Protein Phosphotyrosine Phosphatase 1B: Structure, Function, Role in the Development of Metabolic Disorders and Their Correction by the Enzyme Inhibitors

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Abstract—Protein phosphotyrosine phosphatase 1B (PPTP1B) dephosphorylates receptor and nonreceptor forms of tyrosine kinases, causing the inhibition of their activity and thus regulating appropriate signaling cascades. Increased PPTP1B activity leads to insulin and leptin resistance, being among the causes of type 2 diabetes mellitus and many other metabolic and functional disorders. Selective PPTP1B inhibitors normalize functions of insulin, leptin and some other systems comprising different forms of tyrosine kinases as signaling components, and their development is a promising approach to treat and prevent metabolic disorders. Currently, an active search is in progress for “binary” PPTP1B inhibitors able to interact simultaneously with the catalytic and allosteric sites of the enzyme, providing thereby high efficiency and selectivity of their action. This review focuses on the status quo of the problem of studying the structure, functions and regulatory properties of PPTP1B, its role in the development of metabolic disorders, as well as on recent advances in designing selective PPTP1B inhibitors.

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INTRODUCTION

In the recent years, studies of etiology and pathogenesis of type 2 diabetes mellitus (DM2), metabolic syndrome (MS), nonalcoholic hepatic steatosis and other metabolic and endocrine dysfunctions pay ever increasing attention to the role of changing activity of protein phosphotyrosine phosphatases (PPTP) in the development of these pathologies [1, 2]. Increased activity of these enzymes causes dephosphorylation of many receptor and nonreceptor tyrosine kinases and disrupts thereby transmission of appropriate hormonal signals to the cell. The consequence of this disruption is the development of tissue resistance to hormones, growth factors and cytokines, which, in turn, leads to dysregulation of fundamental cellular processes. All the above-said indicates that a study of the structural and functional organization of PPTP and molecular mechanisms of their interplay with other signaling proteins as well as the development of novel approaches to selective
regulation of their activity are tasks of high priority for contemporary biochemistry, physiology and medicine. The greatest interest among other PPTP attracts protein phosphotyrosine phosphatase 1B (PPTP1B), which controls activity of multiple signaling cascades regulated by such important hormones and growth factors as insulin, leptin, epidermal growth factor (EGF), insulin-like growth factor 1, platelet-derived growth factor (PDGF) [3–5]. Despite numerous studies of PPTP1B, there are still many blank spots and unsolved issues in understanding the molecular mechanisms of PPTP1B action and the role of this enzyme in the genesis of metabolic and endocrine disorders. Currently, many inhibitors of PPTP1B having different chemical identity, specificity and efficiency are developed [6, 7]. However, there is only a handful of real medicines based on selective PPTP1B inhibitors that were brought to the clinical trial stage. This review addresses the status quo of the problem of studying the structure, functions and regulatory properties of PPTP1B, its role in the development of metabolic disorders (primarily, DM2 and MS), and recent advances in designing selective PPTP1B inhibitors.

STRUCTURAL AND FUNCTIONAL ORGANIZATION OF PROTEIN PHOSPHOTYROSINE PHOSPHATASE 1B, ITS TARGETS AND REGULATORY PROPERTIES

PPTP1B is a representative of the large family of tyrosine phosphatases, which encompasses about 100 isoforms and is subdivided into two classes—“classical” PPTP specific to phosphotyrosine (pTyr) and dual-specificity phosphatases that dephosphorylate not only pTyr, but also phosphoserine and phosphothreonine residues. Depending on the localization in the cell, the “classical” PPTP themselves are subdivided into two subclasses—membrane-anchored receptor forms and cytosolic forms with no transmembrane domains; it is the latter that include PPTP1B. Catalytic sites in all PPTP, including PPTP1B, accommodate two hydrophilic loops—the P-loop (I/V) HCXAGXXR(S/T)G with the highly conserved cysteine residue responsible for the specific interaction with the phosphate group of the substrate, and the WD loop that provides dephosphorylation.

PPTP1B, encoded by the PTPN1 gene, is the most studied enzyme in the PPTP family due to its utmost importance for the regulation of multiple signaling and effector proteins, controlling a wide range of biochemical and physiological functions. In 1994, based on X-ray diffraction analysis, the three-dimensional structure of PPTP1B has been identified, having triggered an intensive research on deciphering the molecular mechanisms of the enzyme’s functioning and creating selective regulators of its activity [8]. The enzyme contains 435 amino acid residues and the catalytic domain 30–278 as well as the hydrophobic COOH-terminal region, containing 35 amino acid residues and anchoring the PPTP1B molecule on the cytoplasmic side of the endoplasmic reticulum (ER). Despite the ER localization, PPTP1B can interact with substrate proteins located near or anchored in the plasma membrane as well as with substrate proteins that translocate in the ER cisternae during their synthesis and endocytosis [5].

The PPTP1B catalytic site is deepened by 8–9 Å relative to the enzyme’s surface and comprises the phosphate-binding loop His–Cys–Ser–Ala–Gly–Ile–Gly–Arg214–221 (P-loop). The phosphate group of the substrate forms several hydrogen bonds with hydrogen atoms in amide bonds and with the Arg221 residue in the P-loop. After binding the enzyme to the substrate, the WD loop (sequence 79–187) shifts by 10 Å, affording to cover the pTyr phenylphosphate group and provide a rapprochement between the Asp181 residue and phosphoether bond in the pTyr molecule with subsequent protonation of its oxygen atom. At the same time, the Cys215 residue approaches the phosphorus atom and forms a covalent bond with it, leading to the cleavage of the P–O bond and formation of the phosphocysteine intermediate; the latter is then hydrolyzed, releasing the phosphoric acid residue. It should be noted that the cysteine residue located in the depth of the catalytic site, due to its unique setting, has an unusually low pK_a value (about 5.4) and functions in the enzymatic reaction as a nucleophilic agent [9]. At the same time, however, the Cys215 resistance to oxidation diminishes, providing one of the mechanisms that regulate functional activity of PPTP1B. The specificity of interaction with the pTyr-containing sites