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Role of protein tyrosine phosphatases in the modulation of insulin signaling and their implication in the pathogenesis of obesity-linked insulin resistance

Elaine Xu · Michael Schwab · André Marette

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Abstract Insulin resistance is a major disorder that links obesity to type 2 diabetes mellitus (T2D). It involves defects in the insulin actions owing to a reduced ability of insulin to trigger key signaling pathways in major metabolic tissues. The pathogenesis of insulin resistance involves several inhibitory molecules that interfere with the tyrosine phosphorylation of the insulin receptor and its downstream effectors. Among those, growing interest has been developed toward the protein tyrosine phosphatases (PTPs), a large family of enzymes that can inactivate crucial signaling effectors in the insulin signaling cascade by dephosphorylating their tyrosine residues. Herein we briefly review the role of several PTPs that have been shown to be implicated in the regulation of insulin action, and then focus on the Src homology 2 (SH2) domain-containing SHP1 and SHP2 enzymes, since recent reports have indicated major roles for these PTPs in the control of insulin action and glucose metabolism. Finally, the therapeutic potential of targeting PTPs for combating insulin resistance and alleviating T2D will be discussed.

Keywords Protein tyrosine phosphatase · Obesity · Diabetes · Metabolism · Insulin signaling

Abbreviations

aPKC	Atypical protein kinase C
ABC	ATP binding cassette transporter
ACD	Acyl CoA dehydrogenases
ACO	Acyl CoA oxidase
AGC	Protein kinase A G, and C
Akt	Protein kinase B
AP	Adaptor protein
aPKC	Atypical protein kinase C
AT2	Angiotensin II subtype 2 receptor
Cbl	Casitas B-lineage lymphoma
Cdk	Cyclin-dependent kinase
CEA	Carcinoembryonic antigen
CEACAM	CEA-related adhesion molecules
CNS	Central nervous system
COP1	Caspase recruitment domain-containing protein 16
CPT	Carnitine palmitoyl transferase
CVD	Cardiovascular diseases
ER	Endoplasmic reticulum
FA	Fatty acids
FAS	Fatty acid synthase
FFA/NEFA	Free fatty acids/non-esterified FA
Fkhr/FoxO1	Forkhead transcription factor
G6Pase	Glucose-6-phosphatase
Gab	Grb2-associated-binding protein
GLP	Glucagon-like peptide
GLUT	Glucose transporter
Grb2	Growth factor receptor-bound protein 2
GSK3	Glycogen synthase kinase 3
IGF	Insulin growth factor
IL	Interleukin
IR	Insulin receptor
IRR	Insulin receptor-related receptor
IRS	Insulin-receptor substrate
JAK	Janus kinase
KO	Knockout
LAR	Leukocyte common antigen-related (phosphatase)
LMW-PTP	Low molecular weight PTP

E. Xu · M. Schwab · A. Marette
Department of Medicine, Cardiology Axis of the Institut Universitaire de Cardiologie et de Pneumologie de Québec (Hôpital Laval), Ste-Foy, Québec, Canada G1V 4G2

A. Marette (✉)
Cardiology Axis of the Institut Universitaire de Cardiologie et de Pneumologie de Québec (Hôpital Laval), Ste-Foy, Québec, Canada G1V 4G5
e-mail: andre.marette@criucpq.ulaval.ca

MAPK/ERK	Mitogen activated protein kinase/ Extracellular signal-regulated kinase
MCK	Muscle creatine kinase
MEK	MAPK kinase
mRNA	Messenger ribonucleic acid
mTORC	Mammalian TOR complex
NAFLD	Non-alcoholic fatty liver disease
NEFA	Non-esterified fatty acids
NO	Nitric oxide
$p60^{dok}$	60-kDa tyrosine phosphorylated protein
PAF	RNA polymerase II associated factor
PDK	PDH kinase or Phosphoinositide-dependent kinase
PGC-1	PPARγ co-activator 1
PH	Pleckstrin homology
PHLPP	PH-domain leucine-rich repeat protein phosphatase
PI3K	Phosphatidylinositol 3-kinase
PIP2	Phosphotidylinositol-4,5-bisphosphate
PIP3	Phosphotidylinositol-3,4,5-triphosphate
PKB	Protein kinase B (also known as Akt)
PM	Plasmic membrane
PP	Protein phosphatase
PPAR	Peroxisome proliferator-activated receptor
Prep	PBX-regulating protein
PTB	Phospho-tyrosine binding domain
PTEN	Phosphatase with sequence homology to protein-tyrosine phosphatases and the cytoskeleton protein tensin
PTP	Protein tyrosine phosphatase
Raf	Proto-oncogene serine/threonine-protein kinase
Ras	G-protein and/or a family of related proteins discovered from rat sarcoma
RPTP	Receptor-like PTP
RTK	Receptor tyrosine kinases
S6K1	S6 kinase 1
SCD	Stearoyl-CoA desaturase
SH	Src homology
Shc	SH2-domain containing proteins
SHP	2-SH2-domain containing protein tyrosine phosphatase
SNARE	Soluble NSF attachment protein receptor
SOS	Son-of-sevenless exchange protein
SREBP	Sterol response element binding protein
STAT	Signal transducer and activator of transcription
STP	Serine/threonine phosphatase
T2D	Type 2 diabetes
TAO	Thousand and one amino acid kinase
TC-PTP	T-cell PTP
TF	Transcription factors
TNF	Tumor necrosis factor
TOR	Target of rapamycin
WHO	World Health Organization
Wnt	Wingless and int-1

1 Introduction

Obesity, once considered an endemic medical condition of the rich or a featuring syndrome of several unfortunate genetic variants, has now become one of the greatest global pandemics of the 21st century. The prevalence of obesity has doubled between 1980 and 2008 with the WHO estimates of over 300 million clinically obese adults in 2004 [1], which poses a serious health threat with the associated non-communicable diseases, including atherosclerosis, metabolic syndrome, non-alcoholic fatty liver diseases (NAFLD), type 2 diabetes (T2D), and even some cancers. As a common link between obesity and type 2 diabetes [2–8], insulin resistance is believed to be a *sine qua non* in the pathogenesis of obesity-associated metabolic diseases [9].

The development of insulin resistance in obesity is due to various conditions, mostly initiated by adipose tissue dysfunction [10–13]. Elevated circulating levels of NEFA (non-esterified fatty acids) or free fatty acids (FFA) released in abnormally high quantity by the adipose tissue and decreased FFA clearance in obesity [14–16] has been shown to be one main cause of insulin resistance [17]. By attenuating insulin signaling, FFA impair insulin-mediated glucose uptake in muscles and fat [18–21], suppression of glucose production from the liver [13, 21–23], and pancreatic insulin secretion [24–26]. In addition, adipocyte-derived hormones, metabolites, and inflammatory cytokines released from the overly expanded adipose tissue also down-regulate insulin sensitivity in all major insulin-target cells [11, 13, 27]. Altogether with compensatory hyperinsulinemia and overactivation of nutrient sensing mechanisms such as the mTOR/S6K1 pathway [28], insulin resistance develops along with impaired insulin secretion, leading the way to T2D and other related metabolic disorders. In order to understand this syndrome, the insulin signaling pathways and their regulation have been investigated intensively to unravel this complex machinery. One crucial part of the regulation of insulin signaling pathways is the negative feedback mechanism provided by phosphatases, especially the protein tyrosine phosphatases (PTPs). With only a few PTPs being extensively investigated in the field of metabolism, the importance of many other PTPs remains in the shadow. In this review, we will briefly update the major insulin signaling pathways involved in metabolic regulation, and then discuss the role of PTPs in the modulation of insulin action and energy metabolism, with a particular focus on recent findings that

have unraveled an unsuspected metabolic role for the SH2-domain-containing PTPs, namely SHP1 and SHP2.

2 Insulin action and signaling

2.1 Insulin's metabolic actions

In clinical applications, the most important function of insulin is to maintain glucose homeostasis, as insulin is the most potent endogenous blood glucose-lowering endocrine factor. Regardless of the fasting, feeding, or intermediate states, blood glucose is controlled within a narrow window of 4 to 7 mM in normal individuals. This tight regulation of glucose results from a balance of intestinal absorption, hepatic storage and production, and uptake/metabolism in peripheral tissues, which is fine-tuned by insulin. Through stimulating the translocation of GLUT4 glucose transporters from intracellular locations to the cell surface, insulin induces glucose uptake in fat and skeletal muscle, the latter accounting for up to 75 % of whole-body glucose disposal in the post-absorptive state [29]. In many cell types, insulin promotes glucose storage by increasing glycogenesis and, in some organs such as the liver, by suppressing glucose output via inhibition of glycogenolysis and gluconeogenesis.

From an integrative physiological point of view, insulin exerts multiple functions in many tissues to promote anabolism and proper growth as well as differentiation [30–33]. Besides its anabolic actions in glucose metabolism, insulin also stimulates the uptake of fatty acids and amino acids. By increasing the expression and/or activity of enzymes responsible for glycogen, lipid, and protein synthesis and inhibiting the expression and/or activity of those that catalyze degradation in major tissues, insulin promotes the storage of nutrients and at the same time inhibits their release via its ability to suppress glycogenolysis, lipolysis, and proteolysis [34]. In terms of energy homeostasis, insulin regulates many proteins and enzymes involved in various metabolic pathways in part through inhibiting the release of glucagon [35], a catabolic hormone secreted by the pancreatic α cells. Insulin also directly acts in the CNS to regulate body weight, reproduction, peripheral glucose and lipid metabolism [36–41]. In cardiac muscle, insulin induces relaxation with a positive inotropic effect [42, 43]. Electrolyte homeostasis is also regulated by insulin, as it stimulates potassium uptake while inhibiting renal sodium excretion [44, 45]. In the vasculature, insulin acutely stimulates endothelial function, but when its levels are abnormally elevated, such as in insulin resistance states, it can also promote atherogenenesis through enhancement of vascular smooth muscle cell proliferation [46]. Insulin also plays an important role in aging by down-regulating autophagy [47]. Finally, insulin can regulate its own expression and secretion by an autocrine action in the pancreatic β-cells [48, 49] and by promoting GLP-1 secretion from the intestinal L-cells [50].

Given the vast functions of insulin in numerous sites of action, regulation of insulin signaling is hence a vital process that can be targeted by multiple pathways implicated in the development of metabolic disorders such as insulin resistance.

2.2 Insulin signaling

The insulin receptor (IR) is a member of a highly conserved subfamily of receptor tyrosine kinases (RTK), including the insulin-like growth factor (IGF)-I receptor and the insulin receptor-related receptor (IRR). Functional hybrids of IR, IGF-I receptor, and IRR also exist in many different cell types [51], and the activity of each receptor is dependent on the other partner within the hybrid [52]. In a stable tetrameric form with allosteric enzymatic functions, IR consists of an extracellular domain containing two α-subunits able to inhibit the intrinsic tyrosine kinase activity of the two transmembrane β-subunits with multiple tyrosine residues. Upon insulin binding to the α-subunits, the repression of the β-subunits is lifted and their kinase activity increases as they phosphorylate each other on specific tyrosine sites in an intramolecular reaction (transautophosphorylation) followed by a rapid conformational change [53, 54]. This is an important event, as it enables the insulin receptor to phosphorylate and activate docking effectors (IR substrates) for propagation of insulin signaling. Any reduction in IR tyrosine phosphorylation leads to decreased signal transduction downstream and results in down-regulation of its metabolic actions.

So far, at least nine immediate IR substrates have been identified. Four out of six identified members of the IRS protein family, IRS-1, -2, -3, and -4, have been confirmed to propagate IR signal transduction in known mechanisms. The other five IR substrates are Gab-1 (Grb2-associated-binding protein), $p60^{Dok}$ (60-kDa tyrosine phosphorylated protein), Cbl (Casitas B-lineage lymphoma), APS (adapter protein with a PH and SH2 domain), and isoforms of Shc (SH2-domain containing proteins) [34, 55–58].

A critical step in insulin signaling is the activation of the IRS proteins, especially IRS-1 and IRS-2 which are predominantly expressed in metabolic tissues. Although both isoforms are major signal transducers that are regulated in a similar fashion and involved in insulin-mediated functions, IRS-1 and IRS-2 exert specific functions in different tissues or cell types. For example, IRS-1 predominantly activates pathways leading to general cell growth and GLUT4 translocation in muscle cells whereas IRS-2 is more important in pancreatic β-cell survival/growth, neuronal cell growth, reproduction, food intake, and hepatic insulin action [59–63]. The role of IRS-2 in carbohydrate and lipid metabolism seems more crucial in comparison. IRS-2 knockout mice develop full-blown type 2 diabetes, while

IRS-1 null mice are only mildly insulin-resistant with growth retardation, because its absence is partially compensated by IRS-2 [64–67]. Interestingly, the existence of a dynamic relay between IRS-1 and IRS-2 in hepatic insulin signaling has been proposed in which IRS-2 mainly functions during fasting and immediately after refeeding, while IRS-1 functions primarily after refeeding [68]. Not much is known of IRS-3 and IRS-4, but they have been shown to negatively regulate the IGF-1 signaling pathway by inhibiting the activation of IRS-1 and IRS-2, perhaps by competition [69]. The general structure of an IRS protein consists of a well conserved PH (pleckstrin homology) domain at the extreme N-terminus for membrane localization, a phosphotyrosine binding domain (PTB) for IR binding, the carboxy terminal rich in tyrosine phosphorylation motifs for activation, and special YMXM motifs for docking SH2 domain-containing downstream signaling molecules, such as PI3K and SHP2 (Fig. 1) [70].

Regulation of tyrosine phosphorylation, degradation, or binding of both IR and IRS proteins directly affects three main downstream insulin signaling pathways implicated in metabolic regulation, namely the phosphoinositol 3-kinase (PI3K) pathway, the mitogen activated protein kinase (MAPK) pathway, and the mammalian target of rapamycin (mTOR) pathway [34].

2.3 The major insulin signaling pathways

2.3.1 The PI3K pathway

As an important signaling molecule in many insulin-triggered metabolic processes, PI3K is activated via the catalytic p110 subunit after binding to IRS with its SH2-domain containing p85 regulatory subunit (Fig. 1) [71]. It then phosphorylates phosphotidylinositol-4,5-bisphosphate (PIP2) to produce phosphotidylinositol-3,4,5-triphosphate (PIP3), which binds to PH domains of various signaling molecules and alters their activity or localization [72]. In general, PIP3 activates three classes of signaling molecules, the AGC family of serine/threonine protein kinases, guanine nucleotide-exchange proteins of the Rho family of GTPase, and the Tec family of tyrosine kinases [34, 73–75]. The most well recognized serine/threonine kinase in the AGC family, Akt/PKB, interacts with PIP3 through its PH domain for better membrane localization in order to be catalytically activated upon threonine 308 (T308) phosphorylation by another family member, phosphoinositide-dependent kinase (PDK) 1 [76, 77]. For complete activation of Akt, serine 473 (S473) is phosphorylated by mTORC2, which can further facilitate T308 phosphorylation by PDK1 [78]. Active Akt can also positively reinforce IRS-1 signaling by direct phosphorylation on its PTB domain [79]. PDK-1 also activates the other AGC family members, atypical protein kinase C (aPKC) isoforms ζ and λ, leading to Akt-independent downstream signal transduction [80, 81]. Signaling by Akt and aPKC is essential for different biological responses, including insulin-stimulated translocation of GLUT4 and general protein synthesis [34, 70, 82]. PI3K-Akt signaling also mediates insulin-stimulated glycogenesis by phosphorylation-dependent deactivation of GSK3 (glycogen synthase kinase 3) [83] and relays IR signals to suppress gluconeogenesis by regulating gene expression of important enzymes via phosphorylation-dependent regulation of the Forkhead transcription factor (Fkhr/FoxO1) and PPARγ co-activator 1α (PGC-1α) [84–88].

2.3.2 The MAPK pathway

The other branch of downstream signaling from IRS proteins is the MAPK pathway, leading mostly to the regulation of general gene expression. IRS-1 or Shc can directly interact with growth factor receptor-bound protein 2 (Grb2) to relocate SOS (Son-of-sevenless) to the cell membrane thus activating Ras, a small GTPase that initiates a cascade of serine kinase activation from Raf (proto-oncogene serine/threonine-protein kinase) to MEK (MAPK kinase), then to MAPK/ERK. Once MAPK/ERK is activated, it is translocated into the nucleus to modulate gene expression of various proteins via direct

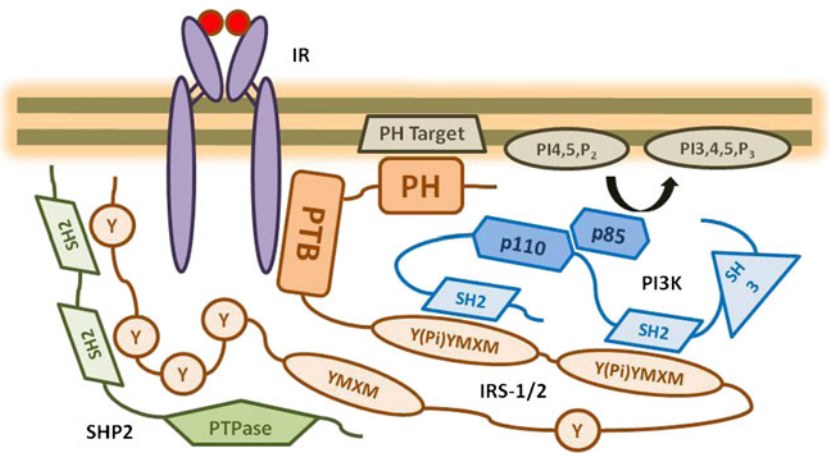

Fig. 1 Example scheme of IR-IRS-PI3K/SHP2 binding. Adapted from White [70]. The IRS-signalling system: a network of docking proteins that mediate insulin action. Mol Cell Biochem. 1998 May;182(1–2):3–11

regulation of transcription factors (TF) [89, 90]. The activation of Ras also requires the stimulation of SHP2 (SH2 domain-containing protein tyrosine phosphatase 2), a known tyrosine phosphatase with multiple positive roles in conducting signal transduction in different pathways, including insulin signaling [34, 70, 91, 92].

2.3.3 The mTOR pathway

Major protein synthesis and degradation-repression actions of insulin, including its inhibition of autophagy [47, 93], are carried out by the activation of the mTOR pathway. The signaling molecule mTOR is a special member of the PI3K family with only serine/threonine kinase capabilities [94, 95]. The detailed activation and downstream signaling of the mTOR pathway is extensive and complex involving the formation, regulation, and downstream signaling of the two complexes, mTORC1 and mTORC2. Comprised of mTOR, GβL, PRAS40, deptor, and raptor, mTORC1 controls transcription, ribosome biogenesis, protein/lipid synthesis, nutrient transport, autophagy, and other processes related to cell growth, with the help of its downstream effectors including ribosomal protein S6 kinase (S6K) and eukaryotic initiation factor 4E binding protein (4E-BP). On the other hand, mTORC2, formed by mTOR, GβL, protor-1/2, mSIN1, deptor, and rictor, regulates cytoskeleton and cell survival via activation of Akt and PKCα [78, 95–98]. Both mTORC1 and mTORC2 are activated by insulin and other growth factors through the IRS-PI3K-Akt pathway, as mTOR itself is a direct target of Akt [99–102]. A key role of mTOR signaling in insulin action is to provide a negative feedback inhibition at the level of IRS-1. Chronic activation of the mTORC1/S6K1 signaling by nutrients or prolonged insulin treatment increases the inhibitory serine phosphorylation of IRS-1, leading to reduced IRS-1 function and impaired activation of the PI3K-Akt pathway [28, 103]. On the other hand, acute inhibition of mTORC1 by rapamycin restores insulin-stimulated activation of the PI3K-Akt pathway and sensitizes insulin-mediated glucose transport in muscle and adipose cells [104, 105].

2.4 Inhibition of insulin signaling and insulin resistance

Throughout evolution, almost all biological processes are efficiently maintained by both positive and negative feedback mechanisms, especially in the regulation of energy homeostasis, and this holds true for insulin-mediated metabolic processes. In normal physiological conditions in healthy individuals, the inhibitory regulations of insulin signaling is essential for protecting the system from over-stimulation and for fine-tuning the signal transduction to produce the appropriate physiological effects. In disease states such as obesity, however, this balance is disturbed as insulin resistance develops from the overactivation of the negative regulators by various internal and external stimuli, including nutrients and inflammatory cytokines such as FFA and TNFα (tumor necrosis factor-α), respectively [106, 107].

3 Phosphatases: Impact on insulin signaling

Contrary to the action of phosphorylases and kinases, phosphatases are enzymes that remove the phosphate entity from cellular substrates. Phosphatases dephosphorylate their substrates mostly via direct binding followed by hydrolyzing the target phosphate into a phosphate ion. Dephosphorylation by phosphatases is as important as phosphorylation, because it regulates normal cellular processes that impact all physiological systems. Phosphatases discovered to date are divided into different classes according to their substrate preferences. The major classes are histidine phosphatases, lipid phosphatases, serine/threonine phosphatases (STPs), protein tyrosine phosphatases (PTPs), and dual-specificity phosphatases that target both phospho-Tyr and phospho-Ser/Thr residues. In the insulin signaling pathways, phosphatases take the regulatory control in almost every step of the cascade.

3.1 Lipid phosphatases

Phospholipids and sphingolipids are signaling molecules whose activities are regulated by five groups of different lipid phosphatases. In the signal transduction from PI3K to Akt, the two best known negative regulators, lipid phosphatases PTEN (phosphatase and tensin homologue) and SHIP2 (SH2 domain-containing inositol-5-phosphatase 2) interfere by dephosphorylating PIP3 at the 3′ and 5′ positions, respectively [108–111]. PTEN has also been reported to directly dephosphorylate Akt [112]. In the mTOR pathway, Lipin 1, a phosphatase with the ability of a transcriptional coactivator, down-regulates mTORC1-stimulated expression of genes involved in *de novo* lipogenesis (SREBP-1, FAS, SCD), while promoting FA oxidation by up-regulating the expression of PGC-1α/PPARα target genes (ACO, PPARα, CPT-1, medium and very long chain ACD) [113, 114].

3.2 Serine/threonine phosphatases (STPs)

Several STPs have been shown to regulate insulin signaling pathways. PP1 is a positive mediator of insulin, as it inhibits glycogen phosphorylase activity and stimulates glycogen synthase activity as well as SREBP-1 mobilization [115, 116]. PP2A selectively impairs hepatic insulin glucoregulation through dephosphorylation-mediated activation of FoxO1 and deactivation of Akt, which can also occur through other STPs such as PHLPP1/2 and PP2B (calcineurin) [112, 117, 118]. Increased PHLPP levels are detected in obese subjects with insulin resistance

[119]. Phosphorylation of Akt at T308 and S473 can be directly down-regulated by PP1, PP2A, and PHLPP [120–122].

3.3 Protein tyrosine phosphatases (PTPs)

In normal physiological conditions, the phosphorylation of tyrosyl residues on all signaling molecules is controlled with a balanced activity between the tyrosine kinases and phosphatases. Since the discovery of the zinc inhibition on a phospho-tyrosyl-protein phosphatase in 1981 [123], PTPs have been found to play an important role in this steady-state balance by catalyzing tyrosine dephosphorylation. PTPs can be divided into four groups based on their catalytic domains; class I, II, and III cysteine-based PTPs and class IV aspartate-based PTPs [124]. Characterized by a conserved active signature motif, the cysteine-based PTPs are subdivided into either classical phospho-tyrosine (pY)-specific PTPs or dual specificity PTPs; the classical PTPs are further classified as receptor-like PTPs (RPTP), non-RPTP, and cytosolic PTPs [125, 126]. Tyrosine phosphorylation is the key activation of IR and IRS proteins, but it is easily undone either directly or indirectly by PTPs, such as LAR, PTP1B, SHP1 and SHP2 [127–133]. The inhibitory regulation of insulin signaling by these PTPs will be discussed in details below.

4 Protein tyrosine phosphatases and insulin resistance

PTPs have been shown to play a role in the development of insulin resistance in classic metabolic tissues through inhibiting the activation of several molecules in the insulin signaling cascade. However, there is growing evidence that PTPs also modulate insulin sensitivity and metabolism through their actions in the central nervous system (CNS), the immune system, the gastrointestinal tract, particularly the intestinal microbiota [134–142]. These actions of several PTPs will be briefly reviewed in the following sections.

4.1 LAR and PTP1B: Historically featured PTPs

4.1.1 LAR and the family

Leukocyte common antigen related (LAR), encoded by *PTPRF*, is one of the first tyrosine phosphatases identified to directly associate with the insulin receptor to negatively regulate insulin signaling [127, 143]. Being the most abundant PTP in the liver and endothelial cells, LAR is also expressed in insulin target tissues, the skeletal muscles and adipose tissue, at low or moderate level, respectively [144]. The general reduction in LAR activity enhances insulin-stimulated insulin-receptor autophosphorylation and downstream substrate activation and signaling [133, 145, 146]. Although one murine model with complete LAR deficiency exhibits a paradoxical phenotype of heightened insulin sensitivities and secondary abnormalities resulting in resistance to insulin-stimulated glucose disposal and inhibition of hepatic glucose output [147], increased LAR in obesity has been observed, and its overexpression in muscle induces insulin resistance and IRS-2 deactivation [148–150]. In the CNS, LAR, together with its two other family members, PTPδ and PTPσ, have been recognized to be important synaptic adhesion molecules and responsible for basic neuronal functions [151], which can potentially affect the central control of energy homeostasis. LAR activity in the hypothalamus has been found to associate with central insulin resistance [152]. PTPσ is crucial for the growth and development of the hypothalamo-pituitary axis, a key regulatory center of glucose homeostasis [153–155].

4.1.2 PTP1B

Being the primary human PTP with hereditary variants associated with T2D and metabolic disorder [156], PTP1B, encoded by *PTPN1* and expressed ubiquitously in almost all tissues [144], has been the most well studied PTP involved in the insulin signaling pathway. Increased activity and expression of PTP1B have been observed in skeletal muscle, liver and brain in obese and insulin-resistant animal models [157–159]. Systemic deficiency of PTP1B results in augmented insulin sensitivity along with a protection against diet-induced weight gain [160], as it is known to directly dephosphorylate IR and IRS-1 [129, 130]. In the liver, hepatocyte-specific PTP1B deficiency prevents diet-induced hepatic steatosis and insulin resistance [161, 162], and the inducible knockdown improves glucose and lipid homeostasis in adult mice [163]. In adipocytes, PTP1B modulates insulin-stimulated glucose uptake by scrambling insulin signaling and GLUT4 vesicle trafficking via Munc18c, an essential regulator of SNARE-mediated budding and fusion of GLUT4 vesicles [164]. PTP1B also negatively regulates adipocyte development and may mediate TNFα action to impair adipocyte differentiation in obesity [165]. However, mice with adipocyte-specific deletion of PTP1B exhibit mild glucose intolerance with larger adipocyte size and decreased leptin sensitivity [166]. In muscles, *MCK-Cre* driven depletion of PTP1B augments systemic insulin sensitivity and glucose homeostasis [167]. During obesity-associated chronic inflammation, PTP1B, with further induced expression [159, 168], either promotes or protects against insulin resistance through modulation of immune cell functions and cytokine production [169–171]. In the CNS, PTP1B activity is associated with hypothalamic insulin resistance and leptin signaling [152, 172–174], as neuronal deletion of PTP1B improves both leptin and insulin signaling as well as general energy homeostasis [175, 176]. Within the cells, PTP1B

contributes to the development of insulin resistance by potentiating ER stress both peripherally and centrally [142, 177]. By controlling cellular filament organization via the regulation of keratin 8 solubility [178], PTP1B can also affect cellular trafficking signaled by insulin [140].

4.2 Other PTPs: Small but big

Although both LAR and PTP1B are well known regulators of insulin's metabolic actions, insulin signaling is also regulated by many other PTPs, which are mostly known to be negative regulators in insulin target tissues (Table 1).

Aside from the direct negative roles in insulin signaling, these PTPs can also attenuate insulin sensitivity indirectly. Since the catalytic and adaptor functions of PTPα are required for IL-1β signaling, PTPα promotes the inflammation-associated deterioration of insulin sensitivity in obesity [196]. TC-PTP shares many similarities in activity and function with PTP1B, especially in the negative regulation of insulin signaling and glucose metabolism, which have been well reviewed [197]. Expressed in great abundance in the liver [144], TC-PTP, together with PTP1B, is known to modulate ER stress, which potentiates the development of obesity-induced insulin resistance [173]. In neuronal cells, similar to PTP1B, elevated expression of TC-PTP in obesity also contributes to central leptin resistance [198]. PTP-PEST binding to Shc down-regulates insulin-induced ERK activation in human cells [190].

Another class of PTP containing two tandem SH2 domains at the N-terminus and a catalytic phosphatase C-terminal domain is composed of only two family members, SHP1 and SHP2, which are discussed in details in the following section.

5 SHP1 and SHP2

Though sharing much similarity in structure and activity, SHP1 and SHP2 have been commonly believed to play opposing roles, with SHP1 being the general negative regulator and SHP2 the positive one, even in the modulation of insulin signaling pathways [131, 199–202]. However, more and more studies have challenged this simplistic view [203].

5.1 Structure, expression and activity

Also known as SH-PTP1, PTP1C, HCP and SHP, SHP1 is encoded by the *PTPN6* gene. Alternative splicing results in two major SHP1 isoforms, the 68-kDa SHP1a (mouse) or SHP1-1 (human) form and the slightly longer form of SHP1b (mouse) or SHP1-2 (human) encompassing two extra amino acids, whose enzymatic activities are fairly comparable [204]. In human, an active 70-kd long form of SHP1, the SHP1L, also exists, although with limited substrate affinity and activity [202, 205]. SHP1 is abundantly expressed in hematopoietic cells, neuronal cells, astrocytes, oligodendrocytes, microglia, the epithelial cells of the prostate, and insulin-sensitive organs

Table 1 Small PTPs implicated in insulin-mediated metabolic regulations

PTP	Gene	Implication	References
LMW-PTP	*ACP1*	Negative regulator of insulin signaling	Chiarugi et al., 1997 [179]
		Reduction improves hyperglycemia and insulin sensitivity in obese mice	Pandey et al., 2007 [180]
PTP-MEG2	*PTPN9*	Negative regulator of hepatic insulin signaling	Cho et al., 2006 [181]
PTPα	*PTPRA*	Negative regulator of IR tyrosine kinase	Moller et al., 1995 [182] Lammers 1997 [183]
		Overexpression in adipocytes decreases insulin-stimulated GLUT4 translocation	Cong et al., 1999 [184]
		Modulator of insulin secretion in INS-1E cells	Kapp et al., 2003 [185]
		Antisense studies and deficiency in mouse models did not affect insulin signaling or glucose homeostasis	Arnott et al., 1999 [186] Le et al., 2004 [187]
PTPε	*PTPRE*	Negative regulator of IR tyrosine kinase	Moller et al., 1995 [182]
		Inhibitory to insulin-induced cell rounding and detachment in BHK-IR cells	Andersen et al., 2001 [188]
		Negative regulator of IR signaling and glucose uptake in skeletal muscles	Aga-Mizrachi et al., 2008 [189]
PTP-PEST	*PTPN12*	Binding to Shc down-regulates insulin-induced ERK Activation in HIRc-B Cells	Faisal et al., 2002 [190]
TC-PTP	*PTPN2*	Dephosphorylates IR	Galic et al., 2003 [191]
		Synergistic with PTP1B action	Xu et al., 2005 [192]
		Promotes hepatic gluconeogenesis by attenuating hepatic STAT3 and insulin signaling	Fukushima et al., 2010 [193]
		Deficiency in muscles does not alter glucose homeostasis	Loh et al., 2012 [194]
		Regulates insulin sensitivity from osteoblasts	Zee et al., 2012 [195]

such as the liver and the skeletal muscle [131, 206–211], with the shorter form being predominant in hematopoietic cells and the longer form in cells of epithelial lineages [204]. SHP2, also known as SH-PTP2, PTP1D, PTP2C and SYP, is encoded by *PTPN11* and only exists in one form [202]. Sharing 50 % similar sequences with SHP1 [202], SHP2 is however ubiquitously expressed [212].

Both SHP1 and SHP2 contain two SH2 domains at the N-terminus (N-SH2 and C-SH2) for substrate binding and the catalytic phosphatase domain at the C-terminus [213]. Inactive forms have a folded structure of the N-SH2 domain directly blocking the catalytic domain (Fig. 2a) [213, 214]. The phosphatase activity of both SHP1 and SHP2 is stimulated upon binding of pY-containing substrate to the SH2 domains (Fig. 2b), hence the substrate specificity determines the binding [213–215]. The active site of the catalytic domain contains important amino acid residues for substrate binding, stabilizing the negative charge of the phospho-tyrosine, and being the proton donor and acceptor in product release [216]. The catalytic pockets of SHP1 and SHP2 are only different in four residues, Arg352, Lys356, Arg358, and Asn359 in SHP1 versus Lys358, Arg362, Lys364, and Ser 365 in SHP2 [217]. The C-terminal end can also regulate PTP activity [202, 218, 219], as it can be phosphorylated on tyrosine residues, which are important for molecule recruitment that directly affects phosphatase activity upon various stimuli [202, 219, 220]. Both Src kinase and the insulin receptor have been shown to stimulate the phosphorylation of SHP1 and SHP2, which was the first observation linking these two PTPs with modulation of insulin signaling [203, 221, 222]. Both SHP1 and SHP2 can also be phosphorylated at certain serine residues in a PKCα-dependent manner [202], and their activity can be disrupted by NO-mediated S-nitrosylation at the active cysteine residue [223]. Interestingly, SHP1 can also exert autoregulation by binding to another SHP1 molecule to be inactivated (Fig. 2c) [224]. Most of the time, SHP1 and SHP2 are cytosolic PTPs, although they can signal from being bound to lipid rafts [202]. More interestingly, both PTPs also localize in the nucleus, indicating their potential role in the regulation of nuclear proteins and transcriptional regulation [225–229].

5.2 Metabolic roles differentiate SHP1 and SHP2 functions

Although increased activity and expression of both SHP1 and SHP2 have been observed in major insulin target metabolic tissues in obese and insulin-resistant animal models [157, 158, 230], their substrate preference and specific pattern of expression and regulation enable them with distinct metabolic roles.

5.2.1 SHP1

The association of SHP1 with insulin signaling through the PI3K-Akt pathway empowers SHP1 as a regulator of insulin action. Under normal conditions, the p85 regulatory subunit of PI3K keeps the p110 catalytic subunit stabilized and inactivated. This inhibitory activity of p85 is relieved by binding of the N-terminal SH2 domain to Src family kinases, which is reversed by the association of SHP1 to maintain the inhibition of PI3K activity [231, 232]. Thus theoretically, in the absence of SHP1, insulin signaling activates the p110 subunit through the tyrosine phosphorylation of p85, allowing further propagation of signal transduction to activate Akt by phosphorylation. SHP1 also selectively binds and dephosphorylates PTEN, subsequently modulating signal transduction in the PI3K-Akt pathway by increasing PIP3 [233]. AT2 receptor-mediated SHP1 activation can lead to inhibition of IRS-2 activation upstream of the PI3K-Akt pathway [234]. However, the best evidence has come from the viable *motheaten* mice. These mice are markedly glucose tolerant and insulin sensitive as compared to their WT

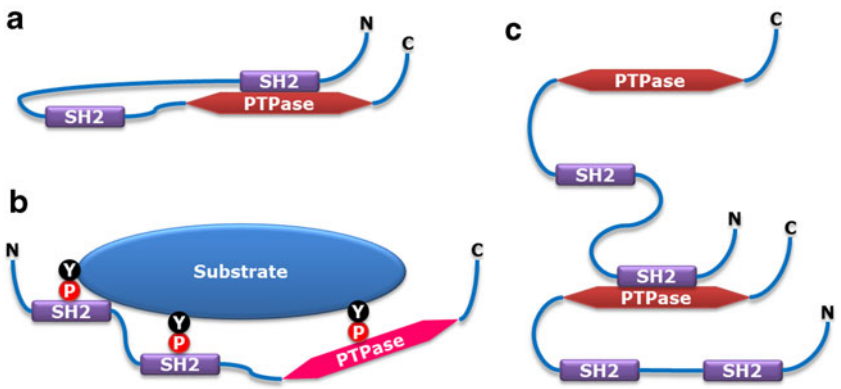

Fig. 2 Protein structures and regulation of SHP1 and SHP2. **a** In the basal state, SHP1 and SHP2 are kept inactive, because the N-terminal SH2 domain (N-SH2) blocks the C-terminal catalytic domain by inserting into the catalytic cleft. **b** SHP1 and SHP2 are activated by binding of Tyr-phosphorylated substrates to the N- and C-terminal SH2-domains thereby releasing the internal inhibition. **c** The activity of SHP1 and SHP2 can also be modulated by forming homodimers via an intramolecular interaction between a N-terminal SH2 domain and a catalytic domain

littermates. This has been found to be a result of enhanced IR signaling through IRS-PI3K-Akt in both liver and muscle [131]. Liver-targeted down-regulation of SHP1 expression and activity in normal mice by adenoviral expression of a catalytically inert mutant of SHP1 or by small hairpin RNA-mediated gene silencing reveals similar findings [131]. In addition, adenoviral introduction of DN-SHP1 containing a C453S mutation increases insulin-induced Akt phosphorylation and augments glucose uptake via GLUT4 up-regulation and glycogen synthesis in L6 myotubes and skeletal muscle tissue, confirming that SHP1 regulates insulin action in a cell-autonomous manner [235].

Interestingly, transcriptional activation of the SHP1 gene (*Ptpn6*) by overexpression of the homeodomain transcription factor Prep1 attenuates insulin signaling and glucose storage in hepatic cells, while Prep1-deficient mice show improved hepatic insulin action in association with reduced SHP1 expression [236], further supporting a key role for SHP1 in the control of liver glucose metabolism. As Prep1 expression is up-regulated in both diet-induced and genetically-driven obesity [236], this indirectly hints a possible increase in SHP1 expression in obesity. Accordingly, SHP1 gene and protein expression is found to be significantly up-regulated in metabolic tissues of mice with diet-induced obesity [230]. On the same diet regime, though hepatocyte-specific SHP1 knockout mice ($Ptpn6^{H\text{-}KO}$) develop obesity as their control WT littermates, they exhibit improved glucose tolerance and insulin sensitivity [230].

SHP1 also modulates insulin action and glucose homeostasis through its ability to inhibit insulin clearance by regulating the IR-associated complex of Cdk2/SHP1/β-catenin/CEACAM1 [237]. Being the primary organ of insulin clearance, liver is responsible for clearing 45–50 % of the insulin secreted from the pancreatic β-cells [238–240]. In the hepatocytes, like many ligand-receptor interactions, insulin-IR complexes are sequestered from the plasma membrane (PM) into the endosomes, where insulin-IR signal transduction takes place before insulin is dissociated from IR. When insulin signaling terminates upon insulin-IR dissociation, insulin is processed and IR is sorted then recycled back to the PM, or both are sent to lysosomes for degradation (Fig. 3) [241, 242].

In general, IR-mediated insulin clearance has a positive role in subcellular insulin signaling and can be defective in abnormal conditions such as obesity, hepatic steatosis, and insulin resistance. Peripheral FFA infusion significantly alters hepatic insulin clearance rate, and portal FFA infusion reduces insulin clearance to an even greater extent [243]. Liver fat content also negatively regulates hepatic insulin clearance and action [244]. Prolonged insulin stimulation of IR and/or hyperinsulinemia also can augment lysosomal IR degradation, leading to IR down-regulation [245, 246]. IDE, the primary insulin degrading enzyme responsible for cellular insulin processing and degradation [247], is increased in insulin-resistant subjects [248]. The rate of IR-mediated insulin clearance is significantly reduced in obese patients, and can be a sign of insulin resistance [248]. In a mouse model of diet-induced obesity, insulin clearance rate is drastically deteriorated [249]. CEACAM1, a key regulator of insulin clearance and insulin action [249, 250], is a direct substrate of SHP1, which binds and dephosphorylates CEACAM1 on tyrosine residues located in the ITIM region of its long cytoplasmic domain [251]. In the viable *motheaten* mice and mice with a temporary SHP1 disruption in the liver, insulin clearance is significantly improved [131]. $Ptpn6^{H\text{-}KO}$ mice with a hepatocyte-specific Shp1 deletion also display a more rapid insulin clearance rate [230].

Taken together, SHP1 negatively regulates glucose metabolism as an inhibitor of insulin clearance and signaling through the PI3K-Akt pathways in contribution to obesity-linked insulin resistance (Figs. 3 and 4 and Table 2).

5.2.2 SHP2

SHP2 can be physically associated with the insulin receptor and IRS-1 [252, 253, 258, 259] and is believed to be a *bona fide* negative regulator of insulin signaling, not only by direct dephosphorylation but also by adapting other inhibitory signaling molecules such as JAK2 and PKC onto IRS [254, 260]. Interestingly, hepatic SHP2 protein expression changes with nutritional status, as it decreases during fasting and increases after feeding, especially after a high-fat diet [263]. Increased activity and expression of SHP2 have been observed in skeletal muscle and liver of obese and insulin-resistant animal models [157, 158], which suggests that this PTP may be implicated in the development of obesity-associated insulin resistance. However, SHP2 was initially thought to positively regulate insulin signaling. Transgenic mice expressing a dominant-negative mutant lacking the PTP catalytic domain (ΔPTP) and inhibiting the insulin-induced association of endogenous SHP2 with IRS-1 show impaired insulin-stimulated glucose uptake and general glucose intolerance, as the activation of the IRS-1/PI3K/Akt pathway is attenuated [255]. This led to the conclusion that the inhibition of endogenous SHP2 function may diminish insulin sensitivity. However further loss-of-function studies, conducted by the generation of tissue-specific SHP2 KO animals further confirmed the negative function of SHP2 in the control of insulin action and glucose metabolism. Indeed, liver-specific SHP2 KO mice (LSHKO) exhibit improved insulin sensitivity and increased glucose tolerance compared with control mice on standard diet. Acute SHP2 deletion by tail-vein injection of adenovirus carrying Ad5-Cre yield comparable results, with improved hepatic insulin signaling via the PI3K/Akt pathway [262]. In diet-induced obesity,

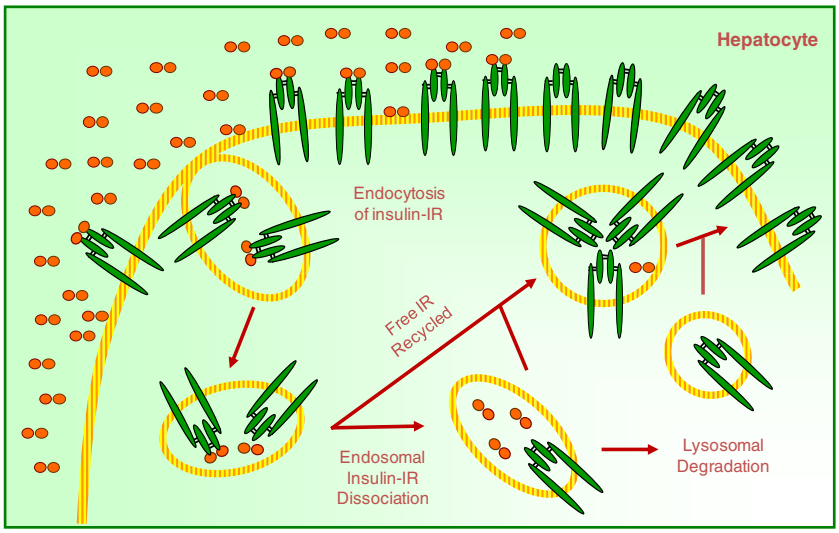

Fig. 3 Simplified scheme of IR-mediated insulin clearance in liver. Activation of IR by insulin binding induces insulin-IR-complex internalization through endocytosis in clathrin-coated vesicles. These complexes are passed from early to late endosomes, still retaining their signaling activity. During this process, insulin is dissociated from its receptor. Insulin degradation is initiated in the endosomes and finalized in the lysosomes, whereas IR can be either degraded after translocation to the lysosomes or recycled back to the plasma membrane

LSHKO show enhanced suppression of hepatic glucose production by insulin and general protection against the development of obesity-linked insulin resistance. Unlike mice with hepatic SHP1 deletion (*Ptpn6*$^{H\text{-}KO}$), LSHKO exhibit less weight gain, increased energy expenditure, and less hepatic steatosis [263]. A potential positive role for the PTP in insulin

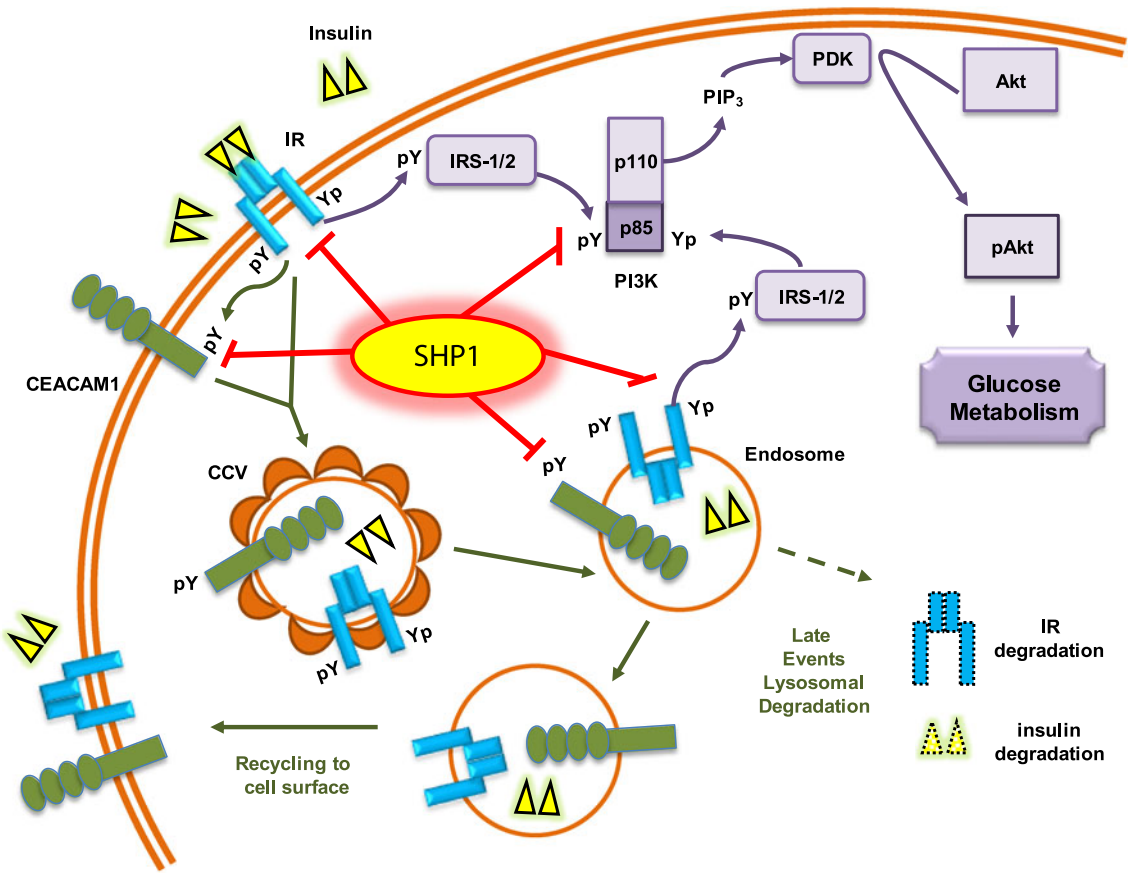

Fig. 4 Known roles of cytosolic SHP1 in the regulation of insulin signaling and of IR-CEACAM1-mediated insulin clearance and glucose metabolism. SHP1 regulates insulin clearance and insulin signaling by targeting several Tyr-phosphorylated molecules in these pathways. It modulates CEACAM1 activity by dephosphorylating it on the plasma membrane thereby down-regulating insulin-IR-complex endocytosis, but also by dephosphorylating it after internalization, thereby preventing its lysosomal degradation and favouring its recycling to the cell surface. SHP1 negatively regulates insulin signaling at different steps. It dephosphorylates the IR both on the plasma membrane and after internalization into the endosomes. It also inhibits PI3K by dephosphorylating the p85 regulatory subunit

Table 2 Summary of SHP1 and SHP2 in insulin-mediated metabolic regulations

PTP	Gene	Implication	References
SHP1	*PTPN6*	Associates with IR	Uchida et al., 1994 [222] Fiset et al., 2011 [237]
		Dephosphorylates PI3K	Yu et al., 1998 [231]
		Dephosphorylates CEACAM1	Huber et al., 1999 [251]
		Negative regulator of insulin signaling in liver and muscle	Dubois et al., 2006 [131]
		Overexpression of inactive SHP1 in muscle increases GLUT4 expression	Bergeron et al., 2011 [235]
		Hepatocyte-specific KO improves insulin sensitivity and promotes insulin clearance	Xu et al., 2012 [230]
SHP2	*PTPN11*	Binds to IR and IRS-1	Rocchi et al., 1996 [252] Walchli et al., 2000 [253]
		Connects JAK2 to IRS	Maegawa et al., 1996 [254]
		Complete KO is lethal; heterozygotes show no defect in glucose homeostasis	Arrandale et al., 1996 [255]
		Overexpression of inactive mutant in mice impairs insulin sensitivity	Maegawa et al., 1999 [256]
		Inactive mutant blocks insulin signaling to RAS	Fukunaga et al., 2000 [257]
		Negative regulator of insulin signaling via direct association with IRS-1	Tanaka et al., 1997 [258] Hayashi et al., 2004 [259]
		Required for IRS-1 S307 phosphorylation by PKC	Mussig et al., 2005 [260]
		Deletion in skeletal muscle results in insulin resistant phenotype	Princen et al., 2009 [261]
		Negative regulator of insulin signaling in the liver	Matsuo et al., 2010 [262]
		Hepatocyte-specific KO protects mice from diet-induced obesity and associated insulin resistance	Nagata et al., 2012 [263]
		Adipose-specific deletion does not alter systemic glucose homeostasis	Bettaieb et al., 2011 [264]

signaling is, however, suggested by another study which shows that SHP2-deficient mice are insulin-resistant and exhibit impaired muscle glucose uptake, which is associated with defective activation of atypical PKCz/l and AMPK [261]. However, these mice also experience severe cardiomyopathy, reflected by multiple cardiovascular disturbances, which may lead to secondary changes in skeletal muscle insulin signaling and attenuated glucose metabolism. In adipose tissue, one study of adipose-specific SHP2 deletion by *adiponectin-Cre* reports no alteration in systemic glucose homeostasis [264], while another study confirms the important role of SHP2 in the promotion of adipogenesis, as mice with adipocyte-specific deletion of SHP2 suffer from premature death, lack of white fat, low blood pressure, compensatory erythrocytosis, and hepatic steatosis [265]. Most recently, a role of SHP2 in the regulation of lipid synthesis has been found, as ubiquitination-mediated degradation of FAS can be facilitated by SHP2, the key adapter PTP for the binding of p38-activated COP1 to FAS in the FAS-SHP2-COP1 complex [266].

6 Role of PTPs in transcription regulation

In many cases, signaling pathways lead to a regulation of transcriptional processes by phosphorylation and dephosphorylation of transcription factors. Although many transcription factors have been shown to be regulated by serine and threonine phosphorylation, tyrosine phosphorylation has not been implicated in the control of many transcriptional processes with one exception. The signal transducer and activator of transcription (STAT) proteins are the prime example for a family of transcription factors whose activity is regulated by tyrosine-phosphorylation [267, 268]. In general, tyrosine-phosphorylation of STATs, which is triggered by cytokines and growth factors via their respective receptors and associated Janus kinase (JAK) proteins, results in dimerization of STAT proteins, translocation to the nucleus and ultimately in activation of transcription. This activation of the JAK-STAT pathway is counteracted by several protein tyrosine phosphatases including SHP1, SHP2, PTP1B and TC-PTP. Although this regulation of the JAK-STAT pathway by PTPs has been extensively studied in hematopoetic and cancer cells and well characterized in the leptin signaling pathway of the CNS [197, 269, 270], very little is known about PTP-mediated control of tyrosine-phosphorylation of STATs in peripheral insulin target tissues. Tyrosine-phosphorylation of STAT3 (Y705) is increased in livers of high fat-fed mice heterozygous for TC-PTP-deletion (*Ptpn2*+/−) and IL-6 treated primary hepatocytes from these mice or in primary hepatocytes where TC-PTP has been knocked-down by shRNA, implying the attenuation of STAT3 by TC-PTP [193]. Tyrosine-phosphorylation of STAT3 (Y705) is also elevated in livers from mice with a liver-specific SHP2 knock-out (*Ptpn11*−/−) fed a high-fat diet, suggesting redundancy in the dephosphorylation of STAT3 in hepatocytes [263].

Independent from STAT3 association, several other transcriptional regulators have been identified as substrates of SHP1 and SHP2. Parafibromin/Cdc73, a core subunit of the nuclear RNA polymerase II-associated factor (PAF) complex, is dephosphorylated by SHP2 and thereby converts into an inducer of Wnt target genes by stably interacting with β-catenin [271]. β-catenin itself is a target for SHP1 in epithelial cells, whose transcriptional activity is negatively regulated by SHP1-mediated dephosphorylation [272, 273]. SHP1 has also been implicated in the regulation of transcriptional processes in insulin target tissues. Down-regulation of SHP1 in muscle cells increases *GLUT4* gene expression, but the exact molecular details of this augmentation still have to be elucidated [235]. In a recent study, we found that SHP1 inhibits PPARγ-dependent transcription and thereby regulates expression of genes involved in lipid metabolism (unpublished data). Indirectly, SHP2 has been proposed to regulate adipogenesis in white adipose tissue via a SHP2-TAO2-p38-p300-PPARγ pathway, which can contribute to defective adipogenesis in obesity [265].

7 PTPs as therapeutic targets for insulin resistance

Some PTP inhibitors may be considered for combating insulin resistance and other disturbances of the metabolic syndrome. Cryptotanshinone, a common CVD drug, has been identified to inhibit SHP2 with 1.76 fold more selectivity than for SHP1 in direct binding to their catalytic pocket [217]. Cembrane diterpenoids from the soft coral Sarcophyton trocheliophorum Marenzeller are a new class of PTP1B inhibitors [274]. Ursolic acid and its derivatives, competitive inhibitors of PTP1B and SHP2, can improve insulin-stimulated glucose uptake by L6 myotubes *in vitro* [275]. PTP1B, SHP1 and SHP2, but not TC-PTP, can be inhibited by S-nitrosylation through NO, which leads to enhancement of insulin responsiveness with increased insulin signaling [276]. The structurally modified phospho-tyrosine mimetic, phosphonodifluoromethyl phenylalanine, a new PTP-MEG2 inhibitor possessing highly efficacious cellular activity to augment insulin signaling and regulation of glucose homeostasis in diet-induced obese mice has been characterized [277].

Whereas it may be worthwhile to develop novel PTP inhibitors for alleviating insulin resistance and T2D, another potential strategy is to identify selective substrates and partners of individual PTP and explore their potential for representing more selective therapeutic targets. Although the function of PTPs in glucose and lipid metabolism has been well established, very few substrates of these PTPs have been identified in insulin target tissues. Given that the nuclear localization of several PTPs has been known for 10 or more years, we are especially missing nuclear targets that are regulated by tyrosine phosphorylation. Three of the PTPs described in this review can shuttle between the cytoplasm and the nucleus. TC-PTP exists as two splice variants, a nuclear 45kD isoform and an endoplasmic reticulum-targeted 48 kD isoform [191, 278]. SHP1 and SHP2 localize to the nucleus in non-hematopoetic cells [228, 272, 279, 280]. We need mass spectrometric approaches to detect new substrates of these PTPs in insulin target tissues. One approach could be to identify the phospho-tyrosine proteome in insulin target cells or tissues with deletions of PTPs to enrich specific targets. Another way would be to identify interaction partners of PTPs in insulin target cells using substrate-trapping mutants of these PTPs in an affinity-purification mass spectrometric approach. A combination of these approaches should give us a comprehensive collection of potential PTP substrates and partners both in the cytoplasm and nucleus. First attempts have been made to detect novel proteins involved in the insulin signaling pathway, but none of them has specifically targeted PTPs [281, 282]. PhosphoSitePlus gives us a collection of many phospho-tyrosine sites in proteins including transcription factors with functions in glucose and lipid metabolism that have been identified by mass spectrometry from cells treated with general PTP inhibitors [283]. Most of these sites have no assigned function, but it could be used as a starting point to elucidate the molecular mechanisms and physiological roles of these tyrosine phosphorylation events in insulin target cells and tissues.

8 Conclusion

We have reviewed how PTPs can inactivate crucial signaling effectors in the insulin signaling cascade by dephosphorylating their tyrosine residues, and their potential implication in the development of insulin resistance and T2D. We have reviewed recent evidence implicating both SHP1 and SHP2 as new potential therapeutic targets. Clearly, we need to further advance our understanding of the mechanisms by which these PTPs regulate insulin signaling and glucose metabolism, and this will be markedly enhanced by the identification of selective partners of these enzymes in key insulin target metabolic tissues.

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Conflict of interest Authors declare no conflict of interest or financial relationship with the organization that sponsored some of the research described in this review article.

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