutic targets in Type 2 diabetes-associated vascular dysfunction.

Protein Tyrosine Phosphatases – major contributors to vascular cells metabolism

For the proper cellular signaling within the vascular wall an efficient balance operates between the phosphorylating kinases, that control the amplitude of signaling proteins activation and the dephosphorylating phosphatases, that regulate both signal amplitude and signal duration [1]. According to the type of phosphorylated aminoacid used as substrate, protein phosphatases are classified in: (i) Protein Tyrosine Phosphatases (PTPs), a very large family of enzymes that dephosphorylate the tyrosine residues, (ii) Serine/Threonine Phosphatases (PSTPs) that dephosphorylate the Ser/Thr residues, and (iii) dual-specificity phosphatases (DSPs) that can dephosphorylate both phosphotyrosine and phosphothreonine residues on MAPKs [2]. Recent analyses suggest that the PSTPs are more ancient than the PTPs [3]. In terms of the enzymatic mechanism, both PTPs and PSTPs perform nucleophilic attack on the targeted phosphate group, but PTPs utilize a catalytic cysteine residue as a nucleophile, whereas the PSTPs nucleophilic attack is facilitated via a metal-activated water molecule positioned in the catalytic groove [4]. Reports indicate that thrombin and vascular endothelial growth factor (VEGF) activation of human endothelial cells (ECs) engage participation of a nuclear MKP-1 that mediate histone H3 (phospho-Ser-10) dephosphorylation [5]. ECs contain also a MKP-3, and its activity is upregulated by sphingosine-1-phosphate [6].

PTPs function in regulation of signals transfer from the cell surface to the nucleus, an essential element for normal function and survival of vascular cells. Thus, PTPs balance and fine-tune the activity of key molecules in the signaling pathways associated with ECs dysfunction, smooth muscle cells (SMCs) growth, vascular wall remodeling, neointima formation, and restenosis. Current emphasis is directed on identification of PTPs classes expressed in vascular cells, on their substrate specificity, and contribution to vascular pathology (Table 1). Type 2 diabetes is associated with vascular wall dysfunction, a condition installed under the effects exerted by hyperglycemia, insulin resistance and oxidative stress among other insults. These stimuli act frequently in concert within vascular cells and imbalance the phosphorylation/dephosphorylation reactions within the signal transduction cascades. Therefore, understanding and manipulating kinases/phosphatases crosstalk is important for adjusting diabetes-associated dysregulation in signaling proteins activation, and for prevention of the deleterious effects of prolonged stimulation.

Receptor and non-receptor vascular PTPs

PTPs constitute a diverse family of receptor-like and cytosolic proteins. These can coexist in a single cell type; as an example, vascular endothelium expresses least 10 different receptor-type and 8 non-receptor-type PTPs [7]. The common features of PTPs consist in the high substrate specificity and in control of activity

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Table 1
Representative vascular PTPs.

	Abbreviation	Cellular substrate(s)	Vascular role(s) in:
Receptor-type PTPs			
Density-enhanced phosphatase-1	DEP-1	VEGFR2	• ECs survival • Contact inhibition of ECs growth
Vascular Endothelial Protein Tyrosine Phosphatase	VE-PTP	VEGFR2 Tie-2, VE-cadherin	• Contact-inhibition of ECs growth • Tubular morphogenesis during angiogenesis • Blood vessel development • Vessel size
Protein Tyrosine Phosphatase β/ζ	RPTP β/ζ	Interacts with pleiotrophin receptor, $\alpha v\beta_3$ integrin	• ECs migration induced by the angiogenic growth factor pleiotrophin
Protein Tyrosine phosphatase α	PTPα	Growth factors receptors	• Multiple signaling systems
Non-receptor-type PTPs			
Src-Homology 2 domain Phosphatase-1	SHP-1	Receptor tyrosine kinases	• ECs-it is induced by the angiogenic hepatocyte growth factor; • Fetal vascular SMCs-it functions in AT 2 receptor signaling
Src-Homology domain Phosphatase 2-containing inositol phosphatase 2	SHP-2	MAP kinases, Akt, VGFR-2	• The cross-talk between Ang-(1–7) and Ang II signaling pathways
Tyrosine Phosphatase Substrate-1	SHPS-1	Growth factors	• Vascular SMCs migration • IGF-I-stimulation of SMCs proliferation
Protein Tyrosine Phosphatase 1B	PTP1B	Phosphorylated IR;EGFR	• Negative regulator of insulin and leptin signaling • Negative regulator of adrenergic contraction in vascular SMCs • Stabilizes ECs junctions maintaining ECs barrier integrity • Lymphocytes transendothelial migration • ECs and SMCs growth and proliferation • Neointima formation • Angiogenesis
Protein Tyrosine Phosphatase Interacting Protein 51	PTPIP51	Interacts in vitro with PTP1B	• Angiogenesis • Vascular remodelingss

by reversible oxidation of the active-site cysteine, or binding of extracellular ligands (for receptor-type PTPs). The available information on receptor and non-receptor vascular PTPs is summarized in Table 1.

Considerable knowledge is accumulated on PTP1B, a widely expressed 50 kDa non-receptor PTP, and the first PTP isolated in homogenous form [8], with regulatory intervention in multiple cellular functions. At cellular level, PTP1B is an endoplasmic reticulum (ER) – resident protein [9], displaying at the carboxy-terminal of the molecule 35 amino acid residues, critical for ER targeting. In rat corneal ECs PTP1B was found associated with vesicular structures subjacent to the plasma membrane [10].

Oxidation and phosphorylation of PTPs

Some 40-odd genes in mammals encode phosphotyrosine-specific, 'classical' Protein Tyrosine Phosphatases [11], and several comprehensive reviews on PTPs chemistry have been published so far [11–14].

Structurally, PTPs possess a conserved 230 amino acid domain with an essential Cys residue in the active site with a lower pK_a than of Cys thiol. At neutral pH, the Cys-thiol groups were deprotonated being susceptible to oxidation by reactive oxygen species (ROS). Moreover, the signaling properties of ROS are largely attributable to the reversible oxidation of the redox-sensitive cysteine of PTPs [15]. Oxidation inhibits the nucleophilic property of PTPs required for substrate dephosphorylation, and makes these enzymes inactive [12,16]. In PTP1B molecule, oxidation of the catalytic **Cys-215** results in formation of a sulfenamide bond between the sulfur atom of the catalytic cysteine and the amide nitrogen of the neighboring serine, accompanied by changes in the tertiary structure at the catalytic site. Upon the addition of antioxidant glutathione the reaction was reversed, indicating that the sulfenamide intermediate could function to protect the cysteine from overoxidation within signaling pathways [17]. In human aortic ECs the NADPH oxidase isoform Nox4, an endogenous source of ROS is localized to the ER where oxidizes and inactivates PTP1B, another ER-resident protein; thus, ROS signaling operates in a spatially restricted microenvironment [9].

Another catalytic Cys is **Cys-459** that in SHP2/PTP was predominantly *S*-nitrosylated when ECs were constantly exposed to blood flow-induced shear stress; *S*-nitrosylation of this Cys residue is reversible, and may protect SHP2/PTP from H_2O_2-induced irreversible oxidation, regulating endothelial responses to various stimuli under flow condition [18].

The subgroup of MKPs, have a common chemical structure with a carboxyl-terminal catalytic domain and an amino-terminal non-catalytic domain that is responsible for binding to MAP kinase substrates [5]. The redox state of **Cys-258** within the catalytic domain of MKP-1 affects the phosphatase activity: it is a target for oxidation and results in enzyme inactivation.

Phosphorylation of PTPs molecule is a process associated with cells migration and vascular remodeling. Thus, phosphorylation of PTP1B is necessary for VCAM-1-dependent transendothelial lymphocyte migration [19]. Reports also indicate that PTPα tyrosine (**Tyr789**) phosphorylation is possibly catalyzed by the PTPα-associated IGF-1 receptor tyrosine kinase; this reaction is required for efficient cell migration in response to IGF-1 [20]. Recruted to the lipid rafts of human vascular SMCs, tyrosine phosphatase SHP-2 is phosphorylated by the co-localized urokinase, an event involved in urokinase-related vascular remodeling [21]. In cultured vascular SMCs, particularly in cells originating from spontaneous hypertensive rats, ROS-induced an impaired interplay between oxidation/phosphorylation and dysregulation of PTP/SHP-2 leads to hyperactivation of downstream AKT signaling pathways, playing a role in redox sensitive vascular remodeling in hypertension [16]. Present data emphasize that transcriptional regulation of PTPs is an important mechanism for controlling onset and termination of receptor tyrosine kinase-dependent tissue remodeling [22].

Effects of high glucose concentration and insulin on vascular PTPs

In diabetes, vascular cells are currently exposed to altered concentrations of circulating molecules and/or to their chemically modified forms, compared to the normal physiological condition. Among the components of the abnormal diabetic milieu are: the high glucose concentration, non-enzymatic glycated proteins and lipids, enhanced ROS levels, and altered insulin concentrations. Recent reports show that in hyperglycemic conditions vascular SMCs respond to Insulin-like Growth Factor-I (IGF-I) by SHPS-1 recruitment of several signaling proteins such as SHP-2, c-Src, Shc and Grb2 [23,24].

Data on the effect of high glucose concentration on PTPs are rather variable. Thus, in mesenteric artery SMCs from WKY and SHRSP rats hyperglycemia and PPAR-gamma inhibition caused an increased expression of PTP1B, along with decreased insulin-stimulated insulin receptor (IR)-β, Akt, and glycogen synthase kinase-3β phosphorylation [25]. Diabetes increased also PTP1B enzymatic activity, reducing the autophosphorylation of retinal IR [26]. However, in assessing the effects of hyperglycemia on vascular PTPs one should also consider the associated enhanced oxidative stress resulting from stimulated mitochondrial ROS overproduction; the consequence is impaired angiogenesis and a reduced number of bone marrow-derived endothelial progenitor cells [27]. To the oxidant environment contributes also growth factor signaling, that increases superoxide anion levels; the latter are further dismutated into H_2O_2, inactivating PTPs such as PTP1B and SHP2. The recent reports appreciate that the type and origin of ROS that inactivates PTPs during growth factor signaling have not been unequivocally identified yet [28].

Under insulin resistant conditions, increased insulin concentrations and/or defects in insulin signaling pathway may contribute to imbalanced secretion of endothelial mediators promoting pathogenesis of vascular abnormalities. The mechanisms underlying insulin resistance comprise: increased serine phosphorylation of IRS proteins, increased degradation of IRS proteins, increased activity of phosphatases (SHP2, phosphatase tensin homolog deleted on chromosome ten [PTEN], and PTP-1B), and decreased activation of insulin receptor downstream signaling molecules including Akt and atypical PKC [29]. In ECs, the abnormal insulin signaling affects insulin-stimulated release of NO, ROS and ET-1, playing a role in endothelial dysfunction [30]. In aortic SMCs, insulin amplifies PDGF-induced motility of the cells by suppressing the expression and function of PTP1B [31].

PTPs inhibitors – still an expectation for Type 2 diabetes therapy

In physiological conditions, protein tyrosine phosphorylation exerted by protein tyrosine kinases (PTKs) is balanced by dephosphorylation reactions exerted by PTPs, whereas their expression is influenced by the overall tyrosine phosphorylation. In cardiovascular diseases such as cardiac hypertrophy, ischemia/reperfusion injury, and atherogenesis an abnormal augmented phosphorylation of various signaling proteins occurs. In an attempt to control protein tyrosine phosphorylation ongoing studies are directed towards PTPs as endogenous inhibitors of PTKs. It was demonstrated that inhibition of PTP1B activity increases both the duration of EGFR autophosphorylation and the relative number of corneal ECs entering the cell cycle [10] and described PTP1B as a potential therapeutic target to promote new vessel formation in ischemic cardiovascular diseases [32]. In this context, recent evidence assess that superoxide dismutase 1 (SOD1) plays an essential role in growth factor-mediated MAPK signaling by intervening in the transient oxidation and inactivation of PTPs. In HUVEC, SOD1 inhibition prevented formation of H_2O_2 protecting PTP1B from oxidation and inactivation, and inhibited ERK phosphorylation subsequent growth factor stimulation [28]. In addition, PTPs activation is still an unexploited therapeutic strategy for vascular restenosis and other diseases involving receptor tyrosine kinases – driven tissue remodeling [22].

As result of increased obesity, Type 2 diabetics are resistant to insulin and leptin, while PTP1B function as a key negative regulator of signaling by both of these hormones. It is obvious that inhibitors of this protein phosphatase may provide promise for correcting endocrine abnormalities in both diabetes and obesity [33]. PTP1B dephosphorylates the autophosphorylated IR returning it to the inactive state, while inhibition of IR–PTP interaction may lengthen the insulin signal. Reportedly, a large variety of PTPs inhibitors have been identified ranging from natural products and their analogs, peptides, phosphonates, non-peptides, mimotopes, metal-containing inhibitors, and redox inhibitors. Other molecules that function as PTPs inhibitors are sodium 2-*O*-carboxymethylpyrogallol derivatives [34], stibogluconate, phenylarsine oxide, alendronate, etidronate, vanadate, gallium nitrate, suramin, or aplidin [35]. At present, attention is focused on small-molecule PTP-1B inhibitors that improve glycemia in a variety of obese rodent models [36]. Thus, 5-Arylidene-2-phenylimino-4-thiazolidinones were synthesized as PTP1B and low molecular weight – PTP inhibitors; it is considered that introduction of a 2-phenylimino moiety onto the 4-thiazolidinone ring enhances the inhibitor/enzyme affinity by favorable interactions with residues in the enzyme active site and surrounding loops [37]. With the goal to encompass possible permeability and pharmacokinetics problems, the ester derivatives of pro-drugs able to deliver the active inhibitors into the cells cytoplasm are now seen as a promising direction. Since in diabetes PTP1B is overexpressed, is become important identification of the pro-drugs that may provide PTP1B inhibitors into the cells, subsequently increasing insulin signaling. Reports show that following 4 days of intraperitoneal dosing in ob/ob mice, one such pro-drug candidate improved insulin sensitivity, and lowered fasting blood glucose and insulin levels [33].

The recent analysis of human protein tyrosine phosphatome may provide an expanded insight into intrafamily PTP diversity, catalytic activity, substrate recognition, and autoregulatory self-association [38]. However, it is essential to have in mind that in vivo individual PTPs can simultaneously intervene in regulating multiple and complex signaling pathways. For drugs development the current studies target either phosphatase catalytic subunits or the phosphatase complexes, such as phosphatase oligomeric holoenzymes and phosphatase-substrate complexes [39]. Enlightening knowledge on PTPs implications in insulin signaling is a provocative task of major clinical significance in insulin resistance and Type 2 diabetes. Even though PTP inhibitors are difficult to develop, phosphatase inhibition is consider of great market potential and further impact [35]. Therefore, designing new selective and sensitive PTPs inhibitors based on structure–activity relationship studies is an aspiration with considerable challenges and exciting opportunities for basic and clinical research.

Instead of conclusion: issues awaiting elucidation

Various features of PTPs chemistry and regulation await rapid investigation, such as: the type and origin of ROS that inactivates PTPs during growth factor signaling [28], the principal mechanisms and the molecular details of the transcriptional regulation of PTPs [22], the identification of PTPs physiological substrates that may bear the key cellular tasks necessary for signaling, allowing the use of PTPs as therapeutic targets [14]. It is interesting to find out to what extent PTP induction by RTK ligands represents a

general mechanism for feedback inhibition of RTK [22]. Then, an urgent imperative remains optimization of PTPs inhibitory activity and selectivity [40].

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