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Review

Mining the function of protein tyrosine phosphatases in health and disease

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ABSTRACT

Protein tyrosine phosphatases (PTPs) play a crucial role in the regulation of human health and it is now clear that PTP dysfunction is causal to a variety of human diseases. Research in the PTP field has accelerated dramatically over the last decade fueled by cutting-edge technologies in genomic and proteomic techniques. This system-wide non-biased approach when applied to the discovery of PTP function has led to the elucidation of new and unanticipated roles for the PTPs. These discoveries, driven by genomic and proteomic approaches, have uncovered novel PTP findings that range from those that describe fundamental cell signaling mechanisms to implications for PTPs as novel therapeutic targets for the treatment of human disease. This review will discuss how new PTP functions have been uncovered through studies that have utilized genomic and proteomic technologies and strategies.

Contents

1. Introduction

Protein tyrosyl phosphorylation is fundamental to the maintenance of numerous cellular functions including gene expression, cell growth, differentiation, migration, adhesion and apoptosis [1]. The net level of cellular protein tyrosyl phosphorylation is balanced by the opposing actions of both protein tyrosine kinases (PTKs) andprotein tyrosine phosphatases (PTPs). The importance of maintaining homeostatic control of cellular tyrosyl phosphorylation is exemplified by the observation that dysregulation of these processes often results in the development of diverse pathophysiological conditions that can include cancer, metabolic, neuronal and immunological diseases [2].

There are a number of excellent reviews that have been published on the PTPs. There are reviews that cover the PTP field from a historical perspective [3]. Whilst others have focused on the role of PTPs in hereditary human diseases [2] as well as viral and bacterial pathogenesis [4]. Comprehensive reviews also exist on PTPs in human cancer [5] and the involvement of lipid-phosphatases in human disease [6]. RPTPs and the biological insight uncovered by the solution of several RPTP crystal structures have also been topics of discussion [7,8]. We direct the reader to these sources for more

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comprehensive discussions since this review will focus largely on the application of non-biased screens as a discovery tool for PTP function.

In many regards PTP research continues to progress rapidly as a function of the emergence of new technological advances in the biological sciences. These include in more recent years the explosion of system-wide non-biased approaches using genomic and proteomic strategies. The goal of this review will be to focus on some of the more recent discoveries in the PTP field that have utilized approaches in genomics and proteomics to uncover PTP function. The application of system-wide non-biased strategies to PTP research has revealed new functions of PTPs in a variety of physiological and pathophysiological settings that highlight the critical role played by these enzymes in cell signaling. This review will focus on the discoveries of PTP function that utilize these types of system-wide non-biased strategies.

2. The PTP superfamily

The classical PTPs include 16 non-transmembrane PTPs and 21 receptor-like PTPs (RPTPs) all of which contain a common conserved core catalytic PTP domain defined by the signature motif $C(X)_5R$ [9] (Fig. 1). The classical PTPs are classified into 17 PTP subtypes: nine non-transmembrane (NT1 to NT9) and eight receptor types (R1/R6, R2a, R2b, R3, R4, R5, R7, and R8) (Fig. 1) [9]. The non-transmembrane PTPs exhibit a variety of non-catalytic domains that mediate functions such as protein–protein interactions (e.g. SH2 and PDZ domains), lipid-binding domains (e.g. FERM) and sub-cellular targeting motifs (e.g. PTP-1B C-terminal ER targeting motif). These non-catalytic domains also play key roles in the regulation of phosphatase activity by coordinating intramolecular interactions that engage in conformational changes that either activate or inactivate PTP catalysis. Furthermore, the post-translational modifications of PTPs, such as proteolysis, phosphorylation, and oxidation, also participate in sub-cellular localization, protein–protein interactions, regulation of catalytic activity, and protein stability [10–13].

RPTPs comprise of variable extracellular domains, a single transmembrane domain, and a cytoplasmic domain containing two, and in some cases, a single PTP domain [14,15]. Since their extracellular domains are similar in structure to the extracellular domains found in cell adhesion molecules RPTPs appear to be involved in cell–cell and cell–matrix communications [7]. Typically, ligand binding to the extracellular domain of an RPTP induces dimerization that leads to the inhibition of its catalytic activity [16–19]. In the dimeric state, reciprocal inhibition of the catalytically competent proximal D1 PTP domain occurs whereby the “wedge motif” of one D1 domain occludes the active site of the opposing D1 PTP domain in the dimer [15,19]. The distal, D2 PTP domain is catalytically inactive although it provides important regulatory functions such as stabilizing substrate interactions, mediating protein–protein interactions and facilitating RPTP dimerization [17,20–23]. Although this mechanism of dimerized-induced PTP inhibition exists for some RPTPs it is still unclear as to how conserved this mode of PTP operation is amongst the entire RPTP family.

The dual-specificity phosphatase (DUSP) family of PTPs comprises of PTPs that dephosphorylate both lipid and protein substrates. The more extensively characterized sub-family of DUSPs are those that catalyze the dephosphorylation of the mitogen-activated protein kinase (MAPK) phosphatases (MKPs). The MKP family comprises of ten catalytically active enzymes that share a common PTP catalytic domain at their carboxyl terminus and a non-catalytic regulatory domain at the amino terminus (Fig. 2) [24–26]. The amino-terminus non-catalytic domain contains a cdc25 homology (CH2) domain and a kinase interaction motif that binds directly to the MAPKs in order to coordinate MKP-MAPK substrate dephosphorylation [27,28]. These enzymes are classified based upon substrate specificity, sequence similarity and sub-cellular distribution into three groups namely; Type I, Type II and Type III [29,30]. Type I MKPs consist of MKP-1, MKP-2, PAC1 and hVH3. This group of MKPs primarily localizes to the nuclear compartment and is induced by many stimuli that activate MAPKs. Type II MKPs, which selectively dephosphorylate ERK, include MKP-3, MKP-X and MKP-4 and they are localized to the cytoplasm. Type III consists of MKP-5, MKP-7, and M3/6, which shuttle between the cytoplasm and nucleus. They selectively dephosphorylate JNK and p38 MAPK but exhibit much less activity toward ERK1/2 [31]. In addition to the classical DUSPs there are also 16 members of the atypical DUSPs that lack the NH2-terminal CH2 domain found in the MKPs but consist of the DUSP catalytic domain (Fig. 2) [32].

3. New approaches to uncovering PTP function

The following sections will highlight how PTPs have been implicated in various processes and their function further realized through the use of unbiased system-wide screening strategies in genomics and proteomics. These approaches include the use of siRNA/shRNA and phosphoproteomics screens coupled with PTP-specific technologies such as substrate-trapping for the identification of PTP substrates.

4. PTP function revealed by siRNA and shRNA screening

Genome-wide siRNA/shRNA screening has proven to be a very powerful tool for the discovery of new gene functions. Recently, these applications have been used to identify new and novel functions of PTPs. One of the major advantages of siRNA/shRNA screening largely revolves around the ability to design strategies that uncover functional effects of genes in an unbiased and system-wide manner. High-throughput screening at the genome-wide level has been performed based on the outcome of specific cellular phenotypes that include cell migration, apoptosis and proliferation in a variety of cell types including epithelial cells, endothelial cells and various cancer cell lines. Collectively, the use of siRNA/shRNA approaches has been a successful strategy for uncovering new PTP functions.

Loss-of-function strategies using siRNA/shRNA approaches have focused predominantly on the identification of genes that have specific cellular phenotypes such as cell migration, apoptosis or proliferation. In contrast, others approaches using siRNA/shRNA screens have employed strategies in which a specific sub-family of genes have been selectively targeted and the analysis of the outcome broad in order to capture new functions for the targeted genes (Fig. 3). In addition, siRNA/shRNA knockdown approaches have been coupled with other methodologies that further enhance the assignment of gene functionality to a specific molecular mechanism, as is the case with the application of substrate-trapping approaches for the PTPs (Fig. 3).

Using a siRNA library targeting 1081 human genes Simpson et al. identified genes that were involved in epithelial cell migration using MCF10A human breast epithelial cells [33]. Of the numerous genes identified several PTPs such as PTPRO, DUSP18, and DUSP24 were found to be involved in either positively or negatively regulating epithelial cell migration. A customized siRNA human kinase library targeted 650 genes, with the phosphatase library targeting 222 genes, which was used to identify new regulators of apoptosis and chemoresistance in cancer cell lines [34]. Of the genes screened, several PTPs were found to be either upregulated or downregulated in chemosensitive states. These included DUSP-5, INPP5A, MTMR7, PPP6C, and PSPH. The SH2