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Review

Low molecular weight protein tyrosine phosphatase: Multifaceted functions of an evolutionarily conserved enzyme

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ABSTRACT

Originally identified as a low molecular weight acid phosphatase, LMW-PTP is actually a protein tyrosine phosphatase that acts on many phosphotyrosine-containing cellular proteins that are primarily involved in signal transduction. Differences in sequence, structure, and substrate recognition as well as in subcellular localization in different organisms enable LMW-PTP to exert many different functions. In fact, during evolution, the LMW-PTP structure adapted to perform different catalytic actions depending on the organism type. In bacteria, this enzyme is involved in the biosynthesis of group 1 and 4 capsules, but it is also a virulence factor in pathogenic strains. In yeast, LMW-PTPs dephosphorylate immunophilin Fpr3, a peptidyl-prolyl-*cis-trans* isomerase member of the protein chaperone family. In humans, LMW-PTP is encoded by the ACP1 gene, which is composed of three different alleles, each encoding two active enzymes produced by alternative RNA splicing. In animals, LMW-PTP dephosphorylates a number of growth factor receptors and modulates their signalling processes. The involvement of LMW-PTP in cancer progression and in insulin receptor regulation as well as its actions as a virulence factor in a number of pathogenic bacterial strains may promote the search for potent, selective and bioavailable LMW-PTP inhibitors.

1. Introduction

Protein tyrosine phosphorylation is involved in many processes in eukaryotic cells, including growth, mobility, differentiation, metabolism, and immune responses. However, several reports published in the last two decades have demonstrated that protein tyrosine phosphorylation is also important in several functions in prokaryotes, including the synthesis of bacterial exopolysaccharides (EPS). Overall, >100 human PTPs are known [1]. They are divided into four distinct classes: class I is the largest group of PTPs and includes "classical" PTPs and the VH1-like ("dual-specific") PTPs; Class II contains only one member, the Low Molecular Weight PTP (LMW-PTP); Class III contains Tyr/Thr-specific PTPs, which are represented by three $p80^{cdc25}$ involved in cell cycle regulation; and Class IV includes Tyr or dual Ser/Thr-specific PTPs. All members of classes I–II–III use a cysteine-based catalytic mechanism, whereas class IV PTPs use a key reactive aspartate residue. This review will focus on LMW-PTP, one of the most ancient enzymes acting as a tyrosine phosphatase, and on its different roles acquired during evolution. LMW-PTPs are found widely in prokaryotes and eukaryotes and have evolved from an ancestral gene common to bacterial arsenate reductases, which are enzymes involved in arsenic detoxification systems. Arsenate reductases and LMW-PTPs are strictly related in terms of both structure (Fig. 1) and catalytic mechanism but acquired peculiar and distinct functions during evolution [2]. LMW-PTP is expressed in all organisms, whereas most PTPs (including PTP1B, CD45, LAR, Shp1, Shp2, PTPα, PTPβ, PTPγ, and others) are expressed exclusively in eukaryotes. LMW-PTP does not share either sequence homology or 3D fold similarity to other PTPs, despite a common catalytic mechanism and a similar P-loop structure. All PTPs contain a sequence signature

Abbreviations: PTP, protein tyrosine phosphatase; PTK, protein tyrosine kinase; LMW-PTP, low molecular weight protein tyrosine phosphatase; LMW-AP, low molecular weight acid phosphatase; ACP1, gene coding for human LMW-PTP; PTP1B, tyrosine-protein phosphatase non-receptor type 1; SHP-2, a SH2-containing PTP; IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus; EGF, epidermal growth factor; PDGF, platelet-derived growth factor; PDGFR, PDGF receptor; VEGF, vascular endothelial growth factor; IGF, insulin-like growth factor; TGFβ, transforming growth factor-β; TAK1, TGFβ activated kinase 1; c-Src, cellular Src tyrosine kinase; FAK, focal adesion kinase; ERK, extracellular signal-regulated kinase; PI3K, phosphatidyl inositol 3 kinase; JAK, Janus kinase; Grb2, growth factor receptor-bound protein 2; p190RhoGAP, a negative regulator of RhoGTPases; VSMCs, vascular smooth muscle cells; ROS, reactive oxygen species; SH3, Src homology 3 domain; LFA-1, lymphocyte function-associated antigen-1; ZAP-70, zeta-chain-associated protein kinase 70; FcγRIIA, platelet low-affinity receptor for immunoglobulin G; NGF, nerve growth factor; STAT, signal transducer and activator of transcription; Eph, ephrin; NFκB, nuclear factor kappa B; EMT, epithelial–mesenchymal transition; Fpr3, a novel FK506- and rapamycin-binding protein; CK2, casein kinase 2; VPS33B, vacuolar protein sorting-associated protein 33B; FN3K, fructosamine-3-kinase; FN3KRP, FN3K-related proteins; BMI, body mass index; wt, wild-type; dn, dominant negative.

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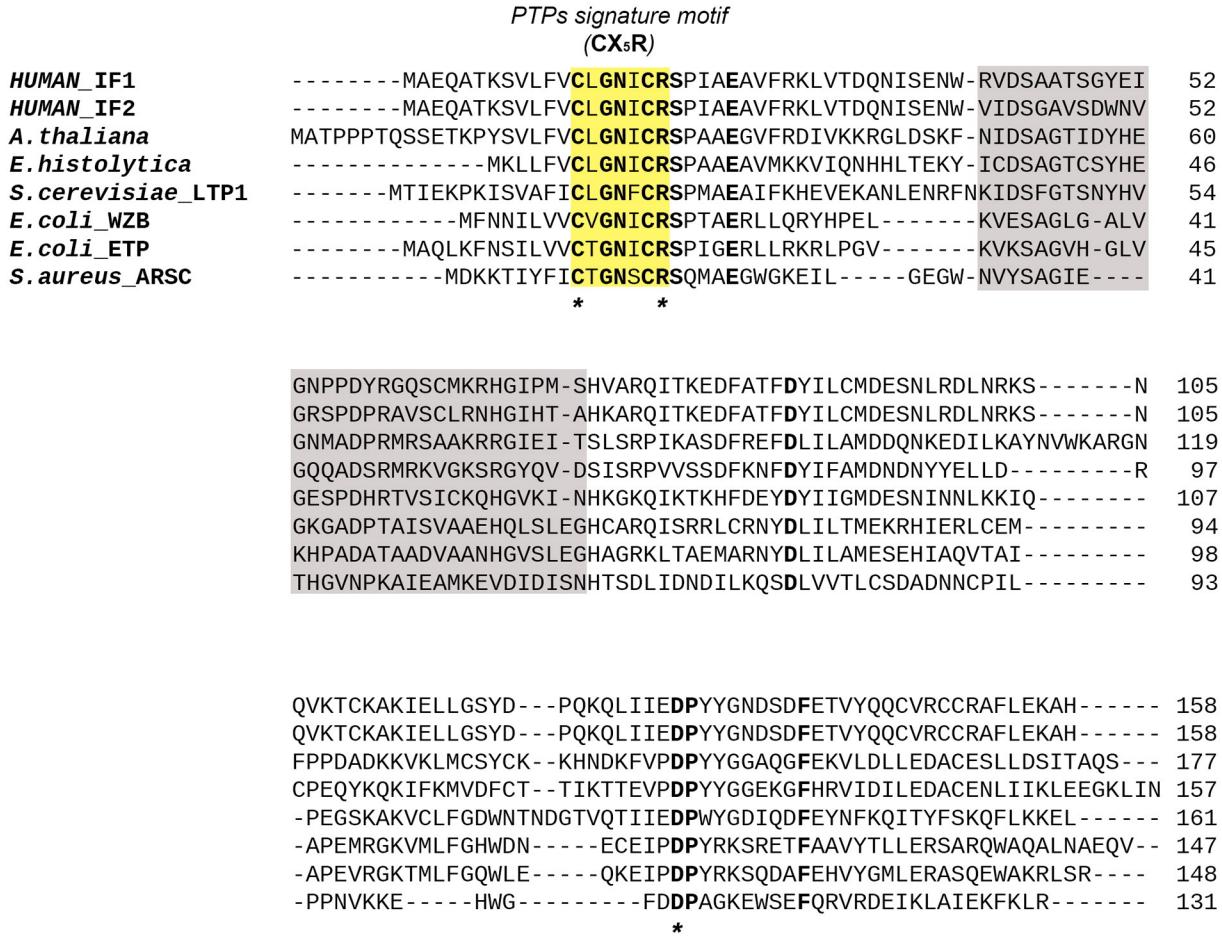

Fig. 1. Alignment of LMW-PTP amino acid sequences. Representative LMW-PTP amino acid sequences of organisms belonging to the five kingdoms are shown. The symbol '*' designates the most important catalytic residues. The isoform-specific sequence domain is highlighted in grey. Residues included in the P-loop and conserved residues are in bold.

motif, CX_5R, in which the cysteine residue acts as a nucleophile in the catalytic mechanism. In animals, LMW-PTP is involved in the dephosphorylation/regulation of many tyrosine kinase receptors as well as in the modulation of a number of cellular proteins involved in important physiological and pathological signalling pathways. In mammals, two active isoenzymes (IF1 and IF2, named also HCPTP-A and HCPTP-B, respectively) are produced by alternative RNA splicing.

2. Early studies on the low molecular weight protein tyrosine phosphatase

For several decades, LMW-PTP was known as low molecular weight acid phosphatase (LMW-AP). The first partial purifications of LMW-AP from mammalian tissues, such as human erythrocytes [3], rat liver [4] and human placenta [5], were published from 1950 to 1960. In 1969, Heinrikson obtained a highly purified bovine liver LMW-AP with an estimated molecular weight of approximately 16,000 Da and found that its p-nitrophenyl phosphatase activity was higher than that toward aliphatic phosphate esters, with the remarkable exception of flavin mononucleotide (FMN) [6]. The relative specificity versus aryl phosphates and FMN was successively confirmed by Van Etten's group, using an apparently pure preparation of bovine liver LMW-AP [7]. These researchers suggested that this enzyme used a covalent catalysis mechanism with a cysteine residue that was essential for catalysis. In 1985, Chernoff & Li described for the first time the protein tyrosine phosphatase activity of a LMW-AP [8]. In fact, these authors observed that the major protein tyrosine phosphatase activity from bovine heart co-eluted via various ion exchange and gel filtration chromatographies and co-migrated on polyacrylamide gel electrophoresis with a LMW-AP, which had molecular and kinetic properties similar to acid phosphatases previously purified from of human liver (cytosolic fraction), placenta and other animal tissues. Successively, other authors confirmed that the LMW-AP was actually a member of the protein tyrosine phosphatase (PTP) family.

2.1. Human red cell acid phosphatase/LMW-PTP: polymorphism and chromosomal localization

Studies on the LMW-AP/LMW-PTP from red cells have permitted the definition of a specific human polymorphism characterized by five distinct phenotypes that exhibit significant differences in catalytic activity [9,10]. These phenotype differences are attributable to three allelic autosomal genes [11]. This complex polymorphism, detectable via a simple electrophoresis technique using a readily available source (red cells), has promoted a great deal of research leading to the discovery of new variants. Red cell acid phosphatase has been widely used as a marker in forensic, genetic, and anthropological studies. In 1973, Ferguson-Smith et al. assigned the genetic locus of acid phosphatase (ACP1) to the short arm of chromosome 2 [12]. Successively, based on extensive linkage data, other authors established the chromosomal localization of the ACP1 gene to the distal portion of 2p25 [13]. In 1993, Lazaruk et al. sequenced substantial portions of the ACP1*A, *B and *C alleles common to Europeans and identified six linearly positioned exons containing codons 14 to 157 as well as two exons of equal length (114 bp) interspaced by a short (41 bp) intron, encoding the specific fast and slow segments of the two variants originated by alternative RNA splicing [11]. A third enzymatically inactive human isoform, designated LMPTP-C, lacks both exons 3 and 4 because LMPTP-C is