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Review article

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

ubiquitin ligase (EDD; E3 identified by Differential Display) that targets and suppresses p53 [29]. Interestingly, p53 plays a survival role in this scenario as B55 alpha mediated support of p53 is required for survival of the cells during the stress of glutamine deprivation [29]. Mitotic exit requires dephosphorylation of Cyclin Dependent Kinase 1 (CDK1), Greatwall (GWL), and CDK1 substrates such as Histone H1 that is mediated by B55 alpha as well as PP1 [30–34,37]. Schmitz and colleagues determined that B55 alpha CDK1 substrates rather than CDK1 were the essential targets for mitotic exit regulation by the PP2A isoform [37]. While pharmacologic inhibition of CDK1 had limited effect on indicators of mitotic exit such as nuclear reassembly and Golgi reformation, genetic suppression of B55 alpha significantly blocked these processes. A key feature of this model was the interplay between Importin 1 and B55 alpha [37]. As will be discussed later, PP2A plays many roles in trafficking proteins including nuclear proteins, For instance, PP2A mediates the transport of GWL between the nucleus and cytoplasm [34]. Greater details on the mechanism behind this process will be discussed later. Cyclic adenosine monophosphate–regulated phosphoprotein 19 (ARPP19) is a PP2A inhibitor that is activated by GWL [30] and can also be activated by CDK1 in a GWL-independent manner [31]. B55 alpha can dephosphorylate ARPP19 [32]. These processes create an effective "On/Off" switch for mitotic exit whereby B55 alpha PP2A inactivates GWL and ARPP19 thus allowing the cell to exit mitosis and enter interphase. The B55 beta subunit has been shown to regulate Cyclin E proteolysis [36]. Regulation of the cell cycle appears to involve a complex network involving the B55 family. B55 alpha negatively regulates AKT survival signaling which impacts apoptotic potential of certain cancer cells and contributes to drug resistance [38–42]. PP2A regulation of AKT is cell type specific as B56 family members beta and gamma has been shown to be AKT phosphatases [43,44]. The B subunit dephosphorylates AKT at threonine 308 [38,41]. B55 alpha also targets PKC alpha [42]. Reduced expression of the B subunit is associated with shorter remission duration and tendency to relapse in AML [41]. The microRNA miR-222 has been shown to support liver cancer cell survival by activating AKT via a mechanism that involves suppression of B55 alpha by the miR [39]. The role for B55 alpha in cells is clearly cell type specific as the B subunit appears to be a tumor promoter in pancreatic cancer [45]. In the study by Hein and colleagues, increased B55 alpha was associated with increased survival signaling including activation of ERK and increased phosphorylation of AKT at serine 473 [45]. The discrepancy between role of the B subunit in pancreatic cancer compared to leukemia and lung cancer likely reflects the composition of the PP2A isoforms in each of these malignant cells. For some PP2A isoforms, the enzyme's components will thrive or be proteolyzed based on which competing B subunits and catalytic cores are present [18–20]. In leukemia cells, B55 alpha and B56 alpha directly compete for catalytic core molecules. Suppression of B55 alpha by shRNA in leukemia induces B56 alpha while shRNA reduction of B56 alpha promotes B55 alpha expression [42,46]. B55 alpha could potentially support B56 alpha function if catalytic core units were present to support the formation of both PP2A isoforms. PKC alpha has been shown to phosphorylate B56 alpha at serine 41 thereby suppressing PP2A function [47]. B55 alpha can dephosphorylates and inactivate PKC alpha [42]. Thus B55 alpha suppression of PKC alpha could promote B56 alpha PP2A function under certain conditions.

If B55 alpha role as tumor suppressor versus tumor promoter relies on AKT signaling then the phosphorylation status of the kinase will be important as threonine 308 and serine 473 phosphorylated AKT have different functions [48]. AKT phosphorylation of mTORC1 relies on threonine 308 and not serine 473 [48–50]. Gallay and colleagues demonstrated that elevated AKT threonine 308 phosphorylation and not serine 473 phosphorylation is prognostic for poor outcome in AML [51]. Thus B55 alpha role as potential tumor suppressor in AML may reflect the importance of AKT signaling regulated by threonine 308 phosphorylation in the disease.

A recent study suggests that B55 alpha is involved in negative regulation of autophagy by serving as a Beclin phosphatase [52]. Interestingly, it appears this mechanism is cell type specific as the phenomenon was observed in skeletal tissue cells but not in cells from the liver. Starvation of skeletal cells resulted in B55 alpha dissociation form Beclin allowing for DAPK phosphorylation of the autophagy molecule [52]. B55 alpha may have a general role in autophagy as the B subunit targets ULK1 [53]. ULK1 is subject to mTORC1 regulation so this suggests an interesting cross-talk between AKT/mTOR components in autophagy. The B55 alpha subunit clearly has diverse roles in sustaining cellular homeostasis. A scheme depicting some of the various B55 alpha targets that have been discussed is presented in Fig. 1.

2.2. B56 family isoforms

The B56 family (PPP2R5 series) is prominent for its regulation of molecules involved in apoptotic control including BCL2, p53, MYC, Glycogen Synthase Kinase 3 (GSK3), the Extracellular Receptor Kinases (ERKs), and beta catenin [46,54–62]. B56 alpha has been shown to dephosphorylate BCL2 at serine 70 in response to stresses associated with ceramide production [46,55,63,64]. BCL2 phosphorylation effect on its anti-apoptotic function is cell type specific though serine 70 phosphorylation is associated with optimal binding to BAX and BAK and is associated with prognosis for poor overall survival in AML [65–68]. The B56 alpha subunit may serve a general role in support of cellular PP2A function by assisting nuclear transport of catalytic subunit mediated by Exportin 1 (XPO1; ref. [69]). Genetic studies to identify PP2A subunit association with SV40 small T antigen transformation identified B56 alpha and B56 gamma as candidates [70]. B56 gamma has been implicated in p53 regulation so a role for this B subunit in cellular transformation is very plausible [71–73]. B56 gamma role in tumor formation could also reflect other targets of the PP2A isoform. A recent study has identified PPP2R6 deletions in lung adenocarcinoma affecting ERK activity [74]. The B subunit also has been shown to dephosphorylate p27KIP1, a negative regulator of cell cycle progression that may have tumor suppressor functions [75]. B56 gamma stabilizes p27 (via T187) and promotes nuclear localization (via T157) suggesting the B subunit is critical to P27 tumor suppressor function [75,76]. AKT has also been implicated in cellular transformation processes involving B56 gamma [77]. B56 gamma, as well as B56 beta, has been shown to be AKT phosphatases [43,44]. Loveday and colleagues propose that mutations in PPP2R5B (B56 beta) and PPP2R5C (B56 gamma) may impact human overgrowth syndromes by possibly affecting AKT signaling in these individuals [78]. In addition to its likely role in tumorigenesis in some cancers, B56 gamma also influences cancer cell migration via Paxillin and other pathways [62,79,80].

Like the B55 family, the B56 family plays an important role in cell cycle progression [81–89]. The interplay between PP2A and PP1 in mitotic processes involves members of the B56 family [81,82]. PP2A B56 family members serve important roles in the process of separating chromosomes during mitosis by controlling the timing of kinetochore assembly and regulating spatial aspects of chromosome alignment with microtubules [81,82,87–89]. B56 PP2A isoforms are required for motor-driven movement of chromosomes to the metaphase plate by a mechanism involving BUBR1 and Kinesin 14 [87]. Depletion of B56 subunits results in impaired chromosome segregation that results from misalignment of chromosomes and is independent of kinetochore assembly [87]. While B55 and B56 can be functional competitors, it appears the two PP2A families cooperate in mitotic regulation [81,82]. Cross-talk between B56 alpha and B55 alpha is depicted in Fig. 1. Grallert and colleagues describe an interesting model where CDK-1 regulates a protein phosphatase relay that involves PP1, and both B55 and B56 PP2A families [82]. Active CDK-1 suppresses the protein phosphatase relay and allows the cell to commit to mitotic entry. CDK-1 phosphorylation of PP1 at threonine 316 prevents association of PP1 with PP2A isoforms but during the metaphase/anaphase transition PP1 auto-dephosphorylates and is re-activated. Active PP1 activates B55 alpha PP2A with subsequent dephosphorylation of B56 family PP2A isoforms at serine 378 [82]. The interplay between

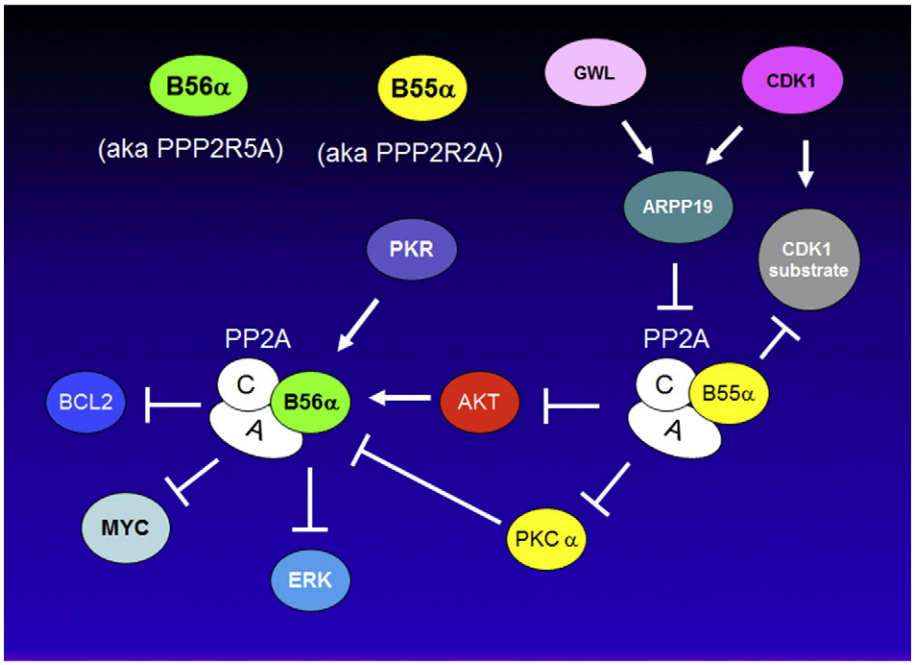

Fig. 1. B55 alpha and B56 alpha PP2A isoforms target a diverse set of substrates involved in cell cycle and cell survival. A number of B55 alpha and B56 alpha targets are depicted.

the protein phosphatases is quite complex as dephosphorylation of B56 family members at serine 378 members allows PP1 to associate with each of the isoforms and dephosphorylate a variety of phospho-sites in each of the subunits that imparts another level of regulation that may involve a diversity of kinases [82].

The B56 family of PP2A isoforms are also critical regulators of molecules like MYC and beta catenin whose protein stability is regulated by a complex regulatory system involving PP2A and GSK3 [90–96]. In both MYC and beta catenin, an initial phosphorylation event at one phosphosite by a kinase like ERK, CDK1, or Casein Kinase stabilizes the protein. However, this initial phosphorylation site primes GSK3 phosphorylation at a second site. Dephosphorylation at the original phosphosite by a PP2A B56 isoform signals for the protein for ubiquitination and degradation. Thorough reviews on the mechanistic aspects of MYC and beta catenin degradation can be found elsewhere [90,91,93,94]. In addition to regulating beta catenin protein stability, the B56 PP2A isoforms have other roles in WNT signaling. B56 beta has been shown to suppress WNT3a and TCF4 activation independent of a role in destabilizing beta catenin protein [97]. However, functional roles for B56 beta in WNT signaling is likely cell type specific as another report found that the B subunit does regulate beta catenin stability [95]. Transgenic expression of B56 gamma using a lung specific promoter results in neonatal death of mice [98]. Examination of lung tissue demonstrated a loss of beta catenin in tissues suggesting that turning off B56 gamma to allow for beta catenin induction is critical for lung development [98]. PP2A regulation of GSK3 could impact both MYC and beta catenin stability though this potential mechanism has not been well studied in cancer. However, Mohan and colleagues identified in cardiac cells that PI3K regulates GSK3 serine 9 phosphorylation via PP2A in an AKT independent manner [99]. In studies investigating Tau phosphorylation in Alzheimer's Disease, PP2A dephosphorylates GSK3 with B56 gamma being a potential GSK3 phosphatase [100,101].

2.3. PR72/PR130 family isoforms

The PR72/PR130 P2A isoforms (PPP2R3 series) are not as well studied as the B55 or B56 PP2A families. PR72/PR130 represents a more evolutionary divergent set of PP2A subunits compared to the B55 and B56 family members [102]. These PP2A B subunits are unique from the other families as they have calcium binding motifs and calcium appears to modulate the activity of these PP2A isoforms [21,103]. PR72 has been shown to regulate dopamine- and cAMP-regulated neuronal phosphoprotein (DARPP-32), a PP1 regulatory subunit important for neurotransmitters [103]. A role for PR72/PR130 B subunits in cancer is unclear though genome screening identified the mouse ortholog of the B subunit is altered in mouse pancreatic carcinoma [104]. Mutation of glycine 90 to aspartate (G90D) in the beta isoform of the A scaffold subunit (PPP2R1B) eliminates binding of B56 gamma but PR72/PR130 binding is maintained [105]. The G90D mutation has been identified in a number of solid tumors and may be clinically relevant [106,107]. Perhaps PR72/PR130 is important to maintain housekeeping PP2A function when PPP2R1B is mutated. PR72/PR130 may have a critical function in maintenance of stem cell pluripotency but its role may not involve protein phosphatase enzymatic activity [108,109]. The mechanism involves binding to the WNT regulator Naked Cuticle (NKD; ref. [108]). IQ-1, a small molecule that prevents differentiation of murine embryonic stem cells (ESC), was shown to work via a mechanism involving the PR72/PR130 regulation of beta catenin/WNT pathway [109]. In that study it was demonstrated that PR72/PR130 prevents beta catenin from switching usage from CBP to p300. The increase in β-catenin/CBP-mediated transcription at the expense of β-catenin/p300-mediated transcription is critical for the maintenance of murine ESC pluripotency [108,109]. The Janssens Laboratory has identified a novel function for PR130 in Epidermal Growth Factor Receptor (EGFR) signaling [110]. In that study they demonstrated that PR130 binds EGFR and SRC Homology 2 domain-containing Inositol Polyphosphate 5-phosphatase.

2 (SHIP2). PR130 has a role in EGFR turnover by preventing degradation of the kinase in response to its ligand [110]. PR130 also supports cancer cell migration and impedes cell adhesion by a mechanism involving LPP (LIM Protein lipoma-preferred Partner [111]). Potential support of metastasis along with support of WNT and EGFR signaling suggest that PR72 and PR130 may act as tumor promoters rather than tumor suppressors [111].

2.4. Striatin family

Striatins (STRN) are a family of 3 proteins (STRN, STRN3, STRN4) that associate with the PP2A catalytic core and were designated as a fourth

PP2A regulatory family (B‴; refs. [13,112,113]). STRN proteins have been found to be associated with complexes that contain PP2A and kinases such as Germinal Center Kinase III (GCKIII) family members Mammalian Sterile 20-Like Kinase 3 (MST3) suggesting a novel signalosome structure, the STRIPAK (STRN Interacting Phosphatase and Kinase) complex, that contains both positive and negative regulatory elements [13,112–120]. The STRIPAK complex may be critical for stem cell differentiation as knockout of Striatin Interacting Protein 2 (STRIP2 also known as FAM40B) in murine embryonic stem cells impairs differentiation of germ layers and blocks cardiomyogenesis [121]. The MST kinases play pivotal roles in cellular homeostasis by controlling cell proliferation, cell death, and other processes [122]. Therefore, the presence of Striatins in the STRIPAK complex can serve as brakes for MST mediated signaling [13]. In that sense the Striatins may be part of a signaling rheostat in signal transduction pathways where STRIPAK complexes are involved.

3. Function and role in cancer

3.1. Regulation of function

Regulation of PP2A function is complex and involves a diversity of players including post-translational modification of subunits, non-PP2A cellular and viral proteins such as SET and SV40 small T antigen, second messenger molecules such as ceramide, and gene regulatory agents such as microRNAs. Phosphorylation, methylation, and other modification catalytic core subunits influences binding affinity of the B subunits and thus modulates PP2A function [4,5]. Phosphorylation of B subunits can affect sub-cellular localization of the PP2A isoform, influence association with the catalytic core or non-PP2A proteins, and these modifications may influence substrate selection by the PP2A isoform. As discussed earlier, serine 378 phosphorylation interferes with B56 family association with PP1 [82]. PP1 was postulated to be a general B56 PP2A protein phosphatase that can reverse phosphorylation of multiple phosphorylation sites in B56 subunits that are introduced by a number of kinases including CDK-1, PLK-1, mitogen activated kinases (MAPKs), and Aurora B kinase [82]. It is thought many of these modifications are important for the myriad of roles B56 PP2A isoforms play in cell cycle. Phosphorylation of B56 alpha is important for its role in apoptosis as a BCL2 phosphatase [46]. When B56 alpha is phosphorylated at serine 28 by dsRNA Dependent Protein Kinase (PKR), the B subunit re-localizes from the nucleus to the mitochondria and dephosphorylates BCL2 at serine 70 thereby reducing the full and potent anti-apoptotic function of BCL2 [46]. Low and colleagues have found that nitration of B56 delta at tyrosine 289 results in impaired PP2A dephosphorylation of BCL2 at serine 70 [123]. Thus cellular homeostasis depends on the cell having the appropriate PP2A isoforms with the required subunit modifications to regulate the signaling cascades that are essential for its cell type. Variation in PP2A isoform stoichiometry or changes in subunit modifications can induce aberrant activation of any number of signal cascades that could promote tumorigenesis or support drug resistance in cancer cells.

3.2. PP2A and tumorigenesis

Suppression of the PP2A family to promote global activation of cellular kinases can be achieved by targeting the catalytic core. Perhaps the best example of PP2A role in tumorigeneis involves transformation of cells by chemical inhibitors of PP2A including okadaic acid and viruses such as polyoma or SV40 [124–132]. PP2A was identified as a tumor suppressor when it was found that malignant transformation of cells by polyoma viruses involved the enzyme [70,126,132]. Simian Virus 40 (SV40) small T (ST) antigen and Murine Polyoma Virus middle T (MT) antigen were found to displace B subunits from the PP2A catalytic core thereby suppressing function. Recent studies have shown that MT can bind Yes Associated Protein (YAP) and when complexed with PP2A the transcription regulator is dephosphorylated [133,134]. In addition okadaic acid class of PP2A inhibitors were found to be carcinogenic [127,131]. These studies verified a role for PP2A dysregulation in tumorigenesis though a mechanism for transformation was not clear. The Hahn laboratory investigated the mechanism how PP2A contributes to SV40 mediated cellular transformation [77,133,135,137]. Expression of the A alpha subunit (PPP2R1A) was modulated in host HEK cells using increasing titer retroviral shRNA to examine contribution of this scaffold subunit [77]. Cells with greatly reduced expression of the PP2A subunit (i.e. >67% reduction) died by apoptosis. Cells with ~50% reduction of A alpha became anchorage independent, were tumorigenic in mice and resembled cells that expressed SV40 ST [77]. PP2A A beta is involved in cell differentiation mediated by AKT so disruption of A beta containing PP2A isoforms could also prove tumorigenic [138]. The A beta scaffold subunit has also been shown to be involved in dephosphorylation and inactivation of the transformation function of the RAS GTPase RalA [137]. RalA has been shown to be a critical component of RAS mediated cell transformation and supports metastasis (reviewed in ref. [139]). The identification of PPP2R1B mutations in lung and colon cancer supports this notion [107]. These findings reveal the requirement for proper balance of PP2A activity within cells with reduced activity promoting transformation but a minimal level of PP2A activity must be maintained for survival.

3.3. Cellular inhibitors of PP2A as tumor promoters

Tumorigenic properties of transforming viruses rely on PP2A inhibition by proteins like the SV40 small T antigen [32,136,137]. Cellular proteins like Cancerous Inhibitor of PP2A (CIP2A) and Inhibitor 2 of PP2A (I2PP2A; better known as SET) are emerging as key players in cancer cell survival and drug resistance [140–145]. CIP2A binds PP2A thus diminishing protein phosphatase catalytic activity though the exact mechanism how CIP2A achieves this suppression is not clear [141]. CIP2A is tumorigenic with a number of oncogenes including MYC being targets [141,146]. Juntilla and colleagues found that overexpression of CIP2A transformed mouse embryonic fibroblasts (with inclusion of mutant RAS V12) as well as HEK-TERV cells [146]. One consequence of CIP2A overexpression was MYC stabilization. These results suggested that CIP2A could serve as a means of suppressing PP2A to promote malignant transformation of cells. To determine physiologic relevance of CIP2A overexpression in cancer, Junttila and colleagues surveyed expression of the PP2A inhibitor in human head and neck cancer and colon cancer and found CIP2A gene and protein expression was significantly elevated in both cancers [146]. Subsequent studies have shown CIP2A expression is elevated in many cancers [141]. Elevated expression of CIP2A is associated with prognosis for poor survival in solid tumor cancers and various leukemias [141,147–151]. The important players in CIP2A mediated tumor promotion are just emerging. MYC mediated transcription as well as MYC amplification in breast cancer is highly correlated with CIP2A suggesting that at least in that malignancy CIP2A activation of the MYC oncogene is important [151].

SET was identified as a PP2A inhibitor associated with acute myeloid leukemia cells [152]. The RNA binding protein hnRNP A2 was shown to bind and activate SET, suggesting that overexpression of the hnRNP protein could stimulate survival signaling by suppressing PP2A via SET in cancer cells [153]. Another RNA binding protein, hnRNP A1, has been shown to positively regulate SET gene expression in chronic myeloid leukemia [154]. An interesting model of SET regulation by sphingolipids has been developed by the Ogretmen group [143,155]. Ceramides, sphingolipid second messenger molecules associated with anti-proliferation and anti-survival signaling, binds and inactivates SET protein [155]. This mechanism suggests that ceramide-mediated apoptosis could involve re-activation of PP2A at least in some cancer cell types. Supporting this notion, the sphingosine analog FTY-720 can potently suppress SET, re-activates PP2A, and induces cell death in many types of cancer [40,142,144,145,156–163]. The Perrotti group

established that SET inactivation of PP2A was critical for BCR-ABL tumorigenic function in chronic myeloid leukemia (CML) and Philadelphia chromosome positive (pH+) acute lymphoblastic leukemia (ALL; refs [140,142,154,157,159]). SET has emerged as a critical target for CML therapy as SET activation is important in blast crisis CML and SET plays a role in Tyrosine kinase inhibitor (TKI) resistance [140,142,154,159]. Janus Kinase (JAK) is another important regulator of SET suggesting that other oncogenic kinases may be important in SET mediated suppression of PP2A. JAK2 promotes PKC mediated phosphorylation of SET at serine 9 that influences its sub-cellular localization [161]. Spingosine Kinase (SK), which is responsible for production of the ceramide antagonist sphingosine 1-phosphate, has been shown to support BCR-ABL protein stability by a PP2A dependent mechanism [163]. These studies reveal a rather complicated regulatory mechanism involving the SET/PP2A axis that contributes to tumorigenesis and drug resistance.

3.4. PP2A mutations in cancer

An initial mutation analysis of PP2A mutations in lung, breast, and melanoma cancers by Calin and colleagues revealed mutations occurred in both scaffold A subunit alpha (PPP2R1A) and beta (PPP2R1B) albeit at low frequency [106]. In that study, mutations in the A beta subunit were mostly exon deletions attributed to abnormal splicing while A alpha subunit mutations were generally conversion of nucleotides including the glutamate (E) 64 [106]. The ability of E64 mutation to suppress potential PP2A tumor suppressor activity was determined PPP2R1A mutant E64D knock-in mice which are more prone to develop lung carcinoma in response to benzopyrene compared to mice with wild-type A alpha subunit expression [164]. The E64D PPP2R1A mutation was shown to block binding of B56 family but not B55 family or PR72/PR130 subunits to the A alpha scaffold [165]. The frequency of A alpha mutations was also found to be low in glioma; however, almost half of glioma samples had A alpha protein expression levels that were 10 fold less compared to counterpart cells [166]. Unlike glioma, PPP2R1A mutations are fairly common in uterine cancers. Whole exome sequencing and DNA copy number analysis of seventy six uterine serous carcinoma samples revealed nearly 20% of patients contained somatic mutation of the A scaffold subunit PPP2R1A; ref. [167]). PPP2R1A mutations vary greatly between ovarian and uterine cancer and mutation frequency depends on the grade of the disease [168,169]. While PPP2R1A mutations are prevalent in high grade uterine cancer, mutations of the A subunit are rarer in high grade ovary cancer. The differences in PPP2R1A mutation frequency in these malignancies clearly demonstrate that they are different diseases [168,169]. A number of mutations in ovarian and uterine cancer have been identified including tryptophan (W) 257 conversion to glycine (G; refs. [167–170]). A recent study of the biological effect of the W257G PPP2R1A mutation in ovarian cancer revealed the mutation promoted cell migration using in vitro assays [170]. The A scaffold subunit with W257G lost the ability to bind B56 subunits with the exception of B56 delta. Cells with PPP2R1A W257G mutation displayed increased phosphorylation of SRC, JNK, and JUN [170]. Inhibition of SRC or JNK with pharmacological inhibitors suppressed cell migration in the cells with W257G mutation suggesting that the PPP2R1A mutation affects this process via a SRC/JNK/JUN axis [170].

PP2A A beta mutations like A alpha mutations alter association with other PP2A subunits [137,171,172]. Based on mutations identified in lung and colon cancer, the PPP2R1B mutations were shown to have various effects. Interestingly, one A beta mutation at aspartate (D) residue 540 (D540G) was found to actually bind more tightly to the catalytic subunit and B56 B subunits compared to wild—type A beta subunit [171]. This mutation raises the interesting possibility that the PPP2R1B D540G mutation is a gain of function mutation that skews binding of B subunits from A alpha toward A beta with consequences that might favor tumor formation.

One of the first PP2A subunit mutations reported was a mutation in the C alpha subunit in okadaic acid resistant Chinese hamster ovary cells [173]. Mutations in either the C alpha (PPP2CA) or C beta (PPP2CB) genes in human have not been reported. However, the PPP2CB gene is located in chromosome 5 q and loss of the C beta subunit has been reported in myelodysplastic syndrome (MDS) where 5q is deleted [174–176]. Lenalidomide has been shown to be an inhibitor of PP2A and part of its efficacy in MDS patients with 5q deletion might be the loss of PP2A function in malignant cells that are haplo-deficient PP2A C beta subunit [174–176].

Reports on mutations in the PP2A B subunits are increasing with more extensive genome sequencing strategies in many of the major medical centers around the world. A number of different mutations in the B56 gamma (PPP2R5C) subunit have been identified in various cell lines derived from solid tumors including melanoma, lung cancer, and embryonic carcinoma [73]. Nobumori and colleagues utilized these various mutations to determine the consequence of each mutation on PP2A B56 gamma isoform structure and function [73]. A number of mutations affected the ability of the B subunit to bind to the catalytic core and interestingly these mutations were scattered throughout the PPP2R5C amino acid sequence (C39R, E164K, Q256R, and L257R; ref. [73]). Two mutations were found to allow association of the B subunit with the catalytic core but binding to p53 substrate was lost. The A383G and F395C mutations lie in the B subunit region where p53 binds and thus ability to dephosphorylate p53 is lost [73,177]. Interestingly, one mutant (S220) lost ability to bind an as yet identified substrate. The S220 mutation suppresses B56 gamma tumor suppressor function and thus suggests that B56 gamma can act as a tumor suppressor by both p53 dependent and p53 independent mechanisms [73]. Mutations of the B55 alpha (PPP2R2A) gene have been reported in prostate cancer [178]. In Mutations of various B56 family members have been found in individuals with intellectual disability and in patients with overgrowth disorders [179,180].

3.5. PP2A and drug resistance

Dysregulation of PP2A by the various mechanisms described above could result in aberrant survival signaling and thus impart survival advantages to malignant cells. A recent study determined that reduced PP2A activity accounted for Bromodomain Containing 4 (BRD4) hyperphosphorylation that was associated with resistance to JQ1 and other BET Bromodomain inhibitors in triple negative breast cancer (TNBC; ref. [180]). BRD4 kinase (i.e. Casein Kinase II) activity was similar in counterpart and TNBC cells so reduced PP2A was suggested. Reduction of PP2A catalytic subunit resulted in increased phosphorylation of BRD4 with increased cell resistance to JQ1 [180]. Use of phenothiazine (a PP2A activator) reduced phosphorylation and sensitized cells to the BET Bromodomain inhibitors. PP2A regulation of BRD4 appears to be important for JQ1 resistance in breast cancer though the B subunit driving the BRD4 phosphatase was not identified [180]. AKT is a major component in survival signaling in many cancers including leukemia [181–183]. In pancreatic cancer, reduced expression of the HEAT repeat-containing protein 1 (HEATR1) is associated with chemoresistance [184]. HEATR1acts to promote PP2A mediated dephosphorylation of AKT in pancreatic cancer cells by a mechanism involving B55 beta. Reduction of HEATR1 in pancreatic cancer cells renders cells resistant to gemcitabine [184]. In colorectal cancer, B55 beta expression is reduced via an epigenetic mechanism [185]. B55 beta negatively regulates AKT in colorectal cancer cells though the mechanism involves targeting the AKT kinase Phosphoinositide Dependent Kinase 1 (PDK1). Reduced PP2A B55 beta promotes rapamycin resistance in the cancer cells in a PDK-1 dependent, AKT independent mechanism that involves MYC [185]. Active AKT is associated with prognosis for poor survival outcome in AML [51,183]. Reduced expression of B55 alpha in AML cells was found to correlate with increased AKT phosphorylation, shorter remission duration, and greater tendency toward

relapse [41,42]. In AML as is likely true in other cancers, activation of multiple survival pathways is associated with increasingly worse survival outcome [183]. Since B55 alpha acts to target both AKT and PKC alpha in AML cells, dysregulation of this B subunit impacts multiple survival pathways [42].

Cellular PP2A inhibitors have been shown to have important roles in drug resistance. Activation of PP2A to reverse resistance to Gleevac and other tyrosine kinase inhibitors (TKIs) has been achieved in CML using the SET activating drug FTY-720 [140,142,144,159,160,186]. CIP2A also plays diverse roles in drug resistance in various cancers. CIP2A mediates resistance to doxorubicin [187]. CIP2A plays a role in PP2A-mediated regulation of MYC which is central in drug resistance mechanisms in many cancers [146,151,188–190]. Consequences of CIP2A stabilization of MYC are complex and impact many survival pathways that contribute to drug resistance including mTOR signaling [190]. CIP2A supports MYC stability by blocking PP2A mediated degradation [191,192].

The B56 alpha PP2A isoform is involved in MYC degradation [93]. Considering that B56 alpha also negatively regulates BCL2 anti-apoptotic function and beta catenin stability, the B56 alpha PP2A isoform can impact many survival pathways [46,55,93,95]. B56 alpha PP2A isoform plays a role in drug resistance in ALL [46,55]. Knockdown of B56 alpha by shRNA renders cells resistant to etoposide, a drug commonly used for ALL therapy [55]. Localization of the B subunit is also important for its role in drug resistance. Overexpression of wild type B56 alpha sensitizes human ALL derived REH cells to etoposide but exogenous B56 alpha with mutant serine 28 converted to alanine (S28A) failed to sensitize cells to the drug at low dose and was less effective augmenting etoposide-induced killing at high dose [55]. While wild type B56 alpha is re-localized to the mitochondria in response to drug challenge, the S28A B56 alpha mutant did so poorly. Thus sub-cellular localization of B subunits may determine if a PP2A isoform acts to support stress signaling, have neutral effect, or oppose stress signaling depending on where in the cell the enzyme is localized.

Notch regulation of PP2A may be important in gamma secretase inhibitor (GSI) resistance in PTEN null T-ALL [191,192]. GSI inhibition of NOTCH promotes AKT activation by a mechanism involving suppression of PP2A [191]. It was postulated that gene expression of PP2A subunits could be affected by loss of NOTCH. Introduction of dominant negative Mastermind Like 1 (MAML1; a co-activator of NOTCH) into Jurkat cells induced AKT phosphorylation similar to when Notch was suppressed suggesting that loss of NOTCH transcription was necessary for induced AKT phosphorylation. However, gene and protein expression of B subunits associated with AKT dephosphorylation or catalytic core PP2A subunits were not changed suggesting NOTCH transcription of PP2A subunits was not involved [191,192]. Dominant negative MAML1 or NOTCH knock down also activated AMPK which is antagonized by AKT so effects on PP2A substrate interaction were postulated [191]. The example of NOTCH regulation of PP2A demonstrates the complexity of PP2A regulatory pathways.

3.6. Therapeutic strategies to target PP2A when it acts as tumor promoter

Studies with the PR72/PR130 subunits reveal that these PP2A isoforms support pro-survival signaling and metastasis (discussed in Section 2.3; refs. [110,111]). At least for these B subunit family members, there could be clinical benefit to inhibiting their function. The List group has found that at least part of the mechanism of action of lenalidomide killing MDS cells with 5q deletion involves suppression of PP2A activity [174–176]. PP2A is required for normal cellular functions so cells with reduced C beta catalytic subunit due to 5q deletion would be sensitive to an inhibitor that targets PP2A catalytic activity. A non-toxic PP2A inhibitor, LB100, has been developed that has shown efficacy in a variety of solid tumors [193–197]. Wei and colleagues demonstrated that LB100 or reduction of A alpha scaffold subunit sensitized pancreatic cell lines to radiation via mechanisms involving disruption of DNA repair [194]. CDC25 emerged as a critical PP2A target that was affected by LB100. LB100 was shown to sensitize ovarian cancer cells to cisplatin by a mechanism that involves at least in part the disruption of cell cycle checkpoint regulation [195]. LB100 augments mitotic catastrophe in radiation treated glioblastoma cells [196]. The Sablina Laboratory has demonstrated that reduced levels of B55 alpha in lung cancer cells was associated with increased phosphorylation of ATM and reduced levels of BRCA1 and RAD51 [198]. Cells with reduced B55 alpha were sensitive to PARP inhibitors as these cells were less efficient at DNA repair. These examples suggest that targeting PP2A can have therapeutic benefits in certain malignancies.

4. PP2A in the microenvironment

4.1. PP2A, metabolism, and TGF beta

The tumor microenvironment can be considered as the collection of cell types that contribute to the malignant state that include the tumor cells themselves, stromal cells, support cells such as tumor associated fibroblast and tumor associated macrophages, immune cells, inflammatory cells and any other cells that provide support for the tumor. It is not hard to imagine that as a master regulator of diverse cellular processes, PP2A will play some role in events that we associate with the microenvironment such as metabolism, metastasis, immune suppression, and stromal induced survival of tumor cells. PP2A appears to have an important role in regulation of cancer cell metabolism [199,200]. A model has been postulated whereby metabolic changes in cancer cells alters PP2A methylation leading to suppressed dephosphorylation of important enzymes such as pyruvate kinase [199]. A recent study has suggested that overexpression of eukaryotic Elongation Factor-2 kinase (eEF-2K) regulates the Warburg Effect in cancer cells by a mechanism involving PP2A and MYC [200]. The eEF-2 protein induces PP2A A subunit expression when active resulting in suppression of MYC but active eEF-2K blocks this function leading to enhanced MYC expression and increased pyruvate kinase M2 activity [200]. PP2A appears to have a role in the hypoxic tumor microenvironment though whether the PP2A isoforms act as tumor suppressors or tumor promoters seems to be dependent on the type of cancer [197,201,202]. At least in liver cancer, use of a PP2A inhibitor (i.e. LB100) sensitizes cells to sorafenib in hypoxic conditions [197]. The mechanism of PP2A mediated survival during hypoxia in hepatocarcioma appears to involve suppression of SMAD3 phosphorylation which supports SMAD3 mediated expression of BCL2 [197]. It is possible the differences in PP2A role in hypoxia induced survival signaling in various cancers will depend on re-localization of PP2A subunits.

Surprisingly the role of PP2A in the tumor microenvironment is understudied though some work has been done on PP2A role in TGF beta mediated signaling [203–206]. TGF beta role in cancer is complex with the molecule demonstrating both tumor suppressor and tumor promoter functions depending on cell type and context [205,207,208]. The cytokine can induce signaling by SMAD-dependent and SMAD-independent pathways with various PP2A family members being involved in both arms [203–206]. TGF beta-induced SMAD2 phosphorylation is regulated positively by B55 alpha but negatively by B55 delta [203]. Neither PP2A family member acts directly on SMAD2. B55 alpha and B55 delta PP2A isoforms target different phosphorylation sites with the B55 alpha stabilizing Activin-Like Kinase 4 (ALK4) while B55 delta destabilizes the kinase [203]. Hypoxia induced PP2A mediated dephosphorylation of SMAD3 but not SMAD 2 resulting in nuclear localization of SMAD3 though the B subunit involved was not identified [204]. A role for B56 alpha in modulating TGF beta response has been suggested by Zhang and colleagues [205]. TGF beta signaling can have pro-survival or pro-apoptotic consequences depending on the cellular context. The model suggests that in early cancer cells TGF beta via the Type I TGF beta receptor recruits B56 alpha to suppress ERK activation resulting in an anti-tumor effect. However, in advanced cancers, B56 alpha induction is lost, ERK remains active, and TGF beta signaling has pro-survival consequences [205]. The role of PP2A in TGF beta signaling is complex

and it is not clear how the various PP2A isoforms interact in this cascade. The effect of TGF beta on B56 alpha and B55 alpha are depicted in Fig. 2.

4.2. PP2A and immune regulation

Currently, there is great excitement about immune based cancer therapies. Diverse strategies to activate the patient's immune system to activate a "host versus tumor" effect include use of vaccines against cancer antigens, monoclonal antibodies against T cell and NK cell checkpoint regulators (e.g. mAbs targeting PD-1 and CTLA4), autologous CAR T cell and CAR NK cells, as well as agents that target immunosuppressive molecules such as arginase [209–211]. PP2A has been found to play a critical role in regulatory mechanisms that control function of T cells, NK cells and myeloid derived suppressor cells (MDSC) [212–226]. SET/PP2A axis is critical for regulation of NK cell function including production of cytokines such as interferon gamma [212,214]. As PP2A family has many targets, there are a myriad of potential mechanisms how the protein phosphatase can influence immune cells. Interestingly, PI3K/AKT axis appears to be a central node in signaling that supports immune activity and blocks resistance in T cells and NK cells [213,222,226]. A number of studies suggest that PP2A regulation of immune function involves control of AKT in the immune cells [213,222,223,226]. Checkpoint inhibitors against CTLA4 and PD-1 have shown efficacy in treatment of solid tumors including melanoma and are being developed for leukemia therapy [209–211]. In T cells, PD-1 and CTLA4 are expressed on the cell surface and suppress AKT mediated signaling upon ligation with their associated ligand (PD-L1 or PD-L2 for PD-1 and CD28 for CTLA4). CTLA4 works to suppress AKT directly via direct activation of PP2A though the mechanism is not clear [227]. A recent report from the Westermarck group used CIP2A deficient mice to demonstrate that the PP2A inhibitor is necessary for the immune adaptive response [225]. Furthermore, mice lacking CIP2A had reduced levels of CD4 and CD8 effector T cells. Roles of PP2A in T cell function relative to the immune cell and the target cancer cell are depicted in Fig. 3, respectively.

A recent paper from Apostolidis and colleagues determined that PP2A is required for T regulatory cell immune suppressor function by a mechanism involving mTOR [217]. In that study the investigators deleted A alpha scaffold in T regulatory cells in mice by crossing Fox3p$^{YFP\text{-}Cre}$ mice with PPP2R1A$^{flox/flox}$ mice. Mice with T regulatory cells lacking PP2A A scaffold developed severe autoimmunity with increases in both CD4+ and CD8+ T cells [217]. CD4+ cells produced greater levels of IL-2 and IL-17 while CD8+ cells produced higher levels of interferon gamma compared to control mice. If T regulatory cells expressed at least half of PP2A A alpha compared to control then autoimmunity was not observed. This finding emphasizes the importance of PP2A in the T regulatory cell function [217]. Interestingly, PP2A activation in T regulatory cells is linked to ceramide metabolism. FoxP3 was shown to suppress expression of SMS1, an enzyme that converts ceramide to sphingomyelin [217]. The accumulation of ceramide in T regulatory cells was suggested to suppress SET protein, which was found to be positively regulated by T cell receptor (TCR), as well as blocking tyrosine phosphorylation of the catalytic C subunit [217]. The study did not look at B subunit involvement so it would be interesting to see if ceramide sensitive B subunits such as B56 alpha are prominent in T regulatory cells and if these B subunits are essential for T regulatory cell suppressor function.

5. Conclusions

PP2A isoforms serve diverse roles in cancer cells. These enzymes can act either as tumor suppressors or tumor promoters depending on the cellular context. Though understudied in cancer, interest in PP2A isoform role in cancer biology is growing. A better understanding of PP2A regulation in cell cycle, cell growth, cell survival, and immune response gives us a greater appreciation of the important role these enzymes play in tumorigenesis, drug resistance, and cancer cell cloaking against immune surveillance. Viral PP2A inhibitors like SV40 small t antigen have been shown to play a pivotal role in viral transformation of cells. The cellular PP2A inhibitors SET and CIP2A are frequently found to influence drug resistance and cancer cell survival in many cancers. Therapeutic strategies to suppress these proteins and re-activate PP2A are being developed for the next generation of cancer therapies.

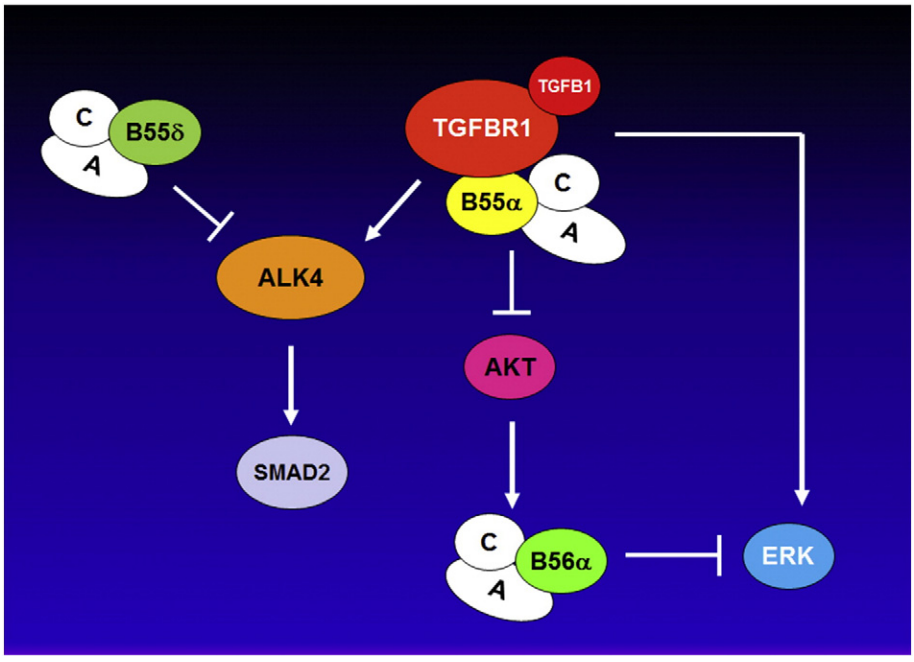

Fig. 2. B55 alpha and B56 alpha PP2A isoforms play important roles in TGF beta signaling. A model of B55 alpha and B56 alpha role in TGF beta signaling is depicted.

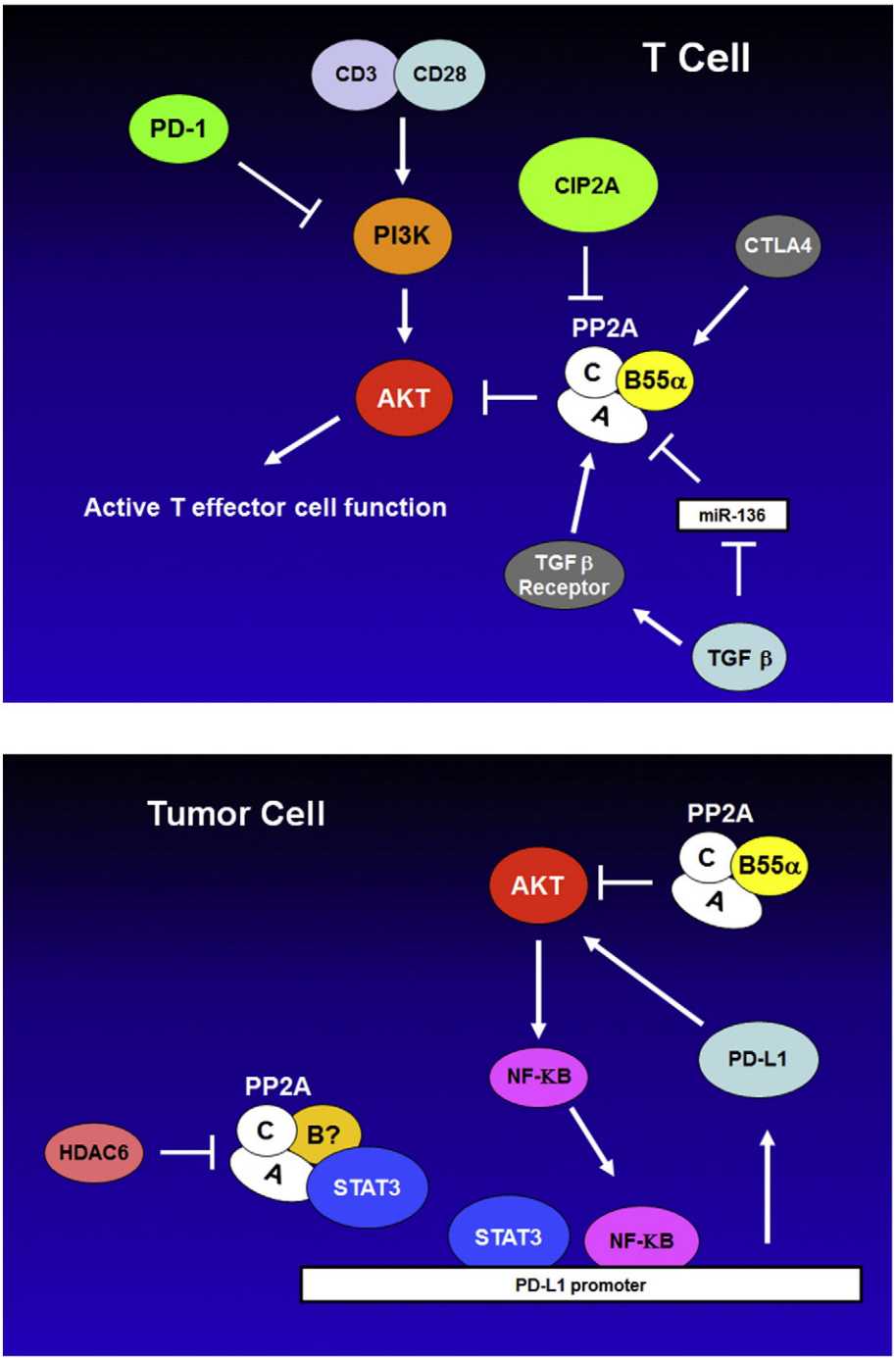

Fig. 3. PP2A isoforms regulate processes that impact immune function. A model of PP2A response to checkpoint inhibitors CTLA-4 and PD-1 in T cell is depicted in the top panel. A model of PP2A regulation of checkpoint ligand PD-L1 expressed in tumor cells is shown in the bottom panel.

Transparency document

The Transparency document associated with this article can be found, in online version.

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