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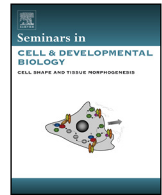

Review

Protein-tyrosine phosphatase 1B substrates and metabolic regulation

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ABSTRACT

Metabolic homeostasis requires integration of complex signaling networks which, when deregulated, contribute to metabolic syndrome and related disorders. Protein-tyrosine phosphatase 1B (PTP1B) has emerged as a key regulator of signaling networks that are implicated in metabolic diseases such as obesity and type 2 diabetes. In this review, we examine mechanisms that regulate PTP1B-substrate interaction, enzymatic activity and experimental approaches to identify PTP1B substrates. We then highlight findings that implicate PTP1B in metabolic regulation. In particular, insulin and leptin signaling are discussed as well as recently identified PTP1B substrates that are involved in endoplasmic reticulum stress response, cell–cell communication, energy balance and vesicle trafficking. In summary, PTP1B exhibits exquisite substrate specificity and is an outstanding pharmaceutical target for obesity and type 2 diabetes.

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Contents

1. Introduction 59
2. PTP1B: cellular location and post-translational regulation 59
3. Identification of PTP1B substrates 60
4. PTP1B substrates and metabolic regulation 60
   4.1. Insulin signaling 60
   4.2. Leptin signaling 60
   4.3. Endoplasmic reticulum stress response 61
   4.4. Cell–cell communication 62
   4.5. Energy balance 62
   4.6. Vesicle trafficking 62
5. Concluding remarks 63
   Acknowledgements 63
   References 63

Abbreviations: PTKs, protein-tyrosine kinases; PTPs, protein-tyrosine phosphatases; pTyr, phosphotyrosine; PTP1B, protein-tyrosine phosphatase 1B; ER, endoplasmic reticulum; EGFR, epidermal growth factor receptor; PDGFR, platelet-derived growth factor receptor; IR, insulin receptor; FRET, fluorescence resonance energy transfer; MVB, multivesicular bodies; BRET, bioluminescence resonance energy transfer; ROS, reactive oxygen species; SH3, Src-homology 3; JAK2, Janus kinase 2; TYK2, tyrosine kinase 2; IRS, insulin receptor substrate; PI3K, phosphatidylinositol 3-kinase; KO, knockout; LepRb, leptin receptor; STAT3, signal transducer and activator of transcription 3; POMC, pro-opiomelanocortin; UPR, unfolded protein response; PERK, protein kinase-like ER kinase; IRE1α, inositol requiring enzyme 1α; ATF6, activating transcription factor 6; eIF2α, eukaryotic translation initiation factor 2; GSIS, glucose-stimulated insulin secretion; ZO1, Zonula Occludens 1; AMPK, AMP-activated protein kinase; PKM2, pyruvate kinase M2; PEP, phosphoenolpyruvate; SNARE, soluble N-ethylmaleimide-sensitive factor attachment protein receptor.

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1. Introduction

Tyrosine phosphorylation is a key post-translational mechanism that regulates a plethora of cellular processes and is required for maintaining homeostasis. Aberrant changes in tyrosine phosphorylation are often associated with disease states such as metabolic disorders, cancer and cardiovascular disease. Tyrosine phosphorylation is tightly controlled by the dynamic and opposing actions of protein-tyrosine kinases (PTKs) and protein-tyrosine phosphatases (PTPs) [1,2]. PTPs are a superfamily of receptor-like and non-transmembrane proteins, whose members are highly specific, tightly regulated and important modulators of cellular signal initiation and termination [2–4]. Classical PTPs contain a 240–250 amino acid catalytic domain specific for phosphotyrosine (pTyr) residues, with a central "signature motif" containing an essential cysteine residue [5]. This review will focus on the prototypical non-receptor protein-tyrosine phosphatase 1B (PTP1B), which has become the subject of intense study and pharmaceutical interest initially owing to its role in metabolic diseases such as obesity and type 2 diabetes. We examine PTP1B cellular location, regulation of enzymatic activity and experimental approaches to identify its substrates. We then highlight the significant findings that implicate PTP1B in metabolic regulation. In particular, insulin and leptin signaling will be discussed as well as PTP1B substrates that are involved in endoplasmic reticulum (ER) stress response, cell–cell communication, energy balance and vesicle trafficking.

2. PTP1B: cellular location and post-translational regulation

PTP1B is an abundant, widely expressed non-receptor phosphatase that was originally purified from human placenta 25 years ago [6]. PTP1B is encoded by the *PTPN1* gene [7] that produces a 435 amino acid protein with a hydrophobic C-terminal sequence that targets PTP1B to the ER [8,9]. Similar to other members of the PTP family, PTP1B contains the conserved sequence [I/V]H**C**XXGXXR[S/T] (X is any amino acid) that contains the essential catalytic cysteine [3]. Due to the unique chemical environment of the phosphatase active site, the catalytic cysteine that is located at the base of the active site cleft, has an unusually low acid dissociation constant (pKa) (~5.4). The low pKa enhances the catalytic function of the cysteine as a nucleophile but renders it susceptible to oxidation [5,10–12], a modification that will be discussed later. Since PTP1B regulates many signaling pathways its function is tightly controlled to avoid aberrant cellular signaling. PTP1B sub-cellular location and post-translational modifications are key modulators of its function.

PTP1B is localized on the cytoplasmic face of the ER by means of a hydrophobic (35 residues) C-terminal sequence [8,9] that imposes topological constraint on PTP1B ability to access substrates [13]. Despite its sub-cellular location, PTP1B can access substrates during (a) endocytosis, (b) biosynthesis and (c) by the ER network movement in close proximity to the plasma membrane (PM) at apparently specialized regions. (a) Genetic and biochemical studies establish that PTP1B dephosphorylates receptor PTKs (RTKs) including the activated epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor (PDGFR) and insulin receptor (IR) [14–21]. These findings raised a question: how can the ER-resident PTP1B dephosphorylate RTKs? Fluorescence resonance energy transfer (FRET) studies demonstrate that most of the activated EGFR and PDGFR interact with PTP1B after their endocytosis at specific sites on the surface of the ER [15]. Subsequent studies extended these findings to the IR [17,21,22]. In addition, PTP1B is a potential regulator of RTKs endocytosis. PTP1B-EGFR interaction occurs through membrane contact between multivesicular bodies (MVB) and the ER, with PTP1B promoting the sequestration of EGFR to MVB [23]. In line with these findings, the endosomal protein STAM2 which regulates sorting of activated RTKs is a PTP1B substrate [24]. Therefore, PTP1B regulates RTKs dephosphorylation and endocytosis that are two key modulators of RTKs signaling. (b) PTP1B is ideally placed to prevent tyrosine phosphorylation of RTKs during their biosynthesis in the ER. FRET and bioluminescence resonance energy transfer (BRET) studies demonstrate basal interaction between PTP1B and IR, which can be enhanced by tunicamycin (an inhibitor of RTKs cell surface maturation) [17]. (c) PTP1B also can access PM substrates at regions of cell–cell contact [25–29]. Why can PTP1B dephosphorylate some substrates (such as activated RTKs) after endocytosis, whereas others are targeted on the PM? Quantitative imaging and modeling of protein mobility demonstrate that the ER network comes in close proximity to the PM at apparently specialized sites of cell–cell contact, enabling PTP1B to engage substrates at these regions [30]. Collectively, these studies establish that PTP1B location limits its ability to access substrates but is still capable of interacting with numerous substrates at diverse sub-cellular locations.

Several post-translational modifications regulate PTP1B function including: (a) oxidation, (b) nitrosylation, (c) sulfyhydration, (d) sumoylation, (e) phosphorylation and (f) proteolytic cleavage. We will briefly highlight some key findings and recent advances (extensively reviewed in [31,32]). (a) PTP1B, similar to other classical PTPs subfamily members, is susceptible to oxidation by reactive oxygen species (ROS) due to the chemical environment of its catalytic cleft [5,12]. Oxidation of the active site cysteine abrogates its nucleophilic properties and inhibits PTP1B activity. Oxidation of PTP1B catalytic cysteine rapidly converts the sulphenic acid (S-OH) to a cyclic sulphenamide and is accompanied by significant changes in the architecture of the active site [33,34]. These structural changes are reversible under physiological conditions and can help protect the enzyme from higher order ($S\text{-}O_2H$ and $S\text{-}O_3H$) irreversible oxidation and facilitate reduction back to its active form. Of note, these conformational changes were utilized to generate conformation-sensing intracellular antibodies that maintain PTP1B in an inactive state, and may have therapeutic applications [35]. ROS functions as an intracellular second messenger and activation of RTKs leads to transient production of H_2O_2 which is needed for receptor activation [36]. Stimulus-induced ROS production transiently inactivates PTP1B, which usually exerts inhibitory effects on the system, to initiate a response to the stimulus. Indeed, epidermal growth factor [37] and insulin [38] stimulation leads to reversible oxidation of PTP1B and attenuation of its enzymatic activity. (b) Similar to ROS, reactive nitrogen species inactivate PTP1B [39]. In particular, *S*-nitrosylation prevents PTP1B active site cysteine from subsequent oxidation when subjected to oxidative stress, and thus plays a protective role against irreversible oxidation [40]. (c) In addition, PTP1B is reversibly inactivated by endogenously generated hydrogen sulphide during the ER stress response through sulfhydration of the active site cysteine [41]. Sulfyhydration of PTP1B provides a potential mechanism for regulating ER stress response. (d) PTP1B is sumoylated on two lysine residues (Lys335 and 347) and its ER-targeting domain is required for maximum sumoylation [42]. Importantly, insulin-induced sumoylation of PTP1B transiently attenuates its enzymatic activity and inhibits the negative effect of PTP1B on insulin signaling [42]. Further, this modification also affects PTP1B-mediated dephosphorylation of emerin, an inner nuclear membrane protein that regulates nuclear architecture [43]. (e) PTP1B is phosphorylated on tyrosine and serine residues, which can either enhance or attenuate its enzymatic activity. Insulin stimulates PTP1B tyrosine phosphorylation (Tyr66, 152 and 153) [44], and results in increased phosphatase activity [45]. On the other hand, insulin induces PTP1B tyrosine phosphorylation and decreases its activity in skeletal muscle and adipose

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