Function of *SP1* in tumors and focused treatment approaches for immune evasion (Review)

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Abstract. Immune escape is a phenomenon in which tumor cells or infections evade detection and clearance by the host immune system in various ways. During an antitumor immune response, cells increase the concentration of pentameric stalk, which enhances antigen presentation and recognition by the immune system. It has been found that both increased and decreased levels of specificity protein 1 (*SP1*) control oncogenes, thereby influencing tumorigenesis and cancer development. Thus, elucidating the mechanism underlying the role of *SP1* in tumors may help identify novel prognostic indicators. However, the immune escape mechanism involved in *SP1* poses new challenges to diagnosis and treatment. The present review used a combination of analogies and summaries to explore the structure, function, regulatory mechanism and biological activity of *SP1* in normal and cancer cells, and aimed to discuss the regulatory function of *SP1* in different tumors, as well as the relevant association between *SP1* and clinical diagnosis and treatment, which revealed the importance of *SP1* in tumorigenesis and cancer development. The novelty of the present review lies in the identification of novel immune evasion mechanisms and immunotherapeutic techniques that provide new insights and approaches for a deeper understanding of the role of *SP1* in malignant tumors.

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Abbreviations: OSMR, oncostatin M receptor; SIRPA, signal regulatory protein α; TAM, tumor-associated macrophage; TBP, TATA-binding protein; SP1, specificity protein 1; Btd, buttonhead; TAD, tight adherence; CDK, cyclin dependent kinase, CXCL, C-X-C motif chemokine ligand; FOXM1, forkhead box M1; SNAI2, Snail family transcriptional repressor 2; LINC00659, long intergenic non-protein coding RNA 659; lncRNA, long noncoding RNA; SNHG7, small nucleolar RNA host gene 7; TUG1, taurine upregulated 1; PTEN, phosphatase and tensin homolog; AKT, protein kinase B; mTOR, mechanistic target of rapamycin; miRNA or miR, microRNA; NF-κB, nuclear factor κB; TNM, tumor-node-metastasis; VEGF, vascular endothelial growth factor; TME, tumor microenvironment; Bcl-2, B-cell lymphoma 2; KRAS, Kirsten rat sarcoma viral oncogene homolog; EMT, epithelial-mesenchymal transition; PD-1, programmed cell death protein 1; HDAC, histone deacetylase; LLPS, liquid-liquid phase separation; MMP, matrix metalloproteinase; RGS20, regulator of G-protein signaling 20; PKM2, pyruvate kinase M2; TMZ, temozolomide

Key words: specificity protein 1, immune escape, tumor, regulatory, mechanism

Contents

1. Introduction

Ovarian cancer has one of the highest mortality rates among gynecological malignancies, largely because early-stage disease lacks reliable diagnostic markers. Research has indicated that overexpression of specificity protein 1 (*SP1*) is strongly linked to ovarian cancer. Previous studies have shown that *SP1* interacts with GC-rich promoters to control gene expression (1). *SP1*-encoded proteins participate in several biological processes, including cell differentiation, apoptosis, immunological responses, chromatin remodeling and DNA damage response. Post-translational changes (such as acetylation, phosphorylation, glycosylation and protein hydrolysis) impact the biological function of this protein (1). Overexpression of *SP1* can drive cancer progression by increasing the expression of genes that enhance cell proliferation, invasion, metastasis

and chemotherapy (2). It has been identified that both the increase and decrease in *SP1* levels control oncogenes, thereby influencing cancer spread and tumor development (3,4). *SP1* accelerates tumor formation by stimulating blood vessel growth and preventing cell death in cancer cells. High levels of *SP1* expression enhance the autophagic flux, which promotes tumorigenesis (5). In addition, the levels of *SP1* in tumor-derived exosomes increase, which favors the secretion of interleukin (IL)-1β by neutrophils through the activation of the Toll-like receptor 4 (TLR4)-nuclear factor-κB (NF-κB) pathway, ultimately aggravating lung metastasis of breast cancer (6). It is expected that research in this area will greatly benefit antitumor treatment.

2. Structure and polymorphism of *SP1*

Structural features of SP1. The structural features of *SP1* were initially identified by Dynan and Tjian in 1983; the protein was recognized as a promoter-specific binding factor necessary for transcribing the crucial immediate early gene of the simian vacuolating virus 40 polyomavirus (7). *SP1* belongs to a group of transcription factor-specific proteins that also include C2H2-type zinc fingers. Members of the SP family exhibit multiple similarities with the Krüppel-like family (KLF) (8). SP family transcription factors bind to the GC-frame of the promoter region of the target gene, while KLF has a preference for the CACCC-frame of the promoter region of the target gene (9). SP family members are categorized into two main groups, namely *SP1-4* and *SP5-9*. *SP1-4* share structural similarities, whereas *SP5-9* are more akin to KLF (10).

SP1 is organized into four structural domains: i) A double-stranded DNA-binding domain; ii) the *SP1* transcriptional activity domain; iii) a buttonhead (Btd) domain; and iv) the SP domain (10). The C-terminus of *SP1* has three standard Cys2His2 zinc finger structures. Two of these structures are located near the N-terminus, and each bind to one of the four bases of double-stranded DNA; the other two bases of DNA are attached to the zinc finger structure close to the C-terminus. This unique configuration enhances the capability of *SP1* to bind to the target gene promoter.

The transcriptionally active part of *SP1* consists of two glutamine-rich transactivation domains [tight adherence (TAD)A and TADB], namely the charged domain and C-terminal domain. These components interact to create a tetramer. The *SP1* tetramer is formed by coordinating TADA, TADB and the D region, causing the DNA in the promoter region of the target gene to bend into a ring. This allows the *SP1* protein to bind to the promoter and initiate target gene expression (11). The Btd and SP domains may influence *SP1* transcriptional activity, which is associated with the hydrolysis of the *SP1* protein (Fig. 1) (12). It has been reported that the transcription factor *SP1* is abundantly present in mammalian cells and controls the expression of several genes and the biological functions of cells. Previous research has classified it as a housekeeping gene (13). *SP1* is also implicated in the regulation of biological processes in colorectal, gastric, breast, ovarian and lung cancer cells. A previous study has demonstrated that *SP1* regulates the expression of genes linked to tissue development (14). Examination of chromosomal gene sequences has revealed that the human genome includes 12,000 binding sites for *SP1*, which control the majority of cellular functions (15). In addition, *SP1* interacts with several proteins and factors in the cell, such as other transcription factors, components of the transcription initiation complex and epigenetic factors (16).

Association of SP1 polymorphisms with its function and tumor process. SP1 function is affected by single nucleotide polymorphisms and structural domain variants, which in turn affect tumorigenesis, metastasis and drug resistance (17). It has been shown that *SP1* interacts with interferon-inducible protein 16, activates heme oxygenase 1 transcription, inhibits iron death and leads to radiotherapy resistance. Therefore, patients with gliomas showing high clinical expression of *SP1* tend to be resistant to temozolomide (TMZ) and have a poorer prognosis (18).

Mutations in the zinc finger (ZNF)3 structural domain of *SP1*, which is essential for liquid-liquid phase separation (LLPS), can affect oncogenic activity. For example, in lung adenocarcinoma, *SP1* promotes metastasis by forming nuclear condensates through phase separation, recruiting coactivators [such as p300 and histone deacetylases (HDACs)], and activating the expression of regulator of G protein signaling factor 20 (RGS20) (19).

Transmembrane structural domain variants also influence the oncogenic effects of *SP1*. It has been shown that, in low-grade fibromucinous sarcoma, FUS-cAMP responsive element binding protein 3 like 2 fusion proteins remodel the endoplasmic reticulum through phase separation, leading to aberrant protein hydrolysis, oncogenic fragmentation into the nucleus and activation of oncogenes (20).

SP1 polymorphisms cause TMZ resistance in glioblastoma. *SP1* inhibits TMZ-induced DNA damage and apoptosis by upregulating cytochrome P450 17A1 family 17 subfamily A member 1, which promotes dehydroepiandrosterone production (21). Betulinic acid inhibits *SP1* and activates the PKR-like ER kinase/CCAAT-enhancer-binding protein homologous protein apoptotic pathway, thereby enhancing TMZ efficacy (22).

SP1 promotes immune escape by regulating programmed cell death-ligand 1 (PD-L1) and metabolic reprogramming. Circular RNA-encoded protein downstream of *SP1* (circPETH-147aa) enhances pyruvate kinase M2 (PKM2) activity through m6A modification and inhibits CD8+ T cell function. However, the natural compound norathyriol blocks circPETH-147aa and restores the efficacy of anti-programmed cell death protein-1 (anti-PD-1) (23). Polymorphisms in *SP1* play a key role in tumorigenesis, metastasis and therapeutic resistance by affecting its transcriptional activity, phase-separation ability and downstream signaling pathways. Future studies should focus on developing precise therapeutic strategies targeting different *SP1* variants.

3. Mechanism of action of *SP1*

Molecular mechanism of SP1. SP1 primarily functions by recruiting the underlying transcriptional complex and interacting with components of the transcription factor II D (TFIID) complex. The TFIID complex comprises the TATA-binding protein (TBP) and other TBP-associated factor proteins. These

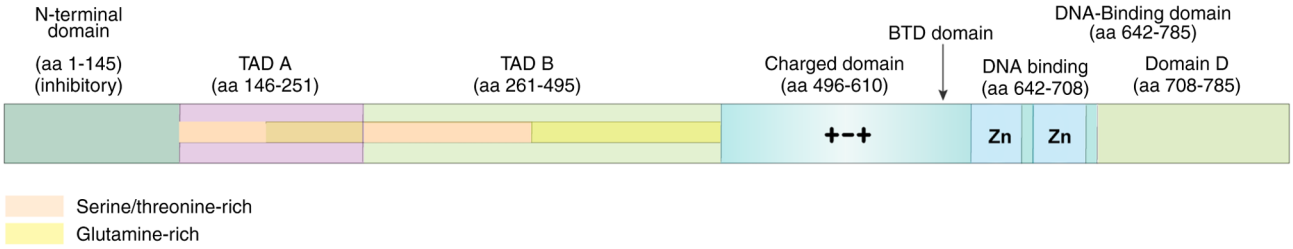

Figure 1. Schematic representation of SP1 structure. The diagram outlines the distinct domains of SP1, including the N-terminal domain (aa 1-145), transactivation domain A (TAD A; aa 146-251), transactivation domain B (TAD B; aa 261-495), charged domain (aa 496-610), DNA binding domain (aa 642-708) and domain D (aa 708-785). The N-terminal domain is marked as inhibitory, while TAD A and TAD B are highlighted with color coding to indicate regions rich in serine/threonine (light orange) and glutamic acid (yellow). The charged domain is represented with a series of positive charges (+) and a series of negative charges (-). The DNA-binding domain (aa 642-785) comprises two zinc finger motifs (Zn, aa 642-708) followed by domain D (aa 708-785), which collectively mediate GC-box recognition. Figure was created using Adobe Illustrator version 28.0 (Adobe, Inc.). Numbers indicate aa positions. aa, amino acid; Btd, buttonhead; SP1, specificity protein 1; TAD, tight adherence.

proteins attach to the gene promoter, initiating the creation and assembly of the transcription start complex. The interaction mechanism of *SP1* can be modulated by various transcriptional activators (24). Previous research indicates that the state of chromosomes can influence the transcriptional activity of *SP1*. *SP1* can directly interact with histone acetylase P300, thereby altering the chromosomal structure to a more relaxed state and increasing the DNA-binding capacity of *SP1* (25). A previous study has demonstrated that *SP1* and P300 can interact in the promoter area of P21 in neural precursor cells to activate P21 expression, which inhibits cell proliferation and induces cell cycle arrest (26). Previous research identified that the activation of reporter genes in the *Drosophila* SE2 cell line was moderate when *SP1* expression vectors were created along with reporter genes and only one *SP1*-binding site was present. However, the presence of two *SP1*-binding sites induced a 78-fold increase in the level of transcription (27). Electron microscopy findings indicated that the cooperative activation of proximal and distal binding sites was facilitated by the bending of the intermediate DNA double strand, allowing *SP1* proteins situated at both ends to engage with each other (28). *SP1* initially assembles into a tetramer in the promoter region of a target gene during transcription initiation. This observation indicates that transcriptional synergy of *SP1* occurs through the formation of a tetramer by multiple *SP1* monomers in the promoter region of the gene (29).

Previous gel blocking experiments have demonstrated that the first *SP1* monomer binds to the promoter of each gene during interactions with the target genes. As the concentration of *SP1* protein increases, a second *SP1* protein molecule sequentially appears on the gene promoter (16). These findings indicate that the synergistic transcriptional activation by SP1 is not attributable to enhanced DNA binding affinity, but rather to a cooperative enhancement of transcriptional output that surpasses the additive effects of SP1 and DNA transcription alone (16). *SP1* is active in all cell types and circumstances; however, its activity is tightly regulated, leading to varied expression results for several tumor suppressor and oncogene genes (16). One of those processes involves interaction with other proteins. For example, octamer transcription factor 1 (Oct1) interacts with structural domain B and the serine/threonine-rich area near *SP1*. This enhances its DNA-binding affinity by binding to distant regulatory genes, thereby enhancing transcription (30). O-GlcNAc in a serine/threonine-rich region of *SP1* prevents the interaction between *SP1* and Oct1, inhibiting the activation of U2 small nuclear RNA genes by these proteins (31). Estrogen can bind to *SP1* to activate transcription. For example, when the endoplasmic reticulum binds to *SP1*, it increases the *SP1*-DNA binding to estrogen response elements even in the absence of estrogen. However, the transcriptional activation of the gene is only enhanced in the presence of estrogen. This indicates that the regulation of *SP1* influences the transcriptional outcome differently (32).

Regulatory mechanism of SP1. Jin *et al* (33) reported that myeloma cells with increased expression of the IQ motif containing GTPase activating protein 1 (IQGAP1) gene stimulate the Ras/Raf/MEK/extracellular signal-regulated kinase (Ras/Raf/MEK/ERK) pathway. A previous bioinformatics study identified *SP1* as an upstream regulator of IQGAP1. *SP1* binding to the IQGAP1 promoter region was confirmed by chromatin immunoprecipitation analysis. The study found that blocking *SP1* or P300 reduced the levels of ERK1/2 and IQGAP1, whereas increasing *SP1* or P300 levels exerted the opposite effect. Increased expression of *SP1* or P300 substantially enhanced the activity of the IQGAP1 gene promoter, with the *SP1*/P300 complex controlling IQGAP1 gene expression in myeloma cells. Zhou *et al* (34) reported that sevoflurane-induced P300 suppressed *SP1* activity by enhancing *SP1* acetylation, reduced cyclin-dependent kinase (CDK)9 expression and stimulated neuronal death. Dong and Gao (35) observed high expression levels of *SP1*, forkhead box M1 (FOXM1), Snail family transcriptional repressor 2 (SNAI2) and C-X-C motif chemokine ligand 12 (CXCL12) in mice and MN9D cells damaged by rotenone. FOXM1 suppression delayed rotenone-induced damage to dopaminergic neurons *in vitro*. Experimental evidence demonstrated that *SP1* contributed to dopaminergic neuronal damage by activating the FOXM1/SNAI2/CXCL12 pathway in living organisms. *SP1* silencing provides a neuroprotective impact on dopaminergic neurons, indicating that dopaminergic neurons rely on the inactivated FOXM1/SNAI2/CXCL12 axis (Fig. 2) (35).

Furthermore, the expression of *SP1* varies over time and under different circumstances within the same malignancy. *SP1* expression is elevated in cancer cells and tissues compared

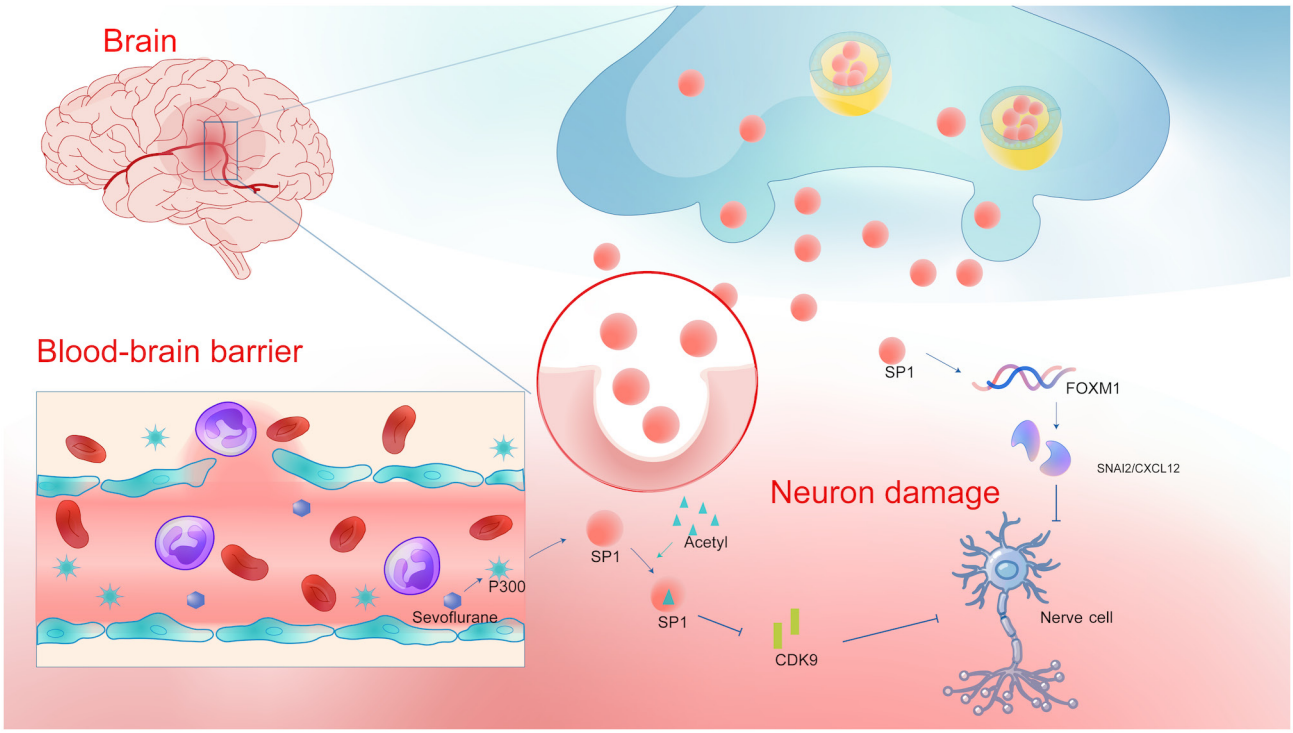

Figure 2. Regulatory mechanism of *SP1* in neuronal injury. Schematic diagram illustrates the interaction between the BBB and neuronal damage. The influx of *SP1*, a transcription factor, affects neuronal integrity. *SP1* interacts with FOXM1, promoting the expression of SNAI2 and CXCL12, which are associated with neuronal damage. Additionally, *SP1* modulates CDK9 activity, further contributing to neuronal impairment. This diagram highlights the molecular pathways involved in the disruption of the BBB and subsequent neuronal damage, providing insights into potential therapeutic targets for neuroprotection. Figure was created using Adobe Illustrator version 28.0 (Adobe, Inc.). CDK9, cyclin dependent kinase 9; CXCL12, C-X-C motif chemokine ligand 12; FOXM1, forkhead box M1; SNAI2, Snail family transcriptional repressor 2; *SP1*, specificity protein 1; BBB, blood-brain barrier.

with normal cells and tissues. However, *SP1* is closely regulated during both the initial and advanced phases of tumor development, thus impacting the evolution of cancer. Its expression levels are significantly increased in lung cancer cells exhibiting low invasiveness and in individuals diagnosed with stage I lung adenocarcinoma. *SP1* expression was decreased in lung cancer cells exhibiting high invasiveness and in stage IV lung adenocarcinoma. Furthermore, *SP1* has an inverse regulatory effect on the migration, invasion and metastasis of lung cancer cells in living organisms. The expression levels of *SP1* were reduced in highly invasive lung cancer cells because the *SP1* protein became unstable. Enhanced *SP1* expression in highly invasive lung adenocarcinoma cells upregulated E-calmodulin, a metastasis inhibitor, and attenuated the translocation of β-catenin into the cell nucleus that leads to tumor malignancy (36). Previous studies on lung cancer cohorts have demonstrated that *SP1* is elevated and stimulates cancer progression in the majority of patients with early-stage lung cancer. In advanced lung cancer, low *SP1* levels are linked to a negative prognosis. E2 raises RING finger protein 4 (RNF4) to decrease *SP1* levels, which enhances CD44 expression by reducing microRNAs (miRNAs or miRs), thereby resulting in a poor prognosis for young women with lung cancer (37). Therefore, treatment approaches aimed at suppressing *SP1* may not be appropriate for all patients with lung cancer, regardless of their stage of disease.

Molecular mechanisms of SP1 in migration and invasion. *SP1* is a widely expressed transcription factor. A previous study has revealed that *SP1* plays a key role in the migration and invasion of numerous cancer types; its main molecular mechanisms include transcriptional regulation of pro-metastatic genes, modulation of the WNT signaling pathway to promote metastasis, enhancement of cancer-promoting transcription by LLPS, metabolic reprogramming to promote invasion and immune microenvironmental regulation (38). *SP1* promotes cancer cell migration and invasion through direct activation of several genes associated with epithelial-mesenchymal transition (EMT) and extracellular matrix remodeling. For example, the promoter of vimentin binds to *SP1* to promote expression and enhance cancer cell migration (38). In addition, *SP1* inhibits E-cadherin, and promotes cancer cell dedifferentiation and invasion by upregulating Snail/Twist (39). Regarding the regulation of the WNT signaling pathway, *SP1* drives the activation of WNT/β-catenin signaling, and promotes the dynamic communication between cancer cells and the microenvironment, which enhances the invasiveness of cancer cells. In addition, WNT signaling can further activate c-Myc and cyclin D1, thus promoting cancer cell proliferation and metastasis (40).

SP1 enhances pro-oncogenic transcription through LLPS. A previous study has shown that the demethylase inhibitor GSK-J4 disrupts *SP1* phase separation and inhibits its pro-metastatic activity (19), suggesting that targeting *SP1*-LLPS may be a new anti-metastatic strategy. *SP1* regulates key enzymes of glycolysis, such as PKM2 and lactate dehydrogenase A to promote the Warburg effect, enhance cancer cell energy supply and support migration (41).

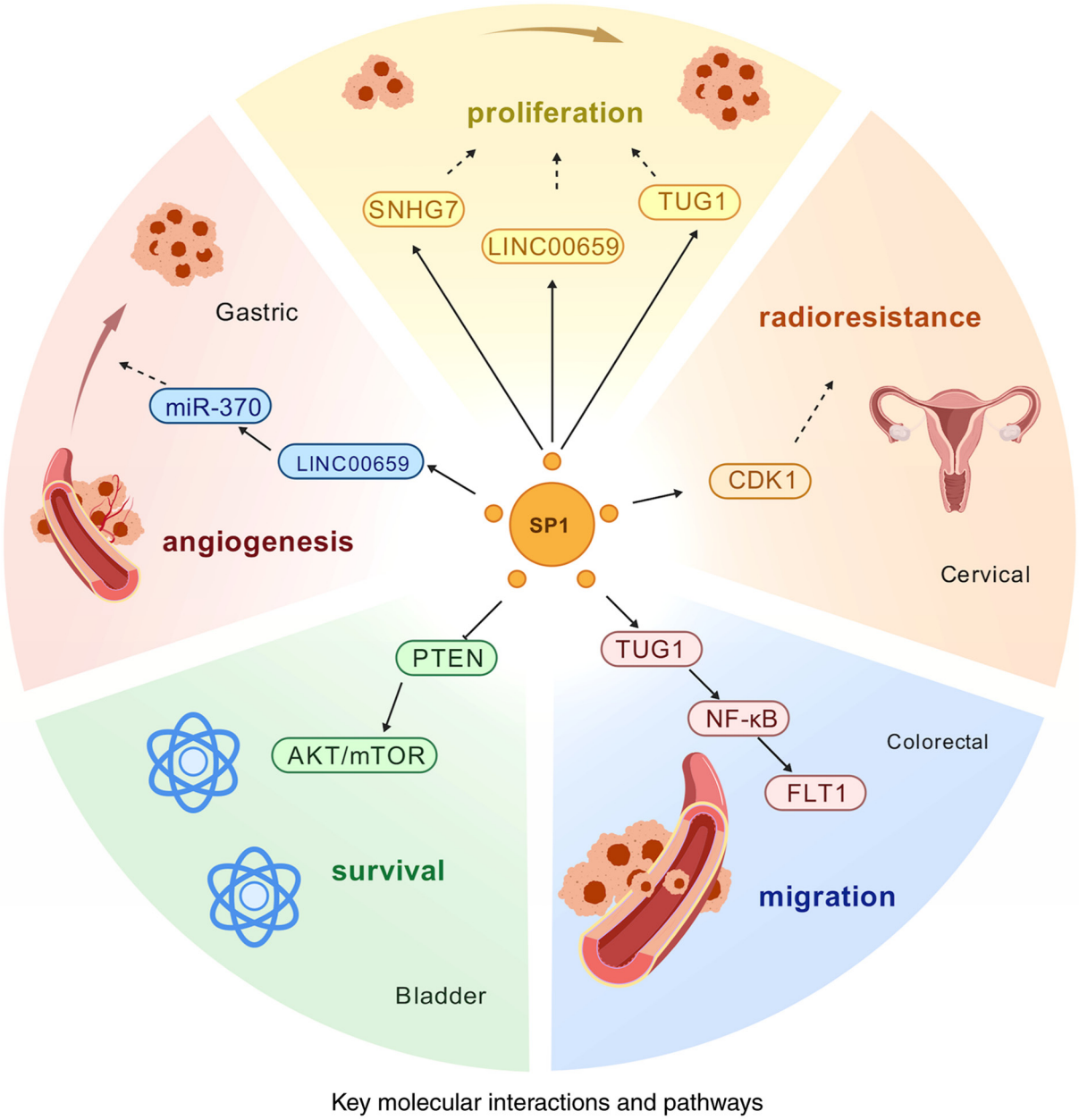

Figure 3. Key molecules and pathways regulated by *SP1* in tumorigenesis and cancer progression. The key molecules and pathways annotated in this figure demonstrate the pleiotropic roles of *SP1* in tumorigenesis and cancer progression, highlighting its potential as a therapeutic target. Figure was created using Adobe Illustrator version 28.0 (Adobe, Inc.). NF-κB, nuclear factor κB; PTEN, phosphatase and tensin homolog; SNHG7, small nucleolar RNA host gene 7; *SP1*, specificity protein 1; TUG1, taurine-upregulated gene 1; miR, microRNA; LINC00659; long intergenic non-protein coding RNA 659; AKT, protein kinase B; mTOR, mTOR, mechanistic target of rapamycin; CDK1, cyclin dependent kinase; FLT1, fms-related tyrosine kinase 1.

In conclusion, *SP1* promotes cancer cell migration and invasion through transcriptional regulation, phase separation and other mechanisms. Targeting *SP1* or its downstream effector molecules, such as WNT and PKM2, may become a new direction for anti-metastatic therapy. However, challenges such as off-target effects and drug resistance remain to be addressed (Fig. 3).

SP1 is associated with cardiomyopathy. *SP1* is important in controlling tumor growth and is a major factor in the development of common illnesses. Ström *et al* (30) observed that mice with reduced *SP1* levels developed hypertrophic cardiomyopathy, which was characterized by significant cardiac hypertrophy, interstitial fibrosis and disorganized myofilament fibers. Furthermore, inhibition of *SP1* led to a significant increase in the cell area of the human induced pluripotent stem cell-derived cardiomyocytes and caused intracellular myofibrillar disorganization similar to that of hypertrophic cardiomyocytes in hypertrophic cardiomyopathy. Tuftelin 1 was identified as an essential target gene for *SP1*. *SP1* overexpression inhibited the progression of hypertrophic cardiomyopathy in myosin heavy chain R404Q/+ mutant mice and corrected the hypertrophic characteristics in human induced pluripotent stem cell-derived cardiomyocytes with hypertrophic cardiomyopathy. *SP1* may be a promising target for the treatment of hypertrophic cardiomyopathy.

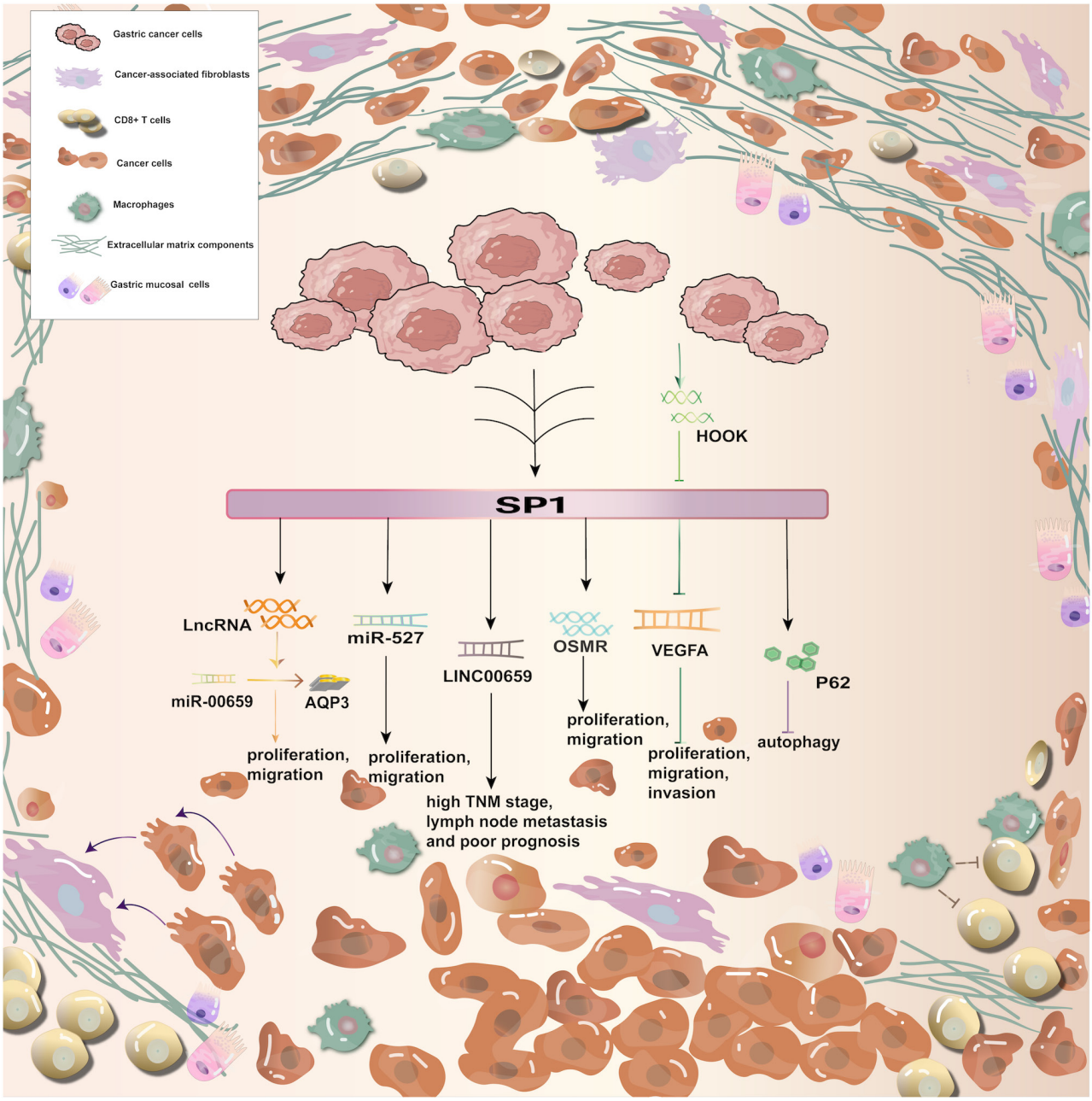

Figure 4. Regulatory mechanism of *SP1* in gastric cancer. *SP1*, a transcription factor, interacts with various molecules and pathways that promote cancer cell proliferation, migration and invasion. Specifically, *SP1* influences the expression of lncRNA, miR-527, miR-00659 and circular RNA LINC00659, which in turn regulate the activity of downstream targets such as AQP370, OSMR, VEGFA and P62. These targets are associated with tumor growth, migration, invasion and autophagy. The diagram includes a legend identifying various cell types involved in the tumor microenvironment, including gastric cancer cells, cancer-associated fibroblasts, CD8+ T cells, macrophages, extracellular matrix components and gastric mucosal cells. Figure was created using Adobe Illustrator version 28.0 (Adobe, Inc.). LINC00659, long intergenic non-protein coding RNA 659; lncRNA, long noncoding RNA; OSMR, oncostatin M receptor; *SP1*, specificity protein 1; TNM, tumor-node-metastasis; VEGFA, vascular endothelial growth factor A; miR, microRNA; HOOK, hook microtubule tethering protein; AQP3, aquaporin3.

4. *SP1* and regulation of the tumor microenvironment (TME)

Involvement of SP1 in the formation of an immunosuppressive microenvironment. Upregulated miR-21 in tumor-associated mesenchymal stem cells diminishes the DNA methylation level of the miR-21 promoter region via the *SP1*/DNA methyltransferase 1 pathway, thus facilitating the elevated expression of miR-21 and augmenting the immunosuppressive capacity of myeloid-derived suppressor cells (42).

Immunosuppressive function of tumor-associated macrophages (TAMs). TAMs suppress T-cell function both directly and indirectly through multiple effects, including the expression of immunological checkpoints such as PD-L1, the production of inhibitory cytokines (such as IL-10 and transforming growth factor-β) and modifications in metabolic activity. TAMs restrict T-cell infiltration by modulating the vascular architecture and extracellular matrix, thereby preventing T cells from accessing intratumoral regions. Exosomal miR-21-5p in hepatocellular carcinoma (HCC) cells

influences HCC cell progression via modulating *SP1*/X-box binding protein 1 (XBP1) and facilitating the M2 polarization of TAMs, consequently impacting the unfavorable prognostic outcomes of patients with HCC (43).

Regulation of neutrophil function. Chronic stress leads to increased *SP1* levels in tumor-derived exosomes, which are internalized by lung neutrophils, thereby stimulating the release of IL-1β via the TLR4-NFκβ-κB pathway. This results in an immunosuppressive milieu that aggravates lung metastasis of breast cancer (6).

Influence on macrophage polarity. The polarity of macrophages, as indicated by CXCL9 and SPP1, is a crucial characteristic of the TME (44). The CXCL9:SPP1 ratio can delineate the prevalence of antitumor immune cells within a tumor, the gene expression profiles of each tumor-infiltrating cell type, and can quantify tumor control or progression, the modulation of communication networks and the response to immunotherapy (45).

Influence on immune cell infiltration. In HCC, SPP1+ macrophages and cancer-associated fibroblasts co-localize in the tumor periphery, creating a tumor immune barrier that obstructs T-cell infiltration into the tumor core, resulting in suboptimal immunotherapy outcomes. Conversely, in a mouse model with SPP1 knockdown, the therapeutic efficacy improved following anti-PD-1 treatment, indicating that SPP1 may modulate the immunological milieu by affecting immune cell infiltration (46).

5. *SP1* in immune escape

Role in gastric cancer. Chemotherapeutic drugs enhance chromatin accessibility and facilitate self-activation of the *SP1* gene promoter region in gastric cancer cells. Activated *SP1* enhances the expression of solute carrier family 6 member 6 (SLC6A6), leading gastric cancer cells to absorb increased quantities of taurine from the microenvironment to mitigate the effects of chemotherapeutic agents. Concurrently, this results in taurine depletion within the microenvironment, which diminishes the expression and functionality of immune checkpoints in CD8+ T cells, ultimately yielding a suboptimal response to immune checkpoint inhibitors in patients. The *SP1*-SLC6A6 regulatory axis is a crucial element connecting chemotherapy and immunotherapy resistance. It offers a clear molecular rationale for the clinical observation of diminished effectiveness of immune checkpoint inhibitors following treatment with numerous chemotherapy regimens (47).

Role in colorectal cancer. Histone demethylase Jumonji domain containing 2D (JMJD2D) functions as a transcriptional coactivator for the factors *SP1*, signal transducer and activator of transcription 3 (STAT3) and interferon regulatory factor transcription factor (IRF)-1. The interaction between JMJD2D and the DNA-binding domain of *SP1* results in increased production of the interferon-γ receptor 1 gene. STAT3 and IRF1 collaborate with the coactivator JMJD2D to increase PD-L1 gene expression, resulting in immune evasion in colorectal cancer (48).

Role in cellular pyroptosis. The transcription factor SP1 binds to the promoter region of gasdermin-E (GSDME), thereby enhancing the expression of GSDME, a crucial execution protein in tumor cells experiencing pyroptosis. This process is initiated by the cleavage of the upstream caspase-3 (CASP3) protein, leading to the formation of a detrimental pore-like structure in the cell membrane, resulting in cell death, rupture and release of inflammatory mediators. This procedure is critical for the survival of tumor cells and their method of cell death. Inhibition of this system increases tumor cell resistance to chemotherapeutic agents, exhibiting a synergistic interaction with the STAT3 transcriptional regulatory pathway and an antagonistic association with DNA methylation. Silencing of *SP1* or pharmacological inhibition diminishes GSDME expression, thereby decreasing the N-terminal levels of GSDME, which is cytotoxic during pyroptosis. This effect eventually reduces cell death and the release of cellular contents (49).

6. Role of *SP1* in different tumors

SP1 is linked to a diverse array of malignancies (≥20 types), most notably colorectal, breast, pancreatic, lung and liver cancer.

SP1 in colorectal cancer. Multiple studies have indicated that *SP1* serves as a connector between crucial oncogenic and metastatic signaling pathways in colorectal cancer. It is involved in tumor cell movement, invasion, EMT and response to treatment. Huang *et al* (50) demonstrated that *SP1* interacted with the taurine upregulated 1 (TUG1) promoter to control its expression, leading to the upregulation of TUG1. This upregulation contributes to the oncogenic characteristics of colorectal cancer.

Previous studies employed immunoblotting to confirm that the colon cancer 1 (MACC1)/MET signaling pathway associated with oncogenic metastasis is deactivated due to miR-320a-induced *SP1* downregulation, which enhances MACC1 transcription (51). Inhibition of miR-320a by *SP1* leads to proliferation and invasiveness of colorectal cancer cells (51). Based on cell function studies, Li *et al* (52) found that miR-1224-5P suppressed colorectal cancer cell motility, invasiveness and EMT by targeting *SP1*. Furthermore, *SP1* stimulated the phosphorylation of P65, thereby promoting the advancement of EMT in colorectal cancer cells. In summary, *SP1* facilitates the NF-κB signaling pathway to enhance metastasis and EMT in colorectal cancer (52). Xu *et al* (53) demonstrated that miR-375 limits the growth of colorectal cancer cells via targeting *SP1*. Yu *et al* (54) showed that *SP1* increased the levels of long noncoding RNA (lncRNA) terminal differentiation-induced noncoding RNA (TINCR), leading to the advancement of colorectal cancer by acting as a sponge for miR-7-5P. Chen *et al* (55) showed that *SP1* stimulated ZNFX1 antisense RNA 1 to increase vascular endothelial growth factor A (VEGFA) levels via binding to miR-150-5P, thereby enhancing the development of colorectal cancer (55). Sun *et al* (56) reported that *SP1* played a role in the suppressive impact of miRNA-382 on cell proliferation and movement in colorectal cancer. Furthermore, *SP1* plays a vital role in colorectal cancer migration and invasiveness

through several pathways, including the miR-150-5P/VEGFA axis (55), the death receptor 4/neurofibromin 1 switch axis (57) and the WNT/β-collagen pathway (58). It was established that *SP1*-dependent promoter progenitors stimulate FOXO3A gene transcription in colorectal cancer cells, and upregulation of the FOXO3A gene by *SP1* is necessary for the development of colorectal cancer (59). The aforementioned experimental investigations concerning *SP1* offer a foundation for prospective targeted treatment in patients with colorectal cancer.

SP1 in gastric cancer. Shi and Zhang (60) determined that *SP1* expression was positively correlated with the degree of tumor infiltration, tumor-node-metastasis (TNM) stage, lymph node metastasis and Lauren stage; however, it was not correlated with tumor differentiation. Kaplan-Meier analysis demonstrated that *SP1* mRNA expression was inversely related to the overall and progression-free survival of patients with gastric cancer. Additionally, *SP1* protein expression was elevated in gastric cancer tissues compared with normal tissues, and was linked to the depth of infiltration and TNM stage of gastric cancer. The inverse association between tripartite motif containing 25 (TRIM25) and *SP1* protein levels in human gastric cancer tissues confirms that elevated *SP1* levels and decreased TRIM25 levels are associated with a worse outcome for patients with gastric cancer (61). Xu *et al* (5) revealed that *SP1* activated P62, subsequently reducing the autophagic flux of the cells. Furthermore, the absence of *SP1* led to an elevated autophagy rate in gastric cancer cells. That study presented evidence of a new method for controlling autophagy in gastric cancer cells. Wang *et al* (62) validated that *SP1* could increase the expression of long intergenic non-protein coding RNA 659 (LINC00659) in gastric cancer. Clinical analyses revealed a correlation between elevated LINC00659 levels and TNM stage, lymph node metastasis and a worse prognosis. The authors also experimentally verified that *SP1* triggered the increase of lncRNAs, which controlled the miR-00659/aquaporin 3 axis, consequently fostering the progression of gastric cancer. Zhang *et al* (63) demonstrated that *SP1* is important in advancing gastric cancer, and its participation in the miR-527/*SP1* axis enhances the proliferation and spread of gastric cancer cells. Yu *et al* showed that *SP1* interacts with the promoter region (-255 to -246 region) of the human oncostatin M receptor (OSMR) gene, as well as with OSMR that is overexpressed in gastric cancer cells. Consequently, *SP1* has a positive regulatory function in promoting the development and metastasis of gastric cancer cells through this gene (64).

Pan *et al* (49) showed that *SP1* promotes the spread of gastric cancer through fatty acids. Previous research verified that miR-149 reduced the expression of zinc finger and BTB domain containing 2 and *SP1*, thus suppressing the cancer-promoting activity of gastric cancer associated transcript 1 (53). *SP1* can increase urothelial cancer associated 1 expression in gastric cancer, and enhance gastric cancer cell proliferation by engaging enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2) and activating the protein kinase B (AKT) pathway specific to gastric cancer (57). Recent research indicates that hook microtubule tethering protein 3 (HOOK3) controls VEGFA expression in gastric cancer cells by suppressing *SP1*, and restrains the proliferation, movement and infiltration of gastric cancer cells. The mechanism via which HOOK3 controls *SP1* remains unidentified and requires further investigation (65). *SP1* is essential for the development and spread of gastric cancer. Further studies are warranted to fully understand the mechanisms of *SP1* and its role in regulation (Fig. 4).

SP1 in breast cancer. Previous studies have shown that *SP1* increases the expression of TINCR, leading to enhanced cell proliferation, growth anchoring and decreased apoptosis in breast cancer cells (66). Monteleone *et al* (67) reported that STAT3 and *SP1* may act together to promote increased Ras homolog family member U levels and enhance the migration of breast cancer cells. Li *et al* (68) observed that miR-212-3p suppressed VEGFA expression through *SP1*, leading to decreased angiogenesis in breast cancer. *SP1* is responsible for epigenetic dysregulation, and is involved in determining the responsiveness of human epidermal growth factor receptor 2-overexpressing breast cancer to treatment with HDAC inhibitors (69). It was reported that miR-539 functioned as a tumor suppressor by targeting *SP1* (70). Zhang *et al* (71) noticed the involvement of TIMELESS circadian regulator and *SP1* in sphingolipid metabolism, with *SP1* playing a role in promoting the development of breast cancer. *SP1* is implicated in several signaling pathways in breast cancer, including the miR-2110/*SP1* axis (72) and ERK/*SP1* signaling network (73). Previous research has shown that miR-506 decreases the methylation of maternally expressed 3 through a *SP1*/SP3-dependent process, leading to a decrease in breast cancer cell motility and invasiveness (74). *SP1* is essential in several signaling pathways related to breast cancer, including the miR-539/*SP1*, miR-212-3p/*SP1* and miR-2110/*SP1* axes, and the ERK/*SP1* signaling pathway.

SP1 in ovarian cancer. Bai *et al* (75) found that the *SP1* molecule triggered the activation of lncRNA small nucleolar RNA host gene (SNHG)7 and interacted with EZH2 to enhance the development of ovarian cancer. Cui *et al* (76) demonstrated that *SP1* stimulated differentiation antagonizing non-protein coding RNA to facilitate ovarian cancer development. Previous studies have demonstrated a strong positive correlation between the expression levels of exosomal CUB domain containing protein 1 (CDCP1) and *SP1* in patients with ovarian cancer. Both proteins are highly expressed in ovarian cancer cells. Furthermore, *SP1*-regulated matrix metalloproteinase (MMP)2 and MMP9 proteins are positively correlated with CDCP1, suggesting a synergistic association between CDCP1 and *SP1*. However, the exact mechanism underlying this association remains unknown (77). Previous research suggests that exosomal miR-21-5p in HCC cells can affect HCC cell development by controlling *SP1*/XBP1 and encouraging the M2 polarization of TAMs, ultimately influencing responses associated with poor prognosis in patients with HCC (43).

Wang *et al* (78) demonstrated that ferritin-1 hindered cisplatin-induced ovarian damage and granulosa cell death both *in vivo* and *in vitro*, thus expanding on the connection between *SP1* and ovarian illness. The expression levels of acyl-CoA synthetase long chain family member 4 (ACSL4) and glutathione peroxidase 4 were considerably and simultaneously altered. The ACSL4 inhibitor rosiglitazone reduced

ovarian damage in mice treated with chemotherapy. Cisplatin enhanced the expression of *SP1*, which in turn bound to the promoter of ACSL4 to boost transcription (78). *SP1* is crucial in the development of ovarian cancer, as well as in ovarian damage and granulosa cell death. However, additional studies are required to identify the precise mechanism involved in these processes.

SP1 in lung cancer. SP1 is closely controlled at various stages of lung cancer, influencing cancer cell advancement in diverse ways at different points in time. Young *et al* (37) found that decreased *SP1* expression in premenopausal patients with advanced lung cancer was associated with a poor prognosis. The study verified that estradiol suppressed *SP1* levels, resulting in decreased miR-3194-5P expression and increased CD44 expression, eventually promoting cancer advancement. Cancer stem cell-related proteins can enhance *SP1* activity. In non-small cell lung cancer, resistance to pemetrexed was closely linked to *SP1* activity (79). Hu *et al* (80) showed that the decaprenyl diphosphate synthase subunit 2 (PDSS2) promoter harbored binding sites for *SP1* and GATA binding protein 1. *SP1* and PDSS2 expression are negatively regulated, and increased *SP1* expression and decreased PDSS2 expression are strongly linked to a poor prognosis in lung cancer. In lung cancer cells, the suppression of PDSS2 transcription by *SP1* leads to pathogenicity. Previous research has shown that *SP1* is involved in the AKT and ERK1/2 signaling pathways in non-small-cell lung cancer, promoting cancer cell proliferation and migration (81). In addition, the miR-326/*SP1*/KLF3 axis plays a role in the development of lung cancer (82). These findings demonstrate the important contribution of *SP1* to lung cancer advancement.

SP1 in prostate cancer. Wang *et al* (83) demonstrated that *SP1* increased SNHG4 expression in prostate cancer. The elevated SNHG4 levels were strongly associated with lymph node metastases, tumor stage and worse overall survival in patients with prostate cancer. Experimental evidence revealed that *SP1* enhanced the progression of prostate cancer by increasing the expression of SNHG4. Previous research indicated that *SP1* triggered the WNT/β-cyclin signaling pathway and facilitated EMT, leading to increased proliferation and invasiveness of prostate cancer cells. Furthermore, overexpression of glypican 5 (GPC5) counteracted this effect, suggesting that GPC5 exerts a cancer-suppressing effect by inhibiting *SP1*. In summary, GPC5 can have a cancer-suppressive impact by blocking *SP1*, and *SP1* affects lymph node metastasis and tumor stage in prostate cancer by increasing SNHG4 expression. Additionally, *SP1* triggers the WNT/β-linker protein signaling pathway, leading to EMT. This process enhances the proliferation and invasiveness of prostate cancer cells, and reduces overall survival in patients.

SP1 in cervical cancer. Previous research has demonstrated that the activation of lung cancer associated transcript 1 by *SP1* contributes to the development of cancer in the cervix by enhancing the proliferation, migration and invasiveness of cervical cancer cells (84). Deng *et al* (85) reported a notable correlation between high *SP1* expression and advanced International Federation of Gynecology and Obstetrics stage, lymph node metastases, and lymph node interstitial infiltration in cervical cancer. Expression of *SP1* in cervical cancer cell lines increased in a dose-dependent manner at both the mRNA and protein levels. *SP1* impacted the longevity of cervical cancer cells following radiotherapy. Suppression of *SP1* caused cell cycle arrest at the G_2/M phase in cervical cancer cells, which led to a significant improvement in cell response to radiotherapy. Increased *SP1* expression decreased G_2/M cell cycle arrest in cervical cancer cells, which was associated with increased expression of CDK1. *SP1* may hinder G_2/M phase arrest and enhance the effectiveness of radiotherapy for cervical cancer by affecting CDK1 (85). Previous research indicated that magnolin (MGL), a chemical derived from the magnolia plant, exhibited inhibitory effects on tumor cell invasiveness and proliferation. MGL hindered cellular metastasis by affecting IL-10/IL-10 receptor B expression, which reduced the JUN N-terminal kinase/*SP1*-mediated production of MMP15, thereby influencing the cervical cancer microenvironment (86). *SP1* plays an oncogenic function in cervical cancer by enhancing the proliferation, migration and invasiveness of cervical cancer cells. It also impacts the survival of these cells following radiotherapy, which is detrimental to patients. The introduction of MGL significantly reduced the negative effects of *SP1* on the cervical cancer microenvironment. Further investigation should uncover the precise mechanism involved in this process, offering a theoretical foundation for the treatment of cervical cancer.

SP1 in osteosarcoma. Signal regulatory protein α (SIRPA) is increased in osteosarcoma tissues, particularly in metastatic tissues, and is linked to a worse prognosis. Reducing SIRPA levels results in decreased stability of *SP1* and arginine absorption, which impacts the migration of osteosarcoma cells. SIRPA activates ERK to phosphorylate *SP1*, preventing its degradation by the proteasome. *SP1* boosts solute carrier family 7 member 3 (SLC7A3) expression by attaching to the SLC7A3 promoter, which leads to increased arginine absorption and encourages the migration of osteosarcoma cells. Arginine improves the stability of *SP1*, creating the '*SP1* stabilization loop'. Previous research demonstrated that increased SIRPA expression enhanced osteosarcoma migration through the '*SP1* stability circle' and SLC7A3-mediated arginine absorption (87). Lysine demethylase 3A (KDM3A) is abundantly present in osteosarcoma tissues and cells. KDM3A boosts *SP1* gene expression by removing methyl groups from its promoter region. *SP1* interacts with the 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 4 (PFKFB4) promoter to stimulate its transcription and enhance its expression. Overexpression of PFKFB4 markedly enhanced the proliferation and metastasis of osteosarcoma cells, and increased the glycolytic activity in these cells. Activation of the KDM3A-*SP1* axis increased the expression of PFKFB4, which led to improved aerobic glycolysis in osteosarcoma and the promotion of tumor growth (88). Mi *et al* (89) showed that the *SP1* gene was upregulated in osteosarcoma, facilitating osteosarcoma progression by increasing LINC00514 expression through competitive binding to miR-708. Hu *et al* (90) showed that the transcription factor *SP1* functioned as a tumor promoter in osteosarcoma by increasing the interleukin enhancer binding factor 3-antisense 1 levels through the control of the

miR-212-SRY-box transcription factor 5 pathway. Another study on osteosarcoma revealed that trans-chalcone impacted the expression of *SP1* and P53 in transcription and proteasome regulation, respectively, thereby influencing the development of this cancer type (91).

SP1 in pancreatic cancer. LIM domain-containing protein Ajuba is a recently identified transcriptional co-regulator that is involved in the development of various types of cancer. Elevated protein and mRNA expression levels of Ajuba and *SP1* in pancreatic cancer tissues are positively connected, and are associated with a worse prognosis in patients. Ajuba binds to the C-terminus of *SP1* and functions as a coactivator to increase *SP1* gene expression and stimulate cell proliferation. The Ajuba promoter includes active *SP1* response elements, and Ajuba is a target gene of *SP1*. The Ajuba/*SP1* complex can create a feed-forward loop that stimulates the transcription of *SP1* target genes and enhances cell proliferation in pancreatic cancer. Ajuba and *SP1* may serve as diagnostic markers and potential targets for the treatment of pancreatic cancer (92). The nuclear factor of activated T cells (NFAT) transcription factor plays a major role in the oncogenicity of pancreatic cancer. Tumor necrosis factor α (TNFα) is a target gene for the interaction between NFATc2 and *SP1*. It has been demonstrated that small interfering RNAs (siRNAs) decrease cell proliferation by blocking NFATc2, *SP1* and TNFα (93). Through survival analysis, Xu *et al* (53) showed that adenylate kinase 4 pseudogene 1 (AK4P1) was a significant predictor of poor prognosis in patients with pancreatic cancer. Subcellular localization studies revealed that AK4P1 was mostly found in the cytoplasm, and may compete for binding with miR-375 in pancreatic cancer cells. *SP1* has been identified as a possible gene that is regulated by miR-375 in pancreatic cancer. Previous expression analyses confirmed that *SP1* could enhance AK4P1 levels in pancreatic cancer. The AK4P1/miR-375/*SP1* pathway is crucial for the progression of pancreatic cancer (94). Previous research showed that protein phosphatase 3 catalytic subunit β inhibited pancreatic cancer progression by promoting atonal bHLH transcription factor 8 translocation and transcriptionally regulating *SP1* (95). Yang *et al* (96) analyzed the transcription of Yes-associated protein 1 (YAP1) in pancreatic cancer cells, and found that the transcription factor *SP1* was upregulated by the atypical protein kinase C isoform t and subsequently bound to multiple sites in the YAP1 promoter to drive the transactivation of YAP1 in pancreatic cancer cells carrying mutant KRAS (Kirsten rat sarcoma viral oncogene homolog (KRAS). Gao *et al* (97) suggested that propofol represses pathological biological behaviors associated with pancreatic cancer cells through the suppression of *SP1*.

SP1 in endometrial cancer. Shao *et al* (74) reported that *SP1* was a direct target of miR-490. Knocking down *SP1* could counteract the impact of miR-490 inhibition on the aggressive behavior of cancer cells. Knockdown of deleted in lymphocytic leukemia 1 (DLEU1) suppressed the phosphoinositide-3-kinase/AKT/glycogen synthase kinase 3β (PI3K/AKT/GSK3β) pathway induced by miR-490 suppression, while *SP1* knockdown may counteract this pathway. These findings indicate that DLEU1 facilitates the development of endometrial cancer by controlling *SP1* expression (98). Liu *et al* (99) identified natural killer cell-related genes involved in cytotoxicity, including CASP3. Further analysis indicated that CASP3 reduced the expression of poly (ADP-ribose) polymerase 1 (PARP1). In addition, analysis of data from the Transcriptional Regulatory Relationships Unraveled by Sentence-based Text database indicated that *SP1* regulated CASP3. By conducting an in-depth investigation on uterine natural killer cell-related genes, it was suggested that the *SP1*-CASP3-PARP1 axis leads to recurrent miscarriage. Previous research has demonstrated that elevated *SP1* levels promote the development of endometrial fibrosis (100), which is an important characteristic in individuals experiencing recurrent miscarriage (101). Elevated levels of *SP1* were detected in ovarian endometriosis, and it was shown that miR-25-3p directly interacted with *SP1*. This evidence indicates a new miRNA/*SP1* pathway in the development of endometriosis, although further investigation is warranted to determine the precise underlying mechanism (102).

SP1 in bladder cancer. Bladder cancer cells overexpress *SP1*. Suppression of *SP1* hindered bladder cancer cell proliferation, migration and invasion, while enhancing programmed cell death. Phosphatase and tensin homolog (PTEN) enhanced tumor cell survival, migration and invasion, while decreasing cell death; these effects were reversed by *SP1* depletion. Reducing *SP1* levels lessened the activation of the AKT/mechanistic target of rapamycin kinase (AKT/mTOR) pathway induced by PTEN reduction. Previous *in vivo* experiments showed that reducing *SP1* expression suppressed tumor development, elevated PTEN levels and reduced the expression of proteins linked to the AKT/mTOR pathway. *SP1* enhanced the progression of bladder cancer by blocking the PTEN-mediated AKT/mTOR pathway (103). Elevated *SP1* mRNA expression was observed in urothelial bladder cancer tissues compared with normal bladder tissues using reverse transcription-quantitative PCR. Immunohistochemistry revealed a strong correlation between elevated *SP1* expression and histological grade, tumor stage, vascular invasion, lymph node metastasis and distant metastasis ($P<0.05$). According to the results of log-rank test, elevated *SP1* expression in cancer tissues was associated with worse overall survival and disease-free survival compared with low *SP1* expression ($P<0.05$). High levels of *SP1* expression in bladder urothelial carcinoma may serve as a marker for identifying patients with a poor prognosis and aggressive disease (104). Yan *et al* (105) found that miR-300 suppressed the migration of bladder cancer cells via controlling the *SP1*/MMP9 pathway. The study revealed that miR-300 directly targeted *SP1* and suppressed its expression by selectively binding to its 3'-non-coding region. Reducing MMP9 led to the migration of bladder cancer cells. *SP1* promoted bladder cancer progression by inhibiting the PTEN-mediated AKT/mTOR pathway. Overall, the aforementioned findings indicate that *SP1* has a significant impact on bladder cancer (Table I).

7. *SP1* and clinical treatment

As a widely expressed transcription factor, *SP1* regulates several pro-oncogenes, such as survivin and VEGF. However, direct inhibition of *SP1* may affect the physiological functions

Table I. Role of SP1 in various tumor types.

Cancer type	Key molecular targets/ pathways	Role of *SP1*	Clinical/functional outcome
Colorectal	TUG1, miR-320a, miR-1224-5p, NF-κB, VEGFA, WNT/β-catenin	Upregulated; promotes EMT, metastasis and chemoresistance	Poor prognosis; enhances cell proliferation and invasion
Gastric	LINC00659, P62, OSMR, UCA1, HOOK3/VEGFA	Overexpressed; linked to autophagy suppression and metastasis	Correlates with TNM stage, lymph node metastasis and poor survival
Breast	TINCR, RhoU, VEGFA, miR-539, ERK/SP1, HDAC	Drives proliferation, angiogenesis and HER2 signaling	Associated with therapy resistance and poor outcomes
Ovarian	SNHG7, DANCR, CDCP1, ACSL4/GPX4	Activates lncRNAs to promote proliferation and chemoresistance	High SP1 expression correlates with aggressive tumor behavior
Lung	PDSS2, AKT/ERK, miR-3194-5p/CD44	Suppresses PDSS2; enhances stemness and pemetrexed resistance	Poor prognosis; promotes metastasis and therapy resistance
Prostate	SNHG4, WNT/β-catenin, GPC5	Upregulates SNHG4 to drive EMT and invasion	Linked to advanced stage and lymph node metastasis
Cervical	LUCAT1, CDK1, IL-10/ MMP15	Promotes radioresistance and metastasis via CDK1	High SP1 expression correlates with FIGO stage and reduced survival
Osteosarcoma	SLC7A3, PFKFB4, LINC00514, miR-708	Stabilizes the 'SP1 loop' to enhance arginine uptake and glycolysis	Drives metastasis; poor prognosis
Pancreatic	Ajuba/SP1 loop, NFATc2/ TNFα, AK4P1/miR-375	Forms feed-forward loops to sustain proliferation	Overexpression linked to worse survival
Endometrial	DLEU1/miR-490, PI3K/ AKT, CASP3-PARP1	Promotes fibrosis and immune evasion	Associated with recurrent miscarriage and aggressive tumors
Bladder	PTEN/AKT/mTOR, MMP9, miR-300	Inhibits PTEN to activate AKT/ mTOR; drives invasion	High SP1 expression correlates with advanced grade/stage and poor survival

SP1, specificity protein 1; TUG1, taurine upregulated 1; miR, microRNA; NF-κB, nuclear factor κB; VEGFA, vascular endothelial growth factor A; LINC00659, long intergenic non-protein coding RNA 659; OSMR, oncostatin M receptor; UCA1, urothelial cancer associated 1; HOOK, hook microtubule tethering protein; TINCR, terminal differentiation-induced noncoding RNA; RhoU, Ras homolog family member U; ERK, extracellular signal-regulated kinase; HDAC, histone deacetylase; SNHG, small nucleolar RNA host gene; DANCR, differentiation antagonizing non-protein coding RNA; CDCP1, CUB domain containing protein 1; ACSL4, acyl-CoA synthetase long chain family member 4; GPX4, glutathione peroxidase 4; PDSS2, decaprenyl diphosphate synthase subunit 2; AKT, AKT, protein kinase B; GPC5, glypican 5; LUCAT1, lung cancer associated transcript 1; CDK, cyclin dependent kinase; IL, interleukin; MMP, matrix metalloproteinase; SLC7A3, solute carrier family 7 member 3; PFKFB4, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 4; NFAT, nuclear factor of activated T cells; TNFα, tumor necrosis factor α; AK4P1, adenylate kinase 4 pseudogene 1; DLEU1, deleted in lymphocytic leukemia 1; PI3K, phosphoinositide-3-kinase; CASP3, caspase-3; PARP1, poly (ADP-ribose) polymerase 1; PTEN, phosphatase and tensin homolog; mTOR, mechanistic target of rapamycin; ETM, epithelial-mesenchymal transition; HER2, human epidermal growth factor receptor 2; lncRNA, long noncoding RNA; PDSS2, decaprenyl diphosphate synthase subunit 2; TNM, tumor-node-metastasis; FIGO, International Federation of Gynecology and Obstetrics.

of normal cells and lead to toxicity. In addition, due to the lack of highly selective *SP1* inhibitors, existing drugs such as mithramycin A have limited clinical application due to side effects; thus, there is a certain degree of complexity in targeting *SP1* inhibition (106).

SP1 promotes chemoresistance by upregulating anti-apoptotic proteins such as B-cell lymphoma 2 (Bcl-2) and metabolic reprogramming such as enhanced glycolysis (107). In addition, *SP1* can synergize with KRAS signaling, thereby exacerbating immunosuppression in the TME and decreasing immunotherapeutic response, making resistance challenging (108). When the TME is impaired, the dense fibrotic mesenchyme of pancreatic cancer can hinder drug delivery (109), and *SP1*-driven EMT further promotes invasion and metastasis (110). EMT and metastasis can be reduced by developing *SP1* inhibitors such as mithramycin A, which has inhibited *SP1*-DNA binding in preclinical models; however, further optimization is needed to reduce toxic effects such as myelosuppression. Additionally, efficacy can be enhanced by screening natural compounds such as curcumin derivatives, possibly by blocking *SP1* phosphorylation, including in the AKT/ERK pathway (111).

Combination targeted therapy could be a promising approach. For example, *SP1* combined with KRAS inhibition may be an option. *SP1* is dependent on KRAS signaling, and co-inhibition can overcome drug resistance (112). Previous research has shown that DNA nanocarriers such as tubular DNA origami structures (~70 nm) can selectively deliver *SP1* siRNA or chemotherapeutic agents to KRAS-mutant tumors to reduce off-target effects. Therefore, the development of nanodelivery

technologies could be a promising intervention (113). In terms of immune microenvironment regulation, *SP1* knockdown enhanced CD8+ T-cell infiltration; if combined with PD-1 inhibitors, it may reverse immune escape (114).

In the future, *SP1* subtype- or structural domain-specific inhibitors, such as zinc finger domain blockers, could be developed to precisely target therapy and reduce systemic toxicity. In addition, the dynamic regulatory network of *SP1* in tumor heterogeneity may be resolved by combining single cell sequencing and chromatin immunoprecipitation sequencing. Phase 1 clinical trials can also be advanced by optimizing the pharmacokinetics of *SP1* inhibitors. Furthermore, *SP1* inhibitors plus epigenetic drugs, such as HDAC inhibitors or lysoviruses, may be utilized to enhance tumor cell killing (115).

8. *SP1* and clinical treatment

New strategies for immunotherapy. Regarding the role of circular RNA derived from PIAS1 (circPIAS1) in melanoma, a previous study revealed that the 108 amino acid peptide encoded by circPIAS1 markedly inhibited immunogenic iron death triggered by immune checkpoint inhibitor therapies by modulating the equilibrium between the SUMOylation and phosphorylation of STAT1, thus facilitating immune evasion. This finding offers an innovative approach to enhance the effectiveness of immune checkpoint inhibitor therapy (116). PD-1/PD-L1 immune checkpoint inhibitors represent an important advancement in cancer treatment; they work by blocking the interaction between PD-1 and PD-L1, thereby releasing T cells from inhibition and restoring their ability to attack cancer cells (76).

SP1 inhibitors and clinical therapy. In recent years, *SP1* inhibitors, such as plicamycin/plicamycin/mithramycin A and IMB-S7, have been investigated for antitumor therapy. *SP1* inhibitors inhibit the transcription of the oncogene RGS20 by blocking *SP1*-DNA binding. Furthermore, they inhibit super-enhancer-driven oncogene expression by disrupting the LLPS of *SP1* (such as GSK-J4), in addition to enhancing the sensitivity of chemotherapy or immunotherapy by modulating the downstream PI3K/AKT signaling pathway (19).

Plicamycin inhibits the binding of *SP1* to DNA by directly binding to its zinc finger structural domain. In lung adenocarcinoma, plicamycin inhibits the *SP1*-RGS20 axis and reduces tumor metastasis (19). In HCC, procamycin decreases GSDME expression, reduces chemotherapy-induced focal death and enhances drug resistance (49). Due to myelosuppression and hepatotoxicity, the clinical application of plicamycin is limited, and this drug is mainly used for adjuvant treatment of osteosarcoma and testicular cancer. Low-dose combination chemotherapy is currently being explored to minimize side effects.

A novel *SP1* small molecule inhibitor called IMB-S7 inhibits the transcriptional activity of *SP1* without affecting other GC-box binding proteins. In pancreatic cancer, IMB-S7 enhances sensitivity to gemcitabine, and reduces EMT and metastasis. In glioma, IMB-S7 combined with TMZ reverses chemoresistance (117). Preliminary data from ongoing phase 1/2 clinical trials show some antitumor activity in solid tumors. However, further validation of safety is needed.

The demethylase inhibitor GSK-J4 inhibits the expression of pro-metastatic genes, such as RGS20, by disrupting the LLPS of *SP1*. In lung adenocarcinoma, GSK-J4 inhibits *SP1*-mediated super enhancer activation and reduces tumor aggressiveness (19). This agent has not yet been investigated in clinical trials; however, it may become an important strategy for *SP1*-targeted therapy in the future due to its high specificity.

Procamycin blocks *SP1*-DNA binding and is used as a broad-spectrum antitumor agent that can reverse drug resistance. However, it can produce myelosuppression and hepatotoxicity. This drug is mainly used in the treatment of osteosarcoma, testicular cancer and lung adenocarcinoma. IMB-S7 can selectively inhibit *SP1*, and is associated with lower toxicity than other drugs. It can be used in combination with chemotherapy, although the clinical data on its usefulness are limited. It is currently used in the treatment of pancreatic cancer and gliomas. The mechanism of action of the chemotherapeutic agent gemcitabine/cisplatin is DNA damage. This is often used as a standard chemotherapeutic regimen; however, it is linked to high drug resistance rates and side effects. At present, it is used against a variety of solid tumors. The immunotherapeutic agent PD-1/PD-L1 activates T cells and has a long-lasting response. However, it is only effective in a proportion of patients. It is commonly used in the treatment of melanoma and non-small-cell lung cancer. KRAS inhibitors are targeted drugs that block oncogenic signals and are used for precision therapy. However, they are prone to secondary drug resistance. Currently, they are mainly used in KRAS-mutant cancers.

In conclusion, the use of *SP1* inhibitors, for example, the combination of IMB-S7 with gemcitabine, may enhance chemosensitivity. However, the toxicity of pro-camptothecin limits its widespread use. Combined use of *SP1* with KRAS signaling (such as IMB-S7 plus sotorasib) may overcome resistance (117). *SP1* inhibitors have shown antitumor potential in preclinical studies. However, challenges, including toxicity and resistance, remain for their use in clinical practice. In the future, drug design needs to be optimized, and combination therapy strategies should be explored to improve efficacy and reduce side effects.

9. Conclusion

The clinical importance of *SP1* in cancer has gained increasing attention, with its expression levels closely correlating with prognosis, invasiveness and metastatic potential across numerous tumor types. Exploring the link between *SP1* and tumors, as well as its correlation with clinical outcomes, is of paramount importance. Previous research indicates that elevated *SP1* expression is typically linked to unfavorable prognosis in patients with cancer. In HCC, the expression levels of *SP1* are markedly elevated compared with normal liver tissues, and its increased expression is strongly associated with microvascular invasion, recurrence rate and reduced survival time (118). This indicates that *SP1* could serve as an independent prognostic indicator for HCC. Similarly, elevated *SP1* expression correlates with reduced survival in other digestive tract malignancies, including gastric, pancreatic and esophageal cancer.

SP1 plays an important role in the proliferation, invasion and metastasis of tumor cells. Previous research has found that *SP1* promotes tumor angiogenesis by regulating angiogenic factors such as VEGF, thus enhancing tumor invasiveness (119). In colorectal cancer, the high expression of *SP1* is significantly correlated with the depth of tumor invasion and lymph node metastasis (120). In addition, *SP1* is closely associated with cell cycle regulatory molecules and growth signaling pathways, which further promote the malignant transformation of tumors (85).

Due to the significant function of *SP1* in various malignancies, targeted therapeutic techniques for *SP1* are currently under investigation. Inhibition of *SP1* activity may significantly diminish tumor angiogenesis, consequently impeding tumor growth and metastasis (87). This therapeutic approach has potential for clinical implementation and may offer novel therapy alternatives for patients with cancer.

A previous meta-analysis revealed a marked association between *SP1* expression and tumor clinicopathological characteristics, including TNM stage and lymph node metastasis (120). The expression levels of *SP1* serves as a crucial marker for assessing survival rate and treatment response in patients with tumors, thus assisting clinicians in formulating personalized treatment strategies.

Plicamycin (mithramycin A) is a specific inhibitor of *SP1* that suppresses the proliferation of certain malignancies by diminishing the expression levels of the *SP1* protein (121). IMB-S7, a *SP1* inhibitor, is being developed by the Institute of Medicine and Biotechnology of the Chinese Academy of Medical Sciences for the treatment of liver fibrosis (117).

In colorectal cancer, the elevation of *SP1* binding activity is a primary event in tumor invasion and metastasis, and *SP1* expression is an independent prognostic factor for patients with colorectal cancer (120). The *SP1*-Luc luciferase reporter gene plasmid has been used to assess the transcriptional activity of *SP1* within the *SP1* signaling pathway in pharmaceutical research and gene overexpression studies (122). The assessment of GSDME expression levels is crucial in disease management: *SP1* modulates cellular pyroptosis by regulating GSDME expression. Silencing of *SP1* or its pharmacological inhibition diminishes GSDME expression, thereby influencing cellular sensitivity to chemotherapeutic agents (49).

SP1 participates in immune evasion via several mechanisms, including i) upregulation of SLC6A6, which facilitates competitive taurine uptake and induces CD8+ T-cell depletion; ii) increase of PD-L1 expression, which enhances immunosuppression through interactions with STAT3 and IRF1; and iii) modulation of cellular localization, which alters the mode of cell death by influencing GSDME expression, thereby increasing tumor cell resistance to chemotherapeutic agents. *SP1* exhibits intricate and varied methods of action in tumor immune evasion, facilitating the immunological escape of tumor cells through interactions with various proteins and the regulation of gene expression and metabolic pathways. The identification of novel immune evasion mechanisms and immunotherapeutic techniques may offer novel insights and methodologies for a more profound understanding of the role of *SP1* in malignancies (123).

SP1 has been implicated in macrophage polarization in silicosis, where silica-induced *SP1* activation upregulates pro-fibrotic cytokine expression, exacerbating lung fibrosis and impairing immune clearance (124). Combining *SP1* inhibitors such as mithramycin with immune checkpoint blockers (ICBs) disrupts immunosuppressive signaling, as observed in *in vivo* models where dual therapy reduced tumor growth by 60% compared to ICB monotherapy (125). Nanoparticle-mediated delivery of *SP1*-silencing RNAs reprograms TAMs, reversing T-cell exhaustion in melanoma (126). These findings suggest that targeting *SP1* could enhance immunotherapy efficacy, for instance, by disrupting its role in immune checkpoint regulation or combining *SP1* inhibitors with existing immunotherapies to counteract immune suppression.

Currently, cytogenetic testing is the only dependable method for the detection of cancer (127). While numerous regulatory systems are well studied, certain aspects related to poor prognosis and survival remain unclear. *SP1* is tightly regulated at various stages of lung cancer, influencing the advancement of cancer cells in varying ways at different points in time. Thus, treatment approaches targeting the suppression of *SP1* may not be suitable for all situations. It can be proposed that tailored DNA-binding methods may be utilized to prevent diseases and prolong patient survival. In addition, future research should also explore *SP1*'s dynamic interactions within the tumor-immune microenvironment and its potential as a biomarker for immunotherapy response stratification.

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Authors' contributions

XW wrote the original draft of the manuscript; PC and YD contributed to writing, reviewing and editing the article; BZ imade substantial contributions to conception and design; ZG was involved in drafting the manuscript; TL made substantial contributions to acquisition of data, and interpretation of data; YY and JL contributed to writing, reviewing and editing the article, and were involved in supervision, project administration and funding acquisition. All authors read and approved the final version of the manuscript. 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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