

# Phosphoprotein Phosphatases (Tyrosine)

## Key References

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## Overview

Protein tyrosine phosphatases (PTPs) and related enzymes (more than a hundred coded by the human genome) are more numerous than serine/threonine phosphatases. They belong to four families, three of which possess a conserved cysteine for catalysis and some conserved features of 3-dimensional structure. The catalytic mechanism of these PTPs involves the transient formation of a covalently phosphorylated enzyme.

Class I cysteine-based PTPs include "classical" PTPs and dual specificity phosphatases (i.e. able to dephosphorylate serine or threonine residues, as well as tyrosines). The "classical" PTPs are further subdivided into receptor-like PTPs (RPTP), which possess a single transmembrane domain and a large extracellular domain, and non-receptor PTPs (NRTPs) which lack such domains. Although the structural features of RPTPs suggest that they may function as receptors, their putative regulatory ligands remain to be identified. RPTPs are involved in cell-cell or cell-matrix interactions and have properties in common with adhesion molecules. Thus, the main role of the extracellular receptor-like domain may be to enrich tyrosine phosphatases at specific locations. RPTPs are implicated, among other functions, in neurite outgrowth, and focal adhesions and adherens junctions regulation.

Many non-receptor PTPs have targeting domains, including SH2 (Src-homology 2), FERM (four-point-one, ezrin, radixin, moesin), and membrane targeting domains. In lymphocytes, for example, SH2-containing PTPs are recruited to specific tyrosine phosphorylated motifs (ITIMs - immunoreceptor tyrosine-based inhibition motifs) and participate in the modulation of the immune response. PTP1B is targeted by its

hydrophobic C-terminus to the cytoplasmic face of endoplasmic reticulum membranes. Dual specificity phosphatases are related to the product of the vaccinia virus H1 gene (VH-1). Members of this group, termed MAP-kinases phosphatases (MKPs), dephosphorylate MAP kinases. Several MKPs are induced by MAP kinase pathways and provide a negative feedback mechanism. VH-1 gene family also includes enzymes (PTENs and myotubularins) that have a specificity for other substrates such as phosphatidylinositol-3-phosphate.

Class II cysteine-based PTPs include a single member in the human genome, the "low molecular weight PTP". Although this enzyme can dephosphorylate a number of tyrosine kinases and their substrates, its precise physiological role is still poorly understood.

Class III cysteine-based PTPs include the three Cdc25 cell cycle regulators. These enzymes are structurally related to a group of sulfurtransferases termed the rhodanases. Cdc25 plays a critical role in the control of the cell cycle by dephosphorylating the dually phosphorylated N-terminal Thr-Tyr motif of cyclin-dependent kinases (Cdks). The last and distinct class IV of potential PTPs, characterized by an aspartate-based, cation-dependent catalysis, comprises the EyA gene products. The physiological role of these enzymes in the control of tyrosine phosphorylation is not yet known.

While many phosphatases inhibit the activities of phosphorylation cascades, some activate them. CD45, for example, activates Src family tyrosine kinases by dephosphorylating an inhibitory phosphotyrosine residue, while Cdc25 activates Cdks. In addition to their physiological role, PTPs are used as

weapons by pathogenic microorganisms. For instance, one of the virulence genes of *Yersinia* bacteria (to which belongs the agent of bubonic plague) codes for a PTP.

The specific activities of PTPs are very high and these enzymes are tightly regulated within cells. Mechanisms of control include protein-protein interactions and restriction to specific locations by precise targeting. Reactive oxygen species reversibly inactivate the catalytic cysteine of PTPs and their role in the physiological regulation of PTPs is supported by several studies. Most of the pharmacological inhibitors of PTPs are nonspecific and include agents that mimic phosphorylated residues or oxidize the catalytic cysteine. Since PTP1B opposes insulin action and Cdc25 controls cell cycle, research for specific inhibitors of these enzymes is very active. Some interesting compounds have been identified, including benzofuran/benzothiofene biphenyl oxo-acetic acids and sulfonyl-salicylic acids derivatives as inhibitors of PTP1B.

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	← CLASS 1 CYSTEINE-BASED PTPs →			CLASS II CYS-BASED	CLASS III CYS-BASED
<b>GENE FAMILY</b>	Classical PTPs Receptor-like	Classical PTPs Non-receptor	VH-1 group	Low MW PTPs	Cdc25 A, B, C
<b>MOLECULAR WEIGHT (kDa)</b>	Variable	Variable	30-50	~18	30-40
<b>SUBSTRATE SPECIFICITY</b>	P-Tyr, broad	P-Tyr, broad	Dual specificities, MAP-kinases	P-Tyr, broad	Dual specificities, Cdks
<b>INHIBITORS</b>	Orthovanadate ( <b>S6508</b> ), Pervanadate, bpV(phen), Phenylarsine oxide ( <b>P3075</b> ), Dephostatin ( <b>D8065</b> ), Ethyl-3,4-dephostatin ( <b>E1904</b> ), PTP inhibitors I, II, III	Orthovanadate ( <b>S6508</b> ), Pervanadate, bpV(phen), Phenylarsine oxide ( <b>P3075</b> ), Dephostatin ( <b>D8065</b> ), Ethyl-3,4-dephostatin ( <b>E1904</b> ), PTP inhibitors I, II, III	Vanadate ( <b>S6508</b> )	Vanadate ( <b>S6508</b> )	Vanadate ( <b>S6508</b> ) NO H <sub>2</sub> O <sub>2</sub> ( <b>H1009</b> )
<b>TISSUE EXPRESSION</b>	Variable	Variable	Ubiquitous	Ubiquitous	Ubiquitous
<b>PHYSIOLOGICAL FUNCTION</b>	Inhibit, sometimes activate signaling	Inhibit, sometimes activate signaling	Negative feedback on MAP-kinases	Inhibit tyrosine kinase signaling	Cell cycle regulation
<b>DISEASE RELEVANCE</b>	Possible role in cancer, immune disorders diabetes, immune disorders target in diabetes (PTP1B)	Yersinia toxin possible role in cancer,	Not known	Not known	Possible oncogene

## Abbreviations

**BpV(phen):** Bisperoxo(1,10-phenanthroline)oxovanadate (V)

**Cdk:** Cyclin-dependent kinase

**PTP:** Protein tyrosine phosphatase

**VH-1:** Product of vaccinia virus gene H1

## FOOTNOTES