REVIEW ARTICLE

Protein phosphatase 1 catalytic isoforms: specificity toward interacting proteins

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The coordinated and reciprocal action of serine-threonine protein kinases and protein phosphatases produces transitory phosphorylation, a fundamental regulatory mechanism for many biological processes. Phosphoprotein phosphatase 1 (PPP1), a major serine-threonine phosphatase, in particular, is ubiquitously distributed and regulates a broad range of cellular functions, including glycogen metabolism, cell cycle progression, and muscle relaxation. PPP1 has evolved effective catalytic machinery but in vitro lacks substrate specificity. In vivo, its specificity is achieved not only by the existence of different PPP1 catalytic isoforms, but also by binding of the catalytic moiety to a large number of regulatory or targeting subunits. Here, we will address exhaustively the existence of diverse PPP1 catalytic isoforms and the relevance of their specific partners and consequent functions. (Translational Research 2014;164:366–391)

Abbreviations: ASPP = apoptosis-stimulating protein of p53 family, also known as PPP1R13; BAD = Bcl-2-associated death promoter; BCL2 = B-cell lymphoma 2, also known as PPP1R50; BRCA1 = breast cancer 1, early onset, also known as PPP1R53; CEP250 = centrosomal protein of 250kDa; CTD = carboxy-terminal domain; FCP = transcription initiation factor IIF-stimulated CTD phosphatase; GADD34 = growth arrest and DNA damage induced gene-34, also known as PPP1R15A; HDAC6 = histone deacetylase 6; LRRC67 = leucine-rich repeat-containing protein 67, also known as PPP1R42; MLCP = myosin light chain phosphatase; MYPT1 = myosin phosphatase target subunit 1, also known as PPP1R12A; PIP = phosphoprotein phosphatase 1 interacting protein; PKB = protein kinase B, also known as AKT; PP1G = muscle-specific glycogen-associated phosphatase; PPEF = protein phosphatase with EF-hand calcium-binding domain; PPM = metallo-dependent protein phosphatases; PPP = phosphoprotein phosphatase; PPP1C = phosphoprotein phosphatase 1 catalytic subunit; PPP1R = phosphoprotein phosphatase 1 regulatory subunit; RB1 = retinoblastoma 1; RGL = glycogen-targeting subunit, also known as Gm or PPP1R3A; SARP = several ankyrin repeat protein; SCP = small CTD phosphatase; STPP = serine-threonine protein phosphatase; URI1 = prefoldin-like chaperone

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INTRODUCTION

Reversible protein phosphorylation plays a major role in cell physiology with both protein kinases and phosphatases participating in the process by, respectively, adding or removing the phosphate group of target substrates.[1]

Protein phosphatases can be divided in serine-threonine protein phosphatases (STPPs), tyrosine phosphatases, and dual-specific phosphatases that dephosphorylate all 3 amino acid residues. STPPs achieve specificity toward the substrates not only by the existence of different catalytic subunits, which are in one order of magnitude less than the kinases, but also especially through the diversity of the binding partners.[2]

This is particularly true for phosphoprotein phosphatase 1 (PPP1) that exists as a holoenzyme composed of a catalytic subunit (PPP1C) and a regulatory subunit (generally known as PPP1R or PPP1 interacting protein, PIP). PPP1 was identified in the early 1940s as the enzyme responsible for the conversion of phosphorylase a to phosphorylase b, but has later been shown to be involved in a wide range of cellular functions including meiosis and cell division, apoptosis, protein synthesis, metabolism, cytoskeletal reorganization, and the regulation of membrane receptors and channels.[3] In the last 2 decades, it has become clear that more than 200 PIPs confer specificity to PPP1C, by targeting it to a specific subcellular compartment (targeting subunits), modulating its specificity (substrate specifiers), inhibiting the catalytic activity (inhibitory subunits), or serving as substrates.[2-4]

In mammals, PPP1C is encoded by 3 separate genes (*PPP1CA*, *PPP1CB*, and *PPP1CC*), each suffering alternative splicing contributing to the PPP1 holoenzyme diversity. The *PPP1CC* gene, in particular, undergoes tissue-specific splicing, giving rise to a ubiquitously expressed isoform, PPP1CC1, and a testis-enriched and sperm-specific isoform, PPP1CC2. The strictly difference between these isoforms resides in the carboxyl-terminus (C-terminus)[2] (Fig 1).

Although many research groups have made great efforts to identify novel PIPs, little attention has been given toward the specificity of those PIPs to a particular PPP1C isoform. Although PPP1C isoforms typically display similar functional properties, especially when assayed in vitro, the fact that they are differentially expressed, depending on the cell type or tissue and even during development, suggests that they can perform distinct but sometimes overlapping physiological functions.[5] This feature is evident in PPP1CC isoform knockout.[6,7]

Most studies have not directly addressed the significance of the different isoforms and simply refer to the phosphatase as PPP1C. Hence, identifying the isoforms' specific roles has proven to be a challenge. Some studies have shown diverse localization patterns for the different PPP1C isoforms and have demonstrated that several PIPs discriminate among the isoforms.[8] Even more complex is that the PIPs themselves have alternative splice variants, thus different combinations of PPP1C-PIPs complexes can be formed taking into account tissue and cell-specific alternative splice of both PPP1C and the PIPs.

In this article, the differences between the different PPP1C isoforms at the DNA, messenger RNA, and protein level will be highlighted and each isoform-specific function will be discussed. We anticipate this work will have a major impact on the scientific community by focusing on PPP1 isoform-specific functions associated with isoform-specific PIPs.

THE PPP FAMILY OF SERINE-THREONINE PHOSPHATASES

Serine-threonine protein phosphatases (STPPs) are crucial for the regulation of many cellular events, from metabolism to sperm motility.[2,9,10] The nomenclature of STPPs was first proposed in 1983 by Ingebritsen and Cohen[11] based on biochemical parameters. Now, by means of recombinant DNA techniques, STPPs are classified into 3 structurally unrelated families: PPP, PPM (metallo-dependent protein phosphatases), and FCP/SCP (CTD aspartate-based protein phosphatases). In this article, we will not address the PPM and FCP/SCP serine-threonine phosphatases. For details on these STPPs please see Cohen.[12]

The PPP family of STPPs comprises catalytic subunits from PPP1C to PPP7C (Table I). Further, functional diversity is also achieved by the existence of several isoforms for each catalytic subunit.[13] PPP1 will be addressed in detail in the next sections. There are 2 genes coding for PPP2C (*PPP2CA* and *PPP2CB*), which are highly conserved in nature. PPP4C and PPP6C share 65% and 57% identity with PPP2C, at the amino acid level, respectively. PPP6C has 3 isoforms originated by alternative splicing. PPP3C possesses 3 isoforms coded by 3 different genes, A, B and C with each gene giving rise to 3 different alternative spliced isoforms. PPP5C and PPP7C belong to the PPP family because they have the common PPP catalytic domain, although they have different N and C termini, implicated in the targeting and regulation of their activity. There is a single gene coding for PPP5C and 2 genes coding for PPP7C (also named protein phosphatase with EF-hand calcium-binding domain [PPEF]) originating 6 isoforms. Most PPP family members are ubiquitously expressed, although some isoforms are tissue specific, for example, PPP7C1 is retina and brain specific.[14] Nevertheless, the panoply