Review

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Protein tyrosine phosphatases: molecular switches in metabolism and diabetes

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Protein tyrosine phosphatases (PTPs) are a large family of enzymes that generally oppose the actions of protein tyrosine kinases (PTKs). Genetic polymorphisms for particular PTPs are associated with altered risk of both type 1 diabetes (T1D) and type 2 diabetes (T2D). Moreover, recent evidence suggests that PTPs play crucial roles in metabolism. They can act as regulators of liver homeostasis, food intake, or immune-mediated pancreatic β cell death. In this review we describe the mechanisms by which different members of the non-receptor PTP (PTPN) family influence metabolic physiology. This 'metabolic job' of PTPs is discussed in depth and the role of these proteins in different cell types compared. Understanding the pathways regulated by PTPs will provide novel therapeutic strategies for the treatment of diabetes.

PTP function

PTPs were initially described as a small family of ubiquitously expressed enzymes with generalized housekeeping roles. They are responsible for the modulation of PTK activity through dephosphorylation of various tyrosine residues on intracellular proteins, thus regulating cellular events such as ligand-mediated receptor signaling as well as cell cycle events [1]. Although initially overlooked, it is now clear that PTP actions have great implication in modulation of cellular function [1], which became apparent as the importance of stringent protein phosphorylation levels in signaling events to maintain cellular homeostasis was recognized. Loss of this tight regulation in protein phosphorylation results in over- or underactivation of key signaling pathways which have been implicated in the pathogenesis of various diseases including diabetes [1].

Over 100 members in the PTP family have been described that are divided into four classes (I–IV) depending on substrate specificity and protein structure [2] (Box 1). Class I PTPNs are currently the most understood subfamily with significant implications in metabolism [1,3]. While other phosphatases, including the receptor-type PTPs, also have reported roles relevant to diabetes, these have been reviewed elsewhere [4,5]. In this review we will discuss the actions of the class I PTPNs in insulin-responsive tissues and cells, during insulin resistance and in the development of diabetes. A better understating of PTPN function during disease development will aid the discovery of novel therapeutic approaches to treating diabetes.

PTP polymorphisms and diabetes

The class I non-receptor PTPs are encoded by 17 genes located on 12 different chromosomes (Table 1). Important members for metabolic regulation include PTPN1, PTPN2, PTPN6, PTPN9, PTPN11, and PTPN22. Analysis of genomic sequence suggests that these PTPs are generally well conserved between human and mouse, with several common polymorphisms being found in the human population in the 5′, 3′, and intronic regions of these genes [6,7]. A perfunctory analysis of expression profiles based on expressed sequence tags (ESTs) also points to possible transcript isoforms that are likely to exist for these various PTPs, but are not yet characterized [7]. More recently, genetic studies have identified various polymorphisms within a select number of *PTPN* genes that are associated with either T1D or T2D (Table 2). Polymorphisms for *PTPN2* and *PTPN22*, the latter encoding a lymphoid tyrosine phosphatase, in particular, exhibit strong association with T1D, a metabolic disease brought on by autoimmune destruction of insulin-producing β cells [8–15]. *PTPN11* is also located within a region for which polymorphisms are associated with T1D, but the candidate gene harboring the strongest associated polymorphisms within this region is *SH2B3*, a gene that encodes a protein regulator of cell growth and cytokine receptor-mediated signaling [12,15]. In contrast to these *PTPN* genes, polymorphisms for *PTPN1* have been associated with T2D, a metabolic disease characterized by obesity and an inadequate β cell response to progressive insulin resistance [16]. Nonetheless, these associations for *PTPN1* polymorphisms have not been replicated in all diabetic populations tested [16], suggesting that further refinement of patient phenotypes and genetic heterogeneity may be required to identify the role of PTPs in T2D. Moreover, functional studies are now required to confirm the effects of particular polymorphisms, and whether or not they are causative mutations for T1D and/or T2D.

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Box 1. PTP structure

The similarity between the structures of PTP enzymes became apparent after the structures of PTPN1/PTP1B [94] and *Yersinia* PTP (Yop51) [95] were resolved. Additional crystal structures then enabled vertebrate PTPs to be superimposed, further demonstrating a high conservation of tertiary structure [1]. This allowed evaluation of a Cα-backbone located on the second α-helix, through which the evolution of PTPs could be tracked by amino acid derivatives in the coding sequence. The tertiary structure of these enzymes is typically composed of a central highly twisted β-sheet core, flanked by α-helices on both sides [2]. The PTP signature loop is located between the C-terminus of the β-sheet and a neighboring α-helix. The activity of PTPs resides in the iconic signature motif encoded by the sequence Cys-X_5-Arg (Figure I). This sequence forms the active phosphate-binding domain where phosphorylated residues interact with the nucleophilic Cys residue, allowing hydrolysis and removal of the phosphate group. Because this sequence is vital for catalytic activity, it is highly conserved throughout all species in the enzyme family. Interestingly, the Cys residue is highly susceptible to oxidation and inactivation by reactive oxygen species (Box 2). The signature motif also contains a highly conserved Arg residue. This residue has been found to interact with the oxygen residues of the substrate phosphate group, forming bidentate hydrogen bonds to help stabilize the substrate once it enters the binding pocket [96].

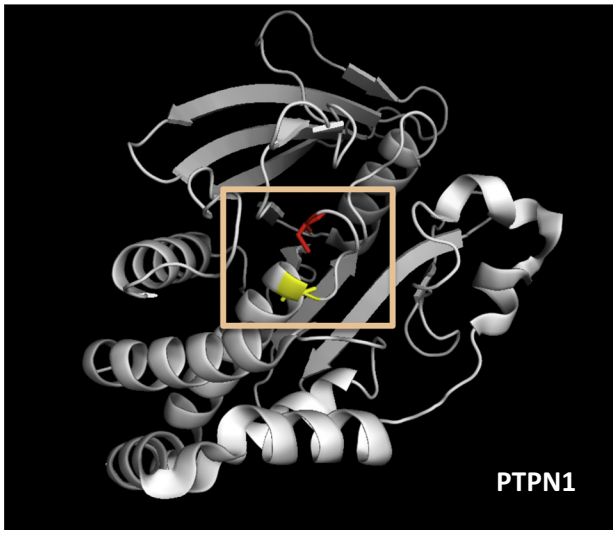

Figure I. Human PTPN1 crystal structure. PDB ID code 3A5J with the motif Cys (red)-X_5-Arg (yellow) highlighted. The model was prepared using the PyMOL molecular graphics system.

The role of PTPs in β cell and immune cell function associated with T1D

A role for the function of PTPs in both immune and β cells has been implicated in the development of T1D. In early stages of the disease, T cells and antigen-presenting cells (APCs) infiltrate the pancreas and secrete proinflammatory cytokines such as interferons (IFNs) that contribute to β cell dysfunction and apoptosis (Figure 1) [17,18]. Signal transduction via IFN receptors on the surface of β cells activates the tyrosine kinases JAK1 and JAK2, which phosphorylate the transcription factor STAT1. Phosphorylated STAT1 dimerizes and translocates to the nucleus where it activates the transcription of chemokines and pro-apoptotic molecules (Figure 1). There is extensive evidence that this transcriptional pathway modulates immune-mediated β cell dysfunction and death. First, deficiency of STAT1 in non-obese diabetic (NOD) mice prevents islet inflammation and the development of hyperglycemia [19]. Second, disruption of STAT1 protects β cells against immune-mediated destruction induced by multiple low doses of streptozotocin [20]. Finally, overexpression of the STAT inhibitor suppressor of cytokine signaling-1 (SOCS-1) in β cells dephosphorylates and inhibits STAT1 action and IFN signaling, and protects NOD mice from insulitis and diabetes [21]. Thus, excessive activation of JAK/STAT signaling in β cells during the inflammatory process contributes to the demise of the β cell itself. Inactivation of PTPN2, a susceptibility gene for T1D (noted above), in β cells results in enhanced STAT1 phosphorylation and sensitization to apoptosis induced by IFN-α, IFN-β, and IFN-γ [22–24]. Silencing of the pro-apoptotic molecule Bim prevents β cell death induced by knockdown of PTPN2 and IFN treatment (Figure 1) [23]. Intriguingly, inactivation of *BACH2*, another T1D susceptibility gene [15], results in downregulation of PTPN2, activation of Bim, and subsequent β cell apoptosis, after exposure to proinflammatory cytokines [25]. These combined observations indicate that PTPN2 plays an important role in β cell survival by regulating IFN-induced STAT1/Bim activation and apoptosis caused by islet inflammation.

PTPs also affect the function of self-reactive T cells, which participate in β cell destruction [17]. For example, PTPN2-deficient T cells exhibit enhanced activation and proliferation by negatively regulating T cell receptor (TCR) signaling via dephosphorylation of lymphocyte-specific protein tyrosine kinase (LCK) (Figure 1) [26]. Moreover, $CD8^+$ T cells lacking PTPN2 and cross-primed by β cell self-antigens escape tolerance and acquire cytotoxic T cell activity, resulting in β cell destruction in the RIP-mOVA mouse model of autoimmune diabetes [27]. Allelic variation for the gene encoding lymphoid tyrosine phosphatase PTPN22 also demonstrates strong association with autoimmune diseases, highlighting its crucial role in lymphoid-derived cells ([28] for comprehensive review). In particular, the missense *C1858T* polymorphism for *PTPN22* leads to a R620W substitution and is associated with an increased risk of T1D [8–13]. Similarly to PTPN2, PTPN22 negatively regulates TCR signaling by dephosphorylating LCK and the T cell surface protein ζ-chain-associated protein kinase 70 (ZAP-70) (Figure 1) [29]. However, the function of PTPN22 and the effect of the R620W mutation during the development of T1D are still not well understood. On one hand, overexpression of PTPN22 has been shown to attenuate the deleterious effects of TCR signaling in NOD mice [30]. On the other hand, PTPN22 silencing confers protection from autoimmunity in NOD mice [31]. Moreover, *in vitro* and *in vivo* studies of T cell development and function show that the R620W mutation confers loss of function [32,33], gain of function [34,35], or abnormal function [36] upon TCR signaling. Hence the effect of this mutation remains unclear in both human disease and mouse models of T1D. Further studies are still