Biochimica et Biophysica Acta 1812 (2011) 1498–1507

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

Review

PP2A targeting by viral proteins: A widespread biological strategy from DNA/RNA tumor viruses to HIV-1

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ARTICLE INFO

Article history:
Received 12 May 2011
Received in revised form 22 June 2011
Accepted 5 July 2011
Available online 10 August 2011

Keywords:
Viruses
Cancer
Neurodegeneration
PP2A holoenzymes
PP2A and human therapy

ABSTRACT

Protein phosphatase 2A (PP2A) is a large family of holoenzymes that comprises 1% of total cellular proteins and accounts for the majority of Ser/Thr phosphatase activity in eukaryotic cells. Although initially viewed as constitutive housekeeping enzymes, it is now well established that PP2A proteins represent a family of highly and sophistically regulated phosphatases. The past decade, multiple complementary studies have improved our knowledge about structural and functional regulation of PP2A holoenzymes. In this regard, after summarizing major cellular regulation, this review will mainly focus on discussing a particulate biological strategy, used by various viruses, which is based on the targeting of PP2A enzymes by viral proteins in order to specifically deregulate, for their own benefit, cellular pathways of their hosts. The impact of such PP2A targeting for research in human diseases, and in further therapeutic developments, is also discussed.

1. Introduction

An estimated one third of the cellular proteins is reversibly phosphorylated on specific serine/threonine (Ser/Thr) residues. Reversible protein phosphorylation, a dynamic process controlled by the coordinated action of phosphorylating (kinases) and dephosphorylating (phosphatases) enzymes, is a key regulatory mechanism that regulates multiple intracellular pathways. There are many different Ser/Thr-specific kinases, each of them being subjected to a specific regulation, that phosphorylate Ser/Thr residues on specific protein substrates. In contrast, to antagonize kinase activities through specific dephosphorylation of Ser/Thr residues, cells used a very limited number of phosphatase catalytic subunits that rely on specific interactions with regulatory proteins to generate a large diversity of phosphatase holoenzymes.

The Ser/Thr phosphatases were originally classified into type-1 (PP1) or type 2 (PP2), according to their substrate specificity and sensitivity to pharmacological inhibitors. In addition type-2 phosphatases were subdivided into major classes, including PP2A, calcium-dependent calcineurin (PP2B) and magnesium-dependent PP2C [1]. Today, based on sequence and structural homology of catalytic subunits, and enzymatic mechanisms, Ser/Thr phosphatases are divided into two large families, known as PPP (Phospho-Protein Phosphatases) and PPM (Protein Phosphatases Metal-dependent). Moreover, other related PPP proteins, such as PP4, PP5, PP6 and PP7, that occurred at low abundance and are expressed in a tissue-and development-specific manner, have also been characterized [2].

Numerous viruses ranging from DNA-Tumor viruses to retroviruses have developed sophisticated strategies in order to deregulate cellular functions via PP2A. This review summarizes our recent knowledge on cellular PP2A proteins and discusses the functional relevance of interactions between PP2A and viral-proteins and their impact on deregulation of cellular pathways. Starting from the biological consequences of these interactions and their ability to specifically target the deregulation of particular cellular pathways, we also discuss how the mimicry of PP2A binding and viral proteins may also serve to evolve new therapeutic developments.

2. Structure of cellular PP2A holoenzymes

PP2A refers to a large family of dimeric and heterotrimeric Ser/Thr phosphatases that account for the majority of Ser/Thr phosphatase activity in eukaryotic cells [3]. $PP2A_D$, the PP2A core dimeric enzyme comprises a 36 kDa catalytic PP2Ac (also called PPP2C) and a structural A subunit, also known as PR65 or PPP2R1 (Fig. 1). In

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doi:10.1016/j.bbadis.2011.07.001

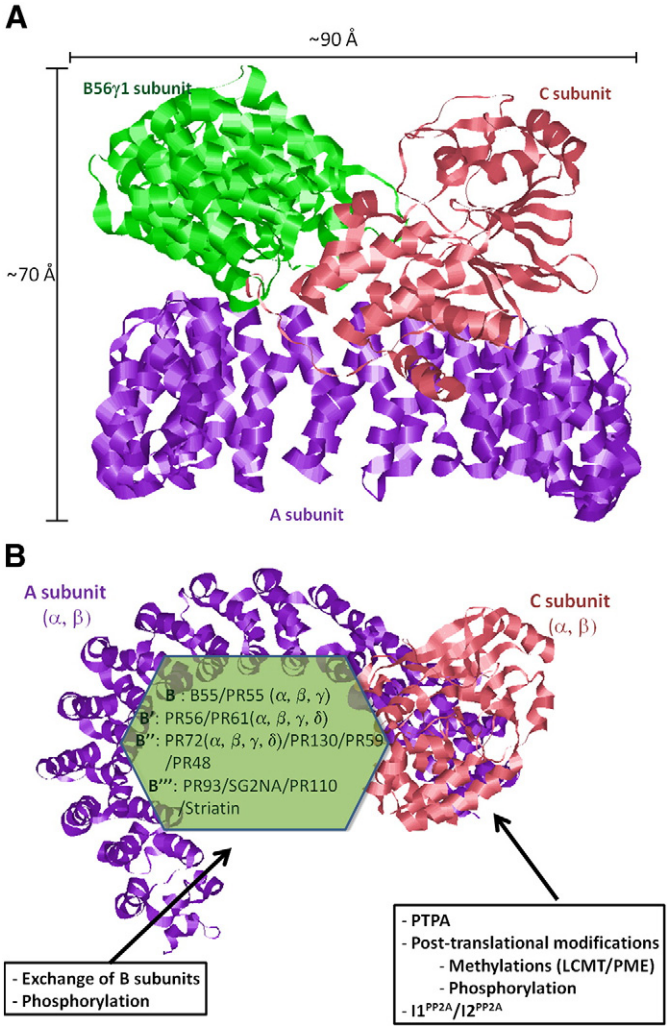

Fig. 1. Structure and regulation of dimeric and trimeric cellular PP2A holoenzymes. A) Three-dimentional crystal structure of a trimeric PP2A holoenzyme bound to microcystin-LR (ref [175] see also ref [11] for recent published crystal structure of the $PP2A_1$ holoenzyme). The scaffold (Aα), catalytic (Cα), and regulatory B (Bα) subunits are shown in blue violet, pink and green respectively. (B) Regulations of dimeric and trimeric cellular PP2A holoenzymes: The catalytic subunit PP2Ac has never been found as a free molecule, but is usually associated to the A structural subunit constituting the dimeric core A/C (illustration is based on 2ie3.pdb structure) or, alternatively, to mammalian a4 protein, an orthologue of the yeast Tap42 protein. The binding of a structurally unrelated third variable (B/B′/B″/B‴) subunit to $PP2A_D$ generates the diversity of trimeric holoenzymes. Reversible methylation of PP2A-C leu_{309} by leucine carboxyl methyltransferase (LCMT) and phosphatase methylesterase (PME-1) regulates the binding of the third variable type B subunits. In addition binding of the phosphatase regulator PTPA to the PP2A–PME-1 inactive complex, provokes a conformational change leading to dissociation of PME-1 allowing the formation of trimeric holoenzyme [161].

mammals the A and C subunits of the core enzyme are constitutively expressed and two distinct genes encode closely related versions of the PP2A A (Aα and Aβ) [4,5] and C (Cα and Cβ) subunits [6,7].

Cells contain a pool of dimeric $PP2A_D$ enzyme that can exist alone [8] or also be associated with a third partner corresponding to a variable "type B" subunits. PP2A B-type subunits contain a split A subunit-binding domain allowing competition with other B-type subunits for A subunit binding [9]. As illustrated in Fig. 1, four major classes of "type B" subunits have been characterized and referred as B, B′, B″, and B‴. In addition, each of the "type B" subunits of PP2A can exist in several isoforms that potentially generate a multitude of (N>75) holoenzyme compositions.

3. Regulation of cellular PP2A holoenzymes

3.1. Regulation by B subunits

Regulation of PP2A primarily involves a combinatorial assembly of type-B subunits with $PP2A_D$ core enzyme and, in addition, PP2A activity, substrate specificity and cellular localization depend on the nature of a B subunit. For example, in contrast to dimeric $PP2A_D$, the trimeric ABαC holoenzyme efficiently dephosphorylates the brain microtubule-associated protein Tau, suggesting that Tau-dephosphorylation is critically regulated by specific Bα targeting of the trimeric holoenzyme [10,11]. However, as illustrated in Fig. 1, in addition to type-B subunits both specific cellular regulators and post-translational modification also regulate PP2A activity. For example binding of α4 protein (Tap42 in yeast) to the PP2A catalytic subunit generates a specific heterodimer [12]. This dimeric Tap42/α4-PP2A phosphatase can repress apoptosis in mammalian cells through negative regulation of c-Jun and p53 [13].

3.2. Regulation by post-translational modifications of the catalytic subunit

Methylation and phosphorylation, two distinct post-translational modifications of the PP2Ac C-terminus $_{304}$-TPDYFL-$_{309}$ sequence, regulate subunit composition of PP2A as well as catalytic activity and substrate specificity of holoenzymes. PP2A phosphorylation on both Thr and Tyr residues inactivates PP2A and its reactivation requires intramolecular autodephosphorylation catalyzed by PP2A [14,15]. Thr_{304} phosphorylation is dependant on an autophosphorylation-activated protein kinase [16]. Tyr_{307} phosphorylation was found in fibroblasts overexpressing pp60 v-src and in chronic myelogenous leukemia cells that overexpress the PP2A inhibitor called SET or $I2^{PP2A}$ [17].

Reversible methylation regulates the binding of the third variable type B subunit [18]. The free carboxyl group of the C-terminal Leu_{309} residue is methylated by the S-adenosylmethionine-dependent LCMT1 (leucine carboxyl methyltransferase 1) [19,20]. Demethylation is catalyzed by a specific phosphatase methylesterase, PME-1 [21,22].

3.3. Regulation by PTPA

The Phosphotyrosyl phosphatase activator (PTPA) was initially considered as a B subunit that interacted with AC core to specifically activate a phosphotyrosyl phosphatase (PTPase) activity [23]. However later findings indicate that PTPA, also renamed PP2A Phosphatase Activator, functions as a chaperone able to reactivate the Ser/Thr phosphatase activity of inactive PP2A [24,25]. Indeed, ATP–Mg^{2+} stimulated peptidyl prolyl cis/trans isomerase activity of PTPA is required to reactivate inactive PP2A and PTPA binding to the PP2A-PME–1 inactive complex, provokes a conformational change leading to dissociation of PME-1 that permits the formation of an active trimeric holoenzyme [26].

3.4. Cellular interacting proteins

In addition to type-B subunits a large and still growing number of cellular proteins can interact with one or more PP2A subunits or can associate with a specific holoenzyme. As illustrated in Table 1 [10,27–85], several cellular partners including protein kinases, cytoskeleton, structural, regulatory proteins such as receptors or transcription factors controlling major intracellular pathways (Hox, Wnt, Ras,…), can form stable active complexes with PP2A. The formation of such complexes represents a major way to regulate PP2A activity and PP2A-mediated intracellular pathways.