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The broken "Off" switch in cancer signaling: PP2A as a regulator of tumorigenesis, drug resistance, and immune surveillance

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ABSTRACT

Aberrant activation of signal transduction pathways can transform a normal cell to a malignant one and can impart survival properties that render cancer cells resistant to therapy. A diverse set of cascades have been implicated in various cancers including those mediated by serine/threonine kinases such RAS, PI3K/AKT, and PKC. Signal transduction is a dynamic process involving both "On" and "Off" switches. Activating mutations of RAS or PI3K can be viewed as the switch being stuck in the "On" position resulting in continued signaling by a survival and/or proliferation pathway. On the other hand, inactivation of protein phosphatases such as the PP2A family can be seen as the defective "Off" switch that similarly can activate these pathways. A problem for therapeutic targeting of PP2A is that the enzyme is a hetero-trimer and thus drug targeting involves complex structures. More importantly, since PP2A isoforms generally act as tumor suppressors one would want to activate these enzymes rather than suppress them. The elucidation of the role of cellular inhibitors like SET and CIP2A in cancer suggests that targeting these proteins can have therapeutic efficacy by mechanisms involving PP2A activation. Furthermore, drugs such as FTY-720 can activate PP2A isoforms directly. This review will cover the current state of knowledge of PP2A role as a tumor suppressor in cancer cells and as a mediator of processes that can impact drug resistance and immune surveillance.

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1. Introduction

1.1. Background

Signal transduction is a dynamic process and so components are required to both initiate signaling and also to stop the cascade at the appropriate time. While we have a very good understanding of many survival kinases in cancer, the protein phosphatases that serve as the "brakes" for most if not all cellular signaling cascades are understudied [1]. On June 1, 2016 if you use PubMed to search for articles using terms "serine threonine protein phosphatases cancer", you will find 1660 papers on this topic. In contrast, a PubMed search using terms "serine threonine protein kinase cancer" identifies 75,070 reports. Thus for every cancer related paper involving serine threonine protein phosphatases, there are 45 papers on kinase role in cancer. That is not to say protein phosphatases are any less important than kinases in signaling pathways. To some extent the serine threonine protein phosphatases are understudied because they are more difficult to work with compared to kinases. While many major kinases like Protein Kinase B (AKT), Extracellular Signal Regulated Kinase (ERK), and Protein Kinase C (PKC) are monomers, serine threonine protein phosphatases like Protein Phosphatase 1 (PP1) and Protein Phosphatase 2A (PP2A) are multimers. The subject of this review, PP2A, is a hetero-trimer. The PP2A hetero-trimer consists of a catalytic core comprised of the A and C subunits (the functional portion of the enzyme that is responsible for the dephosphorylation event) as well as a regulatory B subunit that controls substrate specificity and cellular localization [1–6]. Thus for a proof-of-principle experiment where one might overexpress a protein or suppress its gene expression by siRNA, shRNA, or CRISPR, one has to account for three subunits rather than one. Further complicating matters is the fact that each subunit in the hetero-trimer has multiple isoforms [7–9]. There are two isoforms of the catalytic (PPP2CA aka Cα and PPP2CB aka Cβ), two isoforms of the scaffold A subunit (PPP2R1A aka Aα and PPP2R1B aka Aβ) and at least 17 different B subunit proteins that are members of predominantly of three families identified as B family (aka B55; gene symbol PPP2R2), B′ family (aka B56; gene symbol PPP2R5) and B″ family (aka PR72/130; gene symbol PPP2R3) [7–13]. Striatins (B‴ family; gene symbol STRN) are a fourth regulatory subunit family [1,13]. Each PP2A subunit is located on separate chromosomes in humans. A list of the human regulatory and core PP2A subunits that have been identified and their chromosomal location is presented in Table 1. Though for both A and C subunits the isoforms are >80% homologous by protein sequence, there are distinct differences between each isoform [8,9]. For simplicity, PP2A isoforms are identified by the B regulatory subunit they contain. The B regulatory subunit determines the substrate specificity and cellular localization of the resulting PP2A isoform so identification of enzyme isoform by these subunits is appropriate. The diversity of subunits involved in assembling the active protein phosphatase reveals that PP2A is not a single enzyme but rather a family of enzymes.

Table 1
List of PP2A subunit genes and their chromosomal location in human.

Common name	Symbol	Chromosome location
A α	PPP2R1A	19q13.41
A β	PPP2R1B	11q23.2
B55 α	PPP2R2A	8p21.2
B55 β	PPP2R2B	5q32
B55 γ	PPP2R2C	4p16
B55 δ	PPP2R2D	10q26
B56 α	PPP2R5A	1q32.2
B56 β	PPP2R5B	11q13
B56 γ	PPP2R5C	14q32
B56 δ	PPP2R5D	6p21
B56 ε	PPP2R5E	14q23
PR72	PPP2R3A	3q22.1
Striatin	STRN	2p22
Striatin 3	STRN3	14q12
Striatin 4	STRN4	19q13
C α	PPP2CA	5q31.1
C β	PPP2CB	8p12

1.2. Regulation of PP2A expression

Mechanisms regulating gene expression of PP2A subunits are poorly understood. Little is known of transcription regulating B subunit expression though the role of microRNAs (miRs) in this process is emerging [14]. Transcription factors regulating A alpha and C alpha have been identified [15–17]. A comprehensive analysis of transcription factors regulating A alpha gene expression was performed and identified CREB and SP-1 as a major regulators of the alpha scaffold gene [15]. In hepatocellular carcinoma (HCC), a single nucleotide polymorphism (SNP) mutation in the A alpha promoter revealed involvement of NF kappa B [16]. Ikaros suppression of transcription of the C alpha subunit has been reported [17]. Little if anything about how PP2A B subunit genes are transcribed is known.

A better understanding of proteolytic regulation of PP2A B subunit expression is known. Some PP2A B subunits are subject to proteolysis if they are out competed for binding to catalytic core components. Thus change in expression of one B subunit can impact expression of another B subunit. The Virshup group demonstrated in *Drosophila* that reduction of A subunit using siRNA resulted in loss of C and B subunit expression [18]. Likewise, reduction of C subunit by siRNA resulted in loss of A and B subunit expression. As mRNA levels of A and B subunit were unaffected in the presence of C subunit siRNA, this suggested that PP2A isoform expression is regulated by proteolysis [18]. Strack and colleagues determined that proteolytic regulation of certain PP2A B subunits also occurs in mammalian cells and degradation of some PP2A monomers involves ubiquitin/proteasome pathway [19,20]. While B55 alpha and B56 alpha appear to be unstable as monomers, members of the B″ family and Striatins are stable when free of the catalytic core [20,21]. Hetero-trimer assembly relies on association of the B subunit with the catalytic core [1,4,19–23]. However, PP2A isoform specificity does not rely on the catalytic C subunit [24]. An interesting mechanism regulating catalytic subunit stability involves its association with the alpha 4 protein which is also known as Immunoglobulin (CD79A) Binding Protein 1 (IGBP1). Alpha 4 binds the catalytic subunit and prevents its poly-ubiquitination and degradation [25–29]. Alpha 4 is necessary for stability of PP2A as well as PP4 and PP6, suppresses apoptosis, and the protein is essential for activity of all PP2A isoforms [25–28]. The role for Alpha 4 in PP2A regulation is confusing as catalytic subunits bound to Alpha 4 are stable but inactive [27]. Based on structural analysis of PP2A catalytic subunit complex with Alpha 4 and comparison with the structure of the PP2A holoenzyme, a model was proposed by Jiang and colleagues where Alpha 4 is proposed to act as a scavenger chaperone for monomeric PP2A C subunits [28]. The model suggests that Alpha 4 prevents uncontrolled phosphatase activity by the C subunit. In addition, methylation of the C subunit may be critical to displace the catalytic subunit from Alpha 4 and promote association with the scaffold subunit to create the PP2A catalytic core [28]. Alpha 4 may also direct preferential B subunit association with the catalytic core under certain physiologic conditions. For example, glutamine deprivation promotes PP2A isoforms containing B55 alpha in an Alpha 4 dependent manner [29].

2. B subunit proteins as the drivers of PP2A function

2.1. B55 family isoforms

While B55 family (PPP2R2 series) targets involve a broad range of physiologic functions, a major focus of study involves the role of the B55 alpha isoform as a stress survival protein and as a cell cycle regulator [30–36]. Alpha 4 mediated activation of B55 alpha during glutamine deprivation results in dephosphorylation and inactivation of an E3