

Review

Protein serine/threonine phosphatases in tumor microenvironment: a vital player and a promising therapeutic target

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Abstract

The tumor microenvironment (TME) is involved in cancer initiation and progression. With advances in the TME field, numerous therapeutic approaches, such as antiangiogenic treatment and immune checkpoint inhibitors, have been inspired and developed. Nevertheless, the sophisticated regulatory effects on the biological balance of the TME remain unclear. Decoding the pathological features of the TME is urgently needed to understand the tumor ecosystem and develop novel antitumor treatments. Protein serine/threonine phosphatases (PSPs) are responsible for inverse protein phosphorylation processes. Aberrant expression and dysfunction of PSPs disturb cellular homeostasis, reprogram metabolic processes and reshape the immune landscape, thereby contributing to cancer progression. Some therapeutic implications, such as the use of PSPs as targets, have drawn the attention of researchers and clinicians. To date, the effects of PSP inhibitors are less satisfactory in real-world practice. With breakthroughs in sequencing technologies, scientists can decipher TME investigations via multiomics and higher resolution. These benefits provide an opportunity to explore the TME in a more comprehensive manner and inspire more findings concerning PSPs in the TME.

The current review starts by introducing the canonical knowledge of PSPs, including their members, structures and posttranslational modifications for activities. We then summarize the functions of PSPs in regulating cellular homeostasis. In particular, we specified the up-to-date roles of PSPs in modulating the immune microenvironment, adopting hypoxia, reprogramming metabolic processes, and responding to extracellular matrix remodeling. Finally, we introduce preclinical PSP inhibitors with translational value and conclude with clinical trials of PSP inhibitors for cancer treatment.

Keywords: PSP superfamily; tumor microenvironment; immune therapy; PSPs inhibitors; clinical translation

Introduction

Protein phosphatases, together with protein kinases, mediate reversible and dynamic phosphorylation and dephosphorylation in various biological processes [1]. They are classified into

protein serine/threonine phosphatase (PSP), protein tyrosine phosphatase (PTP), and haloacid dehalogenase phosphatase (HAD) superfamilies on the basis of the catalytic mechanism. PSPs, such as

phosphoprotein phosphatases (PPPs), and PTPs, such as dual-specificity phosphatases (DSPs), dephosphorylate phospho-serine/threonine and phospho-tyrosine residues, respectively. HADs, such as FIIF-associating component of RNA polymerase II C-terminal domain (CTD) phosphatase (FCP), small CTD phosphatase (SCP) and four eyes absent phosphatase, dephosphorylate phospho-serine/threonine and phospho-tyrosine residues [2-4]. The PSP superfamily consists of two groups: the PPP and metal-dependent protein phosphatase (PPM) families [2, 4]. Studies have revealed the essential roles of PSPs in regulating cell growth, differentiation, signal transduction, and intercellular communication [5-8].

Recently, advanced technologies have been applied to decipher the intrinsic crystal structure of PSP complexes. For example, investigations of the PP1-SHOC2-MRAS complex provide a deeper understanding of RAS biology and the RAS/MAPK signaling pathway [9]. Furthermore, the selective targeting of PSPs has better inhibitory effects on oncogenic processes [10]. Due to their extensive and diverse functions, dysregulated and aberrantly expressed PSP proteins are considered important mediators of the occurrence and development of various diseases, including cancers [11].

The tumor microenvironment (TME) can be traced back to the “seed and soil” concept and has been updated in recent years [12, 13]. The TME consists of cellular and acellular components. In fact, the development and fate of tumors depend not only on the intrinsic features of tumor cells but also on the organ where the tumor arises, the stromal cell composition, the extracellular matrix (ECM) and other aspects [14]. Jin MZ *et al.* summarized several hallmarks of the TME: hypoxic, acidic and innervated niche, immune, metabolism and mechanical environment [13]. Single-cell and spatial transcriptomic data suggest that cancer-TME interactions involve tumor cell evolution and the formation of the tumor ecosystem. For example, tumor cells gain oncogenic mutants, immune evasion ability and organotropism *via* crosstalk with stromal cells [15]. Numerous reports have suggested that PSPs are present in the TME and serve as key regulators to modulate hypoxic adaptation, metabolic transition, immune modulation, ECM remodeling, angiogenesis, and intercellular communication [16-20]. The substrate specificity and functions of PSPs may result in diverse outcomes in the TME. For example, high levels of PPP1R16B indicate increased immune cell infiltration and improved overall survival (OS) and disease-free survival (DFS) [21]. High expression of PPP1R14B contributes to the immunosuppressive TME [22]. To obtain a comprehensive understanding

of the roles of PSPs in the TME, advanced technologies, such as single-cell transcription analysis, provide new perspectives on their functions, as well as potential drug treatments [23].

In this review, we summarize the roles of PSPs in the TME. Moreover, classical and novel therapeutic approaches are shedding light on the prospects of PSPs in the TME, from the laboratory to the bedside.

Overview of the PSP superfamily

Seven enzymes are classified as PPPs: PP1, PP2A, PP3/PP2B/calcineurin, PP4, PP5, PP6 and PP7. The sequences identified in the PPPs share a high degree of homology, suggesting that each catalytic subunit may be derived from a common ancestor [24]. Previous studies have demonstrated that the majority of PPPs exist as holoenzymes, with catalytic subunits binding to regulatory and/or scaffold subunits [2]. PP5 and PP7 exist in monomeric forms and are generally inactive because of their self-inhibiting domains [2, 25]. Research on binding proteins with the catalytic subunits of PPPs has established specific domains termed short linear motifs (SLiMs). Several common SLiMs are thought to be involved in phosphatase binding and metal coordination [25]. Further investigations revealed that every PPP has specific SLiMs, and the sequence diversity of their amino acids accommodates a range of affinities with various PPP regulators [26].

The majority of PPMs are single-unit phosphatases containing manganese/magnesium ions (Mn^{2+}/Mg^{2+}) at their activation sites, such as PP2C enzymes. The others are heterodimeric pyruvate dehydrogenase phosphatases (PDPs). Metal ions play a catalytic and central role in the activation of the dephosphorylation reaction for both PPP and PPM. Compared with PPPs, PPMs may rely on additional domains and conserved sequence motifs rather than regulatory subunits to determine substrate specificity. The sequences of the catalytic sites are highly conserved. The PPMs are divided into 12 classes according to their similarity in the sequences of their catalytic domains [25].

Inhibitors, such as okadaic acid, calyculin-A, and tautomycin, can occupy the active sites or SLiMs in PPPs [27]. Calcineurin, however, is insensitive to these inhibitors but is vulnerable to cyclosporin (CSP) and FK506 [28, 29]. For PPMs, specific inhibitors are peptides with sequences that emulate the consensus substrate sequences, such as the AP4-3E peptide, or compounds that bind the specific structure near the catalytic sites, such as GSK2830371 [30-32]. Additionally, PSPs are regulated by posttranslational modifications (PTMs). Phosphorylation, methyl esterification, protein acetylation, and ubiquitination

are the most common PTMs that influence the activity, assembly, expression levels, and other aspects of PSP [2, 33].

Structures of PSPs

The majority of PPPs function as heterometric dimers with diverse catalytic subunits, regulatory subunits, and/or scaffold subunits. Most PPMs are single-unit enzymes with unique sequences. We use the following well-studied subjects as examples to introduce the structural features of PSPs.

The PP1 holoenzyme is composed of a catalytic subunit (PP1-C) and one or two regulatory subunit(s) (also known as regulatory interactors of PP1, RIPPOs) (Figure 1) [34, 35]. PP1 is encoded by three genes, PPP1CA, PPP1CB and PPP1CC, and consists of three diverse isoforms: PP1A, PP1B, and PP1G. These sequences of PP1-C are quite similar, with several amino acid differences in the N-terminal and C-terminal regions [2, 36]. Phosphorylation of PP1 by cyclin A or cyclin B kinases leads to decreased activity *in vitro*, as CDKs can phosphorylate Thr320 in PP1A and Thr311 in PP1G [37]. The best-known SLiM is the RVxF motif found in skeletal muscle [38]. SLiMs are

considered binding sites for distinct RIPPOs. To date, numerous regulatory subunits, such as PUNTS, GADD34/PPP1R15A and MYO18A, have been reported to mediate the specificity of PP1 in various biological processes [7, 39, 40].

PP2A is a heterotrimeric enzyme composed of a catalytic subunit, PP2A-C (encoded by PPP2CA or PPP2CB); a scaffold subunit, PP2A-A (encoded by PPP2R1A or PPP2R1B); and various regulatory subunits, PP2A-B (Figure 1). PP2A-B can be classified into four subfamilies: B55, B56, PR70/72, and striatin (STRN) [41, 42]. Like PP1, phosphorylated Tyr307 on the PP2A-C C-terminal tail inhibits the function of PP2A [43]. Additionally, reversible carboxymethylation of Leu309 controlled by LCMT-1 and PME-1 regulates holoenzyme assembly [44, 45]. The best-known SLiM for PP2A is LSPIxE, which binds B56 for substrate recruitment. Unlike PP1, PP2A-C combines PP2A-A with specific helical repeats rather than SLiMs [25]. In addition to postmodifications of PP2A-C, the multiple regulatory subunits direct the specificity of PP2A substrates and may lead to varying outcomes.

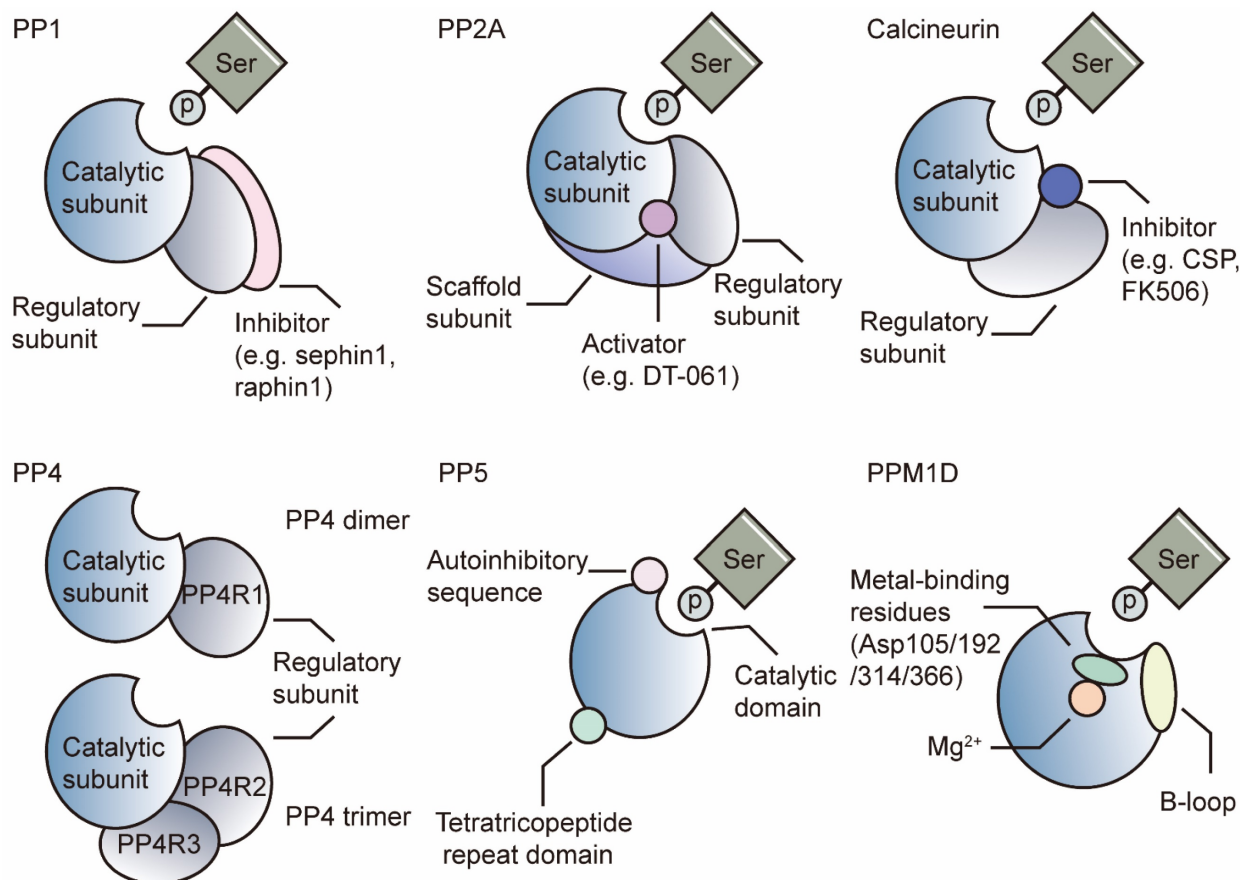


Figure 1. Structure of the PSPs. PP1 is comprised of catalytic and regulatory subunits. It can be inhibited by regulatory subunit-specific inhibitors. PP2A is comprised of catalytic, regulatory and scaffold subunits. Activators can stabilize the holoenzyme. Calcineurin is comprised of catalytic and regulatory subunits, which can be inhibited by inhibitors such as CSP and FK506. PP4 can form the dimer with PP4R1 or trimer with PP4R2/PP4R3. PP5 functions as a single subunit enzyme. It features a tetratricopeptide repeat domain and an autoinhibitory sequence. PPM1D is a single-unit enzyme with the B-loop facing the catalytic center. Four Asp residues facilitate the binding of metal iron. Asp: aspartic Acid, CSP: cyclosporin

Calcineurin comprises an A catalytic subunit and a Ca²⁺-dependent B regulatory subunit (Figure 1). The activation of calcineurin requires Ca²⁺-dependent binding of calmodulin and a subsequent conformational change that displaces the auto-inhibitory domain [46]. SLiMs are binding sites in catalytic and regulatory subunits for substrate recognition. The well-known substrate of calcineurin is the transcription factor nuclear factor of activated T cells (NFAT), which plays critical roles in T-cell maturation and the normal immune environment [47]. The binding site in NFAT has been identified as the PIXIT sequence, which is located in the catalytic A subunit [29]. Another SLiM is LxVP, which is mapped at the interface between the catalytic A subunits and regulatory B subunits. The LxVP sequence can be occupied by substrates of calcineurin or two immunosuppressive drugs: CSP and FK506 [28, 29].

PP4 complexes consist of a catalytic subunit (PP4-C) and a regulatory subunit (PP4R1) as dimers or PP4R2/PP4R3 as trimers (Figure 1) [48]. Like PP2A, PP4 is modified by LCMT-1, which mediates methyl esterification on PP4-C Leu307. Loss of LCMT-1 results in a reduction in the PP4/PP4R1 complex [49].

Unlike those of other PPPs, the catalytic and regulatory domains of PP5 are located on a single peptide [25]. PP5 comprises an N-terminal tetratricopeptide repeat (TPR) domain for substrate recognition and a C-terminal PPP catalytic domain [2]. The autoinhibitory α helix in the C-terminal domain results in low activity of PP5, whereas artificial truncation or depletion of the helix can restore the activity of the catalytic domain (Figure 1) [50, 51]. Once HSP90 binds to the TPR, PP5 is activated [52]. Subsequent recruitment of Cdc37, a cochaperone, results in the formation of the HSP90-Cdc37-PP5 complex and promotes its combination with various substrates [53].

PPMs function as single subunits with metal ions (Mn²⁺ or Mg²⁺) in the active sites [54]. Unlike PPPs, PPMs contain single catalytic subunits (PP2C enzymes) with additional domains and sequences. PP2C enzymes share a highly conserved sequence and are insensitive to PPP inhibitors, such as okadaic acid or microcystin [25]. We take PP2C δ (PPM1D) as an example to introduce the PPMs.

PPM1D is also known as the wild-type p53-induced phosphatase Wip1 because its transcription is induced by P53. PPM1D contains two domains, a carboxy (C)-terminal domain for nuclear translocation signals and a highly conserved amino-terminal phosphatase domain homologous to those of other PP2C enzymes (Figure 1) [55]. PPM1D recognizes and dephosphorylates substrates with a diphosphorylated peptide pTXXpY sequence, such as

MAPK kinases [56]. Another sequence, p(S/T)Q, is for substrates, such as ataxia telangiectasia mutated (ATM) kinases [57]. PPM1D contains 2 unique inserts in its catalytic domain: the P-loop and B-loop. The P-loop faces the side opposite of the catalytic center, while the B-loop faces the catalytic center [33]. The B-loop is the target of some inhibitors, such as GSK2830371 [32].

Among PPMs, several amino acid residues have been suggested to ensure the formation and stabilization of the catalytic structure, including Gly61/126/145/198, Glu171, and Arg174/195 in PPM1A [33]. In addition, Arg33/186 in PPM1A is essential for substrate recognition [58]. Some members, such as PHLPPs, lack the first metal-binding Asp residues (Asp38 of PPM1A), whereas PP2D1 and TAB1 lack the second and third Asp residues (Asp60 or Asp239 of PPM1A), which results in reduced catalytic activity [33].

Biological function of PSPs

PSPs have multiple functions and participate in various biological and oncogenic processes. Additionally, the regulatory effects vary from combinations with different subunits. In this section, we summarize the results in Table 1 and list several well-studied phosphatases as examples.

PP1 modulates Rb dephosphorylation in the G1/S phase and PTMs of P53 during the cell cycle. In addition, PP1 also functions in cell proliferation and apoptosis, DNA damage, the cellular stress response, glycogen and protein metabolism, and cytoskeleton regulation, among many other processes [5, 11]. Multiple combinations of regulatory subunits lead to different signaling pathways and processes. Diverse PP1/RIPPO complexes may have beneficial or detrimental effects on tumors. For example, the PP1-PUNTS complex can prevent the proteasomal degradation of the MYC oncoprotein [59]. The PP1-MYO18A-SMAD4 complex dephosphorylates PAK1-Thy423 and inhibits tumor progression in cholangiocarcinoma [7]. As a result, the modulation of PP1/RIPPO complexes is considered a feasible and promising approach for tumor treatment [60].

PP2A is involved in many biological processes, including mitosis, the cell cycle, cell proliferation, apoptosis, DNA damage repair (DDR) response, and cell differentiation and development [61, 62]. Previous studies have revealed that the PP2A-B55 enzyme can prevent Cyclin B/CDK 1 activation in the G2 phase and stop the G2/M phase transition [63]. PP2A-B56 is required for cardiomyocyte maturation and survival, whereas knocking out the B56 regulatory subunit leads to cell apoptosis [64]. Additionally, PP2 participates in DDR *via* γ -H2AX dephosphorylation

[65].

Table 1. Biological function of PSPs

Enzyme	Type of cell	Function	Ref.
PP1	Various tumor cells	Cell cycle, proliferation	[59, 188]
	Epithelial cell	Cytoskeleton regulation, cell adhesion	[189]
	Various tumor cells	Signal transduction	[9]
	Various tumor cells	DNA damage repair	[190]
	Ovary cell	Cell stress response	[191]
	Breast cancer	EMT, invasion	[192]
	Cholangiocarcinoma	Chemosensitivity	[7]
PP2A	Cervical carcinoma	Cell cycle, proliferation	[10, 63]
	Cardiomyocyte	Cell differentiation	[64]
	Melanocytic cells	senescence	[193]
	Cervical carcinoma	DNA damage repair	[65]
	Various tumor cells	Oxidative stress	[194]
	Gastric cancer	Signal transduction	[10]
	Colon cancer	Metastasis	[195]
Calcineurin	T cell	Cell differentiation and maturation	[47]
	Keratinocyte	Signal transduction	[196]
	Endothelial cell	Proliferation	[197]
PP4	Various cells	Cell cycle, DNA damage repair, cell differentiation	[75]
PP5	Various cells	Cell cycle and growth, DNA damage repair, signal transduction, tumor growth and metastasis	[74]
PP6	Various cells	Cell cycle and growth, DNA damage repair, signal transduction, cell differentiation, tumor formation and progression	[73]
PPM1A	Various cells	Cell migration, proliferation, signal transduction	[33]
PPM1B	Various cells	Necroptosis, senescence, systemic inflammatory response	[33]
PPM1D	Various cells	Cell cycle regulation, metabolism, cell differentiation, tumor progression	[33]

In tumor cells, the PP2A-B56 and PP2A-B55 complexes are considered antitumor players, whereas the PP2A-STRN3 and PP2A-STRN4 complexes are deemed oncogenic [61, 66, 67]. Therefore, interventions on PP2A-B can transform PP2A from being beneficial into an oncoprotein and vice versa. In fact, numerous articles have reported that interventions targeting diverse types of PP2A-B could change the role of PP2A in tumor development, which provides possible and feasible approaches for cancer treatment. Oncoproteins such as cancerous inhibitors of PP2A and SET can inhibit the tumor suppressive effects of the PP2A-B56 complex, whereas cAMP-regulated phosphoprotein 19 interferes with the protective activity of the PP2A-B55 enzyme [61, 66, 67]. However, a selective inhibitor of the PP2A-STRN3 complex, SHAP, has antitumor effects on YAP-activated gastric cancers [10]. In addition, PP2A regulates Hippo signaling pathway by forming the striatin-interacting phosphatase and kinase (STRIPAK) complex. STRIPAK is a conserved complex containing PP2-C, PP2-A, STRNs,

STRN-interacting proteins, sarcolemma membrane-associated protein (SLMAP) and members of the STE20 family of kinases [68]. SLMAP recognizes phosphorylated MST1/2, thereby recruiting STRIPAK to dephosphorylate and inactivate MST1/2 and regulating downstream factors of Hippo signaling pathway [69].

The functions of calcineurin, which is a well-known regulator of NFAT, are to mediate T-cell maturation and ensure normal function in benign and malignant diseases [47, 70, 71]. Due to their critical role in immune modulation, calcineurin inhibitors have been applied for immunosuppression in various diseases [72]. Other PPPs also function in DNA repair, inflammatory modulation, lymphocyte development, tumor growth and survival, and other aspects [2, 73-75].

PPMs participate in vital biological processes, such as cell cycle control, DDR, cell differentiation and immune responses [33]. For example, PPM1D mRNA is regulated in a P53-dependent manner. Fibroblasts in PPM1D-deficient mice exhibit a decreased proliferation rate, suggesting an impaired ability to initiate mitosis [76]. Furthermore, increased expression of truncated PPM1D also leads to reduction of phosphorylated H2AX, and impairs the P53-mediated G1 cell arrest in breast and colorectal cancer (CRC) [77].

Additionally, PPM1D regulates DDR during tumor development. Phosphorylation of Ser139 in H2AX forms a docking site for subsequent recruitment of other DNA during DDR, while PPM1D disturbs the process by dephosphorylating H2AX [78]. Moreover, evidences show that PPM1D is linked with chemo-/radio-resistance. In fact, Miller PG et. al. demonstrates that PPM1D inhibition is a possible approach to enhance chemo-sensitization and response to DDR in P53 wild-type myeloid malignancy [79]. Recent study indicates that increased PPM1D protects cells from ionising radiation. In cells with truncated PPM1D, frequent chromosome bridges are observed after radiation exposure. Genome rearrangements protect the cells from radiation-induced cell cycle arrest and senescence and proliferate in the presence of low doses of DNA damage [80].

PPM1D is also required for the optimal functions of T cells and B cells. Mice with PPM1D exhibit increased CD4⁺ T cells and decreased CD8⁺ T cells. The lower proliferative rate of T cells and B cells are detected compared with normal mice. Furthermore, PPM1D knockout mice present skin ulcerations, abnormal lymphoid histopathology and pathogen susceptibility [76].

In addition, widespread participation in tumor immunity, intercellular communication, hypoxic adaptation, and metabolism border the interpretation of PPMs [81-83]. The contents will be detailed in the following sections.

Biological function of other phosphatases

PTPs and HADs are important players to mediate various biological processes in normal cells and tumor cells. In this section, we briefly introduce several typical PTPs and HADs and discuss their biological processes.

PTPs are single-unit enzymes to dephosphorylate Tyr residues, which are divided into Cys-based and His-based families due to the chief catalytic residues involved in nucleophilic substrate attack during catalytic processes [4]. Src homology 2 domain-containing inositol polyphosphate 5-phosphatase 2 (SHIP2) is a non-receptor PTP which is ubiquitously expressed and associated with poor prognosis in glioma, melanoma, colon cancer, and breast cancer. Studies have suggested that SHIP2 is a major modulator of PI3K/AKT pathway *via* converting PI(3,4,5)P₃ to PI(3,4)P₂. Another modulator PTEN converts PI(3,4,5)P₃ to PI(4,5)P₂. The transduction of PI(3,4,5)P₃ to PI(3,4)P₂ further triggers downstream targets, such as AKT, mTORC1 and RAF, to ensure cellular survival and proliferation for tumor cells. [84]. Furthermore, SHIP2 is reported to interact with c-Cbl ubiquitin ligase to suppress EGRF degradation. [85, 86].

Phosphatase of regenerating liver 3 (PRL3) is a PTP, classified as dual-specificity phosphatase. Studies demonstrate that RPL3 is involved in multiple oncogenic processes, such as activation of EGFR and VEGF pathways [87]. PRL3 is demonstrated to reduce IL-4 expression and diminish the inhibitory effects on endothelial cells, thus promoting angiogenesis [88]. In addition, PRL3 is demonstrated to mediate lysosomal exocytosis and create an acidic niche to reshape TME [89].

HAD contain a DxDx(V/T) active-site signature motif and work with Asp residue as a catalytic nucleophile and Mg²⁺ as a cofactor [3]. The typical HADs are members of FCP and SCP family. The primary substrate of FCP/SCP is the CTD of RNA polymerase II, which contains tandem repeats of a serine-rich heptapeptide [25]. FCP1 is the primary phosphatase targeting CTD to dephosphorylate both pSer2 and pSer5 [90]. Conversely, Scp1 demonstrates minimal catalytic activity towards pSer2, exhibiting a marked preference for pSer5, with a preference ratio of approximately 70 to 1 [91].

Roles of PSPs in the TME

To date, numerous advantages have been identified to illuminate the significance of the TME, from tumor imitation to metastasis outgrowth [14]. PSPs widely function in several typical features of the TME to determine the fate of tumors. We introduce the regulation of the TME by PSP in the following two parts: nonimmunological and immunological aspects (Table 2). In nonimmunological aspects, we focus on the interaction of tumors with acellular environment and nonimmune cells. In immunological aspects, we focus on the interaction of tumors with various immune cells.

Nonimmunological aspect

Hypoxic adaptation

Studies have revealed that hypoxia is a constant feature and that various cancerous properties are involved in hypoxic adaptation. Hypoxia-inducible factors (HIFs) and HIF signaling are classical and essential components of fitness under low-oxygen conditions [13]. PSPs have been demonstrated to regulate the expression of HIF1A and downstream effects. For example, the PP2A-B55 α complex directly dephosphorylates PHD2 at Ser125, which protects HIF1A from hydroxylation and degradation. Intact HIF1A promoted autophagy-mediated cell survival and colorectal cancer (CRC) development [92] (Figure 2A). In addition, activation of calcineurin by the ion channel TRPM8 leads to RACK1 dephosphorylation and inhibition of its dimerization. This process facilitates the accumulation of HIF1A for the adaptation of prostate cancer cells in the hypoxic niche [93] (Figure 2A). PPM1G negatively regulates the transcriptional activity of HIF1A and promotes its degradation under normoxia and acute hypoxia, thus regulating the hypoxic response [94].

HIF1A can act on PSPs to maintain their cancerous properties. Tiwari A *et al.* reported that HIF1A downregulates the expression of PPP1R1B. Decreased PPP1R1B expression restores the activity of PP1, thus facilitating the protection of P53 from degradation by MDM2 dephosphorylation and regulating invasion and metastasis in pancreatic cancer [16]. In ovarian clear cell carcinoma, reduced HIF1A leads to significantly decreased PP2A activity and triggers the Ras pathway [95]. PHLPP is a PPM that is negatively regulated by HIF1A. Reduced PHLPP levels contribute to hypoxic adaptation and drug resistance in colon cancer cells [96].

Table 2. Functions of PSPs in TME

Related properties	Enzyme	Type of cell	Mechanism/pathway	Ref.	
Hypoxic adaption	PP1	Pancreatic cancer	PPP1R1B promotes P53 degradation	[16]	
	PP2A	CRC	PP2A-B55 α protects HIF1A from hydroxylation and degradation	[92]	
		Glioblastoma multiforme	PP2A mediates cell cycle inhibition and reduced ATP consumption	[103]	
	Calcineurin	Prostate cancer	Calcineurin facilitates accumulation of HIF1A	[93]	
	PP5	Various tumor cells	PP5 suppresses ASK-1/MKK4/JNK pathway	[104]	
	PPM1B	Kidney cancer	PPM1B regulates TBK1 signaling	[105]	
	PPM1G	Renal adenocarcinoma	PPM1G negatively regulates HIF1A expression	[94]	
Metabolic reprogramming	PHLPP	Colon cancer	PHLPP is negatively regulated by HIF1A	[96]	
		Gastric cancer	PP1 regulates AKT/HIF1A pathway	[110]	
	PP1	Lung adenocarcinoma	PP1 inhibits STAT3 signaling	[111]	
	PP5	Bladder cancer	PP5 activates PPAR γ signaling	[108]	
	PDP1	Various tumor cells	PDP1 regulates glycolysis and TCA cycle	[17, 83, 114]	
ECM remodeling and angiogenesis	PDP2	Breast cancer	PDP2 dephosphorylates ACSL4	[109]	
		Leukemia	PP2A regulates MMPs expression	[115]	
		Endothelial cell	PP2A regulates YAP activation	[118]	
	Calcineurin	Endothelial cell	Calcineurin/NFAT/angiopoietin-2 pathway promotes angiogenesis	[120]	
	PP4	CRC	PP4 is associated with MMPs expression	[19]	
	PP5	Melanoma	PP5 inhibits Hsp90 α secretion	[116]	
	PPM1A	Fibroblasts	PPM1A regulates P38/MAPK pathway	[82]	
	Stromal cell interactions	PP1	HCC	PP1 regulates P38/MAPK pathway	[20]
			AML	PP1 regulates osteoblast-mediated protective effects	[122]
		Various tumor cells	PP1-MYPT1 activates YAP signaling	[123, 124]	
Immune response	PP2A	Breast cancer, endothelial cell	EV-derived PPP1R1B activates endothelial cells	[125]	
		HCC	PPP2R2A regulates forkhead box O3, P27 and P21	[8]	
	PP1	Multiple myeloma	PP1-GADD34 dissociation promotes immunogenic cell death	[131]	
		Various immune cells	PP1-GADD34 mediates integrated stress response	[23]	
		B cell	PP1 regulates to Fc clustering	[156]	
	Macrophage		PP1 inhibits IRF3 signaling	[157]	
		DC	PP1-GADD34 regulates IFN production	[162]	
	PP2A	Various tumor cells	PP2A inhibits STING signaling	[18, 127]	
		Pancreatic cancer, NSCLC	Inflammatory stimuli regulate PP2A expression in tumor cells	[133, 134]	
		CD4 ⁺ /CD8 ⁺ T cell	PP2A suppresses T cell proliferation, glycolysis and cytokines production	[6, 142, 144]	
Treg cell		PP2A mediates maturation of Treg cells	[149]		
B cell		PP2A ensures optimal functions	[153]		
TAM		SET regulates metabolism, migration, M1 to M2 polarization and STING signaling	[106, 158-160]		
MDSC		PP2A terminates AKT/ β -catenin pathway	[161]		
Calcineurin	Treg cell	Calcineurin/NFAT pathway regulates Treg differentiation	[70, 71]		
	PP4	DC	Calcineurin/NFAT pathway regulates cytokines production	[163]	
PP4	OC	PP4 regulates inflammatory factors secretion	[128]		
	T cell, lymphoma	PP4-PP4R1 inhibits NF- κ B signaling	[147]		
	Normal/leukemic T cell	PP4 dephosphorylates PEA-15	[148]		
PPM1B	NSCLC	PPM1B regulates NF- κ B signaling	[129]		
PPM1D	HCC	PPM1D is correlated with ICB inhibition	[139]		
PPM1H	CRC	PPM1G is correlated with immune cell infiltration	[138]		
PPM1K	Pancreatic adenocarcinoma	PPM1K is correlated with immune cell infiltration	[81]		
	breast invasive carcinoma	PDP1 is negatively correlated with CD8 ⁺ T cells infiltration	[140]		
PDP1	Breast invasive carcinoma	PDP1 is negatively correlated with CD8 ⁺ T cells infiltration	[140]		

In addition to the HIF-related pathway, other approaches involving hypoxic adaptation involve tumor cells. A few decades ago, a study demonstrated that a hypoxic environment promoted the activity of PP1 toward RB dephosphorylation, thus regulating cell proliferation [97]. Later studies revealed that this biological process was due to the reduced expression level of PUNTS, the negative RIPPO [98, 99]. In addition, PP1 facilitates fitness in low-oxygen conditions that overexpress GADD34 in ovarian

cancer (OC) and is correlated with worse overall survival under hypoxic conditions [100]. Previous studies have indicated that PP2A expression levels are increased under hypoxia, whereas hyperoxia hampers the activity of PP2A via posttranslational modification, rather than increasing the abundance of PP2A [101, 102]. The overexpression of PP2A has been reported to mediate PLK dephosphorylation, resulting in G1/S phase inhibition and reduced ATP consumption under hypoxia, which contributes to the

dormancy and drug resistance of glioblastoma multiforme cells [103] (Figure 2A). The expression level of PP5 is also elevated under hypoxia. The overexpression of PP5 suppresses the hypoxia-induced ASK-1/MKK4/JNK signaling cascade to prevent the apoptotic response [104]. In kidney cancer, under normoxia, PPM1B binds to TANK-binding kinase 1 (TBK1) and decreases its activity, whereas under hypoxia, PPM1B cannot dephosphorylate TBK1. TBK1 triggers the downstream Factor P62 and promotes tumorigenesis [105] (Figure 2A).

In addition, SET, an inhibitor regulatory subunit of PP2A, is retained in the cytoplasm of macrophages under hypoxia, thus suppressing the function of PP2A but increasing ERK and P38 signaling, thus regulating the migration and functions of macrophages in the immune response [106].

Metabolic reprogramming

Cell metabolism contributes to energy consumption by tumor cells and the homeostasis of the TME [13]. For example, single-cell sequencing data suggest that PPP2R1A, an LDL-related signature, is involved in lipid metabolism and is associated with worse OS in cutaneous melanoma patients [107]. PP5 also plays a tumor-promoting role *via* positive modulation of PPAR γ . Once dephosphorylated by PP5, activated PPAR γ regulates metabolism-related genes and provides a tumor-promoting TME [108] (Figure 2B). Additionally, PDP2 diminishes lipid peroxidation and inhibits ferroptosis *via* ACSL4 dephosphorylation [109].

For glycogen metabolism, previous reports indicate that inhibition of PP1 activity triggers the AKT/HIF1A pathway and consequent aerobic glycolysis in gastric cancer [110] (Figure 2B). In addition, NSD3 is reported to bind PP1B, leading to STAT3 dephosphorylation, as well as the consequent inhibition of HK2 transcription. This process facilitates glycolysis in lung adenocarcinoma [111]. Apart from PP1, more research on glycolysis has focused on PDP1, an activator of pyruvate dehydrogenase (PDH) [83, 112]. Fan J *et al.* demonstrated that Lys202 acetylation inhibits PDP1 *via* ACAT1 acetylation, contributing to glycolysis and the Warburg effect in hypoxia [83] (Figure 2B). Moreover, PDP1/PDH histone acetylation has been implicated in glycolysis as well as the consequent radio-resistance of CRC [113].

Recently, PDP1 was reported to play a dual role in maintaining homeostasis. When the expression level of PDP1/PDH is too low under hypoxia, subsequent inhibition of HIF1A transcriptional activity and a reduction in its target gene, pyruvate

dehydrogenase kinase 1 (PDK1), partially restore the activity of PDH for cancer cell proliferation. When PDP1/PDH is hyperactivated, the subsequent increase in PDK1 promotes anaerobic glycolysis and lactate production for energy consumption. The intrinsic modulation ensures a stable level of acetyl-CoA, which contributes to adaptation in various TMEs [114]. Additionally, in FLT3-ITD-positive acute myeloid leukemia (AML) cells, PDP1 facilitates cellular respiration, even under hypoxic conditions. During reoxygenation, PDP1 promotes the tricarboxylic acid (TCA) cycle for the positive subgroups, which ensures adaptation to variations in oxygen availability in AML bone marrow [17].

Cancer-associated fibroblasts and ECM remodeling

Cancer-associated fibroblasts (CAFs) are essential components that modulate stiffness and intercellular crosstalk *via* the secretion of TGF- β , IL-6, and TNF- α , among many other factors [14]. For example, fibroblast-to-myofibroblast conversion is reported to nurture the TME and promote migration, invasion and epithelial-to-mesenchymal transition (EMT) in tumor cells *via* TGF- β secretion. Moreover, TGF- β secreted by tumor cells further promotes myofibroblast differentiation, collagen production and ECM stiffness regulation. During this process, PPM1A is the major regulator that can stop it by deactivating the P38/MAPK pathway [82] (Figure 3A). MMPs play important roles in breaking down ECMs [14]. PP2A-C upregulation leads to RNA decay of MMPs, whereas inhibition of PP2A can keep MMP2 and MMP9 RNA stable [115]. PP5 provides an antitumor environment in various cancers by inhibiting Hsp90 α secretion, which synergizes with MMP2 to form an invasive TME [116]. In contrast, PP4 acts as a tumor promoter, which is associated with increased MMP gelatinase activity and increased MMP2/MMP9 expression in CRC cells [19].

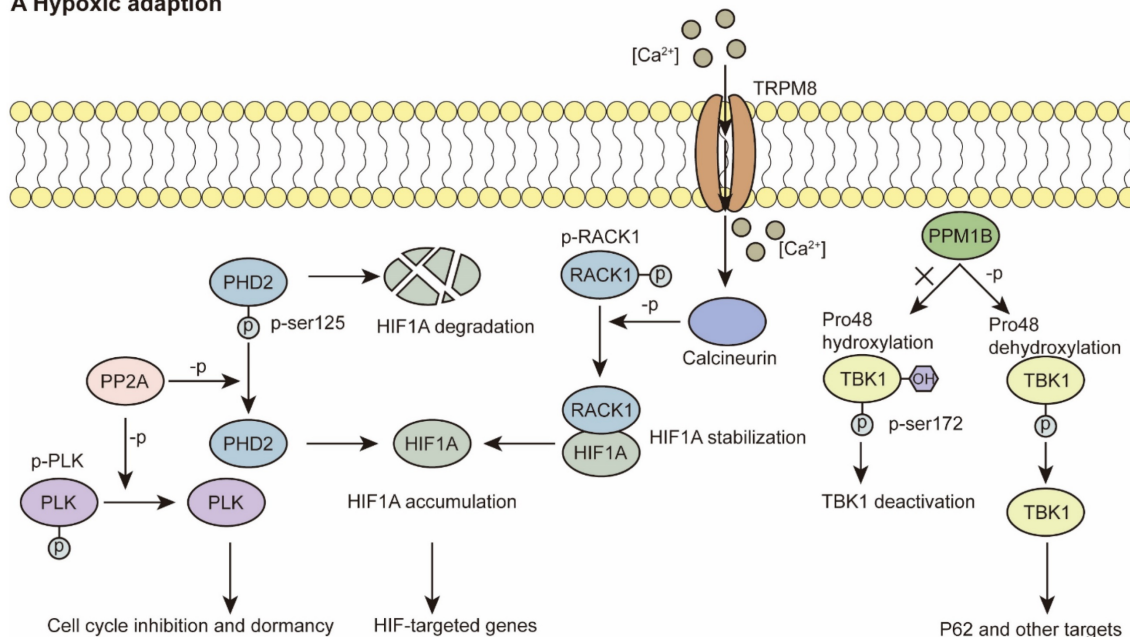
Angiogenesis

In addition to CAFs, endothelial cells are also key regulators of the TME. Previously, Martin, M *et al.* reported that PP2A dephosphorylates class IIa HDACs and promotes their nuclear translocation. Downstream factors, such as MMP10, contribute to the formation of vascular-like networks [117]. PP2A reportedly modulates ECM stiffness and angiogenesis through VEGF-mediated YAP activation [118]. Recent studies have demonstrated the essentiality of PP2A-B55 α for endothelial cell survival. PP2A-B55 α protects endothelial cells from reactive oxygen species-induced apoptosis by dephosphorylating

PHD2 and P38. Vascular network formation provides opportunities for tumor metastasis [119]. Depletion of the endogenous calcineurin inhibitor Dscr1 in lung endothelial cells leads to angiogenesis *via* the

calcineurin/NFAT/angiopoietin-2 pathway, which provides an optimal premetastatic niche for lung metastasis. Furthermore, excessive VEGF in the TME promotes this process [120] (Figure 3B).

A Hypoxic adaption



B Diverse metabolism

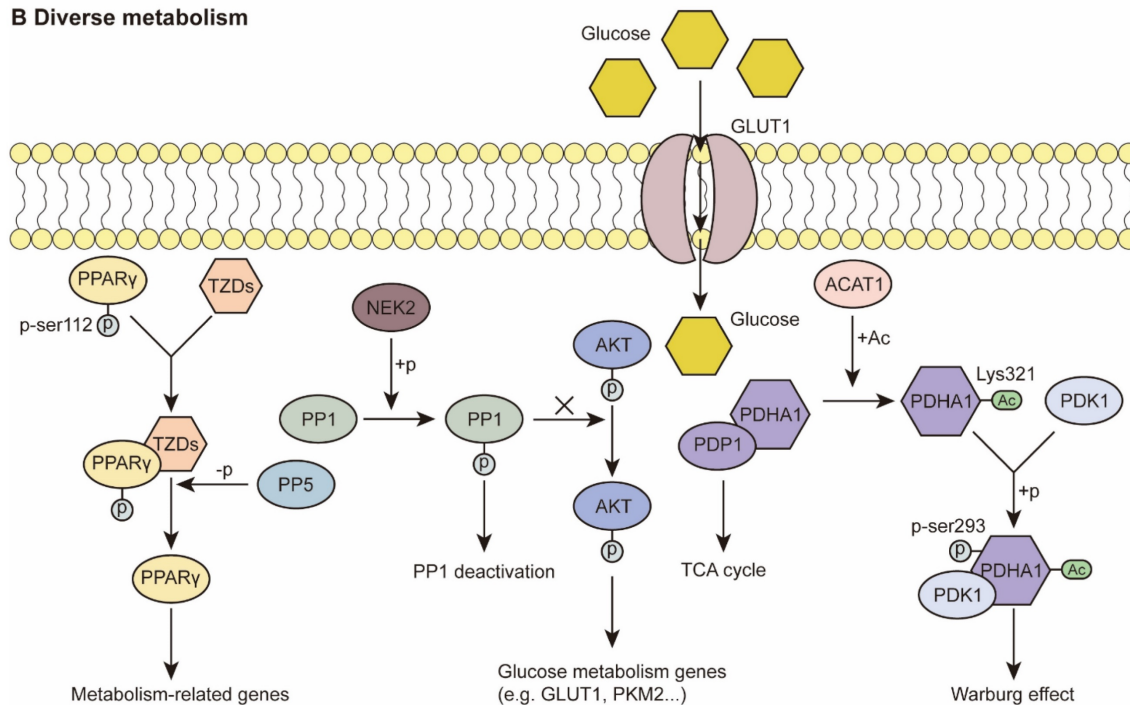


Figure 2. PSPs in hypoxic adaption and diverse metabolism. (A) Hypoxic adaption: PP2A dephosphorylates PLK to inhibit cell cycle and promote dormancy. Dephosphorylation of PHD2 at Ser125 leaves HIF1A accumulation. The iron channel TRPM8, acts as a Ca²⁺ inflow channel, which facilitates the activation of calcineurin. Dephosphorylated RACK1 binds to HIF1A and stabilize HIF1A. Intact HIF1A regulates relative genes which contribute to hypoxic adaption. In normoxia, TBK1 is hydroxylated at Pro48, and can't be dephosphorylated by PPM1B. Under hypoxic conditions, dehydroxylated TBK1 can be dephosphorylated at Ser172, which leads to activation of downstream factors. **(B)** Diverse metabolism: TZDs can bind to PPAR_γ, which recruits PP5 to dephosphorylate PPAR_γ at Ser112. Dephosphorylated PPAR_γ is activated and targets various metabolism-related genes. PP1 is phosphorylated by NEK2. PP1 deactivation facilitates AKT regulation of glucose metabolism genes. PDP1/PDHA1 complex contributes to TCA cycle. Once acetylated on Lys321 by ACAT1, PDHA1 dissociates from PDP1 and binds to PDK1, which leads to Ser293 phosphorylation and the subsequent Warburg effect.

Stromal cell interactions

In bone marrow, PP1A downregulates osteoprotegerin *via* the P38/MAPK pathway in hepatocellular carcinoma (HCC). Reduced osteoprotegerin (OPG) levels disturb the balance between osteoblasts and osteoclasts, leading to bone resorption and consequent metastasis [20] (Figure 3C). In bone marrow, a previous study demonstrated that differentiated osteoblasts can protect AML cells from SPF-1-induced apoptosis [121]. After HDACi treatment, upregulated Nherf1 binds to PP1A to dephosphorylate TAZ in osteoblasts, which inhibits osteoblast-mediated protection against AML [122].

Intercellular communication has been demonstrated to provide tumor cells with cancerous features, increasing their adaptability in various TMEs [14]. Recent studies have demonstrated that the PP1–MYPT1 complex in OC cells can be triggered by dephosphorylation of Thr696 and Thr853 when the complex is incubated with platelets. The functional PP1–MYPT1 complex in ovarian and colon cancer cells dephosphorylates YAP1 and promotes cancer metastasis [123]. Moreover, platelet-derived growth factors (PDGFs) in the TME can activate YAP signaling, whereas PP1 inhibition can counteract this process [124] (Figure 3D). Single-cell RNA sequencing analysis revealed that breast cancer cells can transfer PPP1R1B to tumor endothelial cells *via* extracellular vesicles (EVs), which activate endothelial cells and promote blood vessel formation to alleviate hypoxic conditions [125]. In the liver environment, senescent hepatocytes secrete miR-222-5p in exosomes. The microRNA represses its target gene PPP2R2A, leading to decreases in forkhead Box O3, P27 and P21 and accelerating the proliferation and migration abilities of HCC [8].

Immunity modulation

The TME comprises malignant cells and immune cells, such as T cells, B cells, natural killer (NK) cells, tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), mast cells, granulocytes, dendritic cells (DCs), and other chemokines. The regulation of antitumor immunity is closely associated with tumor development and prognosis [13]. Immune checkpoint blockade (ICB) treatments, such as anti-PD1/PDL1 and anti-CTLA4 therapies, which are correlated with immune regulation, showed value in reinvigorating “exhausted” T cells and controlled tumor growth, which have succeeded in some clinical tumor treatments [126]. Aberrant expression and dysfunction of PSPs in cancer or immune cells can disturb TME homeostasis, leading to an anti-ICB

response and cancer progression.

Tumor cell-mediated immune response

The immune response in tumors involves multiple steps, from immune signal activation and chemokine secretion to immune cell recruitment and the antitumor response [126]. Indeed, PSPs are demonstrated to regulate signaling pathways and mediate various chemokine productions. Mondal *et al.* reported that PP2A deficiency contributed to the accumulation of double-stranded DNA and the activation of cGAS–IFN signaling in glioblastoma. Increased IFN production sensitized tumor cells to ICB treatment (Figure 4A) [127]. Consistent with these results, the PP2A–RACK1 complex has been demonstrated to dephosphorylate and inactivate TBK1, impeding STING-initiated antitumor immunity in patients with mutant Neurofibromin 2 [18]. In OC, PP4 inhibition with fostriecin or PPP4C knockdown activates NF- κ B and STAT1 pathway. As the results, PP4 inhibition leads to increased secretion of proinflammatory factors, such as CCL5, CXCL10 and IL-6 (Figure 4A). Furthermore, cocultured NK-92 cells with PP4-inhibited OC cells presented significantly elevated IFN- γ production, increased degranulation, and increased NK cell-mediated cytotoxicity. Tumors with PPP4C knockdown exhibit increased infiltration of NK, NK T, CD4⁺ T and CD8⁺ T cells when combined with carboplatin [128]. Ubiquitination and degradation of PPM1B trigger NF- κ B activation, leading to the secretion of various chemokines, such as CXCL1, CXCL8, and CCL2, and subsequent TAM infiltration, angiogenesis, T-cell dysfunction and resistance to ICB therapy. These results may explain how diverse oncogenic mutations create an immunosuppressive TME in non-small cell lung cancer (NSCLC) [129].

Antigen processing and presentation is a prerequisite for DC-mediated T cell priming and T cell-mediated killing [130]. Dissociation of the PP1–GADD34 complex facilitates the cell surface translocation of calreticulin. Exposure to calreticulin is a signal for the recruitment and activation of DCs, CTLs and macrophages, leading to subsequent immunogenic cell death [131]. PP2A/PP5 inhibition by LB-100 promotes alternative splicing, which leads to neoantigens presented by MHC- I at the surface of colon cancer cells [132].

The inflammatory microenvironment has been implicated in the modulation of PSP activity and subsequent oncogenic processes for tumor cells. Inflammatory stimuli repress the expression level of PP2A *via* NF- κ B pathway activation. Reduced PP2A expression in pancreatic cancer cells contributes to ERK, PKC and JNK phosphorylation and promotes

cancer development [133]. Decreased PP2A expression in NSCLC cells was detected in response to treatment with macrophage culture medium *via* the NF- κ B pathway. Furthermore, an activated NF- κ B pathway contributes to chemokine production, TAM infiltration, tumor growth and migration in NSCLC [134] (Figure 4A). In addition, inflammation is considered a contributor to changes in intestinal stem cells toward oncogenic phenotypes. This process is associated with PP2A-mediated GSK-3 β activation [135].

Evidence from single-cell analysis and clinical data suggests that PSPs are correlated with immune cell infiltration in tumors and patient prognosis. Research suggests that PP2A deficiency in glioblastoma results in enhanced CD8⁺ T cell, DC, and NK cell infiltration and decreased the number of immunosuppressive TAMs [127]. In endometrial

cancer, high PPP1R16B expression levels indicate the infiltration of B cells, CD4⁺ T cells, CD8⁺ T cells, neutrophils, macrophages and DCs, as well as improved OS and DFS [21]. Increased expression of PPP1R14A in gastric cancer is correlated with poor antitumor immunity and poor outcomes [22]. High expression levels of PPP1R14B are related to increased MDSC infiltration across cancers [136]. In lung adenocarcinoma, PPP1R3G has been suggested to be positively correlated with the infiltration levels of B cells, CD4⁺ T cells and macrophages [137]. Some PPM members also indicate tumor outcomes. In CRC, the expression level of PPM1H is negatively correlated with tumor grade. A high level of PP1M1H indicates greater infiltration of M1 macrophages, CD8⁺/CD4⁺ T cells, and activated NK cells and a better survival rate [138].

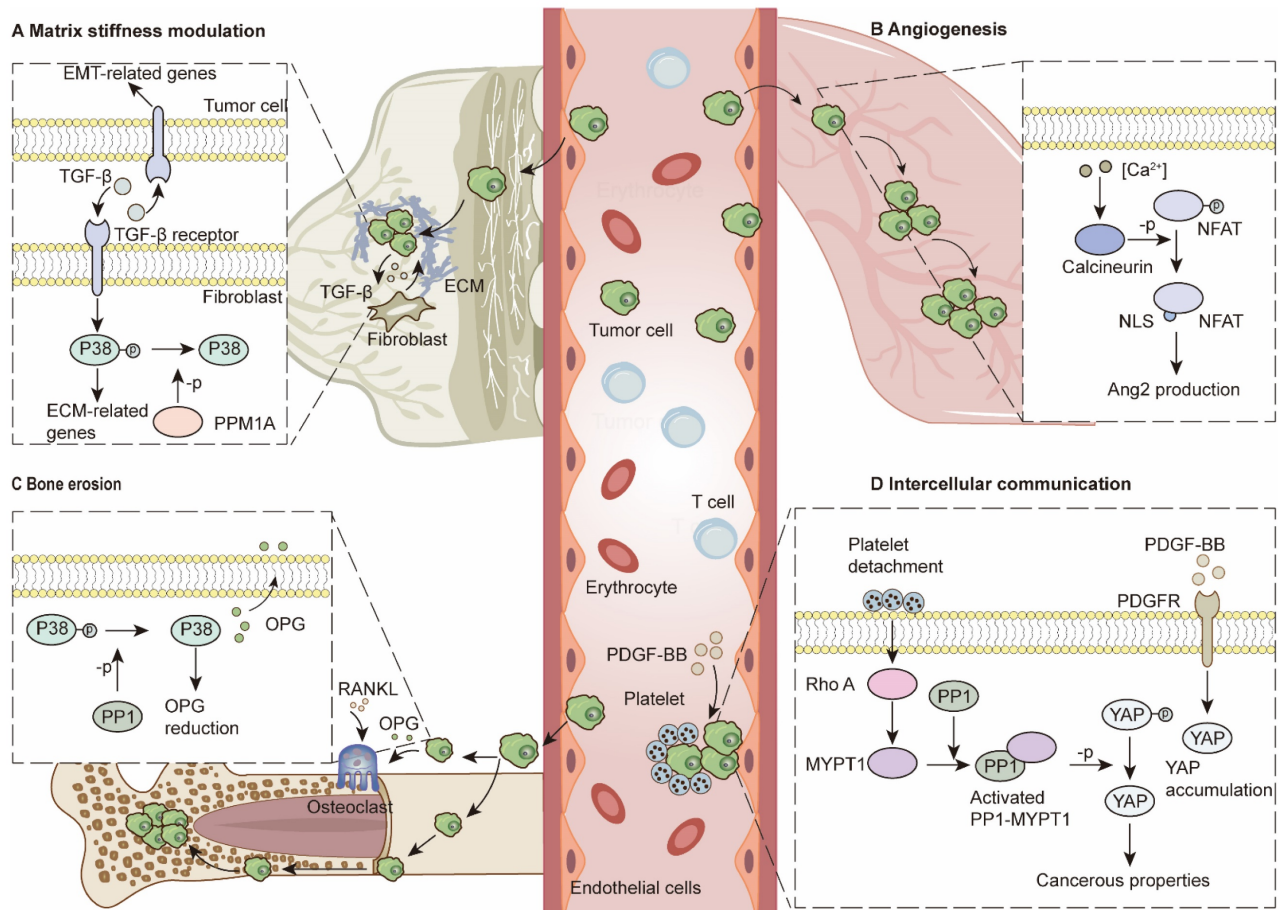


Figure 3. PSPs in ECM modulation and intercellular communication. (A) Matrix stiffness modulation. Fibroblasts and tumor cells regulate ECM-related genes and EMT-related genes through TGF- β pathway. PPM1A can dephosphorylate P38 to terminate this process. **(B)** Angiogenesis. Activation of calcineurin/NFAT/Ang2 pathway in endothelial cells contributes to angiogenesis, which provides pre-metastatic niches for lung metastasis. **(C)** Bone erosion. In tumor cells, PPI dephosphorylates P38 and reduces OPG production. Reduced OPG levels lead to enhanced bone erosion and further bone metastasis. **(D)** Intercellular communication. Platelet detachment contributes to PPI-MYPT1 complex activation, which can dephosphorylate YAP for cancerous properties.

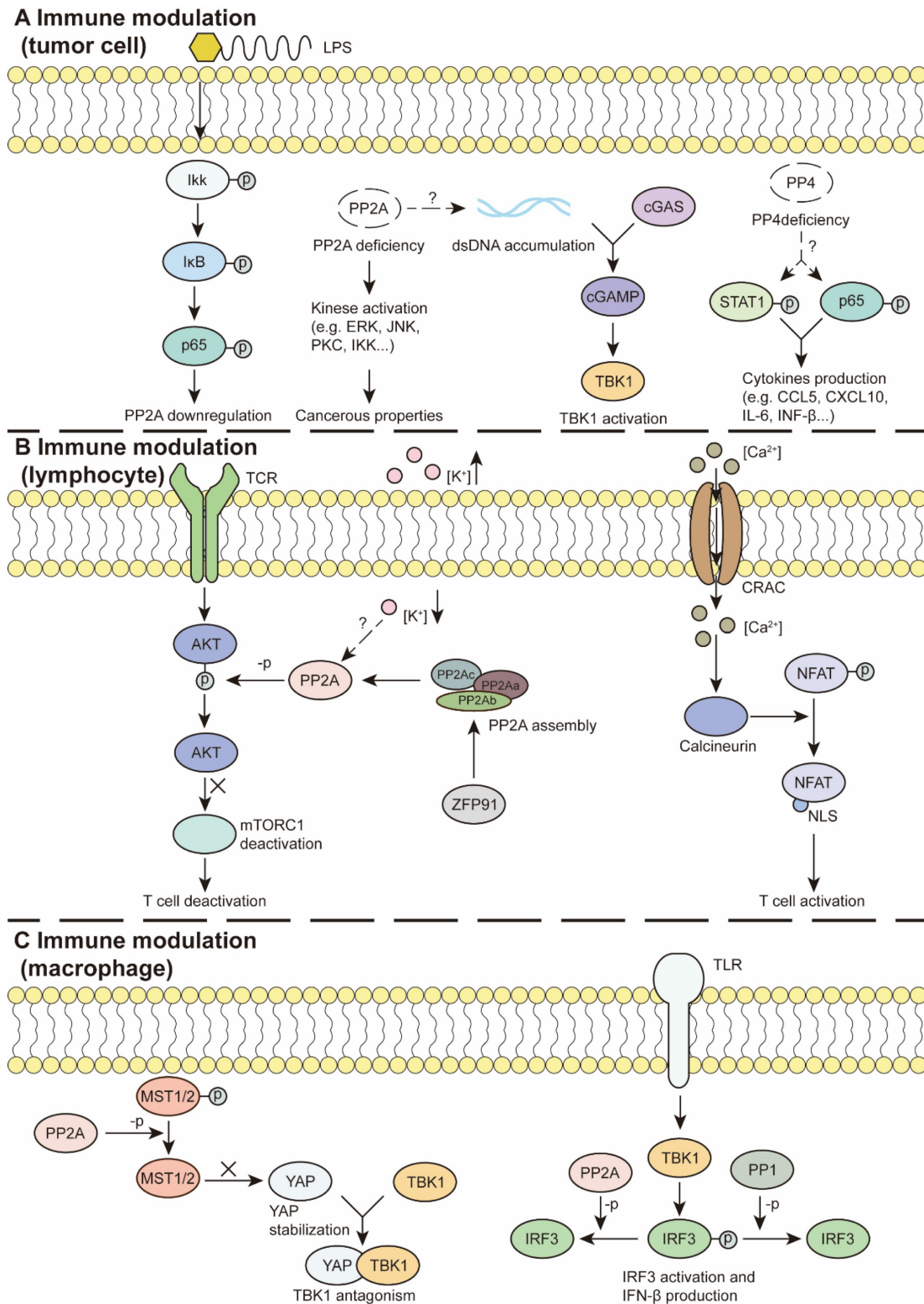


Figure 4. PSPs in immune modulation. (A) In tumor cells, inflammatory factors, such as LPS activate NF-κB pathway and reduce PP2A expression. PP2A deficiency promotes kinase activation and acquires cancerous properties. PP2A deficiency activates the GAS-STING pathway to modulate immunity. PP4 deficiency facilitates STAT1 and P65 activation and cytokine production. (B) In lymphocytes, PP2A can inhibit TCR-induced mTORC1 activation and T cell activation. Moreover, elevation of the extracellular K⁺ concentration can suppress T cell functions, which is required for intact PP2A. ZFP91 promotes PP2A holoenzyme assembly and downstream effects. Besides, Ca²⁺ flows through the iron channel CRAC and activates calcineurin, which dephosphorylates NFAT and exposes the NLS. Activated NFAT regulates T cell activation. (C) In macrophages, TLR/TBK1/IRF3 pathway promotes IFN-β production, whereas PP1 or PP2A can interrupt the process by IRF3 dephosphorylation. Additionally, PP2A dephosphorylates MST1/2 to stabilize YAP, which antagonizes TBK1 and its subsequent effects. LPS: Lipopolysaccharide, NLS: nuclear localization signal, ZFP91: Zinc finger protein 91

These inconsistent results may occur within different tumor types. For example, in HCC, high

expression of PPM1D is correlated with the expression of inhibitory immune checkpoint markers

and worse progression free survival and OS in patients with HCC. In addition, studies have shown that PPM1D contributes to the infiltration of TAMs, Th1 cells, Th2 cells and Tregs [139]. Whereas high levels of PPM1D in pancreatic cancer indicate better outcomes [81]. Similarly, the expression level of PDP1 in tumors is negatively correlated with CD8⁺ T-cell infiltration, whereas it is positively associated with tumor stage and poor prognosis in invasive breast carcinoma [140]. Decreased expression of PDP1 indicates better outcomes in patients with pancreatic adenocarcinoma [81].

The expression levels of some PSPs are correlated with the effects of ICB treatment. The low PPP1R16B expression group had a worse response to anti-PD1/PD-L1 and anti-CTLA4 treatments [21]. In pancreatic adenocarcinoma, PPM1K acts as an antitumor agent to negatively regulate the expression level of PD-L1. Decreased expression of PPM1K is associated with reduced infiltration of B cells, mast cells, CD8⁺ cytotoxic T cells, and various CD4⁺ T cells [81].

Effector T lymphocytes

Previously, PP1 and PP2A were shown to modulate the G0/G1 transition during lymphocyte activation [141]. Furthermore, single-cell transcriptome and immune profiling demonstrated that the PP1-GADD34 complex contributes to antitumor immunity. The use of the GADD34 inhibitor Sephin1 is considered to activate the integrated stress response, which leads to decreased CD8⁺ T cells and NK cells and reduced MHC-I, LCK, and SELPLG pathway crosstalk but increased M1 to M2 polarization and immune suppression [23]. For PP2A, Zhou P *et al.* demonstrated its participation in T-cell-mediated tumor immunity, as PP2R2D-silenced CD4⁺ and CD8⁺ T cells exhibit increased viability and increased production of interferon- γ (IFN- γ), IL-2 and GM-CSF [6]. ZFP91 facilitates the assembly of PP2A, which disturbs mTORC1 activity and restricts glycolysis and T-cell proliferation. The dysfunction of T cells results in an immune-suppressive environment [142] (Figure 4B). In addition, PP2A synergizes with cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) in immune evasion, as CTLA-4 can bind to PP2A for ataxia-telangiectasia mutated autophosphorylation in T-cell apoptosis [143]. Furthermore, the contents of the TME also regulate immune activity. An increase in the extracellular potassium concentration due to tumor necrosis leads to PP2A-mediated T-cell suppression (Figure 4B). Inhibition of PP2A with an inhibitor, okadaic acid, or PP2R2D knockdown can restore CD8⁺ T-cell functions [144].

Calcineurin activation dephosphorylates NFAT and induces its nuclear translocation in functional T cells [47] (Figure 4B). The calcineurin-NFAT pathway has been demonstrated to inhibit Treg cell differentiation and improve the immunosuppressive TME [70, 71]. Accordingly, targeting calcineurin is considered a possible strategy for treating T-ALL [145]. PP4 is required for thymocyte survival and maturation. Depletion of PP4 in T cells leads to aberrant pre-T-cell receptor signaling and can be lethal in mouse embryos [146]. Furthermore, PP4R1 reportedly bridges PP4-C to the inhibitor of the NF- κ B kinase (IKK) complex, where IKK is dephosphorylated and inactivated. PP4R1 silencing leads to hyperactivation of T cells and malignant properties in cutaneous T-cell lymphoma [147]. Additionally, PP4-C reportedly induces apoptosis in leukemic T cells and normal T cells *via* the dephosphorylation of the apoptosis regulator PEA-15 [148].

Regulatory T cells

For Treg cells, Apostolidis SA *et al.* reported that PP2A targeted mTORC1 signaling in a ceramide-dependent manner, which was required for normal functions. Their report suggested that PP2A inhibition in Treg cells may contribute to antitumor immunity [149]. Similar results were obtained when cells were treated with nanomedicine containing the immunomodulator dimethylcantharidin (DMC) in mice. DMC serves as a PP2A inhibitor in T cells, which activates mTORC1 signaling, thus promoting cytotoxic T lymphocyte (CTL) infiltration and reducing Treg cell differentiation in the bulk of tumors [150]. Moreover, researchers suggest that a multikinase inhibitor, H89, regulates the AKT/PP2A axis, promoting TCR and IL-15 signaling in antitumor immunity [151]. The PP2A inhibitor LB-100 enhances chimeric antigen receptor T-cell therapy [152].

B cells

PP2A is required for the optimal function of normal B cells [153]. Inhibiting the mTOR-mediated PP2A/ERK pathway disturbs the proliferation and survival of both normal and malignant B cells [154]. Indeed, PP2A affects malignant B cells, and TGF- β -induced apoptosis depends on PP2A activation and subsequent ERK and JNK dephosphorylation [155]. In B cells, PP1 activity and actin polymerization contribute to Fc receptor clustering, high affinity for IgG and “inside-out” signaling in neutrophils. This process is speculated to mediate antibody-dependent cellular cytotoxicity and enhance the antitumor response [156].

In macrophages and MDSCs

An early study revealed that overexpressed PP1 inhibits TLR- or RLR-triggered IFN- β production *via* IRF3 Ser385 and Ser396 dephosphorylation in macrophages. Moreover, the expression level of PP1 is reduced by stimulation with TLR or RLR ligands [157] (Figure 4C). PP2A is another PSP that has been demonstrated to induce macrophage infiltration *via* Rap1-regulated migration, whereas PPP2CA ablation fails to dephosphorylate STAT6, thus prohibiting M1 polarization and TNF α production [158]. Inhibition of PP2A by cytoplasmic SET stimulates the P38 and ERK pathways and the expression of M2-related genes. Additionally, SET also regulates the mobility and distribution of tumor-associated macrophages (TAMs) in tumor regions, providing an immunosuppressive environment [106]. Previously, PP2A was demonstrated to negatively regulate IFN signaling *via* IRF3 dephosphorylation [159] (Figure 4C). Similar results indicate that the PP2A-STRN4 complex counteracts STING-IFN signaling *via* the dephosphorylation of the Hippo kinase MST1/2 to maintain the stability of YAP/TAZ in TAMs (Figure 4C). *In vivo* experiments have demonstrated that PP2AC deficiency in macrophages promotes CD8⁺ T-cell infiltration, reduces the number of immunosuppressive TAMs and inhibits tumor growth [160].

The accumulation and activity of MDSCs are increased by the AKT/ β -catenin axis, whereas increased PP2A can terminate the pathway and improve the immunosuppressive TME [161]. Additionally, inhibition of the PP1-GADD34 complex hampers the production of type I IFN and proinflammatory cytokines in PAMP-activated DCs [162]. In addition, the calcium/calcineurin/NFAT axis is required for increased IL-2 production and decreased TGF- β production in DCs. DC-derived polarizing cytokines orchestrate the ratio of Foxp3⁺ Treg cells and IFN- γ ⁺ Th1 cells in the TME [163].

PSP-related therapeutic implications

Given the importance of PSPs in both tumor biology and the TME, from the initial stages to the formation of metastases, a variety of therapeutic strategies have emerged and demonstrated efficacy in both laboratory and clinical experiments (Table 3).

Calcineurin-targeted drugs have been developed and used clinically for decades. The first FDA-approved drug targeting a phosphatase was the calcineurin inhibitor CSP [164]. CSP, cyclophilin A, FK506 and pimecrolimus are FDA-approved calcineurin-inhibiting drugs for organ transplantation and atopic dermatitis due to their

immunomodulatory functions [165, 166]. Coadministration of CSP enhances the effectiveness of dasatinib against chronic myelogenous leukemia (CML) but with low tolerance [167]. Recent preclinical studies have demonstrated that rubiginosin B targets calcineurin/NFAT pathway and interrupts Treg cell differentiation. The treatment significantly modulates the immune-suppressive TME and inhibits the growth of CRC cells [70]. Zoledronic acid is a bisphosphonate, which indirectly interferes calcineurin-related signaling by regulating gene expression of calcium channel. In patients suffered from breast, bladder, kidney and prostate cancer with skeletal metastases, treatment with zoledronic acid disrupts Ca²⁺/calcineurin/NFAT pathway in Treg cells and represses their immune-suppressive functions [71]. However, there are increased risks of carcinogenesis during the usage of calcineurin inhibitors. Inhibiting calcineurin/NFAT pathway increases the expression of ATF3, a negative regulator of P53 transcription, and disrupts P53-induced senescence in tumor cells. In fact, treatment with cyclophilin A or FK506 increases the risk suffering from squamous cell carcinoma [168].

Another promising therapeutic implication is the use of PP2A-targeting drugs. FTY720/fingolimod was originally applied for the treatment of multiple sclerosis because of its immunomodulatory effects. Later studies demonstrated that nonphosphorylated FTY720 indirectly activates PP2A by binding to its inhibitor SET, which presents potential benefits against various neoplasms. Moreover, combined therapy with milatuzumab, gefitinib and dasatinib shows anti-tumor effects in mantle cell lymphoma, triple-negative breast cancer and pancreatic cancer [62]. C11 and CM-1231 are analogous to nonphosphorylated FTY720, which has antitumor effects on chronic lymphocytic leukemia (CLL) and AML without immunosuppression or cardiac toxicity [169, 170]. Another activator, DT-061 (known as the small-molecule activator of PP2A, SMAP), specifically stabilizes the PP2A-B56 α complex by binding to its heterotrimeric regulatory pocket and activates PP2A to dephosphorylate its downstream oncogenic proteins, such as C-MYC [171]. Moreover, for those resistant to kinase inhibitors, such as K-RAS-mutant lung cancers, the combination of DT-061 and the MEK inhibitor AZD6244 leads to suppression of the AKT and MYC pathways and attenuation of tumor growth [172]. Similarly, for chronic CLL cells with apoptosis resistance caused by impaired Bax/Bak protein activation, DT-061 treatment triggers apoptosis *via* the induction of permeability transition pores in the mitochondria (mPTPs), which increases the expression of cleaved caspase-9 and cleaved PARP,

independent of the Bax/Bak pathway [173]. In addition, DT-061 activates PP2A and positively regulates GSK3 β , which impairs viability in CLL [174].

LB-100, a small molecule inhibitor of PP2A, has been tested in a phase I trial and has shown acceptable safety, tolerability, and antitumor activity in various carcinomas and sarcomas. Stable of the diseases are achieved for patients with atypical carcinoid of the lung, breast cancer, testicular cancer, malignant thymoma, ovarian cancer chondrosarcoma and fibrosarcoma. One patient with pancreatic cancer has a partial response after LB-100 treatment [175]. Recent studies have demonstrated that LB-100 sensitizes typical and anaplastic meningioma cells to radiation via DNA repair interruption and G2/M cell cycle arrest [176]. LB-100 has been demonstrated to induce chemo-/radio-sensitization in various tumors, such as osteosarcoma, AML, CML and meningioma [177]. Additionally, LB-100 reportedly mediates the perturbation of mRNA splicing and sensitizes colon cancer cells to ICB treatments [132]. In fact, a phase II trial in CRC patients revealed that the combination of LB-100 and ICB therapy led to complete tumor regression [177]. Additionally, preclinical studies revealed that the PP2A inhibitor DMC suppresses Treg cell maturation and promotes CTL infiltration, which alleviates the tumor burden [150]. A novel selective inhibitor of the PP2A-STRN3 complex, STRN3-derived Hippo-activating peptide (SHAP),

exerts antitumor effects by interrupting MST1/2-mediated YAP activation in gastric cancers. For gastric cancers independent of Hippo pathway, SHAP has limited effects [10].

GSK2830371/GlaxoSmithKline is an inhibitor of PPM1D. Preclinical studies suggest its value in the growth inhibition of hematopoietic tumor cells and PPM1D-amplified breast tumor cells with wild-type P53 [32]. CCT007093 is another PPM1D inhibitor that induces lethality in ovarian clear cell carcinoma and potently inhibits growth in medulloblastoma [178, 179].

Due to its wide distribution and essential functions in biological processes, PP1 was once deemed “undruggable”. With a deeper investigation of PP1 and other PPPs, some compounds, such as PP2A inhibitors, have shed light on PP1-targeted therapy. More importantly, drugs that target a specific RIPPO are considered feasible and valuable approaches [11]. Sephin1, a novel GADD34 inhibitor, impedes PP1-GADD34 complex formation and consequent substrate dephosphorylation and inhibits anaplastic thyroid cancer (ATC) growth. Moreover, PPP1R15A inhibition sensitizes ATC cells to conventional chemical treatment [180]. Raphin1 is a PPP1R15B inhibitor. Treating myeloma cells with Raphin1 activates the proapoptotic eIF2 α /ATF4/CHOP pathway. Additionally, the use of Raphin1 potentiates the antitumor effect of bortezomib [181].

Table 3. PSP-related therapeutic implications

Compound	Target	Type of cancer	Activator/Inhibitor	Mechanism/Pathway	Comments	Ref.
Sephin1	PP1-GADD34	ATC	Inhibitor	-	Growth inhibition and chemical sensation	[180]
Raphin1	PP1-PPP1R15B	Myeloma	Inhibitor	Activating EIF2 α /ATF4/CHOP pathway	Apoptosis promotion and chemical sensation	[181]
FTY720/ fingolimod	PP2A- B56 γ	Lymphoma, breast, pancreatic cancer	Activator	Disrupting PP2A-SET interaction	Growth inhibition in various tumor cells, immunosuppression	[62]
C11	PP2A- B56 γ	CLL	Activator	Disrupting PP2A-SET interaction	Growth inhibition in CLL, analog to FTY720 without immunosuppression	[169]
CM-1231	PP2A- B56 γ	AML	Activator	Disrupting PP2A-SET interaction	Growth inhibition in AML, analog to FTY720 without cardiac toxicity	[170]
DT-061 /SMAP	PP2A-B56 α	CLL, lung cancer	Activator	Inhibiting MEK/mTOR and NOTCH1 pathway, mPTPs-mediated apoptosis	Growth inhibition in K-RAS mutant lung cancer, and CLL	[172-174]
LB-100	PP2A	Glioblastoma, CRC, lung cancer	Inhibitor	-	Success in phase I and phase II trials, chemo-/radio-sensitization	[177]
DMC	PP2A	CRC	Inhibitor	Activating PI3K/AKT/mTOR pathway	Immune TME modulation	[150]
SHAP	PP2A-STRN3	Gastric cancer	Inhibitor	Inhibiting HIPPO pathway	Growth inhibition	[10]
CSP	Calcineurin	CML	Inhibitor	Inhibiting Wnt/calcineurin/NFAT pathway	Chemo-sensitization, low tolerance	[167]
Zoledronic acid	Calcineurin	Various cancers with skeletal metastases	Inhibitor	Inhibiting NFAT and IL-2 pathways	Immune TME modulation	[71]
Rubiginosin B	Calcineurin	CRC	Inhibitor	Inhibiting NFAT pathway	Immune TME modulation	[70]
GSK2830371/ GlaxoSmithKline	PPM1D	Hematopoietic, breast cancer	Inhibitor	P53 restoration	Growth inhibition	[32]
CCT007093	PPM1D	Medulloblastoma, OC	Inhibitor	P53 restoration	Growth inhibition and induced lethality	[178, 179]

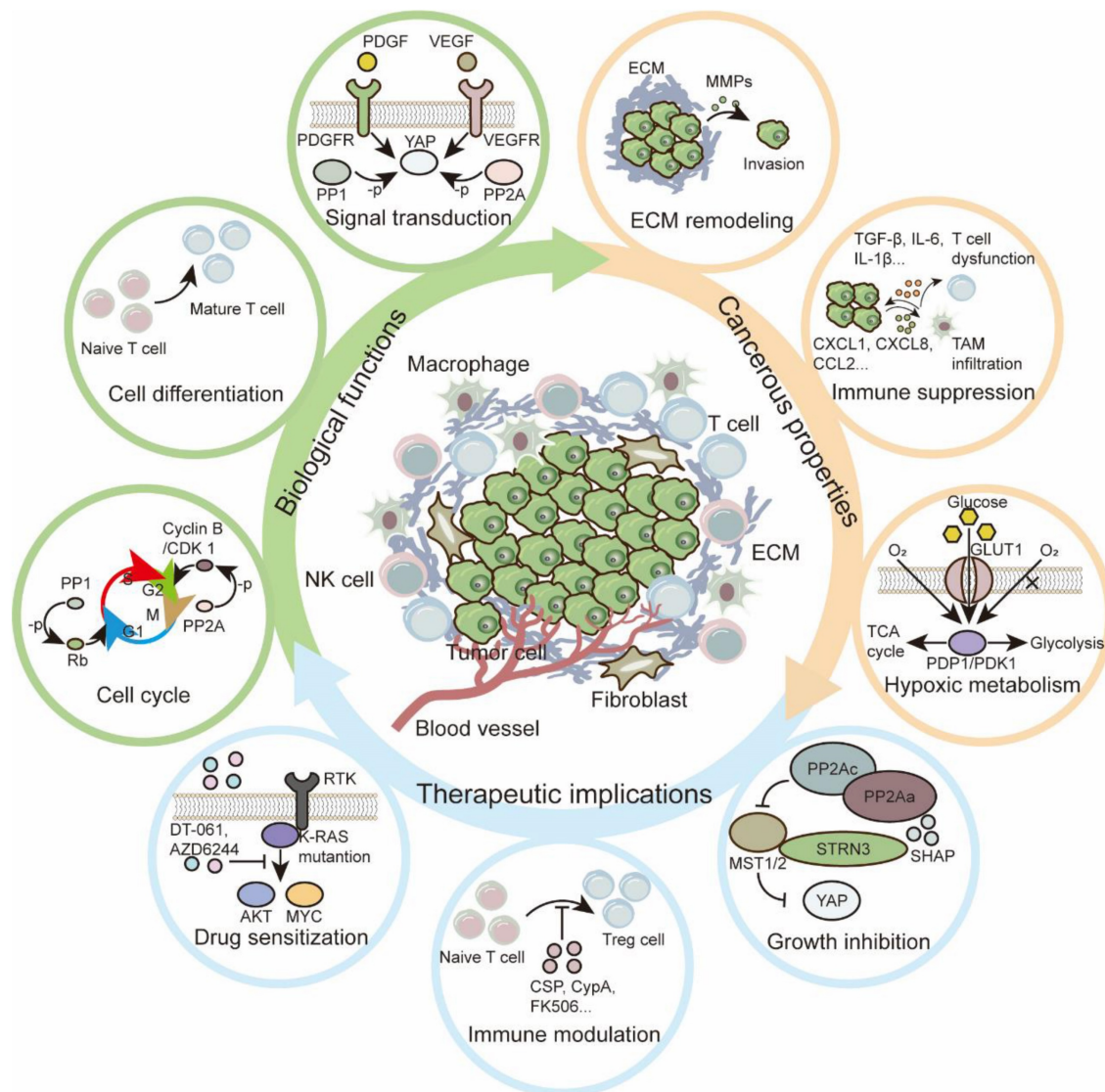


Figure 5. Functions and therapeutic implications of PSPs in TME. In TME, PSPs are required for both biological and cancerous functions. Regarding the essential roles of PSPs, both traditional and innovative therapeutic implications are explored for the treatment of tumors.

Conclusions and prospects

As major participants, PSPs perform versatile functions *via* phosphorylation and dephosphorylation (Figure 5). With an updated theory of tumor biology, PSPs orchestrate the TME by mediating hypoxic adaptation, immune modulation, diverse metabolism, ECM modifications, and intercellular communication, from initiation to outgrowth of metastasis. Some PSPs are modulated by conserved complexes, such as STRIPAK, which forms a conserve complex to recognize phosphorylated MST1/2 and regulates downstream effectors in signaling transduction. In addition, the functions of PPPs may vary within different regulatory subunits. Considering their beneficial or pathological roles in the TME is arbitrary. Indeed, several FDA-approved drugs have shown promising prospects for targeting PSPs and their

subunits; however, several nonnegligible and challenging problems remain unsolved:

First, some PSPs are pivotal players in many biological processes and are widely distributed throughout various cells. Interference with PSPs can be fatal for normal cells. For example, inhibition of the PP2A-B56 complex leads to cardiomyocyte apoptosis [64]. The potential side effects of PSP-targeted therapy must be taken into consideration. Second, the functions of some PSP systems require holoenzymes. Diverse combinations of different regulatory subunits may lead to various outcomes [21, 22]. As for PP1, PP1-NIPP1 acts as a tumor suppressor for tumor growth inhibition, but also acts as a tumor promotor for migration in cervical cancer [182, 183]. Holoenzymes may be beneficial or harmful [60]. Unfortunately, the functions of some subunits in tumors still remain unclear. The specific functions of

regulatory subunit combinations warrant further investigation. Third, due to the multiple functions of regulatory subunits, drugs are expected to target a specific PSP subunit rather than nonspecific inhibitors [11]. Fourth, compensatory effects may occur when phosphatases or kinases are targeted for tumor treatment. In RAS-driven lung cancer, usage of SH2P inhibitors leads to subsequent TGF- β pathway activation, which enhances tumor motility by inducing EMT [184]. Different PSP complexes, or specific enzymes with different catalytic subunits and regulatory subunits, display similar functions and phenotypes [185]. Whether the oncogenic signaling pathway is rescued by another PSPs, nor a new pathway is triggered when we target a specific PSP? The compensatory effects may be troublesome. Fifth, the development of optimal PSP activators is a difficult problem. Sixth, the prospects of PSPs in cutting-edge fields, such as the tumor-nerve-immunity cycle, warrant further research.

Although several challenges exist in PSP-targeted therapy, targeting biological markers is a possible and accessible approach for drug delivery. Therapeutics modified with tumor marker antibodies have shown promise and mild side effects in the laboratory and clinic [186]. Recently, targeting phosphatases with antibody-conjugated nanoparticles successfully delivered drugs to HER2⁺ cancers. Moreover, it makes targeted therapy for “undruggable” disease possible [187].

The wide distribution and pivotal function of PSPs present long-lasting challenges for optimal therapy. With increasing knowledge of the TME, the functions of PSPs will be further elucidated, providing more feasible and valuable drugs for tumor therapy.

Abbreviations

AML: acute myeloid leukemia; ATC: anaplastic thyroid cancer; CAF: cancer-associated fibroblast; CLL: chronic lymphocytic leukemia; CML: chronic myeloid leukemia; CRC: colorectal cancer; CSP: cyclosporin; CTD: C-terminal domain; CTL: cytotoxic T cell; CTLA-4: cytotoxic T-lymphocyte-associated protein 4; DDR: DNA damage repair; DFS: disease free survival; DMC: demethylcantharidin; DSP: dual-specificity phosphatase; ECM: extracellular matrix; EMT: epithelial to mesenchymal transition; EV: extracellular vesicle; FCP: FIIF-associating component of RNA polymerase II CTD phosphatase; HCC: hepatocellular carcinoma; HIF: Hypoxia-inducible factor; ICB: immune checkpoint blockade; IFN: interferon; IKK: inhibitor of NF- κ B kinase; MDSC: myeloid-derived suppressor cell; mPTPs: permeability transition pores in the

mitochondria; NFAT: nuclear factor of activated T cells; NSCLC: non-small cell lung cancer; OC: ovarian cancer; OPG: osteoprotegerin; OS: overall survival; PDGF: platelet-derived growth factor; PDH: pyruvate dehydrogenase; PDK1: pyruvate dehydrogenase kinase 1; PDP: pyruvate dehydrogenase phosphatase; PPM: metal-dependent protein phosphatase; PPP: phosphoprotein phosphatase; PRL3: phosphatase of regenerating liver 3; PSP: protein serine/threonine phosphatase; PTM: post translational modification; SCP: small CTD phosphatase; SHIP2: Src homology 2 domain-containing inositol polyphosphate 5-phosphatase 2; SLiM: short linear motif; SLMAP: sarcolemma membrane-associated protein; STRIPAK: striatin-interacting phosphatase and kinase; RIPPO: regulatory interactor of PP1; SMAP: small-molecule activator of PP2A; STRN: striatin; TAM: tumor-associated macrophage; TBK1: TANK Binding Kinase 1; TCA: tricarboxylic acid; TME: tumor microenvironment; TPR: tetra-trico-peptide repeat.

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Author contributions

Z.H. and Y.L. conceptualized this study. Y.L., F.X., and C.Z. drafted the manuscript. Z.H., B.T., J.S. and B.Z. revised the manuscript. Z.H. obtained funding. All authors read and approved the final manuscript.

Competing Interests

The authors have declared that no competing interest exists.

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