

Multiple roles of S100P in pan carcinoma: Biological functions and mechanisms (Review)

XINLONG WANG^{1*}, DONG ZHAO^{1*}, ERSHU ZHAO¹, YANAN GE¹, FEI CAI¹,
YIDAN XI¹, JIATONG LI², XUEFEI LIU¹ and ZHENDONG ZHENG¹

¹Department of Oncology, General Hospital of Northern Theater Command, Shenyang, Liaoning 110000, P.R. China; ²Department of Periodontics, Stomatological Hospital, School of Stomatology, Southern Medical University, Guangzhou, Guangdong 510000, P.R. China

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Abstract. This article examines the multifaceted roles of the S100P gene in pan-cancer, with the aim of exploring its biological functions and related mechanisms in depth. S100P is a small calcium-binding protein that recent studies have identified as playing a significant role in the occurrence and progression of various cancers. As research on cancer biomarkers advances, the relationship between S100P expression levels and cancer prognosis, metastasis and invasiveness has garnered increasing attention. However, the specific mechanisms underlying the role of S100P in different cancer types remain elusive and related research is still in the exploratory phase. Therefore, this review systematically summarizes the biological functions of S100P, clarifying its signaling pathways and regulatory mechanisms. This work provides new insights and strategies for targeted therapy and establishes a theoretical basis for subsequent clinical applications. Through this summary, the present review aims to enhance personalized treatment approaches for S100P-related cancers and strengthen future explorations of S100P.

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1. Introduction

S100P is a member of the S100 protein family, first purified and characterized from the placenta by Becker *et al* (1) in 1992, with the 'P' denoting its placental origin. Notably, S100P is exclusively found in the genomes of vertebrate species (2). Among vertebrates, the S100 protein family represents the largest group of innate immune proteins containing EF-hand motifs (3,4), where the two alpha helices in these motifs provide calcium (Ca²⁺) binding sites (5). Consequently, S100P participates in mediating Ca²⁺-dependent signaling pathways (6). Uniquely, in humans, the S100P gene is located on chromosome 4 (4p16). Although S100P is present in many mammals, its expression is not universally widespread (7). This phenomenon may be due to incomplete genome sequencing or the loss of corresponding genomic sequences during the process of speciation (8). Research indicates that S100P is related to human evolution; for instance, Zhu *et al* (9) observed the expression of S100P protein during hormonal rhythmic fluctuations in the uterine wall, suggesting its potential involvement in embryo implantation and development, as well as its functional roles in various adult human tissues. Numerous studies have demonstrated that S100P is functionally related to the carcinogenic processes of several cancers, including lung cancer, pancreatic cancer and breast cancer. This underscores its significant potential as a tumor biomarker and therapeutic target (10,11). Although the specific mechanisms remain elusive in numerous areas, this review offers new insights and strategies for targeted therapy. It establishes a theoretical foundation for a deeper understanding of S100P and its applications in personalized cancer treatment, highlighting its significant clinical implications. Information regarding the literature search pertinent to this review is provided in the supplementary information file. Additionally, a detailed literature search flowchart is available in Fig. S1.

Correspondence to: Dr Xuefei Liu or Professor Zhendong Zheng, Department of Oncology, General Hospital of Northern Theater Command, 83 Wenhua Road, Shenhe, Shenyang, Liaoning 110000, P.R. China
E-mail: feiliu6@163.com
E-mail: gcp_zzd@sina.com

*Contributed equally

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2. S100P-related biomarkers

Biomarkers serve as indicators of abnormal signals across multiple biological levels, including molecular, cellular and organismal, which emerge due to the influence of environmental pollutants prior to the onset of significant damage to the organism. The specific expression of S100P in cancer indicates its potential as a histological marker for pan-cancer, with elevated levels typically correlating with poor prognosis, as illustrated in Table I. Research has shown that S100P is highly expressed in various malignancies, such as lung cancer (12), pancreatic cancer (13,14), liver cancer (15,16) and colorectal cancer (CRC) (17). For instance, in intrahepatic cholangiocarcinoma, S100P serves as a highly sensitive diagnostic marker for differentiating its various pathological subtypes (16,18). Furthermore, S100P can function as a screening marker for early biliary tract lesions during bile cytology examinations (19).

Given the high postoperative recurrence rates observed in most cancer patients, effective predictive factors remain elusive. Research conducted by Ji *et al* (20) identified S100P as a promising biomarker for predicting the risk of postoperative recurrence in CRC during follow-up. Similarly, Hwang *et al* (21) demonstrated that S100P functions as a postoperative predictive marker for hepatocellular carcinoma (HCC) within the Asian population. The detection of S100P in body fluids, such as blood or cerebrospinal fluid, is clinically more feasible than in tissue samples. For instance, in HCC characterized by portal vein tumor thrombus and microvascular invasion, serum S100P levels measured via ELISA are regarded as a robust biomarker for this condition (22). Currently, there is a notable absence of effective immunohistochemical (IHC) markers for the diagnosis of pancreatic tumors. Research has indicated that employing S100P classification in conjunction with peptide nucleic acid (PNA)-mediated real-time polymerase chain reaction (PCR) clamp techniques (i.e., PNA clamp PCR) can significantly improve the accuracy of diagnosing histologically challenging cases (23).

3. Upstream regulators of S100P

In the genomes of eukaryotes, the majority of transcriptional genes are composed of non-coding RNAs (ncRNAs). The present study focuses on the regulatory ncRNAs associated with S100P, which include long ncRNAs (lncRNAs), circular RNAs (circRNAs) and microRNAs (miRNAs). ncRNAs are crucial for regulating gene expression and maintaining cellular homeostasis (24,25), and their roles in cancer regulation are receiving increasing attention (26). For instance, in pancreatic cancer, Jiang *et al* (27) demonstrated that both transient and stable transfection of miR-495 led to a reduction in the mRNA and protein expression levels of S100P in pancreatic cancer cell lines (SW1990 and BxPC-3). Experiments involving the overexpression and knockdown of miR-495 confirmed its role in suppressing tumor growth and invasion in a manner dependent on S100P (27). Similarly, another study revealed that miR-671 was sequestered by circ_0092314, which alleviated the suppressive effect of miR-671 on S100P, thereby activating the AKT pathway, as discussed in the earlier section on epithelial-mesenchymal transition (EMT) (28).

In addition to their roles in metastasis-related cellular functions (28,29), miRNAs are also implicated in the development of resistance to conventional chemotherapy, which represents another detrimental characteristic of cancer cells. Gemcitabine, a deoxycytidine derivative, is a standard chemotherapeutic agent used in the treatment of pancreatic cancer (30). Specifically, miR-365 targets the 3'untranslated regions of src homology 2 domain-containing transforming protein 1 (SHC1) and BAX mRNA, resulting in decreased expression of these genes, while simultaneously increasing the expression of the oncogenic factor S100P (29). SHC1 is localized to the mitochondrial intermembrane space and plays a role in the production of reactive oxygen species, which can induce apoptosis (31). Additionally, BAX enhances the sensitivity of ovarian cancer cells to cisplatin (32). These findings suggest that downregulation of SHC1 and BAX may contribute to the development of gemcitabine resistance (29). Although the authors did not perform any follow-up studies to elucidate the interaction mechanisms among S100P, SHC1 and BAX, prior research indicates that this could represent a promising mechanism of action. Similarly, in breast cancer, researchers hypothesized that lncRNAs associated with trastuzumab resistance at the transcriptional level are closely linked to S100P, although no specific in-depth studies have been conducted (33). In both breast and lung cancers, lncRNA non-coding RNA activated by DNA damage (NORAD) is transcriptionally suppressed via the Hippo pathway, and the associated transcriptional co-activator with PDZ-binding motif-TEA domain transcription factors complex, along with the nucleosome remodeling and deacetylase complex, is also found to be downregulated. LncRNA NORAD acts as a decoy to sequester S100P, thereby inhibiting metastasis in these cancers. In cancerous tissues, the suppression of its repetitive sequences results in an increase in S100P expression (34).

4. Metastasis

Tumor metastasis is one of the leading causes of mortality among cancer patients. EMT is a crucial regulatory program in cancer development. Through this process, epithelial cells lose their intercellular connections and polarity, resulting in the loss of epithelial characteristics and the acquisition of mesenchymal traits that confer invasive and migratory capabilities (35). EMT is characterized by alterations in epithelial markers, such as E-cadherin, and mesenchymal markers, including vimentin and fibronectin (36). Furthermore, there is an increasingly recognized association between EMT and drug resistance across various cancers (36-38). It has been indicated that S100P plays a significant role in EMT-related processes and is critical for invasion and metastasis in various tumors (28,39).

In pancreatic adenocarcinoma, circ_0092314 sequesters miR-671, resulting in an increase in S100P, which promotes EMT and cellular invasion. The inhibitory effect of miR-671 on S100P is primarily manifested through reduced cell invasion and spheroid formation, alongside the upregulation of E-cadherin and downregulation of vimentin (28). In CRC, Zuo *et al* (39) identified S100P as a crucial initiating target that interacts with thioredoxin-1, promoting EMT and enhancing cellular invasion and metastasis. Shen *et al* (40,41) validated in murine

Table I. Expression and significance of S100P in different types of tumors.

Cancer type	S100P overexpression	Clinical correlation	(Refs.)
Non-small cell lung cancer	mRNA and protein	OS and PFS	(12,84)
Colorectal cancer	mRNA and protein	EFS	(17,40)
Hepatocellular carcinoma	mRNA and protein	OS and RFS	(21,85)
Intrahepatic cholangiocarcinoma	mRNA and protein	OS and PFS	(15,86)
Lung adenocarcinoma	mRNA and protein	OS and PFI	(51,75,76)
Gastric cancer	mRNA and protein	OS and PFS	(52)
Gallbladder cancer	mRNA and protein	OS	(87,88)
Breast cancer	mRNA and protein	RFS	(89-91)
Ovarian cancer	mRNA and protein	OS	(92,93)

OS, overall survival; PFS, progression-free survival; EFS, event free survival; RFS, recurrence-free survival; PFI, progression-free interval.

models that S100P facilitates EMT in colon adenocarcinoma via the advanced glycosylation end-product receptors (RAGE) signaling pathway. Of note, Hsu *et al* (42) demonstrated that in lung cancer, RAGE does not mediate S100P-induced cancer progression; instead, S100P binds to integrin $\alpha 7$, subsequently mediating cellular invasion and metastasis by activating the focal adhesion kinase (FAK)/AKT/zinc finger e-box binding homeobox 1 signaling axis and promoting the EMT process. Regarding drug resistance, Hamada *et al* (29) discovered that miR-365, associated with EMT, upregulates the expression of the oncogenic molecule S100P, thereby increasing the resistance of pancreatic cancer cells to gemcitabine through the downregulation of SHC1 and BAX; however, further specific studies on the interaction between these factors were not conducted. These findings suggest a close relationship between the S100P-regulated EMT process and drug resistance, indicating significant potential for targeting S100P in therapeutic strategies against resistance in future research.

5. S100P and signaling pathways

S100P is a tumor-promoting factor that primarily regulates the activity of multiple targets within signaling pathways through various modes of interaction, while simultaneously coordinating other target proteins within multiprotein complexes. Additionally, S100P modulates proliferation, apoptosis, invasion, migration and drug resistance in cancer cells (Fig. 1). Furthermore, angiogenesis, the cell cycle and drug resistance in tumors are associated with S100P (Fig. 2). Of note, in certain contexts, S100P can also function as a tumor suppressor in specific cancer types, such as gastric and lung cancers.

The critical regulatory functions of S100P encompass a complex network of interactions, including protein-protein and protein-nucleic acid interactions, which are mediated by signaling pathways and ncRNAs. Consequently, a review of the S100P-related signaling pathways in cancer was provided below to establish a foundation for further clinical translation, as detailed in Table II.

S100P and the PI3K/AKT pathway. The PI3K-Akt signaling pathway represents a crucial signaling network within cells, activated by a variety of cellular stimuli or toxic injuries.

When growth factors bind to receptor tyrosine kinases or G protein-coupled receptors on the cell membrane, they initiate the activation of class Ia and Ib PI3K isoforms, respectively. These activated PI3Ks catalyze the phosphorylation of phosphatidylinositol at the cell membrane, resulting in the production of the second messenger phosphatidylinositol-3,4,5-trisphosphate (PIP3). Subsequently, PIP3 functions as a pivotal molecule in the activation of Akt (protein kinase B). The PI3K-Akt signaling pathway ensures that cells can appropriately respond to external stimuli or damage, thereby maintaining normal cellular function and homeostasis.

In bladder cancer and gallbladder cancer, S100P has been confirmed as a target of the PI3K/AKT pathway, promoting cancer cell invasion and metastasis (43,44). For instance, Hou *et al* (43) demonstrated that Leupaxin upregulates S100P via the PI3K/AKT pathway in bladder cancer. In addition, Li *et al* (44) reported that in gallbladder cancer, LIM and SH3 domain protein 1 downregulates S100P through the PI3K/AKT pathway, leading to cell cycle arrest. Of note, in endometrial cancer, S100P enhances the growth and metastasis of cancer cells by regulating the PI3K/AKT signaling pathway and can serve as a marker to differentiate between the squamous cell carcinoma and adenosquamous cell carcinoma subtypes of endometrial cancer (45).

Knockdown of miR-671 results in the overexpression of S100P, which enhances the signaling expression of the AKT pathway, ultimately promoting the EMT process in pancreatic cancer (28). Similarly, S100P facilitates EMT, migration and invasion of CRC cells by upregulating S100A4, thereby activating the AKT signaling pathway (39). In lung cancer, integrin $\alpha 7$ serves as a binding receptor for S100P, which activates the FAK/AKT axis and promotes EMT. This further demonstrates the role of the AKT signaling pathway in tumor invasion and metastasis (42). Numerous studies have suggested that the activation of S100P within the AKT pathway may contribute to its carcinogenic effects.

S100P and RAGE/ERK pathways. RAGE activates various signaling pathways, including MAPK, ERK, PI3K and NF- κ B, which regulate critical cellular processes such as the cell cycle, gene expression, chronic inflammation and extracellular matrix synthesis. In this context, the role of

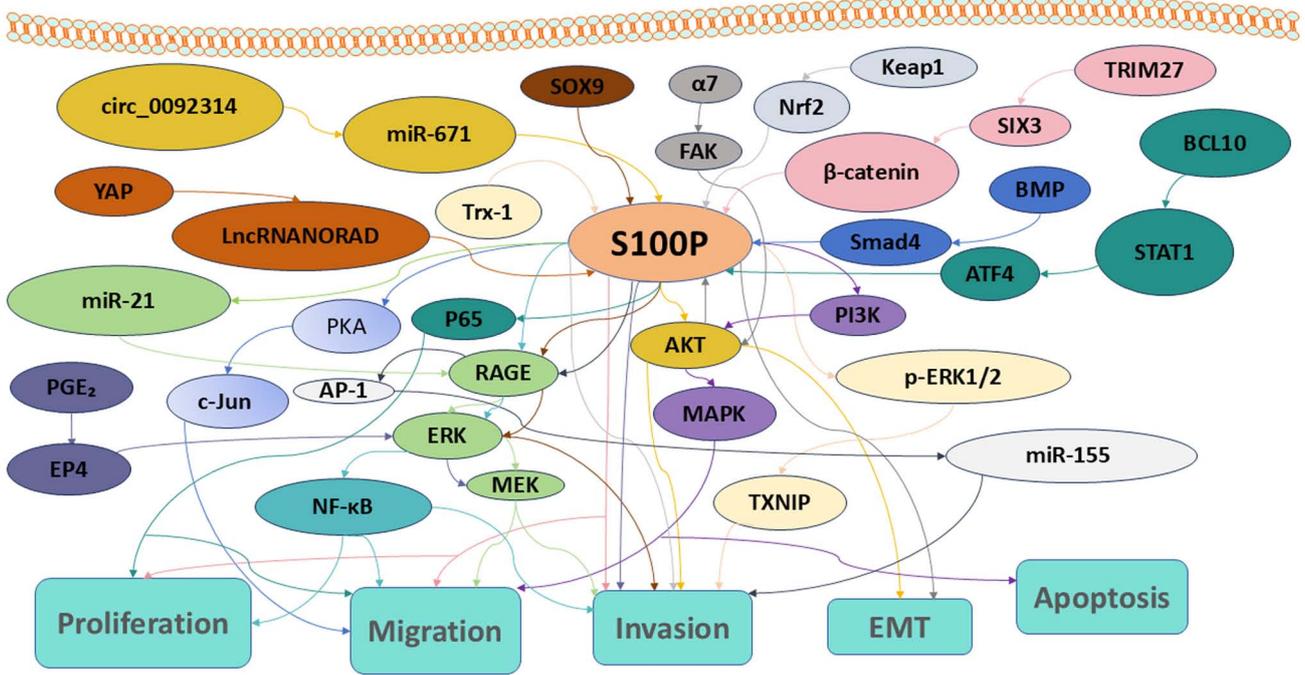


Figure 1. S100P signaling pathways associated with proliferation, apoptosis, migration, invasion and EMT in tumors. EMT, epithelial to mesenchymal transition; miR, microRNA. YAP, yes-associated protein; lncRNA NORAD, long non-coding RNA activated by DNA damage; PGE₂, prostaglandin E₂; EP4, E-type prostanoid receptor 4; Trx-1, thioredoxin-1; PKA, protein kinase A; c-Jun, cellular Jun proto-oncogene; AP-1, activator protein 1; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells.; SOX9, SRY-Box transcription factor 9; RAGE, receptor for advanced glycation end-products; ERK, extracellular signal-regulated kinase; MEK, MAPK kinase; FAK, focal adhesion kinase; MAPK, mitogen-activated protein kinase; AKT, protein kinase B; TXNIP, thioredoxin interacting protein; Keap1, kelch-like ECH associated protein-1; TRIM27, tripartite motif 27; SIX3, sine oculis homeobox homolog 3; BMP, bone morphogenetic protein; Smad4, mothers against decapentaplegic homolog 4; PI3K, phosphoinositide 3-kinase; BCL10, B-cell lymphoma 10; STAT1, signal transducer and activator of transcription 1; ATF4, activating transcription factor 4.

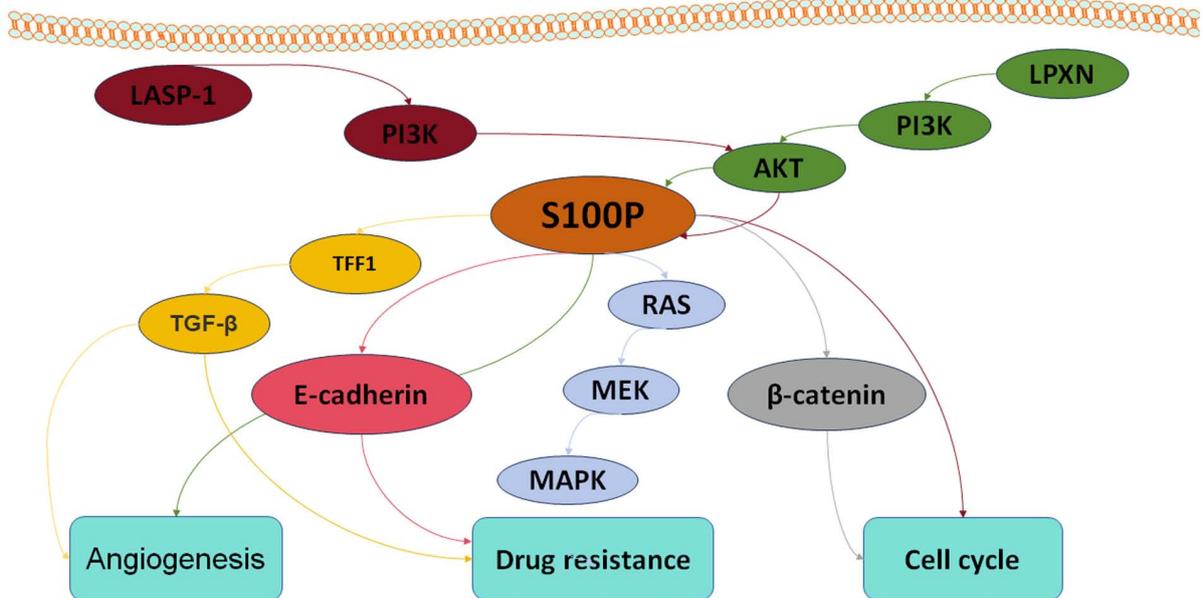


Figure 2. S100P signaling pathways associated with angiogenesis, cell cycle and drug resistance in tumors. LASP-1, LIM and SH3 domain protein 1; PI3K, phosphoinositide 3-kinase; LPXN, leupaxin; AKT, protein kinase B; TFF1, trefoil factor 1; TGF-β, transforming growth factor-β; RAS, rat sarcoma viral oncogene homolog; MEK, MAPK kinase; MAPK, mitogen-activated protein kinase.

S100P as an upstream regulator of the RAGE/ERK pathway in modulating the phenotypic functions of cancer cells may be emphasized. The first study, published by Fuentes *et al* (46) in 2007, focused on colon cancer and revealed that, while RAGE

was present in both normal and malignant tissues, S100P expression was restricted to malignant specimens. The introduction of exogenous S100P to SW480 cells resulted in the stimulation of ERK1/2 phosphorylation and NF-κB activity,

Table II. Signaling pathway in which S100P participates.

Cancer type	Signaling pathway	Role in cancer	Tumor suppressor/promoter role	(Refs.)
Breast cancer	S100P/RAS/MEK/MAPK	Drug resistance	Promotion	(33)
Lung cancer and breast cancer	YAP/LncRNA NORAD/S100P	Migration, invasion	Suppression	(34)
Lung cancer	α 7/FAK/AKT/S100P	Migration, invasion, EMT	Promotion	(42)
Non-small cell lung cancer	S100P/TFF1/TGF β	Proliferation, angiogenesis, drug resistance	Promotion	(12)
	TRIM27/SIX3/Wnt/ β -catenin/S100P	Proliferation, migration, invasion	Promotion	(49)
	Keap1/Nrf2/S100P	Migration, invasion	Suppression	(50)
Lung adenocarcinoma	S100P/PKA/c-Jun	Migration, polarization	Promotion	(51)
Pancreatic cancer	circ_0092314/miR-671/S100P/AKT	EMT, proliferation, invasion	Promotion	(28)
	BMP/Smad4/S100P	Migration	Promotion	(95)
Bladder cancer	LPXN/PI3K/AKT/S100P	Proliferation, invasion, angiogenesis	Promotion	(43)
Gallbladder cancer	LASP-1/PI3K/AKT/S100P	Proliferation, migration, cell cycle	Promotion	(44)
Endometrial cancer	S100P/PI3K-AKT/MAPK	Proliferation, migration, invasion, apoptosis	Promotion	(45)
	S100P/ β -catenin	Proliferation, cell cycle	Promotion	(94)
Colorectal cancer	SOX9/S100P/RAGE/ERK	EMT, invasion, migration	Promotion	(41)
	S100P/RAGE/ERK1/2/NFkappaB	Proliferation, migration	Promotion	(46)
	S100P/RAGE/AP-1/microRNA-155	Invasion, migration	Promotion	(47)
	S100P/RAGE/microRNA-21/ERK/MEK	Invasion, migration	Promotion	(48)
	Trx-1/S100P/p-ERK1/2/TXNIP	Invasion, migration	Promotion	(54)
	PGE ² /EP4/ERK/MEK/S100P	Invasion, colony formation	Promotion	(55)
Gastric cancer	S100P/E-cadherin	Apoptosis, Drug resistance	Suppression/promotion	(52)
Oral cancer	BCL10/STAT1/ATF4/S100P/P65	Proliferation, migration, invasion	Promotion	(53)

EMT, epithelial to mesenchymal transition; miR, microRNA. YAP, yes-associated protein; lncRNA NORAD, long non-coding RNA activated by DNA damage; PGE², prostaglandin E²; EP4, E-type prostanoid receptor 4; Trx-1, thioredoxin-1; PKA, protein kinase A; c-Jun, cellular Jun proto-oncogene; AP-1, activator protein 1; NF- κ B, nuclear factor κ -light-chain-enhancer of activated B cells; SOX9, SRY-box transcription factor 9; RAGE, receptor for advanced glycation end-products; ERK, extracellular signal-regulated kinase; MEK, MAPK kinase; FAK, focal adhesion kinase; MAPK, mitogen-activated protein kinase; AKT, protein kinase B; TXNIP, thioredoxin interacting protein; Keap1, kelch-like ECH associated protein-1; TRIM27, tripartite motif 27; SIX3, sine oculis homeobox homolog 3; BMP, bone morphogenetic protein; Smad4, mothers against decapentaplegic homolog 4; PI3K, phosphoinositide 3-kinase; BCL10, B-cell lymphoma 10; STAT1, signal transducer and activator of transcription 1; ATF4, activating transcription factor 4; LASP-1, LIM and SH3 domain protein 1; LPXN, leupaxin; TFF1, trefoil factor 1; TGF- β , transforming growth factor- β ; RAS, rat sarcoma viral oncogene homolog.

thereby promoting biological processes such as proliferation and migration. Co-immunoprecipitation studies confirmed an interaction between S100P and RAGE; however, the precise mechanism underlying this interaction remains to be elucidated (46). Following this, numerous researchers have further explored this relationship. For instance, Onyeagucha *et al.* (47) demonstrated that S100P activates RAGE, which in turn influences the expression of miRNA-155 through the activator protein-1 (AP-1) in colon cancer cells. Conversely, the inhibition of MAPK kinase (MEK) using dominant-negative c-Jun (TAM67) or through genetic suppression of c-Jun activation attenuated AP-1 activity, leading to a decrease in miR-155 induction by S100P (47). Furthermore, they discovered that S100P enhanced miR-21 expression via the RAGE pathway, with ERK/MEK also playing a regulatory role (48). Additionally, S100P was shown to stimulate the gene promoters of these two miRNAs, enriching c-Fos and AP-1 family members (47,48). Similarly, Shen *et al.* (41) investigated the regulation of SOX9 on S100P and the RAGE/ERK pathway, further substantiating the role of S100P in promoting tumor growth and invasion within this signaling context in colon cancer.

In addition to the two highlighted pathways mentioned above, S100P plays a significant role in various other signaling pathways. In lung cancer, S100P, in conjunction with trefoil factor 1 (TFF1), enhances the activity of the TGF β signaling pathway, thereby promoting the proliferation and angiogenesis of non-small cell lung cancer (NSCLC) through its interaction with spread through air spaces (combined aerospacial diffusion), a recognized aggressive mode in lung cancer (12). Furthermore, in NSCLC, tripartite motif containing 3 in the β -catenin signaling pathway, leading to an increase in S100P expression, which facilitates tumor migration and invasion (49). Notably, overexpression of Keap1 and the knockdown of Nrf2 both aim to decrease S100P expression independently; additionally, Keap1 inhibits Nrf2 expression, which further suppresses the migration and invasion of NSCLC (50). In lung adenocarcinoma, S100P enhances the secretion of chemokines and polarizing factors in tumor-associated macrophages (TAM) by activating the PKA/c-Jun pathway, thereby promoting tumor growth (51). In the context of lung cancer, lncRNA NORAD inhibits the Hippo/ yes-associated protein (YAP) pathway, leading to a reduction in S100P functional expression, which in turn suppresses both the growth and metastasis of lung cancer (34). Regarding gastric cancer, researchers have found that the effect of S100P on the growth and apoptosis of gastric cancer cells is contingent upon the expression of E-cadherin in tumor cells. Specifically, S100P promotes the growth of cancer cells in patients with E-cadherin-negative tumors while inhibiting the expression of E-cadherin in tumor subpopulations, thus affecting the biological behavior of these cells (52). In oral cancer, Wu *et al.* (53) demonstrated that B-cell lymphoma/leukemia 10 enhances the progression of oral cancer by upregulating S100P through the STAT1/activating transcription factor 4 axis, while simultaneously reversing P65 activation. In CRC, Trx-1 activates S100P gene transcription; concurrently, S100P promotes Trx-1 expression and nuclear localization by upregulating phosphorylated ERK1/2 and downregulating thioredoxin-interacting protein expression, facilitating CRC cell invasion and metastasis (54).

Additionally, another study indicated that increased prostaglandin E₂/E-type prostanoid receptor 4 expression of S100P correlates with elevated ERK levels (55). In breast cancer, Merry *et al.* (33) found that epigenomic changes at the enhancer level drive S100P upregulation, activating RAS/MEK/MAPK pathways to compensate for trastuzumab's inhibition of human EGFR2. LncRNA NORAD is repressed by the YAP pathway and suppresses lung and breast cancer metastasis by sequestering S100P (34).

6. Targeting S100P in cancer therapy

The high degree of tumor heterogeneity and the complexity of the tumor microenvironment (TME) significantly influence the occurrence, development and prognosis of cancer therapies. Consequently, this section summarizes the latest advancements in S100P therapy.

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a pleiotropic myelogenic growth factor and pro-inflammatory cytokine that has clinical applications across various indications, making it a promising target for cancer treatment. Vaccines that incorporate GM-CSF in their therapy may stimulate effective anti-tumor responses by promoting the differentiation and activation of dendritic cells (56). One study confirmed that the 'hinge' region of S100P and the F89 residues are involved in GM-CSF recognition. When the same concentration of GM-CSF and S100P was introduced to THP-1 cells, their combined effect resulted in a significant reduction in cell viability. In addition, the study predicted that GM-CSF binding should inhibit S100P from interacting with RAGE (57), which aligns with the above-mentioned descriptions in the signaling pathway section. Under physiological conditions *in vitro*, S100P interacts specifically with GM-CSF and several other four-helical cytokines (58). The similar effects of S100P binding to another four-helical cytokine, IFN- β , on MCF-7 breast cancer cell viability (59,60) suggest substantial potential for GM-CSF therapies targeting S100P. Currently, GM-CSF is utilized either alone or in combination with chemotherapy, and monoclonal antibody/cancer vaccines are undergoing clinical trials against various cancers (56). Building on previous studies regarding the relationship between IFN- β and S100P (59,60), researchers have targeted S100P in prostate cancer treatment by modulating the interferon pathway. This study analyzed differential gene expression in humans and dogs, revealing that S100P and interferon-induced transmembrane protein-like 1 exhibited increased transcript abundance in both human and canine prostate cancer. Furthermore, it was found that members of the S100P co-expressed gene community were enriched in the interferon pathway (61).

Probe technology serves as a crucial instrument for both detecting tumor lesions and targeting single gene therapies. In 2020, Sun *et al.* (62) developed a novel DNA aptamer, AptS100P-1, specifically targeting the S100P protein in CRC. This aptamer exhibits high specificity and affinity, effectively binding to S100P to inhibit tumor growth (62). Although ELISA, IHC and mass spectrometry are widely recognized diagnostic methods for protein biomarkers, they often involve complex procedures that are unsuitable for large-scale sample analyses (63,64). Surface-enhanced Raman spectroscopy, a vibrational fingerprint spectroscopy technique, is renowned for

its exceptional sensitivity and accuracy. Recent studies indicate that scholars have employed this technology in conjunction with molecular probe techniques to detect biomarkers such as S100P, facilitating the early detection and assessment of CRC (65,66).

Targeted therapy operates at the molecular level, focusing on specific carcinogenic targets. It utilizes drugs or other interventions to disrupt, inhibit and prevent the occurrence, growth and spread of tumors. In a recent study by Ahmed *et al* (67), a small-molecule therapy for pancreatic ductal adenocarcinoma was developed. Their approach successfully downregulated the quadruplex expression of S100P using a tetrad sequence designed to target discrete ‘signals’ within S100P. Furthermore, the combination of the naphthalene diimide compound QN-302 with the S100P promoter G-quadruplex significantly reduced tumor proliferation. Although still under development, QN-302 has been granted orphan drug status by the US Food and Drug Administration for the treatment of pancreatic cancer (67).

Additionally, the results of current clinical trials and the breakthrough progress of S100P were summarized based on data from PubMed. Due to the absence of reliable markers for the early diagnosis of pancreatic cancer, the sensitivity and specificity of routine serum CA19-9 are notably low. Furthermore, imaging and minimally invasive tests do not serve as universal screening tools. Consequently, researchers in the US and Japan have made significant advancements in the investigation of S100P in duodenal pancreatic juice as a standard for the early diagnosis of pancreatic cancer (ClinicalTrials.gov ID, NCT01699698).

In breast cancer research, an ongoing clinical diagnostic study has identified S100P as one of the diagnostic criteria. Compared to traditional mammography, Visualized Tissue Metabolism is a functional imaging method that displays metabolic intensity in real time using colors from the visible spectrum. This technique can detect metabolic changes prior to anatomical transformation. It offers advantages such as the absence of radiation, the need for contrast agents, pain or physical contact, and it can be utilized without restrictions on exposure time. Although the study has not yet yielded successful outcomes, it indicates significant potential for detecting S100P before the formation of a lump or tumor (ClinicalTrials.gov ID, NCT06045572).

In addition to the aforementioned S100P therapies, which are still in the development stage, the current studies on the prognostic modeling of S100P following clinical treatment were also analyzed. In lung cancer, the combination of S100P and TFF1 has demonstrated a poor prognostic effect in two clinical trial cohorts [EGFR-tyrosine kinase inhibitor (TKI) therapy and immunotherapy], adversely affecting patient survival (12). Another study elucidates a novel prognostic model incorporating S100P and the TME, which similarly indicates a poor prognosis in the context of immunotherapy (68-70). Researchers have also integrated S100P into the prognostic models of TME and TAM (71,72). Yu *et al* (73) proposed the inclusion of drug sensitivity in the risk prediction model, highlighting that S100P is highly expressed in high-risk patients as a gene associated with drug resistance. Zhou *et al* (74) identified specific drug resistance genes, focusing on the S100P-based model following gefitinib

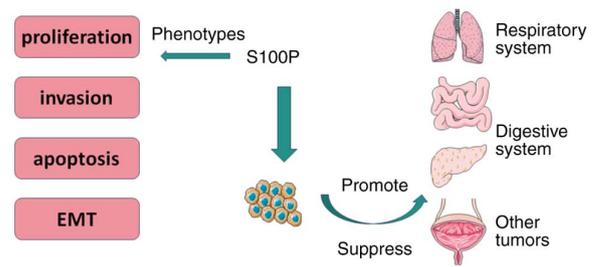


Figure 3. The functional phenotypic roles of S100P in various tumors. EMT, epithelial to mesenchymal transition.

and erlotinib treatment targeting EGFR-TKIs. They found that high-risk patients exhibited a low immune infiltration score, which holds significant potential for predicting drug responses (e.g., Docetaxel and Sorafenib) (74). The study of tertiary lymphoid structures (TLS) plays a crucial role in enhancing therapeutic efficacy and in predicting and evaluating the effectiveness of immunotherapy drugs. Consequently, some scholars have developed a nomogram predictive scoring model based on TLS, elucidating the relationship between S100P, drug sensitivity, tumor mutation burden and cancer stem cells (75). In the context of oxidative regulation, a prognostic model based on oxidative stress factors has demonstrated that S100P correlates with poor prognosis (76). Li *et al* (77) characterized the interplay between immunity and hypoxia within the TME as a prognostic model, revealing that S100P also indicates a poor prognosis. Autophagy serves as a key regulator of programmed cell death; thus, researchers have integrated autophagy and immune subtypes into a two-dimensional index to construct a prognostic model, wherein the high-risk group expressing S100P showed sensitivity to autophagy inhibition (78). In cervical cancer (CC), the nicotinamide adenine dinucleotide (NAD⁺) metabolizing-related gene S100P is thought to contribute to cancer pathogenesis and can predict survival and prognosis in CC. Targeting NAD⁺ is viewed as a promising therapeutic approach in oncology (79). In CRC, researchers have established prognostic models incorporating urea cycle genes and immune-infiltrating cells, substantiating that S100P is a reliable independent risk predictor (80). Given the high recurrence risk associated with cancer, addressing the reduction of recurrence probability post-treatment is a critical concern. The expression model of S100P associated with small extracellular vesicles can effectively predict the risk of CRC recurrence (20). Furthermore, another study highlighted the role of S100P in predicting early recurrence following HCC resection (21).

7. Limitations of S100P

While the significance of S100P in pan-cancer regarding its biological functions and mechanisms has been highlighted in the present review, its role in melanoma remains under-explored. S100P is notably expressed in both primary and metastatic melanoma (81,82); however, one study indicates that its expression level is lower in metastatic melanoma compared to normal tissues (82). This observation suggests that S100P may have a negative role in more aggressive, dedifferentiated melanoma. Furthermore, S100P lacks specificity in

epidermal melanocytes. In normal skin tissue, S100P is highly expressed in the inner layer of the thoracic duct and in the ducts of eccrine sweat glands; however, melanocytes exhibit strong immunoreactivity to S100A4 (83).

8. Other contents of S100P

In contrast to the interrelated research content discussed previously, this section presents relatively independent studies on S100P regarding clinical prognosis and signaling pathways. In small cell lung cancer, S100P is highly expressed and negatively correlates with overall survival (OS) and progression-free survival (PFS) (12,84). In hepatocellular carcinoma, S100P is also highly expressed and negatively correlates with OS and recurrence-free survival (RFS) (21,85). In intrahepatic cholangiocarcinoma, elevated S100P levels are associated with OS and PFS (15,86). In gallbladder cancer, increased S100P indicates a reduction in OS (87,88). In breast cancer, elevated S100P has been shown to negatively correlate with RFS (89-91). In ovarian cancer, an increase in S100P has been found to correlate with a decrease in OS (92,93), as detailed in Table I. Regarding signaling pathways, in addition to the PI3K/AKT and RAGE/ERK pathways discussed earlier, S100P plays significant roles in other pathways as well. For example, in endometrial cancer, S100P promotes cancer cell proliferation by regulating β -catenin (94). In pancreatic cancer, S100P facilitates cancer cell migration through the BMP/Smad4/S100P axis (95), as detailed in Table II.

9. Conclusion

In this review, the potential of the S100P gene as a biomarker was thoroughly explored, highlighting its critical role in cancer metastasis and the associated regulatory mechanisms. S100P is not only upregulated in various tumor types but also closely linked to tumor aggressiveness and metastatic potential (Fig. 3). The upstream regulatory factors of S100P were analyzed and several signaling pathways were identified, including PI3K/AKT and RAGE/ERK, which underscore its multifaceted roles in tumor cell biology, such as promoting cell proliferation, migration and anti-apoptotic processes. This analysis offers a new perspective on understanding the functions of S100P within the TME.

These findings provide new insights into the mechanisms by which S100P is involved in cancer metastasis and establish a foundation for future targeted therapeutic strategies. Targeting S100P presents promising prospects and could yield new treatment options for cancer patients. Furthermore, future research should utilize genomic and proteomic approaches to further explore the functional differences of S100P across various tumor types and its potential for clinical application, with the aim of enhancing cancer patient prognoses. The conclusions drawn from this review offer a novel perspective on the role of S100P in cancer research and clinical practice, and more in-depth findings in future studies may be anticipated.

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Availability of data and materials

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Authors' contributions

All authors contributed to the study conception and design. Data collection and analysis were performed by XW, DZ, EZ and YG. The first draft of the manuscript was written by XW and DZ. FC, YX and JL wrote some of the content and revised the paper. ZZ and XL approved the final version and contributed to the conception of the paper. All authors commented on previous versions of the manuscript. All authors read and approved the final 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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