

Research progress of SPP1 in cancer regulation: Tumorigenesis, metastasis, tumor microenvironment, immunity and therapeutic targets (Review)

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Abstract. Secreted phosphoprotein 1 (SPP1, also known as osteopontin, OPN) is a multifunctional matricellular glycoprotein that is aberrantly overexpressed in nearly all major human malignancies. It functions as a central signaling hub that drives tumor initiation, sustains cancer stemness, accelerates invasion and metastasis, remodels the tumor microenvironment (TME), and mediates immune evasion. SPP1 exerts its oncogenic effects by binding to integrin family receptors ($\alpha\beta3$, $\alpha\beta5$, $\alpha5\beta1$) and CD44 variants, thereby activating canonical oncogenic signaling cascades including PI3K/AKT, NF- κ B, MAPK/ERK and Wnt/ β -catenin. Beyond cancer-cell-autonomous functions, SPP1 orchestrates a complex immunosuppressive TME by

modulating tumor-associated macrophages, cancer-associated fibroblasts, myeloid-derived suppressor cells, regulatory T cells (Tregs) and cytotoxic T-cell activity. Preclinical studies have validated SPP1 as a promising therapeutic target, with strategies including neutralizing antibodies, RNA aptamers, small-molecule inhibitors, RNA interference and combination immunotherapy showing potent antitumor efficacy. The present review systematically summarizes the molecular basis of SPP1, its receptor-mediated signaling, multifaceted regulatory roles in tumor biology, TME remodeling, immune suppression and advances in SPP1-targeted therapy. Current challenges, emerging concepts and future directions to translate SPP1-targeted interventions into clinical practice for cancers were further discussed.

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Abbreviations: SPP1, secreted phosphoprotein 1; OPN, osteopontin; TME, tumor microenvironment; TAMs, tumor-associated macrophages; CAFs, cancer-associated fibroblasts; MDSCs, myeloid-derived suppressor cells; Tregs, regulatory T cells; RGD, Arg-Gly-Asp; PDAC, pancreatic ductal adenocarcinoma; CRC, colorectal cancer; HCC, hepatocellular carcinoma; GC, gastric cancer; BC, breast cancer; LC, lung cancer; OC, ovarian cancer; ECM, extracellular matrix; PTMs, post-translational modifications; CDH1, E-cadherin; CK2, Casein kinase II; MPCs, mesenchymal pancreatic cancer cells; CSCs, cancer stem cells; ApDCs, aptamer-drug conjugates; NSCLC, non-small cell lung cancer; ICB, immune checkpoint blockade; scRNA-seq, single-cell RNA sequencing

Key words: SPP1, OPN, tumor stemness, tumor metastasis, TME, immune evasion, therapeutic target

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1. Introduction

Cancer progression depends on the coordinated interplay between cancer-cell-autonomous programs and non-autonomous remodeling of the tumor microenvironment (TME) (1,2). Identifying master regulators that bridge these processes is critical for developing next-generation therapies. Secreted phosphoprotein 1 (SPP1), also known as Osteopontin (OPN), is a highly phosphorylated glycoprotein belonging to the

extracellular matrix (ECM) protein family, which was first identified in bone matrix as an essential protein for mineralization and bone remodeling (3). Cloning and sequence analysis of rat osteopontin cDNA reveals an Arg-Gly-Asp cell-binding sequence (3-5). Subsequent research has revealed its broader biological functions, including roles in inflammation, wound healing, immune regulation and tissue repair (4). In cancer biology, SPP1 has emerged as a critical multifunctional regulator. Its expression is elevated across diverse malignancies-including pancreatic ductal adenocarcinoma (PDAC), breast cancer (BC), lung cancer (LC), colorectal cancer (CRC), hepatocellular carcinoma (HCC), gastric cancer (GC) and ovarian cancer (OC), where elevated levels correlate with advanced tumor stage, metastatic burden and poor patient survival (6).

SPP1 promotes core cancer hallmarks, including sustained proliferation, evasion of apoptosis, angiogenesis, invasion, metastasis and therapy resistance (7,8). Beyond its direct effects on cancer cells, SPP1 uniquely serves as a central coordinator of the TME, modulating immune cell polarization, cancer-associated fibroblast (CAF) activation, ECM remodeling, and angiogenesis to establish an immunosuppressive and pro-metastatic niche (9,10).

The present review comprehensively examines the research progress on SPP1 in cancer regulation, focusing on its molecular biological basis, receptor interactions and signaling pathways, regulatory roles in tumorigenesis and metastasis, modulation of the TME and immunity, and emerging therapeutic targeting strategies. Challenges and future perspectives to accelerate clinical translation of SPP1-targeted strategies were also discussed.

2. Molecular biological basis of SPP1

Structural characteristics of SPP1 gene. The *SPP1* gene encoding osteopontin (OPN) is located on the long arm of human chromosome 4 (4q22.1) and spans ~5.4 kilobases (kb), comprising 7 exons and 6 introns (11). The coding sequence is mainly distributed across exons 2 to 7, producing 5 major alternative splicing transcripts (12). The gene is evolutionarily conserved across vertebrates, with mammalian SPP1 exhibiting >60% nucleotide sequence identity in the coding region and >70% amino acid identity in cross-species comparisons (11). The 5'-end promoter region contains abundant cis-acting elements, allowing dynamic expression of SPP1 under stimuli such as inflammatory signals, hypoxia and carcinogenesis.

Structural characteristics of OPN protein. OPN is a glycosylated protein encoded by the *SPP1* gene, which is widely present in the ECM and is a key component of bone matrix. The molecular weight of OPN protein ranges from 44 to 75 kDa. Alternative splicing of the *SPP1* gene gives rise to three primary isoforms of OPN, each with distinct structural and functional characteristics (13). OPN-a, the full-length isoform, is the canonical secreted form (sSPP1) and the predominant isoform within the TME (14). OPN-b lacks exon 5 (OPN-b Δ ex5); although it is also secreted, it exhibits enhanced integrin binding and is associated with aggressive tumor phenotypes (15). OPN-c lacks exon 4 (OPN-c Δ ex4) and is often retained intracellularly (iSPP1) or localizes to the nucleus (nSPP1) (16). Functionally, secreted OPN-a and

OPN-b mediate paracrine signaling in the TME, while intracellular/nuclear OPN-c modulates cell cycle progression and transcriptional regulation (14,17).

Structurally, SPP1 contains three functionally defined domains that support its diverse biological activities. The integrin-binding domain is acidic and rich in aspartic acid residues. It serves as the main site of phosphorylation, enhancing integrin binding affinity and promoting cell adhesion and migration (18,19). The central domain contains a conserved Arg-Gly-Asp (RGD) motif, which is responsible for binding to various integrins (for example, α v β 3, α v β 5, α 5 β 1) (20). This interaction triggers downstream signaling cascades such as FAK/PI3K-AKT and MAPK/ERK pathways to regulate tumor cell proliferation, survival and epithelial-mesenchymal transition (EMT). The C-terminal domain contains a non-RGD integrin-binding site (SVVYGLR) and a thrombin cleavage site (21). Under the action of thrombin, proteolysis produces N-terminal and C-terminal fragments with distinct functions: The N-terminal fragment retains RGD-mediated integrin binding, while the C-terminal fragment preferentially interacts with the CD44 receptor, promoting stemness, chemoresistance and immune evasion in the TME (22). The functional diversity of OPN is largely attributed to its extensive and variable post-translational modifications (PTMs), which finely regulate its protein-protein interactions, stability and receptor binding specificity (Fig. 1).

PTMs. SPP1 undergoes extensive PTMs that critically regulate its function:

Phosphorylation: OPN is one of the most highly phosphorylated proteins *in vivo*, with numerous serine and threonine phosphorylation sites, often occurring in acidic clusters. This modification is essential for high-affinity integrin binding and downstream signaling activation. Casein kinase II (CK2) and other kinases phosphorylate specific residues, creating acidic patches that coordinate calcium ions for integrin recognition (23,24). This extensive negative charge is crucial for mediating high-affinity binding to various integrins, especially α v β 3, through coordination with calcium ions and basic residues on the integrin surface. Phosphorylation is a prerequisite for integrin participation in activating downstream pro-survival and migration signaling pathways such as PI3K/AKT and FAK (25).

Glycosylation: OPN undergoes both N-glycosylation and O-glycosylation. These carbohydrate modifications significantly enhance protein stability, increase its resistance to proteolytic degradation, and affect its secretion (26). Most importantly, glycosylation directly regulates the interaction between OPN and its other major receptor, CD44. Specific glycan structures can either promote or sterically hinder binding to CD44 variants, adding an additional layer of regulation that determines whether OPN signals primarily through integrin-mediated or CD44-mediated pathways in a context-dependent manner (27,28).

Proteolytic cleavage: Thrombin cleavage at Arg156-Ser157 generates N-terminal (containing RGD) and C-terminal fragments. The N-terminal fragment retains integrin-binding activity, while the C-terminal fragment preferentially binds CD44 to promote stemness, chemoresistance and immune evasion (29).

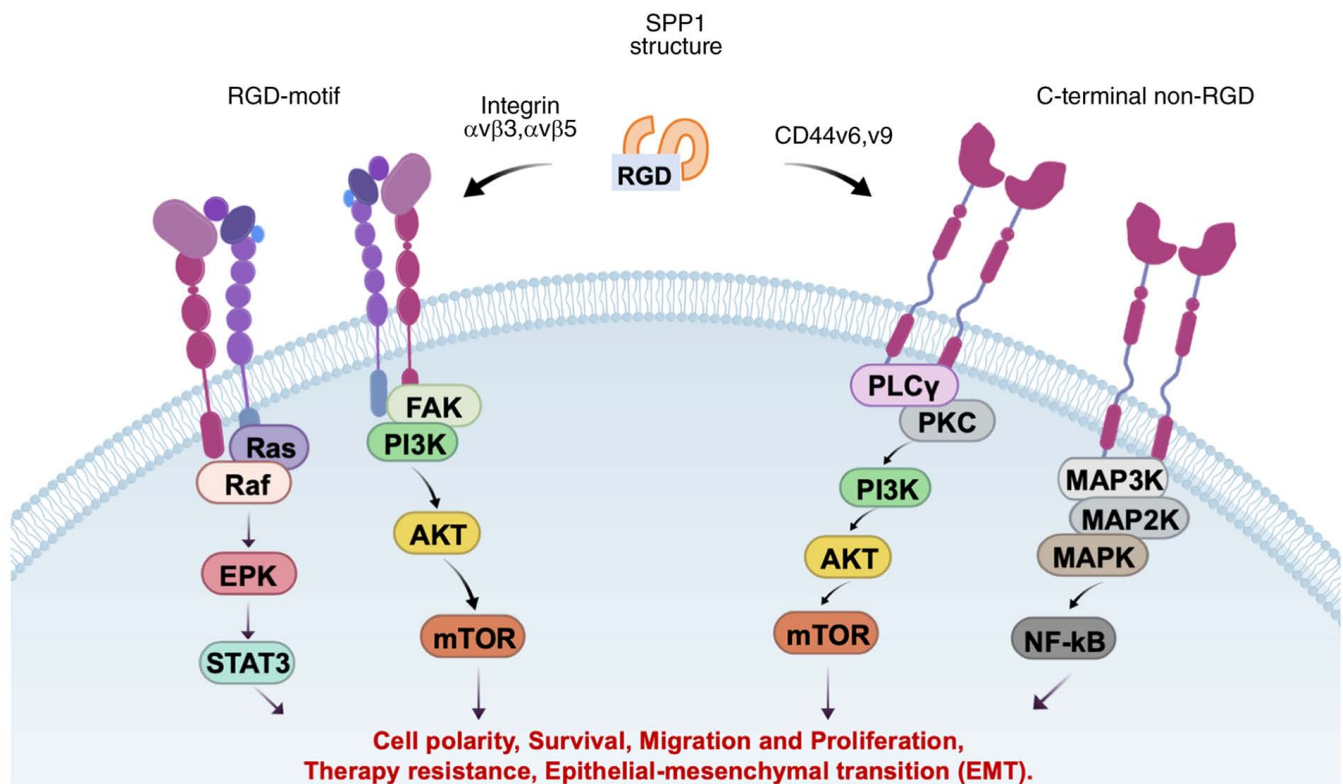


Figure 1. Structural characteristics of SPP1 protein. SPP1, also known as osteopontin, binds to cell surface receptors integrin $\alpha v \beta 3 / \alpha v \beta 5$ via its conserved RGD motif, and to CD44 (especially variant isoforms CD44v6/v9) via its C-terminal non-RGD binding domain. Engagement of integrins triggers the phosphorylation and activation of FAK, which further initiates two core oncogenic cascades: The PI3K/AKT and MAPK/ERK signaling pathways. Activated AKT and ERK converge on NF- κ B to promote its nuclear translocation and transcriptional activity. Meanwhile, SPP1-CD44 binding predominantly activates the JAK/STAT3 signaling axis, and also cross-activates the PI3K/AKT pathway. These signaling cascades coordinately drive the core malignant phenotypes of cancer cells, including uncontrolled proliferation, apoptotic resistance, EMT, enhanced migration and invasion, cancer stem cell maintenance, and therapy resistance. SPP1, secreted phosphoprotein 1; RGD, Arg-Gly-Asp; FAK, focal adhesion kinase; EMT, epithelial-mesenchymal transition.

In summary, the multi-domain structure of OPN combined with its complex PTMs enables interactions with multiple cell surface receptors, forming the structural basis for its functional pleiotropy.

3. Main receptors and downstream signaling pathways of SPP1

As a multifunctional secreted protein, the biological functions of SPP1 depend on its specific binding to various cell surface receptors. Signaling pathways mediated by different receptors play distinct roles at different stages of cancer, collectively constituting the complex regulatory network of SPP1. Currently identified SPP1 receptors mainly include the integrin receptor family, CD44 and its splice variants, as well as other receptors such as CD40 and TLR4. Notably, these receptor interactions are primarily mediated by secreted isoforms (OPN-a and OPN-b), whereas the intracellular/nuclear OPN-c isoform exerts distinct, receptor-independent functions in cell cycle regulation and transcriptional control (13,14,17).

Integrin receptors. Integrins are a class of heterodimeric transmembrane proteins composed of α and β subunits, which are recognized as the main cell adhesion transmembrane receptors. They play multiple roles in transducing biochemical and mechanical signals between cells and the environment

as ECM-cytoskeleton linkers in both health and disease (30). SPP1 binds to several integrins via its RGD motif, including: $\alpha v \beta 3$, $\alpha v \beta 5$, $\alpha v \beta 1$, $\alpha v \beta 6$ and $\alpha I I \beta 3$ (CD61) (31-33). In cancer, $\alpha v \beta 3$ and $\alpha v \beta 5$ are the most extensively studied integrin receptors. They are primarily responsible for regulating the adhesion, migration and invasion abilities of cancer cells (34). After binding to $\alpha v \beta 3$, SPP1 can activate the downstream FAK and PI3K/AKT signaling pathways, promote cytoskeletal rearrangement, and enhance the motility of cancer cells. In addition, $\alpha v \beta 3$ is also involved in SPP1-induced angiogenesis by upregulating the expression of pro-angiogenic factors such as VEGF to promote the formation of tumor neovascularization (35) (Fig. 1).

A landmark study first confirmed that $\alpha I I \beta 3$ (CD61) is the key receptor through which SPP1 regulates stromal cell fate in pancreatic cancer (PC) (36). The study found that SPP1 secreted by epithelial PC cells specifically binds to the CD61 receptor on the surface of mesenchymal PC cells (MPCs), activates the downstream BMP2-GREM1 signaling axis, forms an intercellular positive feedback loop, and maintains the mesenchymal phenotype of MPCs. Knockout of *CD61* completely mimics the phenotype of *SPP1* knockout, leading to the transformation of MPCs into epithelial-like cells and significantly inhibiting the metastatic ability of PC. This discovery reveals a novel mechanism by which SPP1 regulates PC cell plasticity.

CD44 receptor and other receptors. CD44 is a transmembrane glycoprotein with multiple isoforms generated by alternative splicing. CD44v6 and CD44v9 are particularly associated with cancer stem cells (CSCs). SPP1 binds CD44 via a region C-terminal to the RGD motif, overlapping with the SVVYGLR domain (37,38). This interaction activates JAK2/STAT3, PI3K/AKT and MAPK pathways, promoting stemness, chemoresistance and immune evasion (39). Unlike integrins, the binding of SPP1 to CD44 does not depend on the RGD sequence but is achieved through specific regions at its N-terminal and C-terminal ends. CD44 exists in multiple alternative splicing variants, among which CD44v6 plays a specific role in gastrointestinal cancers (40,41), whereas CD44v9 marks CSCs in cholangiocarcinoma and drives stemness, tumor progression, metastasis and chemoresistance by regulating Wnt/ β -catenin, EMT and cellular redox status (42) (Fig. 1).

Existing studies have confirmed that SPP1 secreted by CAFs binds to the CD44 receptor on the surface of PC cells, activates the downstream FAK/PI3K/AKT/ERK signaling pathway, upregulates the expression of stemness transcription factors such as NANOG, KLF4, BMI-1 and ABCG2, and significantly enhances the self-renewal ability and tumor sphere formation ability of pancreatic CSCs (5). CD44v6 is not only involved in SPP1-induced maintenance of tumor stemness but also closely related to invasion, metastasis and chemoresistance of PC (43). In addition, SPP1 binding to CD44 on CAFs activates β -catenin/HIF-1 α -related transcription, leading to increased production of CXCL12 by CAFs (44). This SPP1-CD44- β -catenin/HIF-1 α -CXCL12 axis establishes a feedback loop that promotes cancer progression, creates an immunosuppressive microenvironment, and contributes to both primary and acquired resistance to immunotherapy (44).

Beyond integrins and CD44, SPP1 interacts with several additional receptors and co-receptors that modulate its signaling and functional outcomes. Heparan sulfate proteoglycans serve as co-receptors that modulate SPP1-mediated signaling, while calcium-binding proteins interact with SPP1 through its calcium-binding properties to influence ECM interactions (45).

Notably, CD61 (integrin β 3) has recently been identified as a critical receptor for SPP1 in PC, where it maintains mesenchymal cell fate through the SPP1-CD61-BMP2-GREMI signaling axis (36). These alternative interactions expand the functional repertoire of SPP1 beyond its canonical integrin and CD44 pathways, highlighting its context-dependent roles in the TME.

Key downstream signaling pathways of SPP1. Recent studies have uncovered context-specific roles of these pathways. In the TME, SPP1⁺ macrophages secrete SPP1, which binds to CD44 on CD8⁺ T cells and activates PI3K/AKT signaling. This aberrant activation induces a unique effector-exhaustion intermediate state (T cell stress response), where T cells retain some effector molecules (for example, IFN- γ) but upregulate exhaustion markers (PD-1 and TIM-3), leading to impaired proliferation and cytotoxicity, thereby driving colon cancer liver metastasis (46). In prostate cancer, PTEN deletion constitutively activates PI3K/AKT/mTOR

signaling. Activated AKT phosphorylates and degrades the translation inhibitor PDCD4 (relieving eIF4A inhibition) and phosphorylates 4E-BP1 (releasing eIF4E). These parallel pathways increase eIF4F complex availability and cooperate with MNK/eIF4E to selectively enhance translation of mRNAs with complex 5'-untranslated region structures, promoting SPP1 secretion (47). Collectively, these studies reveal a bidirectional immunosuppressive feedback loop: Tumor cell-intrinsic PI3K/AKT activation drives SPP1 secretion via translational regulation; secreted SPP1 activates PI3K/AKT in immune cells (T cells, MDSCs) to induce immunosuppression; and the resulting immunosuppressive microenvironment sustains tumor cell survival and pathway activation. This loop, validated in colon and prostate cancers, may represent a universal immune evasion mechanism in solid tumors. Targeting this axis, for example, combining AKT inhibitors with SPP1-neutralizing antibodies, could overcome immunotherapy resistance. As depicted in Fig. 1, the PI3K/AKT/mTOR pathway is activated downstream of integrin and CD44 engagement and represents a central node in SPP1-mediated survival signaling.

Beyond PI3K/AKT, SPP1 activates MAPK/ERK signaling to promote c-Myc and Cyclin D1 expression, accelerating cell cycle progression, and upregulates MMP-2/MMP-9 to degrade ECM and enhance invasion (48). SPP1-integrin binding also induces FAK phosphorylation, which not only activates downstream PI3K/AKT and MAPK/ERK but also directly regulates cytoskeletal rearrangement and cell motility (49). Furthermore, the JAK1/JAK3-STAT1 pathway is an upstream regulator of SPP1 expression in macrophages: STAT1 activation drives SPP1 transcription, forming pathogenic SPP1⁺ macrophage subsets. JAK inhibitors (for example, tofacitinib) significantly suppress this pathway, downregulate SPP1, and reduce pathogenic macrophages, showing superior efficacy to TNF inhibitors, while SPP1 paracrine signaling amplifies JAK inflammatory signals in a positive feedback loop (50). Additionally, in tumor-associated macrophages (TAMs), SPP1 promotes angiogenesis through activation of the ERK/p38 signaling pathway, further highlighting the context-dependent utilization of p38 MAPK downstream of SPP1 (5). Moreover, In the TME, SPP1-stimulated macrophages (SPP1⁺ TAMs) promote angiogenesis via NF- κ B activation (5,51). This NF- κ B activation downstream of SPP1 is a critical node linking inflammation to tumor progression (Table I).

In short, SPP1 engagement with integrin or CD44 receptors triggers multiple intracellular signaling cascades critical for tumor progression. The PI3K/AKT/mTOR pathway, activated via FAK, supports cell survival, proliferation, metabolic reprogramming and stemness maintenance (36,52); MAPK/ERK signaling drives proliferation, differentiation and migration; NF- κ B activation promotes inflammation, survival and invasion through upregulation of BCL2, MMP9 and CXCL8 (35,53); and CD44-dependent JAK/STAT3 signaling enhances stemness, immune evasion and angiogenesis, while integrin clustering-induced FAK/Src activation facilitates adhesion and invasion (54-56) (Table I). SPP1 splice variants expressed by breast tumors regulate monocyte activation via MCP-1 and TGF- β 1, promoting an immunosuppressive myeloid phenotype (57,58). This SPP1-MCP-1/TGF- β 1 axis contributes

Table I. Receptors and downstream signaling pathways of SPP1 in various cancers.

First author/s, year	Cancer type	Receptors	Pathways	Function mechanism	(Refs.)
Deng <i>et al</i> , 2025	PDAC	/	PI3K/AKT pathway	Promotes cell mobility and invasion metastasis	(59)
Nallasamy <i>et al</i> , 2021	PDAC	CD44	/	Promotes stemness carcinogenesis	(37)
Li <i>et al</i> , 2025	PDAC	CD61	BMP2-GREM1 pathway	Promotes metastasis	(36)
Huang <i>et al</i> , 2017	CRC	/	p38 MAPK pathway	Promotes cell migration and invasion, and inhibits apoptosis and autophagy	(60)
Cheng <i>et al</i> , 2019	CRC	/	PI3K-AKT-GSK/3 β - β -Catenin pathway	Promotes cell invasion and stem cell-like properties	(61)
Wei <i>et al</i> , 2018	CRC	/	PI3K/AKT pathway	Promotes cell migration and invasion	(62)
	CRC	CD44	β -catenin/HIF-1 α pathway	Promotes metastasis and immunotherapy resistance	(44)
Dong <i>et al</i> , 2016	HCC	/	Vimentin (residues between 246 and 406)	Promotes EMT through stabilizing vimentin protein	(63)
Tong <i>et al</i> , 2024	HCC	CD44	PI3K/AKT pathway	Promotes the differentiation of HSCs into CAFs	(64)
Zhang <i>et al</i> , 2024	HCC	Integrin	PI3K/AKT/mTOR signaling pathway	Attracts MDSCs and Tregs to facilitate immune evasion	(65)
Deng <i>et al</i> , 2021	GC	/	NF- κ B pathway	Promoted TIC-like phenotypes and chemoresistance	(51)
Song <i>et al</i> , 2024	GC	/	PI3K/AKT pathway	Promotes chemoresistance	(66)
Liu <i>et al</i> , 2020	LC	/	PI3K/AKT pathway	Promotes cell viability and reduces cell apoptosis	(67)
Kang <i>et al</i> , 2015	LC	/	FAK/PI3K/AKT pathway	Promotes the lamellipodia formation to allow cell invasion	(68)
Fu <i>et al</i> , 2020	LC	Integrin α V β 3	Integrin α V β 3/FAK pathway	Promotes FAK phosphorylation to enhance cell proliferation	(56)
Jia <i>et al</i> , 2016	LC	/	HIF2 α (target) and AKT1/miR-429/ZEB pathway	Promotes metastasis	(69)
Guo <i>et al</i> , 2024	BC	/	PI3K/AKT/mTOR pathway	Promotes metastasis and invasion, angiogenesis	(70)
Zhang <i>et al</i> , 2014	BC	Integrin α V β 3	PI3K/AKT/mTOR pathway	Promotes metastasis	(71)
Pang <i>et al</i> , 2011	BC	/	p38 MAPK pathway	Inhibits cell apoptosis	(72)
Mi <i>et al</i> , 2013	BC	Integrin α V β 3	Integrin/AP-1	Promotes metastasis	(73)
Blasberg <i>et al</i> , 2010; Sun <i>et al</i> , 2013; Sun <i>et al</i> , 2013	BC	CD44	MCP-1 and TGF- β 1	Promotes immune escape	(57,58)
Song <i>et al</i> , 2008	OC	/	PI3K/AKT pathway	Promotes progression and survival	(74)

SPP1, secreted phosphoprotein 1; PDAC, pancreatic ductal adenocarcinoma; CRC, colorectal cancer; HCC, hepatocellular carcinoma; GC, gastric cancer; BC, breast cancer; LC, lung cancer; OC, ovarian cancer.

to the establishment of an immunosuppressive TME by skewing monocyte differentiation toward a pro-tumorigenic state. As schematically illustrated in Fig. 1, SPP1 functions as a signaling hub that integrates receptor-specific inputs into coordinated oncogenic outputs.

Collectively, these findings position SPP1 as a central signaling coordinator rather than a mere ligand: By engaging

distinct receptor complexes, integrins (α V β 3, α V β 5 and α IIb β 3) and CD44 variants (CD44v6 and CD44v9), SPP1 converges on and amplifies core oncogenic cascades (PI3K/AKT, MAPK/ERK, JAK/STAT3 and NF- κ B) in a context-dependent manner, thereby coordinating proliferation, survival, EMT, stemness and immune evasion as an integrated program (Fig. 1, Table I).

4. Regulatory roles of SPP1 in tumors

SPP1 in tumor cell proliferation and survival. SPP1 promotes cancer cell proliferation through multiple mechanisms. Activation of PI3K/AKT signaling enhances cell cycle progression by upregulating Cyclin D1 and downregulating p27 (36). SPP1-integrin engagement activates the Ras-Raf-MEK-ERK cascade, which translocates to the nucleus and phosphorylates transcription factors including ELK1, c-FOS and c-JUN. The MAPK/ERK pathway increases MYC expression, driving metabolic reprogramming and ribosome biogenesis (75). SPP1 also inhibits apoptosis by upregulating BCL2 and BCL-XL via NF- κ B and AKT signaling (35). SPP1 also upregulates IAP family members that directly bind and inhibit caspases-3, caspases-7 and caspases-9, further suppressing both intrinsic and extrinsic apoptotic pathways (8). SPP1-induced NF- κ B increases c-FLIP expression, which inhibits death receptor-mediated apoptosis by competing with caspase-8 assembly (6) (Table I).

In OC, SPP1-induced STAT3 activation is required for survival under hypoxic and nutrient-deprived conditions (54). Furthermore, SPP1 promotes autophagy under stress conditions, providing metabolic intermediates that support survival. Conversely, excessive SPP1 signaling may suppress autophagic cell death by activating AKT (76).

Together, these mechanisms establish SPP1 as a central coordinator of tumor cell proliferation and survival: It integrates growth factor signaling, stress adaptation (for example, hypoxia and nutrient deprivation), and autocrine/paracrine cues to sustain cell cycle progression, apoptotic resistance and metabolic fitness across diverse cancer types.

SPP1 in EMT and metastasis. SPP1 serves as a potent, multifaceted inducer of EMT, a cellular reprogramming process essential for metastatic dissemination, therapy resistance and stemness acquisition. SPP1 regulates EMT at transcriptional, post-transcriptional and post-translational levels via autocrine and paracrine mechanisms.

SPP1-induced AKT activation stabilizes Snail by phosphorylating GSK-3 β , preventing Snail degradation. Snail directly represses CDH1 (E-cadherin) transcription by binding to E-box elements in its promoter. In CRC, Slug directly binds to the SPP1 promoter, creating a positive feedback loop that amplifies EMT (77). SPP1 signaling upregulates EMT transcription factors including Snail, Slug, Twist and ZEB1/2, leading to downregulation of E-cadherin and upregulation of N-cadherin, vimentin and fibronectin (64,78). Additionally, SPP1 activates matrix metalloproteinases (MMP2 and MMP9) that degrade ECM components, facilitating invasion (79). SPP1 directly binds to and stabilizes vimentin, preventing its ubiquitination and degradation, thereby promoting EMT independent of transcriptional changes (80). SPP1-induced COL11A1 expression drives EMT and metastasis via integrin-mediated FAK signaling. SPP1⁺ TAMs and FAP⁺ CAFs synergistically promote EMT and liver metastasis via β -catenin/HIF-1 α activation (81). Several novel molecular mechanisms underlying SPP1 function in PC have been recently elucidated. Epithelial PDAC cells secrete SPP1, which activates CD61 on mesenchymal cells, thereby inducing BMP2 and GREM1 expression and establishing a bidirectional regulatory loop that maintains cellular heterogeneity (36). Additionally, LINC01133 has been identified as

a long non-coding RNA that binds to Arp3 and reduces SPP1 mRNA degradation, consequently increasing SPP1 expression and promoting EMT in PDAC (82). Furthermore, VSIG4⁺ TAMs epigenetically regulate SPP1 transcription; VSIG4 deficiency reduces lactate production and histone H3K18 lactylation, leading to decreased STAT3-mediated SPP1 transcription and disruption of TAM-neutrophil immunosuppressive interactions (83).

In PC, SPP1 maintains mesenchymal cell fate through the SPP1-CD61-BMP2-GREM1 axis. Epithelial PDAC cells secrete SPP1, which binds to CD61 on mesenchymal PDAC cells, activating NF- κ B and inducing BMP2 expression. BMP2 maintains mesenchymal identity, while GREM1 (BMP antagonist) feeds back to epithelial cells to sustain SPP1 secretion (36).

In summary, SPP1 functions as a master coordinator of EMT and metastatic progression rather than a single-pathway inducer: It orchestrates EMT at transcriptional (Snail/Slug/Twist/ZEB), post-transcriptional and post-translational levels, couples EMT to ECM remodeling and stemness acquisition, and maintains mesenchymal cell fate through reciprocal paracrine axes (for example, SPP1-CD61-BMP2-GREM1 in PDAC), thereby integrating invasion, therapy resistance and metastatic competence into a coordinated phenotypic program.

Epidemiological evidence of SPP1 dysregulation in tumorigenesis. Epidemiological studies of multiple human cancers consistently show that SPP1 expression is dysregulated in tumor tissues. This repeated overexpression emphasizes the potential of SPP1 as a pan-cancer molecule and a promising diagnostic biomarker. Compared with normal tissues, SPP1 is significantly overexpressed in multiple solid tumors, including HCC, GC, PDAC, CRC, esophageal squamous cell carcinoma (ESCC), OC and BC (84-89). Correspondingly, elevated SPP1 protein levels have also been detected in the serum of patients with these malignancies. Clinically, high SPP1 expression is a well-recognized predictor of poor prognosis in cancers such as PC, CRC, clear cell renal cell carcinoma and LC (90-93). In addition, SPP1 overexpression is closely associated with metastatic progression in BC and melanoma (94-96). Overall, these epidemiological and clinical evidence confirm that SPP1 is a molecule that is consistently upregulated in cancer. Its strong correlation with aggressive disease and poor patient outcomes makes it a clinically relevant target for diagnosis, prognostic stratification and therapeutic development.

Roles of SPP1 in different tumors. SPP1 is widely overexpressed across multiple human malignancies and exhibits distinct regulatory mechanisms in different tumor types. This chapter systematically reviews the research progress of SPP1 in PC, GC, CRC, BC, LC and HCC, with particular emphasis on its roles in tumor initiation and progression, metastasis, TME remodeling, immune regulation and therapeutic targeting.

PC/PDAC. PDAC is one of the most lethal malignancies worldwide, with a five-year survival rate below 10%. SPP1 plays a crucial role in maintaining the mesenchymal cell fate in PC. It has been identified as a key downstream effector of PTHrP, activating the EMT program (99). Functionally, SPP1 activates the PI3K/Akt/mTOR signaling pathway to promote the motility and invasive ability of PC cells (59). Additionally, SPP1 induces aberrant angiogenesis, which further hinders T cell infiltration and promotes tumor progression (100).

Long-term co-culture of PC cells with CAF-conditioned medium enriches CSCs, as evidenced by increased proportions of CD44⁺, ALDH⁺ and AF⁺ cells, along with enhanced tumor sphere formation and self-renewal potential. Knockdown of SPP1 in CAFs or CD44 in cancer cells completely reverses CAF-induced stemness and drug resistance, confirming that the SPP1-CD44 axis is a key signaling pathway connecting the stroma to tumor stemness (37).

SPP1 also regulates PDAC progression by remodeling the TME through paracrine signaling. A key mechanism for maintaining epithelial-mesenchymal cell heterogeneity in PDAC involves GREM1, which is secreted by mesenchymal cells. By inhibiting BMP signaling in epithelial cells, GREM1 sustains the continued high expression of SPP1 in epithelial cells, ultimately forming a transcellular positive feedback regulatory loop: Epithelial SPP1 → mesenchymal GREM1 → epithelial SPP1. This loop directly determines the metastatic and invasive potential of tumor cells (36) (Table II).

CRC. SPP1 is a key driver of CRC progression and metastasis, with roles spanning malignant transformation, microenvironment remodeling and immune evasion. In primary tumors, SPP1 directly enhances the invasive ability of CRC cells through the PI3K-AKT-GSK3- β - β -catenin signaling pathway and induces stem cell-like properties, thereby promoting tumor initiation and recurrence (61). More importantly, SPP1 plays a central role in constructing the immunosuppressive microenvironment of CRC. TGF- β signaling induces the generation of immunosuppressive SPP1⁺ macrophage subsets, which form a unique spatial network with CAFs within primary tumors and liver metastases, jointly establishing a dual immune barrier (101). On one hand, these macrophages secrete chemokines that hinder the recruitment and infiltration of effector T cells (102); on the other hand, SPP1⁺ macrophages stimulate CAFs to produce large amounts of CXCL12, further exacerbating immunosuppression and driving resistance to immunotherapy (44).

The role of SPP1 is particularly prominent during CRC liver metastasis. Tumor cell-derived extracellular vesicles enriched with circ-0034880 induce the formation of pre-metastatic niches dominated by SPP1 high CD206⁺ pro-tumor macrophages in distant organs, creating favorable conditions for circulating tumor cell colonization. Following the establishment of liver metastases, the spatial interaction between SPP1⁺ macrophages and fibroblasts further strengthen local immunosuppression, leading to poor response to immune checkpoint blockade (ICB) therapy (103). Therefore, targeting SPP1 and its mediated intercellular communication network represents a promising strategy to improve the therapeutic efficacy of CRC, particularly in metastatic disease.

OC. SPP1 is a core regulatory molecule in the malignant progression of OC. Its roles span tumor cell metabolic reprogramming, microenvironment remodeling, immune exhaustion and metastasis. SPP1 has been confirmed as a reliable prognostic biomarker, closely associated with the composition and functional state of tumor-infiltrating immune cells (104).

Within the TME, the intercellular communication network mediated by SPP1 is particularly critical. In ascites-associated macrophages, PLIN2 significantly promotes lipid accumulation via the HIF1 α /SPP1 signaling pathway, thereby enhancing

the pro-tumor phenotype of macrophages (105). Meanwhile, ubiquitous environmental bisphenol exposure can also accelerate OC progression and remodel the immunosuppressive microenvironment by activating the β -catenin/SPP1 axis (106). More importantly, SPP1⁺ macrophages serve as core executors of immunosuppression in OC. They interact with tumor cells and other stromal cells through the SPP1-CD44 axis to construct a robust immune barrier (38). Targeting this axis has been shown to effectively reverse immunosuppression and inhibit tumor growth.

Notably, SPP1-mediated immune abnormalities are not limited to macrophages. A recent study identified unique SPP1⁺ T cell and NKT cell subsets in OC (107), and their presence is significantly associated with more severe immune exhaustion and more aggressive clinical progression. Furthermore, hypoxia-driven remodeling of SELENOP⁺ macrophages is also closely linked to SPP1 signaling, which collectively affects T cell infiltration and function, ultimately promoting distant metastasis of OC (108). Therefore, targeting SPP1 and its upstream and downstream signaling pathways holds promise as an important breakthrough for breaking immune tolerance and improving therapeutic outcomes in OC.

HCC and GC. SPP1 is a key inducer of invasion and metastasis in both HCC and GC. In HCC, the CSC marker SOX9 regulates the Wnt/ β -catenin signaling pathway to influence SPP1 expression (109), while SPP1 interacts with and stabilizes vimentin to promote EMT (63). Under hypoxic conditions, specific enrichment of SPP1⁺ macrophages in the liver cancer microenvironment is induced via activation of the HIF-1 α pathway. These macrophages form spatial co-localization with CSCs in hypoxic regions and directly enhance the stemness, self-renewal and tumorigenic capacity of CSCs through the SPP1-CD44 axis, representing a key mechanism underlying the poor prognosis of HCC (110).

In GC, SPP1 mainly drives malignant progression, especially tumor metastasis, by mediating intricate crosstalk between TAMs, stromal cells and immune cells. Multi-omics analyses have confirmed a specific interaction between GREM1⁺ fibroblasts and SPP1⁺ macrophages in GC, with both cell types jointly constructing a pro-TME (111). This CAF-macrophage crosstalk is especially critical in GC peritoneal metastasis; it not only remodels the local stromal architecture but also directly determines patient response to ICB therapy (112). Patients with high expression of this interaction signature often show significant ICB resistance.

In metastatic GC, SPP1⁺ TAMs can also engage in direct harmful crosstalk with CD8⁺ exhausted T cells, further amplifying immunosuppression (113). These macrophages secrete factors such as SPP1 to induce CD8⁺ T cells to express exhaustion markers including PD-1 and TIM-3, thereby weakening their antitumor cytotoxic function and ultimately promoting tumor invasion and metastasis. Therefore, blocking the intercellular communication network mediated by SPP1 holds promise as an important strategy to enhance the efficacy of GC immunotherapy and inhibit peritoneal metastasis (Fig. 2, Table II).

LC. In non-small cell LC (NSCLC), SPP1 drives malignant progression by promoting cell invasion, metastasis and therapeutic resistance. Mechanistically, SPP1 induces NSCLC cell invasion via activating the Rho-associated kinase pathway and

Table II. Clinical significance of SPP1 expression in cancers.

First author/s, year	Cancer type	Expression pattern	Major functions	Biomarkers	(Refs.)
Li <i>et al.</i> , 2025	PDAC	Significantly elevated	Maintains mesenchymal cell fate via SPP1-CD61-BMP2-GREM1 axis; promotes metastasis	Diagnostic, prognostic	(36)
Song <i>et al.</i> , 2024	GC	Upregulated	Promotes chemoresistance via POU5F1/SPP1 axis; induces T cell inactivation	Prognostic	(66)
Qi <i>et al.</i> , 2022	CRC	Highly upregulated	Drives liver metastasis; promotes CAF-mediated CXCL12 production; induces T cell stress	Predictive	(81)
Feng <i>et al.</i> , 2025; Liu <i>et al.</i> , 2024	BC	Overexpressed	Promotes stemness and chemoresistance via macrophage-tumor SPP1-CD44 crosstalk; drives lung metastasis	Prognostic	(35,97)
Fu <i>et al.</i> , 2020; Chen <i>et al.</i> , 2023	LC	Elevated	Drives CD8 ⁺ T exhaustion via SPP1 ⁺ malignant-CXCR4 ⁺ TAM crosstalk; promotes migration via COL11A1	Predictive	(56,75)
Xu <i>et al.</i> , 2025	HCC	Elevated	SPP1 ⁺ TAMs impair antitumor immunity; SPP1 ⁺ BCL2A1 ⁺ TAMs promote immune suppression	Prognostic	(98)

SPP1, secreted phosphoprotein 1; PDAC, pancreatic ductal adenocarcinoma; GC, gastric cancer; CRC, colorectal cancer; HCC, hepatocellular carcinoma; BC, breast cancer; LC, lung cancer.

inactivating cofilin (68), and facilitates metastatic dissemination by regulating epithelial-mesenchymal plasticity (69). In terms of drug resistance, SPP1 enhances cisplatin resistance in A549 lung adenocarcinoma cells through PI3K pathway activation and subsequent ERCC1 upregulation (67). In EGFR-mutant NSCLC, aberrant activation of the SPP1/integrin α V β 3/FAK signaling axis mediates resistance to EGFR tyrosine kinase inhibitors (TKIs), which is tightly linked to SPP1-induced EMT (56,75).

5. Regulation of TME by SPP1

TAMs. SPP1 is a key regulator of TAM recruitment, polarization and function, contributing to the formation of an immunosuppressive and pro-TME. It promotes the recruitment and polarization of macrophages toward a pro-tumor M2-like phenotype through signaling pathways such as CD44/PI3K/AKT and CD44/JAK2/STAT3. This leads to increased secretion of factors that support tumor proliferation, angiogenesis, and ECM remodeling, including VEGFA and IL-6 (54,55,114,115). Hypoxia further upregulates SPP1 in macrophages and enhances their pro-tumor functions (116). In CRC, SPP1⁺ TAMs are enriched at the invasive front via the HIF-1 α /STAT3 pathway, and their density correlates with lymph node metastasis (117). Similarly, single-cell RNA sequencing (scRNA-seq) of PDAC organoids showed that SPP1⁺ macrophages are associated with tumor angiogenesis and proliferation (118) (Fig. 2).

SPP1⁺ TAMs engage in critical crosstalk with other stromal cells. They interact with CAFs and neutrophils to promote ECM remodeling, angiogenesis and immune exclusion (83,119,120). In PDAC, spatially co-localized SPP1⁺ APOE⁺ TAMs and CTHRC1⁺ GREM1⁺ myofibroblastic CAFs (myCAF) synergistically form an immunosuppressive micro-environment through active ECM deposition and induction of EMT (121). Analysis of 14 independent CRC cohorts found a positive correlation between FAP⁺ fibroblasts and SPP1⁺ TAMs, which is regulated by chemerin, TGF- β and interleukin-1. This interaction stimulates the formation of immune-excluded, desmoplastic structures that limit T cell infiltration and reduce the efficacy of anti-PD-L1 therapy (81). In HCC, DAB2⁺ and SPP1⁺ TAMs enhance the function of FAP⁺ CAFs through signals such as TGF- β , PDGF and ADM, participating in ECM organization and angiogenesis (122) (Fig. 2). Importantly, the CXCL9:SPP1 macrophage polarity index, defined by the expression ratio of CXCL9 and SPP1 (rather than conventional M1/M2 markers), has a strong prognostic association with survival across multiple cancers and predicts anti-PD-1 response (123). TAM-derived secreted SPP1 (predominantly OPN-a) mediates these paracrine effects, highlighting the isoform- and source-specificity of SPP1 function in the TME.

T cells and immune evasion. SPP1 directly impairs anti-tumor T cell function. Macrophage-derived SPP1 interacts with CD44 on T cells, inducing exhaustion markers (PD-1, TIM-3 and LAG-3) and suppressing cytotoxic activity via the

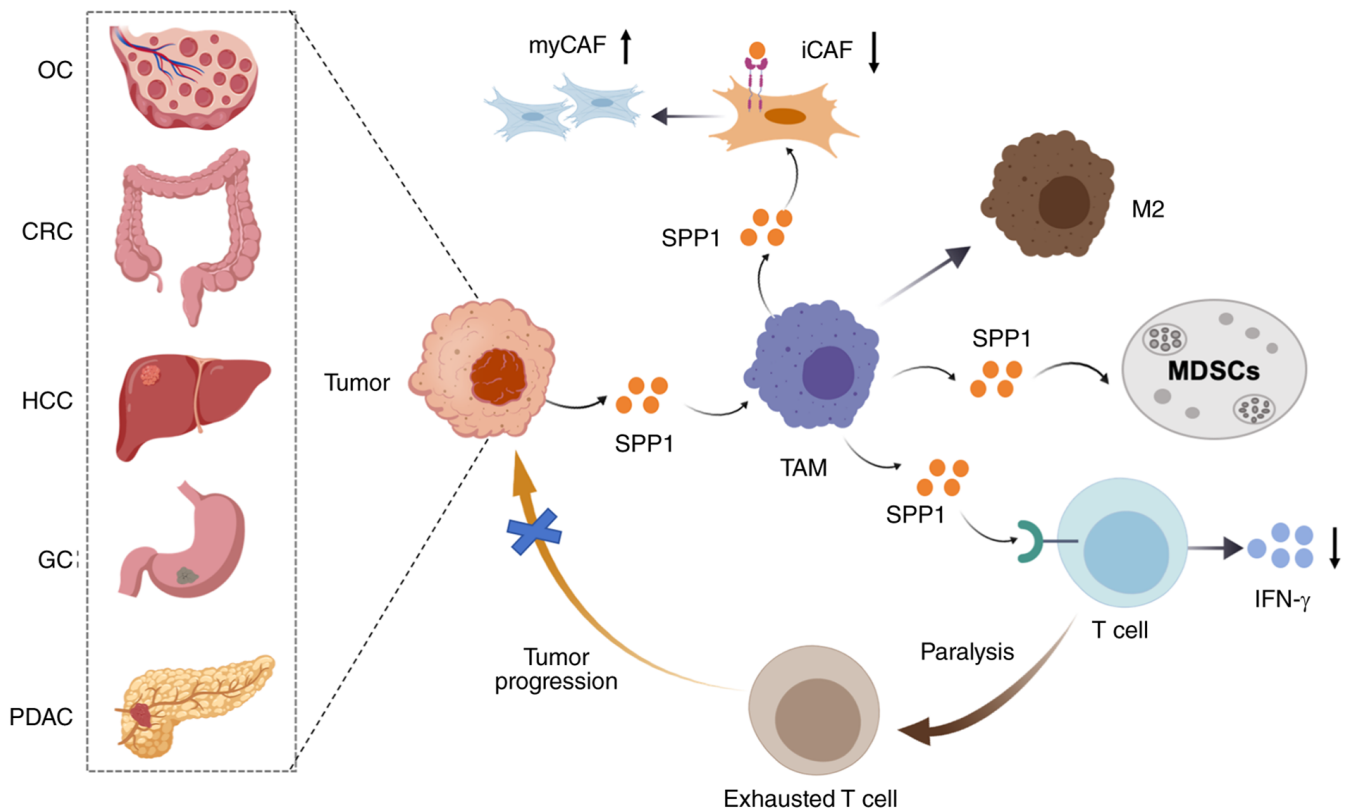


Figure 2. SPP1-mediated crosstalk in the TME. This schematic depicts that SPP1 secreted by TAMs acts as the key effector to mediate paracrine and autocrine intercellular crosstalk via binding to integrins and CD44 splice variants. SPP1 drives CD8⁺ T cell exhaustion and MDSC activation to suppress antitumor immunity; it activates CAFs to promote extracellular matrix remodeling and T cell exclusion; it sustains tumor cell stemness, invasion and metastasis via autocrine signaling; and it amplifies pro-tumor effects by promoting M2-like macrophage polarization. Ultimately, the SPP1-centered regulatory network drives immunosuppressive TME formation, tumor invasion and metastasis, cancer stem cell maintenance, and therapy resistance. SPP1, secreted phospho-protein 1; TME, tumor microenvironment; MDSCs, myeloid-derived suppressor cells; CAFs, cancer-associated fibroblasts; myCAF, myofibroblastic CAF; iCAF, inflammatory CAF; TAMs, tumor-associated macrophages; PDAC, pancreatic ductal adenocarcinoma; CRC, colorectal cancer; HCC, hepatocellular carcinoma; GC, gastric cancer; OC, ovarian cancer.

SPP1-CD44 and CD155-CD226 pathways, thereby limiting tumor elimination (115,124,125). High SPP1 expression in the TME is associated with reduced T cell infiltration and proliferation, while inhibition of SPP1 can restore T cell activation and enhance immunotherapy efficacy (126). In metastatic GC, crosstalk between SPP1⁺ TAMs and exhausted CD8⁺ T cells is the key immunosuppressive mechanism (113). Furthermore, spatial transcriptomics in primary PDAC tissues identified SPP1 as a promoter of the immunosuppressive microenvironment at the tumor front, characterized by accumulation of FOXP3⁺ regulatory T cells (Tregs) (127). SPP1 can also be directly expressed by T cells. SPP1⁺ exhausted T (Tex) cells are associated with NKT cell activity and poor prognosis in OC and may be induced by immune checkpoint inhibition (107). Additionally, CAF-derived SPP1 activates CD44 on tumor cells to enhance stemness features in PC cells, as evidenced by increased CD44⁺, ALDH⁺ and AF⁺ populations and elevated self-renewal and drug-resistance markers (37). Thus, SPP1⁺ TAM-CAF interactions create a desmoplastic barrier that physically excludes T cells from tumor nests. In CRC, SPP1⁺ TAMs and FAP⁺ fibroblasts form immune-excluded structures that limit T cell infiltration and reduce the benefit of anti-PD-L1 therapy (15,81,98). Spatial transcriptomics in PDAC reveals that SPP1 promotes accumulation of FOXP3⁺ Tregs at tumor fronts (64). As depicted in Fig. 2, this SPP1-mediated T cell

exhaustion represents a key node in the immunosuppressive network, where SPP1⁺ TAMs directly impair cytotoxic T cell function through SPP1-CD44 interactions.

Myeloid-derived suppressor cells (MDSCs). SPP1 promotes the formation of an immunosuppressive microenvironment by recruiting and activating MDSCs. It is a key factor for recruiting MDSCs into the TME in prostate cancer (47). In BC models, SPP1 knockdown reduces MDSC infiltration and restores the cytotoxicity of CD8⁺ T cells (15). In monocytic MDSCs, SPP1 expression enhances the activities of arginase 1 and inducible nitric oxide synthase. This consumes local L-arginine and produces nitric oxide, which together inhibit T cell proliferation and function (128). This MDSC recruitment, illustrated in Fig. 2, further amplifies the SPP1-centered immunosuppressive circuit.

CAFs. SPP1 reprograms quiescent fibroblasts into activated, pro-tumor CAFs. SPP1 binds to integrin $\alpha\beta 5$ on fibroblasts, triggering the FAK-Src-Ras-MAPK cascade, which phosphorylates the transcription factor AP-1 and upregulates CAF marker genes including FAP, α -SMA and PDGFR β (129,130). Activated CAFs then secrete dense ECM, increase TME stiffness, and activate YAP signaling in tumor cells, promoting proliferation and invasion (131). Conversely,

a positive feedback loop exists: SPP1-activated CAFs secrete TGF- β and IL-1, which in turn enhance the pro-inflammatory activity of SPP1⁺ macrophages. Conversely, in the context of PTEN deletion, activation of YAP1 in macrophages can directly induce SPP1 secretion through the β 1 integrin-PYK2 pathway, thereby stimulating angiogenesis in glioma (132). Importantly, CAFs themselves can serve as a source of SPP1. In prostate cancer, SPP1⁺ myCAFs promote androgen deprivation therapy resistance through the SPP1-ERK paracrine mechanism (133). In NSCLC, co-culture with SPP1⁺ CAFs increases the metastatic potential of tumor cells (134) (Table II). As shown in Fig. 2, SPP1-induced CAF activation creates a feedforward loop that reinforces ECM deposition and immune exclusion, thereby establishing a physical barrier against T cell infiltration.

ECM. SPP1 fundamentally remodels the ECM to promote an invasive and immunosuppressive TME. SPP1⁺ macrophages and CAFs synergistically remodel the ECM by upregulating metalloproteinases (for example, MMP9, MMP12 and MMP7) that degrade structural components, and lysyl oxidase that cross-links collagen, increasing stiffness (81,116,126). This remodeling is closely related to hypoxic conditions and the maintenance of CSCs. Additionally, SPP1 enhances ECM stiffness, forming a dense desmoplastic barrier that physically excludes cytotoxic lymphocytes and contributes to immunotherapy resistance. In PDAC, SPP1⁺ CAFs are associated with a rigid matrix, and targeting SPP1 reduces this stiffness (135). In HCC, the interaction between SPP1⁺ macrophages and CAFs stimulates the formation of the tumor immune barrier, limiting immune cell infiltration into the tumor core (126). This ECM remodeling, summarized in Fig. 2, physically excludes T cells and creates a niche conducive to tumor invasion and therapy resistance.

Collectively, these findings establish SPP1 as a central orchestrator of the immunosuppressive TME: Secreted predominantly by SPP1⁺ TAMs and CAFs, SPP1 coordinates a multi-component regulatory network, driving M2-like macrophage polarization, CD8⁺ T cell exhaustion, MDSC recruitment, CAF activation and ECM remodeling, through reciprocal paracrine crosstalk that converges to form an immune-excluded, therapy-resistant (Fig. 2, Table III). Its multifaceted interactions with T cells, MDSCs, CAFs and the ECM make it a promising therapeutic target for reprogramming the TME to enhance immune infiltration and improve cancer treatment outcomes.

6. Targeting SPP1 for tumor therapy

SPP1 as a diagnostic and prognostic biomarker. Single-cell transcriptome analyses have revealed that the expression of CXCL9 and SPP1 in TAMs is almost completely mutually exclusive at the single-cell level, forming two macrophage subsets with opposing functions: CXCL9⁺SPP1⁻ antitumor TAMs and CXCL9⁻SPP1⁺ pro-tumor TAMs. Traditional M1 (CD80 and ITGAX) and M2 (CD163 and MRC1) markers cannot distinguish these two subsets and are not significantly associated with patient prognosis, whereas a higher proportion of SPP1-high TAMs correlates with shorter overall survival (OS) (123).

SPP1⁺ TAMs are predominantly distributed in hypoxic regions of tumors and exhibit strong co-localization with GLUT1⁺ cells (a hypoxia marker). *In vitro* experiments have confirmed that hypoxia directly induces high SPP1 expression in macrophages via the HIF-1 α pathway, which is the key regulator of their spatial distribution and functional polarization. Functionally, SPP1⁺ TAMs are highly coordinated with the pro-tumor programs of the entire TME: Their presence is significantly associated with the activation of EMT, angiogenesis, glycolysis and mTOR signaling pathways. As a secreted protein, SPP1 promotes tissue remodeling, angiogenesis and tumor metastasis by acting on integrin and CD44 receptors on the surface of fibroblasts and endothelial cells. Concurrently, SPP1⁺ TAMs inhibit the infiltration of T cells, B cells and dendritic cells, thereby establishing an immunosuppressive microenvironment. SPP1 inhibition combined with ICB synergistically reverses immunosuppression and overcomes immunotherapy resistance (36,38,81). SPP1 inhibition also sensitizes tumors to chemotherapy, targeted therapy and stromal-targeting agents (81). These findings have been validated in more than 10 human cancer types, including head and neck cancer, LC, CRC and liver cancer, indicating that TAM polarity defined by SPP1 is a ubiquitous feature of the TME with significant clinical prognostic value and therapeutic guiding implications (136).

In sum, elevated SPP1 expression in tumor tissues and patient serum correlates with poor prognosis across multiple cancers. Meta-analyses have confirmed that high SPP1 expression is associated with reduced OS and disease-free survival (90).

Therapeutic strategies targeting SPP1. SPP1 is a key driver of tumor progression and immune suppression, making it an attractive therapeutic target. Small molecule inhibitors offer a promising approach for targeting SPP1 in tumor therapy, acting either on SPP1 itself or its receptors (Table IV).

Small molecule inhibitors targeting SPP1 or its receptors

Direct inhibition of SPP1 expression. Emerging studies have identified compounds that directly target SPP1. The lead compound CANDI460, discovered through phenotypic screening, directly inhibits SPP1 in TAMs, thereby reducing tumor burden in preclinical models (144). Additionally, molecular dynamics simulations have identified nilotinib, a TKI, as a high-affinity binder of SPP1, forming multiple hydrogen bonds and pi-pi interactions. This binding significantly reduces SPP1 protein levels in OC models (38). To avoid disrupting physiological OPN-a, targeting cancer-associated OPN-c is preferred (13). Approaches include monoclonal antibodies against unique exon junctions (for example, OPN-c Δ ex4 and OPN-b Δ ex5) and small molecules selective for isoform-specific conformations (14).

Indirect suppression of SPP1 expression. Small molecules can also downregulate SPP1 indirectly by targeting upstream regulatory pathways. For example, the bromodomain and extra-terminal inhibitor NHWD-870 downregulates SPP1 by inhibiting BRD4 and inactivating NF- κ B2 transcription, thereby reducing melanoma growth and metastasis (138). In CRC, the HIF-1 α /STAT3 pathway is critical for activating TAM-derived SPP1 (117); pharmacological inhibition of

Table III. Crosstalk between SPP1 and tumor microenvironment components.

First author/s, year	Cancer type	Cells expressing SPP1	Receptors	Interacting cells	Pathway	Function	(Refs.)
Xu <i>et al.</i> , 2024	Multiple cancers	SPP1 ⁺ TAMs	CD44	Tumor cells	CD44/PI3K/AKT pathway	Promotes TAMs recruitment and polarization	(114)
Qu <i>et al.</i> , 2025	CRC	SPP1 ⁺ TAMs	Integrin $\alpha\beta3$	Tumor cells	Integrin $\alpha\beta3$	Promotes metastasis by activating EMT	(117)
Li <i>et al.</i> , 2024	PC	SPP1 ⁺ TAMs	/	CTHRC1 ⁺ myofibroblastic CAFs	ECM signaling and EMT	Promotes an immunosuppressive TME through active ECM deposition and EMT	(121)
Qi <i>et al.</i> , 2022	CRC	SPP1 ⁺ TAMs	COL1A1/ LAMA1-ITGB1	FAP ⁺ CAFs	/	Promotes immune-excluded desmoplastic structure and limits the T cell infiltration	(81)
Long <i>et al.</i> , 2024	HCC	SPP1 ⁺ TAMs	/	FAP ⁺ CAFs	TGF- β , PDGF and ADM	Promotes ECM organization and angiogenesis	(122)
Cheng <i>et al.</i> , 2023	ICC	Tumor cells	CD44	T cells	CD44	Inhibits T cells proliferation	(125)
Fan <i>et al.</i> , 2024	HCC	SPP1 ⁺ TAMs	CD44 and integrin	Cancer stem cells	CCL3, CCL16, and CCL15	Limits cell infiltration into the tumor core	(110)
Liu <i>et al.</i> , 2023	HCC	SPP1 ⁺ TAMs	/	CAFs	Cytokine receptor interactions, ECM pathways, TNF pathway, and IL-17 pathway	Promotes TIB structure formation and immunosuppressive TME	(126)
Du <i>et al.</i> , 2024	GC	SPP1 ⁺ TAMs	/	CD8 ⁺ exhausted T cells	GDF pathway	Promotes immunosuppressive TME	(113)
Liu <i>et al.</i> , 2025	PC	Tumor cells	CD44	FOXP3-related Treg cells	/	Promotes EMT and liver metastasis	(127)
Wang <i>et al.</i> , 2023	OC	SPP1 ⁺ exhausted T cells	/	NKT cells	Cytokine receptor interactions, ECM receptor interactions, and local adhesion pathways	Promotes immunosuppressive TME	(107)
Wang <i>et al.</i> , 2023	PC	SPP1 ⁺ CAFs	Integrin	Tumor cells	SPP1-ERK paracrine pathway	Promotes castration resistance	(133)
Xu <i>et al.</i> , 2025	LC	SPP1 ⁺ CAFs	CD44 and PTGER4	Tumor cells	SPP1-CD44 and SPP1-PTGER4	Promotes metastasis	(134)

SPP1, secreted phosphoprotein 1; CRC, colorectal cancer; PC, pancreatic cancer; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; GC, gastric cancer; LC, lung cancer; OC, ovarian cancer; ECM, extracellular matrix; TAMs, tumor-associated macrophages; EMT, epithelial-mesenchymal transition; CAFs, cancer-associated fibroblasts; TME, tumor microenvironment.

Table IV. SPP1-targeted therapeutic strategies.

First author/s, year	Strategy	Therapeutic drugs	Preclinical efficacy; Mechanism	Clinical status	(Refs.)
Li <i>et al.</i> , 2025	Neutralizing antibodies	MPIIB10, ASKP1240	Inhibits tumor growth, metastasis; extends survival in PDAC models	Preclinical/Phase 1	(36)
Wang <i>et al.</i> , 2024; Wei <i>et al.</i> , 2019	RNA aptamers	SPP1-targeting aptamers, 4-1BB-SPP1 bispecific	Reduces M2 macrophage infiltration; enhances T cell co-stimulation	Preclinical	(55,137)
Hou <i>et al.</i> , 2025; Deng <i>et al.</i> , 2020	Small molecule inhibitors	CANDI460, nilotinib, NHWD-870, Static	Reduces SPP1 expression; blocks downstream signaling	Preclinical/Early clinical	(38,138)
Krieger <i>et al.</i> , 2021; Xelwa <i>et al.</i> , 2024	Gene silencing (siRNA/shRNA)	SPP1-specific siRNAs	Reduces migration, invasion, chemoresistance	Preclinical	(139,140)
Reardon <i>et al.</i> , 2008	RGD-mimetic peptides	Cilengitide	Inhibits integrin-mediated signaling	Phase II (discontinued)	(141)
Liu <i>et al.</i> , 2025	Combination with chemotherapy	SPP1 knockdown + gemcitabine	Enhanced apoptosis, reduced invasiveness	Preclinical	(142)
Qi <i>et al.</i> , 2022; Zhang <i>et al.</i> , 2026	Combination with immunotherapy	SPP1 inhibition + anti-PD-1	Restores T cell infiltration, enhances immune checkpoint inhibitor efficacy	Preclinical	(81,143)

SPP1, secreted phosphoprotein 1; PDAC, pancreatic ductal adenocarcinoma; siRNA, small interfering RNA; shRNA, short hairpin RNA.

STAT3 with Stattic, a small-molecule STAT3 inhibitor, yields robust antitumor effects across various cancers, and this intervention effectively represses SPP1 expression (145-147) (Table IV, Fig. 3).

Blockade of SPP1-receptor interactions. Another approach is to disrupt the binding of SPP1 to its receptors, such as integrins and CD44. The cyclic RGD peptide cilengitide is a characteristic inhibitor of the key SPP1 receptors $\alpha\beta 3$ and $\alpha\beta 5$ integrins. Cilengitide competitively occupies the ligand binding site, potentially blocking SPP1-integrin interactions (141,148). In addition, blocking this interaction can also inhibit downstream FAK signaling, which is crucial for SPP1-mediated cell migration and invasion. As shown in Fig. 3, inhibition of the key SPP1 receptors $\alpha\beta 3$ and $\alpha\beta 5$ integrins will attenuate downstream FAK signaling, thereby reducing tumor cell migration and invasion, and potentially synergizing with immunotherapy by reversing the immunosuppressive TME (Fig. 3).

In summary, although SPP1 expression can be regulated through various upstream pathways and receptor-blocking drugs show antitumor effects, the research on highly specific, direct SPP1-targeting drugs is still in the early stage, representing a key area for future development.

Nucleic acid aptamers targeting SPP1. Nucleic acid aptamers, especially RNA aptamers, are short, structured oligonucleotides that can bind to SPP1 with high affinity and specificity, thereby blocking its pro-cancer functions. This class of therapeutic agents has the advantages of low immunogenicity and the ability to be chemically modified to enhance stability and delivery (149). Their applications are further expanded, such as

aptamer-drug conjugates (ApDCs) and aptamers constructed entirely from therapeutic nucleoside analogs (150). These modalities enable precise delivery by discriminating isoforms and cellular sources. OPN-c-specific ADCs deliver cytotoxic payloads to tumor cells, improving therapeutic index (144). SPP1 RNA aptamers offer low immunogenicity and modifiability, with preclinical efficacy in esophageal cancer (55). The diverse therapeutic strategies targeting SPP1, ranging from neutralizing antibodies and RNA aptamers to small molecule inhibitors and combination immunotherapies, each with distinct mechanisms of action, are illustrated in Fig. 3.

Preclinical studies have demonstrated the effectiveness of SPP1-targeting aptamers. In ESCC models, SPP1 RNA aptamers significantly inhibited tumor growth and reduced M2 macrophage infiltration (55). In mouse glioblastoma models, systemic administration of 4-1BB (CD137)-SPP1 bispecific aptamers improved survival by triggering co-stimulatory immune responses. Notably, SPP1 aptamers alone did not significantly improve survival, highlighting the benefits of combinatorial approaches (137). Beyond oncology, SPP1-specific aptamers have shown protective effects by regulating immune responses in non-neoplastic diseases such as chronic liver disease (151).

Overall, these findings highlight the great potential and clinical application prospects of SPP1-targeting aptamers in cancer therapy (Table IV, Fig. 3).

Challenges and future directions of SPP1-targeted therapy. The clinical translation of SPP1-targeted therapy faces challenges, mainly due to the complexity of SPP1 interactions with multiple receptors and its indispensable role in normal physiology. SPP1 participates in key processes such as cell

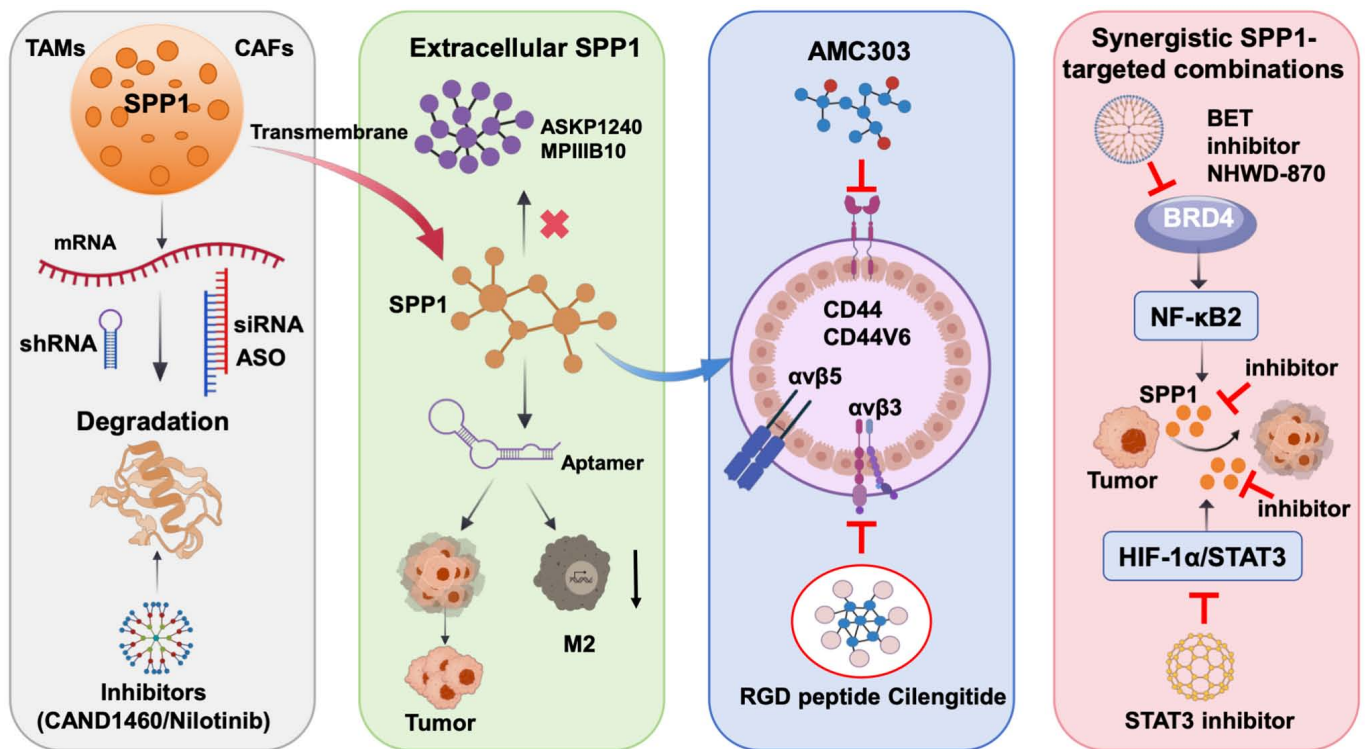


Figure 3. Therapeutic strategies targeting SPP1 in cancer. SPP1/osteopontin is mainly secreted by tumor cells, TAMs and CAFs in the TME. It drives malignant progression by binding to integrin receptors and CD44 splice variants, activating downstream oncogenic signaling cascades, and mediating tumor cell-autonomous malignant phenotypes and non-autonomous TME immunosuppression. This diagram systematically summarizes the intervention nodes of SPP1-targeted therapeutic strategies, including: i) Inhibiting SPP1 transcription and protein synthesis via small molecule inhibitors and siRNA/shRNA; ii) Neutralizing extracellular secreted SPP1 via neutralizing antibodies and RNA aptamers; iii) Blocking the interaction between SPP1 and its membrane receptors via RGD-mimetic peptides and receptor-targeted inhibitors; iv) Synergistic combination therapy, including SPP1 targeting combined with chemotherapy, immune checkpoint inhibitors and pathway inhibitors, to reverse chemoresistance and immunosuppression, ultimately exerting comprehensive antitumor effects. SPP1, secreted phosphoprotein 1; TAMs, tumor-associated macrophages; CAFs, cancer-associated fibroblasts; TME, tumor microenvironment; siRNA, small interfering RNA; shRNA, short hairpin RNA.

adhesion, tissue integrity and immune regulation, affecting the activation and migration of macrophages and T cells (152). Therefore, systemic inhibition of SPP1 has the potential to disrupt these functions, possibly leading to impaired tissue repair and dysregulated immune responses.

Despite these promising therapeutic strategies, the clinical development of SPP1 pathway inhibitors has encountered significant setbacks, underscoring the need for a more circumspect assessment. A cautionary precedent is cilengitide, a cyclic RGD peptide targeting $\alpha v\beta 3/\alpha v\beta 5$ integrins, key receptors mediating SPP1 signaling. Despite robust preclinical evidence of anti-angiogenic and anti-invasive activity and encouraging phase I/II results (141), the phase III CENTRIC trial (EORTC 26071-22072) in newly diagnosed MGMT-methylated glioblastoma failed to demonstrate any survival benefit (median OS 26.3 months in both cilengitide and control arms), leading to the termination of cilengitide development as an anticancer agent (153). The companion CORE phase II trial in MGMT-unmethylated glioblastoma yielded paradoxical results, with standard-dose cilengitide showing modest survival improvement while dose intensification did not improve outcomes, further highlighting the unpredictability of integrin-targeted therapy in clinical settings.

Several interconnected factors likely account for these failures and pose broader challenges to SPP1-targeted therapy. First, off-target toxicity remains a fundamental

concern: SPP1/OPN plays indispensable physiological roles in bone remodeling, wound healing and immune homeostasis. OPN-deficient mice exhibit impaired wound healing with disorganized collagen fibrillogenesis and reduced tissue debridement (154), suggesting that systemic SPP1 inhibition could compromise tissue repair and bone integrity in patients. Second, the failure of integrin-targeted agents such as cilengitide indicates that broad-spectrum blockade of integrin signaling is often compromised by functional redundancy among integrin family members, interference with normal physiological processes, and paradoxical dose-response relationships. These limitations suggest that SPP1-targeted therapy should not aim for global suppression of SPP1 but rather focus on selectively disrupting the pro-tumorigenic signaling axis between SPP1 and key integrins, particularly $\alpha v\beta 3$. $\alpha v\beta 3$ plays a central role in therapeutic resistance by activating FAK/Src and PI3K/Akt pathways, thereby promoting cell survival, DNA damage repair and EMT, which collectively reduce the sensitivity of tumor cells to radiotherapy, chemotherapy and targeted agents. As one of the major ligands of $\alpha v\beta 3$, elevated SPP1 expression is likely to drive acquired resistance through sustained activation of these pathways. Therefore, targeting the SPP1- $\alpha v\beta 3$ interaction may offer greater specificity than direct integrin inhibition, while avoiding broad interference with the physiological functions of other integrins (155,156).

To overcome these hurdles, future drug development must prioritize precision-enhancing strategies, including tissue-specific targeting of tumor-associated SPP1 isoforms or TME-activated therapeutics to minimize off-target effects. Advanced modalities, such as bispecific antibodies co-targeting SPP1 and immune checkpoints, lipid nanoparticle-delivered siRNA for SPP1 silencing and SPP1-directed ApDCs, represent next-generation approaches. Rational combination therapy, pairing SPP1 inhibitors with chemotherapy, TGF- β blockers, or immune checkpoint inhibitors (ICIs; for example, anti-PD-1), may overcome drug resistance. Finally, biomarker-driven patient stratification using predictive biomarkers will ensure that SPP1-targeted therapies are administered to populations most likely to benefit.

7. Limitations and perspectives

In the present review, the well-documented pro-tumorigenic functions of SPP1/OPN were emphasized across a broad spectrum of malignancies. Nonetheless, it is essential to acknowledge that the biological effects of OPN are highly context-dependent, and conflicting outcomes have been reported under certain conditions. Of particular interest, OPN has been established as a direct transcriptional target of the tumor suppressor TP53; activation of p53 in response to DNA damage leads to upregulated OPN expression. This observation implicates OPN in TP53-mediated immune surveillance, where it may function to impede malignant transformation (157). In cutaneous squamous cell carcinoma models, host-derived OPN suppressed early tumor progression by eliciting an acute innate inflammatory response, as wild-type mice exhibited significantly lower tumor incidence than OPN-null mice (158). A landmark study further revealed that OPN exerts dual, source-dependent functions: Host-derived OPN acts as a macrophage chemoattractant to mediate host defense, whereas tumor-derived OPN suppresses macrophage activity and enhances the survival of metastatic tumor cells (159). At the isoform level, overexpression of OPN-c in NSCLC significantly reduced cell proliferation, colony formation and invasive capacity relative to controls, a finding that stands in stark contrast to the pro-tumorigenic activity of the full-length OPN-a isoform (160). These contradictory observations highlight the complexity of SPP1 biology and caution against a unidimensional interpretation of its role in cancer.

Context-dependent and contradictory roles of SPP1 in cancer. Evidence demonstrating that SPP1 can exert opposing functions depending on the cellular and tissue context was discussed. For example, the tumor suppressor Chromobox Homolog 7 (CBX7) has been shown to directly inhibit SPP1 gene expression, and loss of CBX7 correlates with SPP1 overexpression and malignant progression in various carcinomas, including thyroid, breast and lung cancers (161,162). Conversely, the CBX7-interacting protein HMGA1b acts as a positive regulator of SPP1 gene expression, counteracting CBX7-mediated repression and highlighting the complex transcriptional regulation of SPP1 (161). This transcriptional duality reflects a broader theme in SPP1 biology: The same molecule can be co-opted for tumor promotion or tumor suppression depending

on the regulatory networks active in a given cellular context. Additional studies have shown that OPN can act as a tumor suppressor in certain models; for instance, in prostate cancer, OPN has been reported to induce apoptosis in early-stage lesions, while promoting metastasis in advanced disease (163). These paradoxical observations underscore the importance of considering the specific biological context when interpreting SPP1 functions.

Tumor type and disease stage. SPP1 may play fundamentally different roles in early vs. late stages of tumorigenesis, and across different tumor types. While SPP1 is generally pro-tumorigenic in established cancers, its role in early-stage lesions or specific subtypes may differ. For instance, in prostate cancer, OPN has been reported to suppress tumor growth in early stages by inducing apoptosis, yet promote metastasis in advanced disease (163). Similarly, in BC, OPN may exert anti-tumor effects in certain molecular subtypes while promoting progression in others (5). This stage- and subtype-specific functionality highlights the need for careful contextualization when evaluating SPP1's role.

TME composition. Differences in immune infiltration, stromal activation and ECM composition can markedly alter SPP1's functional outcomes. In TMEs dominated by M1-like macrophages, SPP1 may promote antitumor immune responses; conversely, in TMEs enriched with M2-like macrophages, MDSCs and CAFs, SPP1 reinforces immunosuppression (164). The spatial organization of SPP1⁺ cells relative to immune cells, whether they co-localize in immune-excluded regions or infiltrate tumor nests, can also dictate whether SPP1 exerts immune-stimulatory or immune-suppressive functions (5). In hypoxic, macrophage-dominant microenvironments, SPP1 primarily mediates immunosuppression; under other conditions, however, it promotes innate immune activation and contributes to host defense (158,159). Moreover, the dual roles of CXCL9/SPP1-polarized TAMs observed in HCC further illustrate that the microenvironmental context can completely reverse the functional outcomes of this protein (120).

Cellular source of SPP1. Tumor cell-derived vs. TAM-derived SPP1 may exert distinct functions, with differential impacts on tumor progression. Autocrine SPP1 from cancer cells primarily drives cell-intrinsic malignant phenotypes (proliferation, survival and EMT), while paracrine SPP1 from TAMs and CAFs shapes the immunosuppressive TME (163). The distinct PTM profiles of SPP1 secreted by different cell types further contribute to functional divergence.

Isoform detection and functional heterogeneity. Different studies may detect different isoforms or fail to distinguish between OPN-a, OPN-b and OPN-c, leading to conflicting conclusions. OPN-a (secreted) and OPN-c (intracellular/nuclear) have fundamentally distinct functions. Studies that detect total OPN without isoform discrimination may inadvertently conflate isoform-specific activities, leading to contradictory interpretations (13,165). This is particularly relevant for OPN-c, which is often upregulated in cancer but rarely expressed in normal tissues, and may mediate tumor-specific functions not captured by pan-OPN detection. The three major splice variants of SPP1, OPN-a, OPN-b and OPN-c, display distinct subcellular localization patterns and exert non-overlapping, and in some cases even antagonistic, biological functions (13,14,160).

PTMs. Phosphorylation and glycosylation patterns can markedly alter SPP1's receptor binding and function. For instance, extensive phosphorylation of serine and threonine residues is critical for high-affinity integrin binding, while specific O-glycosylation patterns modulate CD44 interaction (166,167). The degree of phosphorylation and the specific glycan structures attached to SPP1 can vary across cancer types, disease stages and cellular sources, thereby influencing receptor preference (integrin vs. CD44) and downstream signaling outcomes. Consequently, studies that do not characterize the PTM status of SPP1 may arrive at different functional conclusions.

Methodological advances for mechanistic studies

Single-cell multi-omics and spatial transcriptomics. Single-cell and spatial multi-omics technologies have revolutionized cancer research by providing unprecedented resolution of TME heterogeneity and cell-cell interactions. These technologies are particularly powerful for studying SPP1-mediated signaling networks. scRNA-seq enables the identification of SPP1-producing cell types and the characterization of SPP1-responsive cell populations, revealing the specific cell states associated with SPP1 signaling (123). Although SPP1 is known to promote M2-like TAM polarization, T cell exhaustion, MDSC recruitment and CAF activation, the precise molecular mechanisms governing these interactions, particularly the receptor utilization and downstream signaling in different cell types, remain incompletely defined. Future studies should integrate single-cell multi-omics, spatial transcriptomics and advanced imaging approaches to map SPP1-mediated intercellular crosstalk in the TME with cellular resolution. Single-cell sequencing is particularly critical for dissecting the functional heterogeneity of SPP1: It can distinguish SPP1 originating from tumor cells vs. immune or stromal cell subsets, resolve isoform expression at single-cell resolution, and identify spatially defined SPP1⁺ niches that drive distinct phenotypic outcomes.

Spatial transcriptomics (for example, 10x Visium and Xenium) adds a crucial spatial dimension, revealing the spatial organization of SPP1⁺ cells relative to SPP1 receptor⁺ cells and immune populations (97,121). This spatial information is essential for understanding whether SPP1-mediated signaling occurs in specific TME niches (for example, tumor-stroma interface, perivascular regions and immune-excluded zones). The integration of multiple omics layers, transcriptome, epigenome and spatial architecture, will be essential for constructing comprehensive models of SPP1 function in cancer.

Future studies should also incorporate multi-omics approaches to profile the SPP1 interactome, including both protein-protein interactions and PTM landscapes. These integrated approaches will provide a holistic view of SPP1 function, bridging the gap between molecular mechanisms and clinical outcomes.

Proteomic and PTM analysis. SPP1 undergoes extensive PTMs, including phosphorylation, glycosylation and proteolytic cleavage, that critically regulate its function. However, these modifications are often overlooked in standard studies, leading to incomplete understanding of SPP1 biology. Advanced proteomic approaches, including mass spectrometry-based

phosphor-proteomics and glycol-proteomics, are essential for comprehensively characterizing the PTM landscape of SPP1 in different cancer types, disease stages and cellular contexts (24,26).

These approaches can reveal modifications that are specific to cancer vs. normal tissues, modifications that are altered by drug treatment, and modifications that determine receptor binding specificity. Furthermore, the development of modification-specific antibodies would enable the detection of particular PTM forms of SPP1 in clinical samples, providing biomarkers of SPP1 activation and receptor preference. The integration of proteomic data with transcriptomic and epigenomic data will provide a multi-dimensional understanding of SPP1 function, enabling the development of more precise therapeutic strategies.

Key challenges and future directions

Isoform-specific functional heterogeneity. The functional heterogeneity of SPP1 isoforms (OPN-a, OPN-b and OPN-c) remains a critical knowledge gap. Most studies treat SPP1 as a single entity despite isoform-specific localization and functions (13,14,17). Key limitations include the scarcity of isoform-specific detection reagents and knockout models, the unknown mechanisms of intracellular OPN-c vs. secreted isoforms, and the need for isoform-targeted therapies to avoid off-tumor toxicity. Addressing these gaps through isoform-specific antibodies, genetic models, and mechanistic studies is essential for clinical translation and precision oncology: i) Detection tools: Lack of isoform-specific antibodies (for example, targeting exon junctions OPN-c Δex4 and OPN-b Δex5) hinders precise quantification and clinical correlation; ii) Genetic models: Current knockout strategies ablate all isoforms; isoform-specific knockout mice are needed to dissect individual contributions to tumorigenesis and metastasis; iii) Therapeutic targeting: Pan-SPP1 inhibition risks disrupting physiological functions (for example, OPN-a in bone); isoform-selective inhibitors (antibodies, aptamers and ADCs) offer greater precision; iv) Intracellular functions: OPN-c's nuclear/cytoplasmic roles in transcription, cell cycle, and DNA repair remain poorly understood. v) Clinical translation: Isoform-specific biomarkers are required for patient stratification in clinical trials. Future research should prioritize isoform-specific knockout models and selective detection reagents to dissect their individual roles and develop isoform-targeted therapies that minimize off-tumor effects.

Development of isoform-specific inhibitors. Preclinical studies have validated SPP1 as a promising therapeutic target, yet clinical translation remains in its infancy, largely owing to the lack of isoform-specific inhibitors. Key challenges include the absence of isoform-specific inhibitors, potential off-target toxicity due to SPP1's physiological roles (bone remodeling, wound healing and immune homeostasis), and limited understanding of resistance mechanisms to SPP1-targeted therapies. Because distinct SPP1 isoforms may exert opposing functions, broad-spectrum SPP1 inhibition not only fails to selectively target pathogenic isoforms but may also inadvertently abrogate isoform-specific protective effects. Future drug development should therefore prioritize isoform-selective small molecules, antibodies, or aptamers to achieve specific targeting of pro-tumorigenic SPP1 isoforms.

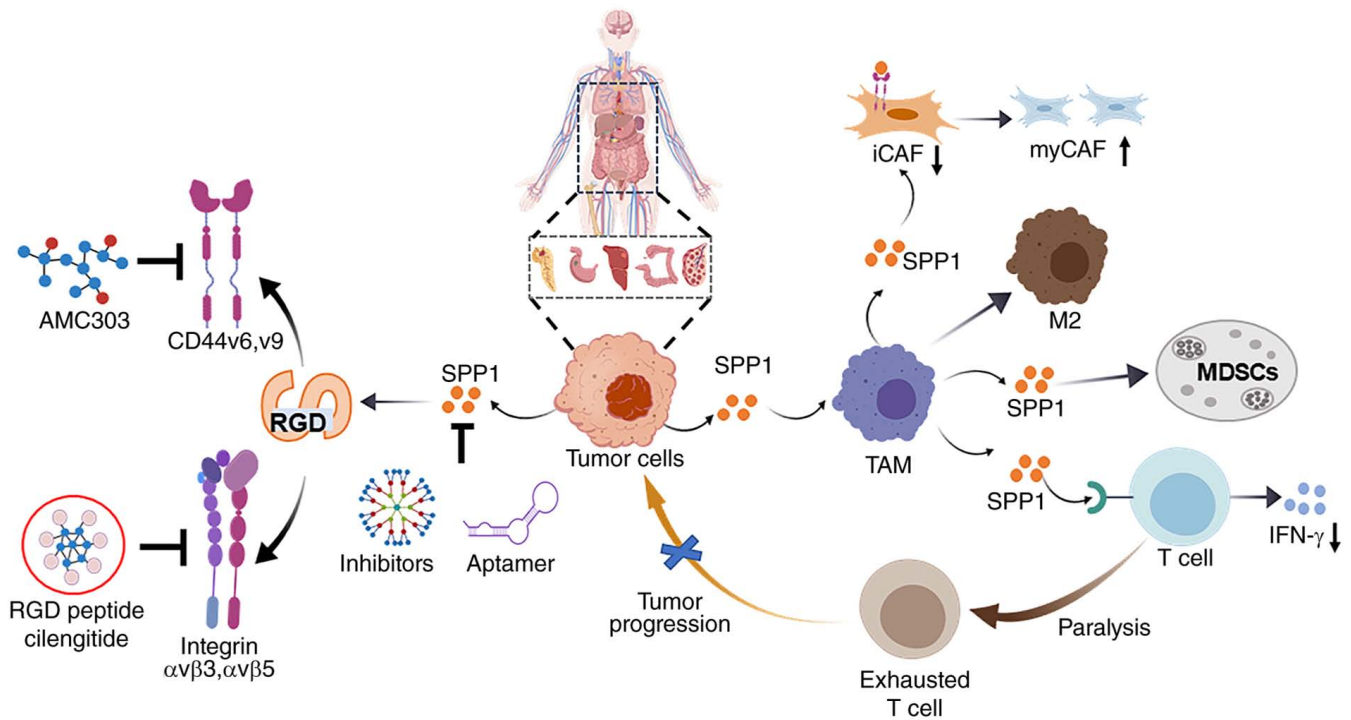


Figure 4. SPP1 as a central oncogenic hub in multiple malignancies: From receptor signaling to therapeutic targeting. The present review systematically delineates the core oncogenic mechanisms of SPP1 (SPP1/osteopontin) in multiple malignancies, including ovarian cancer, colorectal cancer, hepatocellular carcinoma, gastric cancer and pancreatic ductal adenocarcinoma. SPP1 is predominantly produced by tumor cells and M2-like TAMs within the TME. Through its RGD motif, SPP1 binds integrin $\alpha v \beta 3 / \alpha v \beta 5$, and via its C-terminal non-RGD domain, it interacts with CD44 and its splice variants v6/v9, thereby activating PI3K/AKT, MAPK/ERK and JAK/STAT3 signaling cascades. These pathways drive cell-autonomous malignant phenotypes and orchestrate an immunosuppressive tumor microenvironment. Based on these mechanistic insights, the present review further summarizes multi-node targeted intervention strategies against the SPP1 signaling axis, providing a critical theoretical foundation for developing novel antitumor therapies. SPP1, secreted phosphoprotein 1; MDSCs, myeloid-derived suppressor cells; CAFs, cancer-associated fibroblasts; myCAF, myofibroblastic CAF; iCAF, inflammatory CAF; TAMs, tumor-associated macrophages.

Mitigation of off-target toxicity. SPP1 participates in essential physiological processes, including bone remodeling, wound healing and immune homeostasis. Systemic inhibition of SPP1 therefore carries inherent risks of off-tumor toxicity. To address this, future efforts should focus on developing tissue-specific or TME-activated delivery systems, such as antibody-drug conjugates targeting SPP1-producing cells, lipid nanoparticle-encapsulated siRNA with tumor-homing ligands, or hypoxia-responsive prodrugs that are selectively activated in the TME. Additionally, designing rational combination regimens with chemotherapy, targeted therapy and immunotherapy may allow dose reduction of SPP1-targeted agents while enhancing therapeutic efficacy.

Biomarker development for patient stratification

Circulating SPP1 and isoform profiles. The development of reliable circulating biomarkers is essential for patient stratification and monitoring of therapy response. Serum SPP1 levels are already being evaluated as prognostic biomarkers in numerous cancers; however, current assays typically measure total SPP1 without isoform discrimination. The development of isoform-specific ELISA assays for circulating OPN-a, OPN-b and OPN-c would enable more precise assessment of SPP1 isoform profiles and their correlation with clinical outcomes. Studies have shown that serum SPP1 levels are elevated in patients with PDAC, HCC, NSCLC and other cancers, and correlate with tumor stage and poor prognosis (65,75,121,137).

However, the prognostic value of individual isoforms remains unclear. Isoform-specific circulating SPP1 detection could identify patients with OPN-c-driven tumors who may be candidates for OPN-c-targeted therapies. Additionally, changes in serum SPP1 isoform profiles during treatment could serve as early markers of response or resistance.

Spatial signatures and TME architecture. The spatial organization of SPP1-expressing cells within the TME provides powerful prognostic and predictive information. Spatial imaging techniques, including multiplex immunohistochemistry, imaging mass cytometry and spatial transcriptomics, can reveal the density and distribution of SPP1⁺ cells relative to immune cells, CAFs and cancer cells. Key spatial signatures with clinical relevance include: i) SPP1⁺ TAM-CAF co-localization, where high co-localization of SPP1⁺ TAMs and FAP⁺ CAFs predicts poor response to checkpoint blockade (81); ii) the location of SPP1⁺ cells in immune-excluded vs. immune-infiltrated regions, with SPP1⁺ cells in immune-excluded regions contributing to T cell exclusion, while those in immune-infiltrated regions directly suppress T cell function; and iii) SPP1 density at invasive fronts, where high SPP1 density at tumor-stroma interfaces predicts metastatic potential and poor prognosis (117). Together, these spatial signatures could serve as companion diagnostics for SPP1-targeted therapies, identifying patients whose tumors display the immunologically 'cold' and desmoplastic phenotype likely to respond to SPP1 modulation.

Functional immune ratios. Functional immune ratios derived from transcriptomic data provide a measure of the balance between immune activation and immune suppression. The CXCL9:SPP1 macrophage polarity index is a prime example; a low ratio (more SPP1 than CXCL9) indicates strong immunosuppression and predicts poorer response to immunotherapy (123,125). Other functional ratios may also hold predictive value, including the IFNG: SPP1 ratio (reflecting T cell activation vs. macrophage-mediated immunosuppression), the CD8A:SPP1 ratio (indicating cytotoxic T cell infiltration vs. macrophage-derived immune suppression), and the TGFB1:SPP1 ratio (reflecting CAF-mediated fibrosis vs. immune suppression). These ratios could be used to identify patients with ‘SPP1-dominant’ immunosuppression who are most likely to benefit from SPP1-targeted therapies, as well as to monitor therapeutic responses and the emergence of resistance.

Overall, while SPP1 has emerged as a central coordinator of cancer progression and a promising therapeutic target, its context-dependent functional duality, isoform complexity and multifaceted TME interactions present significant challenges; overcoming these limitations through mechanistic dissection, advanced therapeutic modalities and biomarker-guided clinical trials will be essential to translate SPP1-targeted strategies into clinical practice and ultimately improve outcomes for cancer patients.

8. Conclusions

The present review has systematically synthesized the multifaceted roles of SPP1 in cancer, from its structural and molecular basis to its profound impact on tumorigenesis, metastasis, TME remodeling, immune regulation and therapeutic targeting (Fig. 4). Accumulating evidence firmly establishes SPP1 not merely as a bystander but as a central coordinator of cancer progression.

In summary, SPP1 emerges as a pivotal regulator of tumor progression by orchestrating oncogene activation, tumor suppressor inhibition and extensive TME remodeling, including immune cell polarization, CAF activation, angiogenesis and ECM stiffening. Its functional effects are mediated through interactions with key receptors, integrins ($\alpha\beta3$ and $\alpha\beta5$) and CD44, forming a pro-tumor signaling network (Fig. 4). Although SPP1-targeted therapies (small molecules, aptamers and bispecific agents) exhibit therapeutic potential, off-target effects remain a major challenge. Future research should leverage single-cell sequencing to dissect TME heterogeneity, advance tissue-specific drug delivery systems, and validate rational combination strategies (chemotherapy, ICIs) integrated with SPP1-based companion biomarkers. These advances will eventually translate mechanistic findings into improved clinical outcomes for patients with SPP1-driven malignancies.

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Authors' contributions

HL conceived and designed the scope of the review. YX, DH, ST, HY, RZ, BC, PZ and AS performed the literature search and drafted the initial manuscript. YX, DH, and HL revised manuscript. HL provided funding support. All authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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