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Unraveling the complexity: A comprehensive analysis of the PP2A in cancer and its potential for novel targeted therapies

Minireview

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Protein phosphatase 2A (PP2A) is a major serine/threonine phosphatase considered a potent tumor suppressor that critically regulates diverse cellular processes, including cell cycle progression, apoptosis, or DNA repair. PP2A is typically downregulated in cancers but mechanisms for its inactivation in human cancers are poorly understood. PP2A represents a family of more than 60 phosphatases. According to cellular context, each heterotrimeric PP2A holoenzyme exerts a unique role in cancer, and PP2A isoforms can act either as tumor suppressors or as promoters. Due to wide structural diversity, PP2A has been considered undruggable. However, increasing knowledge predisposes PP2A diversity to therapeutical targeting for the treatment of a broad range of cancer pathologies, including drug resistance or cloaking immune surveillance. In this review, we discuss the regulatory role of PP2A in cancer, its regulation by microRNA and hypoxia, its contribution to therapy resistance development, and the therapeutic potential of direct and indirect targeting, or combinatory administration with other anti-cancer drugs to improve cancer treatment outcomes.

Key words: PP2A; phosphatases; dephosphorylation; cancer; hypoxia; miRNA; epigenetics

Protein phosphorylation is a post-translational modification essential for the control of the activity of most enzymes in the cell. A fine-tuned balance between kinases and phosphatases regulates a complex and highly integrated series of phosphorylation and dephosphorylation events, typical reactions controlling signal transductions in cells, including events facilitating DNA damage response. Disturbance of this balance can lead to altered cellular behavior and the development of many diseases, not excluding cancer. In cancer research, the most attention has been devoted to the deregulation of kinases and their activity. Kinases are considered a major mechanism of cancer cells to evade normal physiological growth and survival. Based on this knowledge, specific inhibitors of these enzymes have been developed and proven very successful in cancer therapy [1]. On the other hand, despite their long-term underestimation, phosphatases are now considered equally important and their essential role in controlling cell proliferation and cancer development cannot be overlooked. Phosphatases have been generally identified as tumor suppressors [2]. However, recent research has paradoxically demonstrated their inhibition as a potential targeting option for cancer treatment, therefore considering them as attractive targets for new cancer therapies development [3, 4].

Based on their substrate specificity and catalytic mechanism, protein phosphatases (PP) are classified into two major families and several subfamilies with multiple members. The major families are the protein serine/threonine phosphatases and protein tyrosine phosphatases. The protein serine/threonine phosphatases can be further sub-classified into three structurally distinct families: phosphoprotein phosphatases, metal-dependent protein phosphatases, and aspartate-based phosphatases. Phosphoprotein phosphatases include PP1, PP2A, PP2B, PP4, PP5, PP6, and PP7. PP2C and pyruvate dehydrogenase phosphatase represent the metal-dependent protein phosphatases and FCP1 and SCP aspartate-based phosphatases. Based on their structure and gene sequence, the protein tyrosine phosphatase family is divided into 3

main families (Class I–III) with several sub-families: Class I are classical protein tyrosine phosphatases (transmembrane and non-receptor) and dual specificity phosphatases (mitogen-activated protein kinase /MAPK/ phosphatases, phosphatase and tensin homologs /PTEN/, CDC14s), Class II are CDCs (CDC25A, B, C), and finally Class III are low molecular weight protein tyrosine phosphatases [5, 6].

Drug resistance is a commonly encountered problem in clinical oncology. Multiple mechanisms are involved in cellular response to therapeutics (e.g., platinum agents) including import/export of the drug, its inactivation, or causing DNA damage. In most solid malignancies, cisplatin (CDDP) is the standard first-line therapy. Its cytotoxicity strongly relates to nuclear DNA damage that is repaired by different DNA repair mechanisms. Constitutive phosphorylation of intermediates within signaling pathways and DNA damage response (DDR) mechanisms, has been shown to be a barometer of critical cellular processes that determine the decision of the cell to repair damaged DNA or induce apoptotic cell death [7]. The serine/threonine kinases ATM and ATR are primary coordinators of cellular responses to DNA damage. These kinases are activated upon induction of double-strand breaks (DSBs) or arrest of DNA replication and are involved in the regulation of DNA repair, cell cycle checkpoints, and apoptotic signaling [8]. The effects of ATM/ATR are exerted directly and indirectly through the control of phosphorylation of downstream target proteins like BRCA1, H2AX, checkpoint kinases CHK1 and CHK2. DSBs activate other important kinases mentioning DNA-PKs that belong to the PI3K-related protein kinase superfamily [9], playing a role in therapy resistance [10]. Similarly, WEE1, a protein kinase localized in the nucleus, is extensively involved in DDR signaling [11] that negatively regulates the G2/M transition after the detection of DSB [12]. In addition, increased phosphorylation of many other signaling proteins of the ATM/ATR pathway may correlate with the extent of apoptotic induction [13, 14]. Thus, reversible phosphorylation and dephosphorylation play an important role in modulating cell function and maintaining homeostasis that allows cells to survive, proliferate, and cope with different kinds of stress [15]. Although it is clear that phosphatases antagonize the action of kinases, much less is known about their role in the development and progression of human cancers [16]. Importantly, growing evidence suggests that phosphatases can serve not only as negative regulators but also actively contribute as DDR modulators [17].

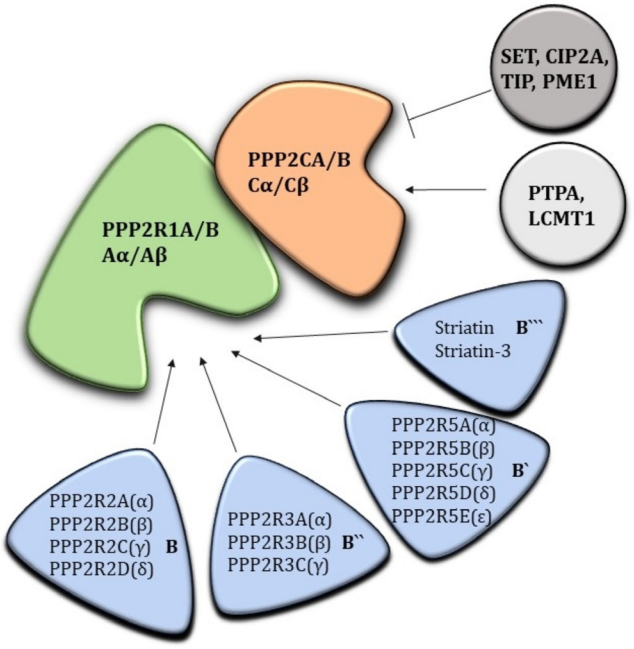

Figure 1. PP2A family of serine/threonine heterotrimeric phosphatases. The PP2A holoenzyme is a heterotrimeric complex composed of a catalytic subunit C, a structural subunit A, and a single regulatory subunit B. Four unrelated families of PP2A B regulatory subunits (B /B′/B′′/B′′′) have been identified so far. The assembly and activity of heterotrimeric PP2A complexes is regulated by intracellular inhibitors of PP2A (SET, CIP2 PME1, and TIP) and activators of PP2A (PTPA and LCMT1).

Protein phosphatase 2 (PP2A)

PP2A is one of the major serine/threonine phosphatases that refers to a large family of heterotrimeric Ser/Thr phosphatases involved in the control of numerous signaling cascades. The core enzyme PP2A consists of a catalytic C subunit and a structural A subunit. In mammals, 2 distinct genes encode closely related versions of the PP2A subunits A (Aα/PPP2R1A and Aβ/PPP2R1B) and C (Cα/PPP2CA and Cβ/PPP2CB). The AC dimer recruits a third regulatory B subunit responsible for the substrate specificity and function of the PP2A heterotrimeric complex. To date, four unrelated families of B subunits have been identified: B/B55/PPP2R2, B′/B56/PR61/PPP2R5, B′′/PR72/PPP2R3, and Striatin/STRN/B′′′ (Figure 1). Approximately 100 different complexes of these subunits can be formed by their combination, and these individual PP2A complexes are thought to mediate specific physiological functions [18]. PP2A is highly conserved, ubiquitously expressed in eukaryotic cells [19] and its catalytic activity is tightly regulated. Functionally, PP2A plays a key role in the cell cycle, cellular metabolism, cell migration, DNA repair, cell survival, and other signaling pathways [20, 21]. Therefore, from the clinical point of view, it is considered an important new therapeutic target in multiple pathologies and diseases [22, 23].

However, approximately 30% of PP2A complexes exist only as a 'core dimer' composed of a catalytic and structural subunit (PP2A-CB) [24]. There are two isoforms of the catalytic subunit (PP2ACα and PP2ACβ), which share 97% sequence homology. The most prevalent isoform is PP2ACα [25]. Importantly, both share a unique C-terminal tail containing a TPDYFL motif, that is located between the structural and regulatory subunits in the holoenzyme [26, 27]. This motif plays a fundamental role in the regula-

tion of catalytic activity and holoenzyme assembly [28]. The structural subunit also has two isoforms (PR65α and PR65β) [18, 26] sharing 87% sequence homology. Structurally, they consist of 15 huntingtin-elongation-A subunit-TOR (HEAT) repeats, which are short pairs of interacting helices linked by a tight 1–3 residue turn that forms a horseshoe shape [29]. It is through the HEAT repeats that the catalytic and B56 regulatory subunits bind to the structural subunit to form the trimeric holoenzyme. The catalytic subunit binds to HEAT repeats 11–15 through a mix of hydrogen, hydrophobic, and ionic bonding [27]. This not only keeps the active site of the catalytic subunit exposed and accessible to the substrate but also facilitates binding of the carboxyl terminus of PP2ACα to a surface groove at the interface between the scaffolding and a regulatory subunit enabling recruitment of the latter [26].

PP2A in cancer

PP2A has been assumed to play a major role as a tumor suppressor and is often misregulated in cancer. However, this phosphatase can also activate several oncogenic pathways and positively participate in the oncogenic process [30, 31].

PP2A enzyme plays a direct role in the negative regulation of DSBs repair proteins, such as γ-H2AX, ATM, CHK1, and CHK2 [32]. However, contrary to the notion that protein phosphatases solely function as negative regulators of DNA repair signaling, the targeted inhibition of PP2A activity hampers DNA repair [33]. PP2A function is also essential for the activation of cell cycle checkpoints in response to irradiation. These apparent discrepancies can potentially be explained by the existence of multiple distinct PP2A complexes that can modulate various stages of the DNA repair process. The diversity of PP2A functions suggests that particular PP2A complexes may contribute independently to different phenotypes, including the DNA damage response [18]. Indeed, knockdown of 4 different PP2A regulatory B subunits (PPP2R2A, PPP2R2D, PPP2R5A, and PPP2R3C) was found to impair DNA repair efficiency, suggesting that these specific PP2A complexes are involved in the control of DNA repair [17]. PP2A also regulates numerous cellular signaling cascades by inhibiting the activity of kinase oncogenes. Recently, a reduction in PP2A activity has been found in various types of human tumors. Loss of PP2A function occurs either through inactivating mutations of PP2A structural subunits or upregulation of endogenous cellular inhibitors of PP2A, such as inhibitor 1 of PP2A (I1PP2A), also known as ANP32A, inhibitor 2 of PP2A (I2PP2A), also known as SET, or cancerous inhibitor of PP2A (CIP2A) [16, 34, 35]. PP2A activity can also be regulated by post-translational modification, e.g. phosphorylation of threonine 304 (T304) residue or tyrosine 307 (Y307) residue can inactivate PP2A [16, 36], while methylation of the carboxyl-terminal leucine 309 (L309) residue can reversibly activate PP2A [14, 15]. In pancreatic ductal adenocarcinoma cells, an increased level of the B55α subunit has been identified correlating with poor survival of pancreatic cancer patients. Consequently, inhibition of the B55α subunit resulted in reduced phosphorylation of Akt and Erk1/2, and lower β-Catenin levels leading to decreased cell growth, clonogenicity, mobility and anchorage-independent growth, pointing to oncogenic effects of PP2A-B55α (PPP2R2A) [37].

PP2A substrate specificity and localization

The mechanism of assembly of PP2A heterotrimeric complexes is not yet fully understood. The PP2A activity and the dynamic exchange of PP2A regulatory subunits could be modulated by reversible methylation and phosphorylation of the carboxyl-terminal end of subunit C. This complexity in the assembly of the holoenzyme trimer provides PP2A with the ability to dephosphorylate a large number of different substrates and mediate a wide range of physiological functions. Since PP2A suppresses tumors by regulating cell signaling cascades opposing kinase oncogenes [18], pharmacological activation of PP2A activity could restrict the activity of kinase oncogenes. Some PP2A activators have been proposed as treatment options for various types of human leukemia. For example, loss of PP2A enzymatic activity contributes to the pathophysiology of p210 and p190BCR/ABL-induced leukemia [16, 38]. Also, a CHEK2 and PPP2R2A fusion study in pediatric teratomas showed that deregulation of CHEK2 and/or PPP2R2A has pathophysiological significance in at least a subset of germ cell tumors [39]. Moreover, PP2A is an attractive target for sensitizing DNA damage repair. Extensive studies in *Xenopus leavis* have shown that PP2A is induced as part of the DDR and is involved in G2-M arrest [40]. The inhibition of PP2A disrupts the normal progression into mitosis, ultimately resulting in mitotic catastrophe and apoptosis. PP2A also regulates CHK1, a critical DDR mediator, through a negative feedback loop that maintains CHK1 in a state of low activity during normal cell division, priming it for a rapid response to DNA damage [41]. This integral relationship is maintained by the continuous phosphorylation and dephosphorylation of CHK1 [14].

The work of several groups highlights the importance of the regulatory subunits in determining substrate specificity and subcellular localization of PP2A. For example, involvement of the B55α (PPP2R2A) subunit in the PP2A holoenzyme is needed for PP2A-mediated dephosphorylation of p107 in human osteosarcoma and glioblastoma cells [42]. The B55α subunit of PP2A also directs its activity toward phospho-β-catenin [43] and an AP-1 complex in tumor cells [44]. It is worth noting that heat shock transcription factor 2 (HSF2) can regulate PP2A activity by obstructing the assembly of the holoenzyme through steric hindrance, as it binds to the same binding site on PP2AC as B55 [45]. Additionally, PP2A-B56 is involved in mediating insulin signaling and lipid metabolism by dephosphorylating Akt in

C. elegans and *Drosophila* [46, 47]. Finally, B56γ determines the PP2A substrate specificity during cardiac development in mice [48]. It is interesting to note that the B subunit composition of PP2A relates with the localization into cellular compartments and intracellular structure of PP2A. In rat brain, B55α and β isoforms localize PP2A to the cytosolic and nuclear compartments, whereas the γ isoform towards cytoskeletal structures [49, 50]. In mammals, B55 has been shown associated with cytoskeletal dynamics and nuclear translocation and is essential for cytokinesis [50]. Similarly, B56α, β, and ε guide PP2A in the cytoplasmic compartment, whereas the δ and γ isoforms direct it towards the nucleus [51] or subnuclear structures associated with transcription factor assembly [52]. It is important to highlight that B56δ exhibits dynamic localization, shuttling between the nucleus and cytosol in a cell cycle stage-dependent manner [53]. This suggests that the localization of B56δ can undergo changes and is not static [23].

Regulation of the PP2A by microRNA

microRNAs (miRNAs) represent a family of short regulatory RNA molecules, which are expressed in a tissue- and time-specific manner and regulate gene expression after transcription. miRNAs hybridize with target mRNA to induce translational repression or mRNA degradation [54]. Functional studies have shown that miRNAs are involved in virtually every physiological process and therefore their deregulation is associated with the development of different pathologies. miRNA expression is deregulated in human malignancies, most often due to chromosomal abnormalities, changes in transcriptional control, epigenetic changes (demethylation or inhibition of histone deacetylases), and due to defects in the mechanism of miRNA biogenesis. Abnormal miRNA expression in malignant cells can result from amplification or deletion of specific genomic regions comprising genes for miRNA. Changes in miRNA expression accompany various processes of tumorigenesis, such as tumor proliferation, migration, angiogenesis, apoptosis, drug transport, or DNA repair [55]. Depending on their target genes, miRNAs act as an oncogene or as a tumor suppressor. A single miRNA can regulate different target genes and one target gene can be regulated by different miRNAs [56]. Approximately 23 miRNAs are implicated in the regulation of the major components of PP2A (Table 1).

Yu et al. [57] performed bioinformatics analysis and found that PPP2R2A is a target of miR-221, which they further confirmed in osteosarcoma (OS) cells using western blot and dual luciferase assay. They found that miR-221 directly targeted, thus downregulated PPP2R2A. Restoration of PPP2R2A in cells overexpressing miR-221 restored sensitivity to CDDP. Another study showed that miR-222 could attenuate CDDP-induced cell death in bladder cancer cells through inhibition of CDDP-induced autophagy by directly targeting PPP2R2A [58], thus suggesting that miRNA-222 could modulate sensitivity to CDDP by targeting PPP2R2A itself. Zhuang et al. [59] provide a view of the role of miR-218 in chemotherapy resistance, specifically in

Table 1. miRNAs involved in regulation of key components of PP2A.

Subunit	Gene Target	miRNA	Tissue/Model	Target and Effect	Notes	References
Catalytic	PPP2AC	miR-1	Rat cardiomyocytes	↓PP2AC protein		[147]
		miR-155	PBMCs	↓PP2AC mRNA	↓miR-155 correlates to ↑PP2AC mRNA in PBMCs from patients with SLE or Familial Mediterranean Fever	[63]
		miR-429	OB6, hFOB1.19	↓PP2AC mRNA/protein	Targets 3'-UTR of PP2AC mRNA	[62]
		miR-520h	Human breast and cervical cancer cell lines	↓PP2AC promoter	Targets 3'-UTR of PP2AC mRNA	[148]
		miR-183	ACHN, A498 renal tumor biopsies	↓PP2ACα and PP2ACβ protein and promoter activity	Regulates cell growth and metastasis in renal cancer	[64]
		miR-133a	CHO	↓PP2ACα and PP2ACβ promoter activity	miRNA overexpression	[60]
		miR-1246	Mesenchymal stem/stroma cells	↓PP2Ccβ mRNA / promoter activity		[61]
Structural	PPP2R1B	miR-200c	Esophageal squamous cell carcinoma	↓PP2A-Aβ protein	↑miR-200c associated with chemoresistance	[65]
		miR-587	HCT1 16, Colorectal cancer biopsy	↓PP2A-Aβ protein	Confers chemoresistance in colorectal cancer	[66]
	PPP2R2A	miR-31	Murine and human lung cancer cell lines	↓PPP2R2A mRNA ↓promoter activity	miR-31 and PPP2R2A expression inversely related in murine and human lung cancer	[67]

Table 1. ***Continued . . .***

Subunit	Gene Target	miRNA	Tissue/Model	Target and Effect	Notes	References
Regulatory		miR-195	Murine and human lung cancer cell lines	↓PP2ABα expression	Represses specific tumor suppressors in lung cancer	[149]
		miR-17-92 miR-20	DLBCL cells and DHL4 cells	↓PP2A promoter activity and mRNA		[68]
	PPP2R2D	miR-133b	HepG2, QGY7701, MHCC97H, HCC97L, Hep3B, Huh7	↓PP2ABδ protein and mRNA	miR-133b binds to 3'UTR enhancing sensitivity of HCC to chemotherapy	[69]
	PPP2R5A	miR-1	Adult rat isolated ventricular myocytes	↓PP2ABα protein	miR-1 enhances cardiac excitation contraction coupling by ↓PP2A-Bα abundance and altering cellular localization of PP2AC	[147]
		miR-133	Cardiomyocytes	see note	miR-1 and miR-133 expression associated with decrease protein levels of B56α/δ and lower PP2A activity	[60]
		miR-155 miR-31	Murine macrophages	↓PP2ABα mRNA ↓PP2ABα promoter	Decreases PP2A activity limiting autophagy	[150]
	PPP2R5C	miR-27a	HBELH		B55γ KO ↑miR-27a mRNA, B55α KO ↓miR-27a mRNA	[75]
		miR-183	ACHN, A498 renal tumor biopsies	↓PP2A B56γ protein/promoter activity	Regulates cell growth and metastasis in renal cancer	[64]
	PPP2R5D	miR-9	HEK293 Pulmonary macrophages	↓PPP2R2A ↓PPP2R5D promoter activity ↓PP2A-Bδ	Inhibition of miR-9 ↑PP2A activity	[70]
		miR-133	Cardiomyocytes		miR-1 and miR-133 expression associated with decrease protein levels of B56α/δ and lower PP2A activity	[60]
	PPP2R5E	miR-19	Lymphocytes	PPP2R5E mRNA, promoter activity, protein		[151]
			DLBCL cells, DHL4 cells	↓PPP2R5E promoter activity and mRNA		[68]
Other	CIP2A	miR-218	A375 SK-MEL-2 cells	↓CIP2A promoter, mRNA and protein	Suppresses proliferation, migration, invasiveness, and the cell cycle	[72]
		miR-375	HEK293, CAL27	↓CIP2A promoter activity, ↓mRNA, ↓protein	Inverse correlation between miR-375 and CIP2A in oral cancer and NCI-60 cells but not in multiple head and neck cancer cell lines	[71]
		miR-383-5p	A549, H1299	↓CIP2A protein, ↓mRNA, ↓ promoter activity	miR-383-5p inversely related to CIP2A expression in lung adenocarcinoma	[73]
	SET	miR-199b	JAR, BeWo	↓SET protein, ↓promoter activity	miR-199b associated with ↑SET in choriocarcinoma	[74]
	PME1	miR-195	Rat hippocampal and cortical regions	↑PME promoter activity		[149]

the response of oral cancer cells to CDDP, through the Wnt signaling pathway by targeting the PPP2R5A phosphatase. miR-218 was significantly upregulated in CDDP-resistant oral cancer cell lines and in oral cancer patients who failed neoadjuvant chemotherapy. The authors demonstrated that miR-218 decreased the levels of PPP2R5A and increased the expression of β-catenin and glycogen synthase kinase-3β (GSK3β). Importantly, inhibition of miR-218 restored the sensitivity of oral cancer cells to CDDP therapy. Moreover, more studies have demonstrated that miR-155, miR-183, miR-429, miR-520h, miR-133a, and miR-1246 can reduce the promoter activity, mRNA expression, and protein expression of PP2AC [60–64]. From a clinical perspective, low expression of miR-155 correlates with high levels of PP2AC mRNA expression in peripheral blood mononuclear cells (PBMCs of patients with systemic lupus erythematosus or familial Mediterranean fever [63]. Regarding the PP2A structural subunits, miR-200c and miR-587 decrease the expression of the PPP2R1B to grant chemoresistance in esophageal squamous cell carcinoma and colorectal cancer

[65, 66]. Multiple studies have emphasized the involvement of miRNAs in regulating the expression of the B55 and B56 regulatory subunits. In murine and human lung cancer cell lines, Liu et al. demonstrated an inverse relationship between miR-31 and PPP2R2A expression [67]. More recently miR-17 and miR-20 have been shown to inhibit PPP2R2A promoter activity, and hence PPP2R2A mRNA expression [68]. In another work, miR-133b was shown to bind to the 3'-UTR of PPP2R2D, and decrease transcription in hepatic carcinoma cell lines; an effect associated with chemosensitization [69]. There is also some evidence showing miRNA regulation of the B56 regulatory subunit. In pulmonary macrophages, miR-9 has been found to regulate steroid-resistant airway hyper-responsiveness by reducing the abundance and promoter activity of PP2A-B'δ, as demonstrated by Li et al. in 2015 [70]. Studies focusing on experimental models of cancer demonstrate that miRNAs also play a key role in regulating the expression of several endogenous inhibitors of PP2A. For example, miR-218, miR-375, and miR-383-5p decrease CIP2A promoter activity, mRNA expression, and protein abundance in skin, oral, and lung cancer cell lines [71–73]. Furthermore, overexpression of miR-199b decreases SET promoter activity, expression, and abundance in choriocarcinoma cell lines [74]. The PP2A holoenzyme, which undergoes post-translational modification, emerges as a target regulated by miRNAs.

Indeed, miRNAs play a significant role in modulating the expression of various components within the phosphoprotein phosphatase system. However, it is important to note that a reciprocal relationship also exists, meaning that the phosphoprotein phosphatase system can, in turn, regulate the expression and activity of miRNAs. In bronchial epithelial cells, knockdown of B56γ upregulates miR-27a [75]. In a more recent study, the silencing of B55α increases the expression of miR-191-5 and reduces the expression of miR-142-3p in AML cells [23, 76].

PP2A and hypoxia

Because of disorganized vasculature developed to supply oxygen to rapidly growing tumors, many solid tumors contain hypoxic regions with reduced oxygen levels. In cancer patients, tumor hypoxia leads to a poor prognosis [77] due to potentially increased malignancy, resistance to both chemo- and radiation therapy, and an increased likelihood of metastases [78]. Compared to healthy tissue, where tissue oxygen levels usually exceed 40 mmHg, tumors can sustain oxygen levels of only 0–20 mmHg [79]. Under physiological conditions, hypoxia typically leads to cell death. However, it can also induce genomic changes and metabolic switch that allow tumor cells to adapt to poor nutrition and a hostile microenvironment, thus remain viable. Hypoxic stress pre-selects subpopulations of viable cells with a genetic mechanism for malignant progression [80]. Cellular adaptation to hypoxia is primarily mediated by the family of transcriptional regulators, hypoxia inducible factors (HIFs). More than 100 genes are regulated directly or indirectly by HIF [81, 82], whose active form binds to the hypoxia-response element (HRE) in the promoter region of the target genes.

The role of epigenetics in cellular responses to hypoxia is becoming widely recognized. This type of control may play a role in tandem with HIF or may maintain the hypoxia-adapted cell phenotype following HIF activation. Epigenetic control is important in the stabilization and binding of HIF to its transcriptional targets and subsequently also after direct activation of HIF. HIF activity is thought to be amplified in the background of epigenetic changes that are a prerequisite for the response to hypoxia. Epigenetic changes at the level of DNA and histones can modulate the specific binding of HIF on the target gene promoter [83]. Crucially, hypoxia is associated with more than 300 different posttranslational modifications such as phosphorylation and nitrosylation [84]. Given the importance of HIF-1α, and posttranslational modification in response to hypoxia, what is the evidence for hypoxia-mediated modulation of PP2A? In line with the transcription-suppressive effects mediated by HIF-1α, intermittent hypoxia, involving alternating periods of normal oxygen levels (normoxia) and reduced oxygen levels (hypoxia), selectively reduces PP2A mRNA levels in a specific pattern within the rat brain. Furthermore, according to Raghuraman et al. [85], this decrease in PP2A levels seems to be specific to the phosphatase itself, as other phosphatases like PP2C, PP4, PP5, and PP6 remain unaffected, at least in the context of intermittent hypoxia. Several groups have shown hypoxia to upregulate PP2A. In human colorectal cancer cells, rat primary alveolar epithelial cells and mouse heart, hypoxia increases PP2A activity [86–88], PP2A mRNA, and protein abundance [89, 90]. Although the increase in hypoxia-mediated PP2A activity could be explained by the increase in PP2A abundance, it more likely reflects post-translational modification of PP2AC. In HT29 human colorectal cancer cells exposed to hypoxia, the increase in the PP2A activity coincided with a decrease in the phosphorylation of PP2AC. Interestingly, this effect was independent of any changes in the levels of PP2A or PP2A Aα/β, as reported by [88] Lin et al. in 2012.

Moreover, it is known that hypoxia modifies the activity of the cytochrome chain responsible for mitochondrial oxidative phosphorylation, resulting in decreased ATP synthesis and increased production of reactive oxygen species (ROS). Several studies indicate that ROS may be responsible for the increase in PP2A abundance [90–92], as the effect decreases after exposure to ROS scavengers (1-10-phenanthroline and superoxide dismutase) [89]. In contrast to the above studies, a couple of groups demonstrated that hypoxia does not in fact alter PP2A expression or protein abundance [93, 94]. Whether coincidental or not, these studies were undertaken in tumor-derived stem cells and mouse embryonic stem cells, respectively. So, is there a link between PP2A and HIF-1α? One of the first studies to establish a link between HIF-1α and

PP2A was by Komatsu et al. in 2007 [95]. In this study, PP2A and PP2ACβ mRNA were found to be lower in fractures of the femur from HIF-1α+/– mice than those with a HIF-1α+/+ phenotype. In a more recent clinical study, PP2A activity was shown to positively correlate with HIF-1α abundance in patients with a high-grade astrocytoma compared to non-neoplastic surgical specimens and was an independent predictor of survival [93]. This is consistent with the observation that the knockdown of HIF-1α increases the proliferation of ovarian cancer cells by reducing PP2A activity but not PP2AC abundance in an ovarian clear cell carcinoma cell line [96]. Recently, work by Elgenaidi and Spiers [23] has shown that the expression of multiple components is suppressed by hypoxia with kinetics that are cell line dependent. There is also a reciprocal interaction, as B55α-associated PP2A attenuates the degradation of HIF-1α through dephosphorylation of PHD2 at Ser125 to increase HIF-1α levels [23, 97].

PP2A in cancer therapy resistance

The emergence of resistant clones following targeted therapy and cytotoxic chemotherapy is a significant challenge in cancer treatment. Various mechanisms can disrupt the normal function of PP2A, leading to abnormal survival signals that provide advantages to cancer cells. Recent research has shown that reduced PP2A activity contributes to hyperphosphorylation of Bromodomain Containing 4 (BRD4), which is associated with resistance to JQ1 drug and other bromodomain and extra-terminal domain (BET) inhibitors in triple-negative breast cancer (TNBC) [98]. In pancreatic cancer, decreased expression of HEAT repeat-containing protein 1 (HEATR1) is linked to chemoresistance [99]. HEATR1 promotes PP2A-mediated dephosphorylation of AKT in pancreatic cancer cells through B55b, and reduced HEATR1 renders cells resistant to gemcitabine. Similarly, in colorectal cancer, epigenetic mechanisms reduce B55b expression, leading to negative regulation of AKT and promoting rapamycin resistance. Active AKT is associated with poor survival outcome in acute myeloid leukemia (AML), and reduced B55α expression in AML cells correlates with increased AKT phosphorylation, shorter remission duration, and higher relapse tendency [100]. Dysregulation of B55α affects multiple survival pathways in AML by targeting AKT and PKCα. Cellular PP2A inhibitors, such as CIP2A, also play diverse roles in drug resistance across different cancers. CIP2A mediates resistance to doxorubicin and supports MYC stability by blocking PP2A-mediated degradation. The B56α PP2A isoform is involved in MYC degradation and affects multiple survival pathways, including BCL2 anti-apoptotic function and b-catenin stability. The subcellular localization of PP2A B subunits is also crucial for their role in drug resistance [101]. Overexpression of wild-type B56α sensitizes cells to etoposide, while a mutant form with altered serine 28 fails to do so effectively [102]. Furthermore, PP2A activating therapy has been explored in lung cancer models with constitutive KRAS activation. Loss of PP2A regulatory subunits and overexpression of SET and CIP2A have been observed in lung cancer, and inhibiting PP2A was found to drive resistance to kinase inhibitors in KRAS-driven lung cancer cell lines [103]. Activation of PP2A via siRNA against CIP2A sensitized cells to MAPK inhibitors, indicating that pharmacological activation of PP2A could overcome MEK inhibitor resistance. A phenothiazine derivative (SMAP) that activates PP2A synergized with the MEK inhibitor trametinib, leading to significant tumor regression in KRAS-driven xenograft mouse models. This study suggests that combining MEK inhibitors with PP2A activators could be a potential strategy to combat resistance mechanisms and suppress the PI3K pathway along with c-MYC stabilization [104].

PPP2R2A and PPP2R5A – important regulatory subunits

The subunit B55α of the PP2A, encoded by the *PPP2R2A* gene, is present in all tissues. Its highest expression levels are found in the developing central nervous system and limbs, as well as in the adult brain, bladder, adrenal glands, ovaries, and placenta [105]. This gene acts as a tumor suppressor and is frequently deleted or under-expressed in various types of human cancers. Loss or inactivation of B55α has been associated with cancer and Alzheimer's disease [106–108]. Therefore, it is important to understand the functional role of B55α in normal physiological processes. In prostate, ovarian, and lung adenocarcinomas, which account for a significant proportion of non-small cell lung cancer cases, the region coding for PPP2R2A frequently undergoes loss of heterozygosity (LOH), leading to reduced PPP2R2A expression in 60% of prostate cancers, 46% of ovarian cancers, and 43% of lung adenocarcinomas [17, 109]. Reduced expression of PPP2R2A is associated with unfavorable outcomes, highlighting the need for treatments targeting PPP2R2A-deficient cancers. Qiu et al. [110] have identified new synthetic lethal interactions between PPP2R2A deficiency and CHK1 or ATR inhibition. They have also shed light on the mechanisms through which PPP2R2A deficiency induces spontaneous replication stress (RS)/DNA damage by upregulating replication initiation and c-Myc activity, even without external DNA-damaging agents. Furthermore, they propose PPP2R2A as a novel predictive biomarker for guiding the development of ATR and CHK1 inhibitor trials. In cellular models, PP2A-B55α complexes have been shown to positively regulate the ERK/MAPK pathway while negatively regulating the PI3K/AKT pathway [111]. PPP2R2A complexes are also involved in DNA damage repair pathways through dephosphorylation of ATM, cell cycle regulation through dephosphorylation and activation of the retinoblastoma-related protein p107, control of mitotic exit by deactivating Cyclin-dependent kinase B-Cdk1 and its target proteins [112–114], and cell adhesion and migration through dephosphorylation of Rac1 and AP-1 [44, 115]. PP2A-B55α has been identified

as a tumor suppressor also in various epithelial and blood cancers. The PPP2R2A gene is commonly deleted in human breast [116] and prostate tumors [117], and the knockdown of PPP2R2A in breast cancer cell lines has been shown to increase tumorigenicity [98]. PPP2R2A is also frequently downregulated in non-small cell lung carcinomas [17]. In a recent study by Panicker et al. [118] using N-ethyl-N-nitrosourea (ENU)-induced mutagenesis, a splice-site mutation in PPP2R2A resulted in reduced PP2A-B55α expression. Generation of double heterozygous mice for this PPP2R2A mutation and a null allele of the gene encoding the insulin receptor resulted in a diabetic phenotype characterized by hyperglycemia, hyperinsulinemia, impaired glucose tolerance, and glycosuria [119]. This suggests that PP2A-B55α may play a role in metabolism and since PP2A-B55α dephosphorylates b-catenin during Wnt signaling, it may also play a role in the development [43].

B56α, designated and encoded as *PPP2R5A* is another important PP2A regulatory subunit. PPP2R5A is involved in the regulation of many key signaling pathways, such as p53, Bcl2, cyclin-dependent kinase (CDK), MAPK, Janus kinase/signal transduction and activating transcription factor (JAK/STAT). Abnormalities of PPP2R5A are often associated with various types of diseases, especially some types of adenocarcinomas and epithelial carcinomas [120, 121]. Similar to other regulatory B subunits, PPP2R5A has eight double-helix units that form a solenoid-shaped structure. All members of the B' family of regulatory subunits are phosphoproteins, meaning that PPP2R5A itself can be regulated by reversible phosphorylation and dephosphorylation. It has been shown that protein kinase C alpha (PKCα), protein RNA-dependent kinase (PKR), CHK, and PP2A itself can regulate the phosphorylation of PPP2R5A and thus modulate its function [15, 121]. PPP2R5A has been reported to be involved in the regulation of DNA repair and apoptosis through multiple pathways. It should also be noted that the effect of PPP2R5A on PP2A is closely related to the phosphorylation state of PPP2R5A; overexpressed PPP2R5A can suppress PP2A function [122].

PPP2R5A is involved in the regulation of cell proliferation, DNA repair, apoptosis, and cell transformation through other pathways related to p53, MAPK, Wnt, c-Myc, JAK, and adenylate kinase 1 (AK1). p53 is an important factor involved in DNA repair, apoptosis, and cell transformation. Under normal conditions, p53 has a low expression level that is tightly regulated by various p53 suppressors that prevent abnormal blocking of proliferation and apoptosis. When DNA damage occurs, p53 is activated and promotes DNA repair or apoptosis [123]. As PPP2R5A is an important regulatory subunit of the tumor suppressor PP2A, it is quite possible that mutation, abnormal expression, or hypofunction of PPP2R5A promote the occurrence and development of tumors. Investigation of somatic mutations in human cancers pointed to abnormal expression of the *PPP2R5A* gene in endometrial carcinoma (heterozygous silent/nonsense substitution) and colon adenocarcinoma (somatic frameshift deletion), while alternatively spliced human mRNA for *PPP2R5A* was found in prostate cancer [124]. In addition, some miRNAs, such as miR-338-5p [125] or miR-218 [59], can alter the expression of PPP2R5A, as often detected in tumors. PPP2R5A generally acts as a tumor suppressor but also has oncogenic functions. Variable functioning of PPP2R5A depends on its regulatory factors, substrates, and the status of PPP2R5A itself (such as expression, phosphorylation level, and mutation) [15]. Furthermore, PPP2R5A is involved in the promotion of mitosis. Interacting with CDK, CHK can ensure the accuracy of mitosis by facilitating stable kinetochore-microtubule attachments and correct sister chromosomes separation. Most CDK-cyclin kinase activities promote DNA replication and cell mitosis [126]. Meanwhile, PP2A regulates the entry into mitosis and exit from mitosis [127]. Cyclin A/CDK can inhibit the function of PP2A through PPP2R5A to promote cell mitosis [128]. PPP2R5A also regulates T cell activation: after being activated, T cells are able to specifically eliminate cancer cells. T lymphocyte cell surface receptors CD28 and CTLA-4 are closely related to T cell activation and the phosphorylation of the cytoplasmic domain of CD28 promotes the transmission of a signal that activates T cells while the phosphorylation of the cytoplasmic domain of CTLA-4 has an opposite function [129]. PP2A is found to associate with the cytoplasmic domains of both CD28 and CTLA-4. The cytoplasmic domain of CTLA-4 has an association with PPP2R5A and may utilize this to CD28, dephosphorylating CD28 or CTLA-4 and impacting the serine/threonine kinase cascades mediated by T cell receptor (TCR) [129, 130]. Another report proves that CIP2A which interacts with PPP2R5A and inhibits PP2A can promote the activation of T cells, which also means PPP2R5A may take part in T cells suppression [15].

Targeting PP2A: clinical implications

In recent years, PP2A targeting has been tested as a promising therapeutic intervention in various diseases, including cancer. PP2A-targeted therapies focus on i) the identification of small molecules that selectively activate PP2A, ii) development of novel drug delivery systems, and iii) the exploration of combination therapies with potent inhibitors of the driver oncogene enhancing the treatment efficacy [4, 131].

The discovery of small-molecule activators of PP2A regulating PP2A activity attracts the most attention. Recently, several compounds have entered clinical testing. FTY720 (Fingolimod) is a sphingosine analogue shown to activate PP2A. FDA approved FTY720 drug for multiple sclerosis in September 2010 [132]. It has been found to activate PP2A by inhibiting its inhibitor SET and appeared as a promising anti-cancer molecule being evaluated in clinical trials for various types of cancer. FTY720 also acts as an immunomodulator and inducer of apoptosis in cancer

cells through PP2A activation [133]. LB-100 is another small molecule inhibitor with PP2A activating properties, used for the treatment of glioblastoma and hepatocellular carcinoma [4, 134, 135]. LB-100 is commonly used in pancreatic, ovarian, and breast cancer as a chemo-sensitizer, showing a low toxicity in patients over a specific dose range [136–138]. Next, CPI-0610 (Pelabresib) is a small molecule inhibitor, currently under investigation in clinical trial in patients with relapsed or refractory lymphoma [139]. CPI-0610 is being evaluated both as a single agent and in combination with other therapies [140]. Also, several natural products, e.g. cantharidin or fostriecin, represent potent inhibitors of PP2A that have shown powerful anticancer activity in preclinical studies, particularly against solid tumors [141, 142]. Both are being investigated in clinical trials for their potential therapeutic benefits in various cancer types. Lastly, okadaic acid is a natural potent and selective inhibitor of PP2A. Although not currently in clinical testing, okadaic acid has provided valuable insights into the role of PP2A in disease and may serve as a basis for the development of novel PP2A inhibitors [143].

A significant advance in PP2A-targeted therapy has been shown in the development of novel drug delivery systems to improve the specificity and efficacy of PP2A activators. Nanoparticle-based drug delivery systems have been designed to encapsulate and deliver PP2A activators specifically to tumor cells. These nanoparticles can enhance the bioavailability and stability of the drugs while minimizing off-target effects [144–145].

Combination therapies involving PP2A-targeted agents have also shown promise in overcoming drug resistance and enhancing treatment efficacy [104]. For example, combining PP2A activators with other anti-cancer drugs, such as chemotherapy or targeted therapies, has been shown to synergistically inhibit tumor growth and improve patient outcomes. Additionally, combination therapies that target multiple components of the PP2A signaling pathway have been explored to overcome the complexity and heterogeneity of cancer cells. Inhibition of PP2A coupled with additional DNA-damaging strategies may be therapeutically beneficial. For example, LB-100 has demonstrated synergistic effects with other anticancer agents, such as DNA-damaging agents and targeted therapies, making it a potential candidate for combination therapy [146].

In conclusion, PP2A isoforms play various roles in cancer cells, exhibiting either tumor-suppressive or tumor-promoting functions depending on the specific cellular context. Although the study of PP2A isoforms in cancer is still limited, there is a growing interest in understanding their role in cancer biology. By gaining a deeper comprehension of PP2A regulation in processes such as cell cycle control, cell growth, and cell survival, we can better grasp the significant contribution these enzymes make to tumorigenesis and drug resistance of cancer cells. Cellular inhibitors of PP2A, namely SET and CIP2A, frequently exert influence on drug resistance and the survival of cancer cells in numerous cancer types. Consequently, therapeutic strategies are being developed to suppress these proteins and reactivate PP2A, aiming to pave the way for the next generation of cancer therapies. The latest advances in PP2A-targeted anti-cancer therapy include the discovery of small molecules that activate PP2A, the development of novel drug delivery systems for targeted delivery of these activators, and the exploration of combination therapies to enhance treatment efficacy. Further research would help to understand the functions of PP2A in various pathological and physiological processes, thus laying the foundation for the use of phosphatases as markers in tumor prevention, in early diagnosis, or in the design of targeted treatment to improve the prognosis of patients. Given the importance of the regulatory and scaffolding subunits in determining the localization and substrate specificity of the PP2A holoenzyme, work in this area as well is required to fill the void.

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