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REVIEW

S100 Protein Family in Lung Cancer: an Updated Narrative Review

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Abstract: The S100 protein family comprises 25 known members that modulate variously basic biological behaviors of cells by binding Ca^{2+} and activating Ca^{2+}-signaling pathways. As the primary cause of cancer-related death, lung cancer is closely associated with several S100 proteins, like S100A2, S100A4, S100A6, S100A8/9, etc. Notably, the functions and mechanisms of different S100 proteins vary in every sub-type of lung cancer. Overall speaking, the abnormal expression of S100 proteins is predominantly observed in lung adenocarcinoma, while their roles are limited in small-cell lung cancer. This review, which presents an update on our previously published review of S100 proteins in lung cancer (2021), aims to enable readers having a deeper understanding of the roles of different S100 proteins in three main sub-types of lung cancer, as well as to facilitate their future researches. It focuses on relevant studies examining the functions of S100 proteins in lung adenocarcinoma, squamous carcinoma, and small-cell lung cancer. This review was conducted based on this standard, and provides a comprehensive evaluation of the literature review on S100 proteins as well as enhances understanding of the relationship between S100 proteins and every sub-type of lung cancer from a new perspective.
Keywords: S100 protein family, lung cancer, adenocarcinoma, squamous carcinoma, small cell lung cancer

Introduction

Lung cancer has a high incidence worldwide and is the primary cause of cancer-related death, leading to an estimated 1.8 million deaths in 2022.[1] Pathologically, lung cancer is classified into non-small cell lung cancer (NSCLC) and small-cell lung cancer (SCLC). NSCLC accounts for approximately 80% of lung cancer cases and is further divided into adenocarcinoma (ADC), squamous carcinoma, and large-cell carcinoma.[2] The poor prognosis is primarily associated with two major factors. First, patients do not typically exhibit specific symptoms in the early stages of the disease, resulting in the diagnosis at an advanced stage.[3] Besides, the majority of lung cancer types have unknown causes and lack effective treatment methods. In recent years, although the prognosis of lung ADC (LADC) with positive driver genes has significantly improved owing to the use of targeted drugs, drug resistance commonly occurs after a period of treatment.[4–6] Therefore, a large number of studies examined the molecular biological mechanisms underlying the occurrence and development of lung cancer.

The S100 protein family, initially discovered by Moore in 1965, comprises 25 small acidic calcium-binding proteins widely expressed in various cell types and tissues.[7] This family was named S100 owing to its solubility in 100% saturated ammonium sulfate.[8] Most of the S100 genes, including S100A1, S100A2, S100A4, and S100A6, are located at chromosome locus 1q21, which is a region frequently rearranged in cancers.[9] Therefore, S100 proteins are abnormally expressed in a variety of cancer types. These proteins participate in a wide range of biological processes of cancer cells and other biological functions by interacting with various signaling proteins.[9] In estrogen receptor alpha (ERα)-positive breast cancer, S100A7 inhibits proliferative capacity by degrading β-catenin through the mediation of glycogen synthase kinase 3β and E-cadherin signaling.[10] In thyroid cancer, S100A6 is regarded as a promoter of cell proliferation and tumorigenicity partly through the phosphoinositide 3-kinase/AKT/mammalian target of rapamycin signaling pathway.[11]

Numerous previous studies demonstrated that S100 protein dysregulation is closely linked with lung cancer development.[12] Several members of the S100 protein family were involved in the development and progression of lung carcinoma. Interestingly, it is notable that, compared to other sub-types, many S100 proteins tend to be abnormally

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expressed in lung adenocarcinoma. In 2017 and 2021, we summarized, reviewed, and updated the discoveries of studies investigating the functions of several S100 family members, such as S100A2, S100A4, S100A6, S100A7, S1008/9, S100B, and S100P, in lung cancer separately.[13,14] As ongoing studies continue to investigate the mechanisms of S100 proteins in lung cancer from 2021 to 2025, and the mechanism of these proteins may vary in different pathological lung cancers, we believe it is necessary to review the relevant researches on S100 protein in lung cancer from the perspective of different pathological types. Therefore, we updated the previous review and comprehensively summarized the role of the S100 protein family in three main sub-types of lung cancer, aiming to enhance the readers' understanding of relevant findings. The literature search for this review was conducted using PubMed, Web of Science, and Scopus, with search terms including "S100 proteins", "lung cancer", "adenocarcinoma", "squamous cell carcinoma", and "small cell lung cancer". The search covered studies published from January 2021 to January 2025.

Function of S100 Proteins in Lung Adenocarcinoma

S100A2

In cancer, S100A2 functions as a tumor suppressor or promoter. In gastric carcinoma, the expression of S100A2 was down-regulated compared with that of noncancerous cells. The decreased expression of S100A2 was associated with poor differentiation, lymph node metastasis, poor survival, and an increased risk for tumor relapse.[15] In cholangiocarcinogenesis, the overexpression of S100A2 was observed in biliary intraepithelial neoplasia and invasive ADC, predicting an advanced clinical stage and poor survival.[16] Similarly, several relevant studies reported conflicting views on the role of S100A2 in LADC. Previous studies showed low expression of S100A2 at the messenger ribonucleic acid (mRNA) and protein levels in either cells (H1792, H157, H1944, and A549) or tissues (0/10) of LADC, while the mRNA level of S100A2 was partially restored by aza-dCyd treatment in LADC cell lines H1944 and A549.[17] At the cellular level, S100A2 exhibited high expression in small airway epithelial cells, low expression in six of the seven LADC cell lines, and modest expression in the H1648 cells.[18] The results of the immunohistochemical analysis of S100A2 in 94 consecutive series of primary small LADCs revealed the absence of S100A2 immunoreactivity in normal lung tissues. However, the expression levels of S100A2 were relatively high in 9/94 (9.6%) patients and low in 24/94 (25.5%) patients.[18] In addition, more similar studies reported the significantly lower expression of S100A2 in LADC than in squamous carcinoma.[19–22] In the cytological examinations of HTB56 and HTB58 LADC cells, S100A2 was observed to enhance transwell migration and transendothelial migration in vitro. Additionally, in vivo experiments confirmed that S100A2 could promote more distant metastasis. However, the conclusions regarding its correlation with clinicopathological parameters are inconsistent. S100A2 expression demonstrated a significant correlation with lymphatic invasion, and its high mRNA expression level was associated with poor survival in patients with NSCLC who underwent surgical resection (138 of 196 had LADC).[23] In LADC, patients with S100A2-positive tumors tended to have better prognoses than those with S100A2-negative tumors.[24] Based on these contradictions, some scholars proposed that S100A2 plays a dual role in NSCLC. S100A2 is highly expressed in the early and advanced stages of cancer; however, it is equally distributed in the middle stages.[25] In the A549 LADC cells, the deletion of S100A2 inhibited the transforming growth factor-β1-induced epithelial–mesenchymal transition (EMT) through Wnt/β-catenin signal transduction. A recent study showed that, S100A2 mediated glutamine metabolism to induce LUAD metastasis and its up-regulated expression could be mediated by the transcriptional regulator TFAP2A. These findings suggest that S100A2 may regulate the development of LADC through relative pathways.[26,27]

S100A4

S100A4 is also referred to as mts1, FSP1, p9Ka, 18A2, and pEL98. The association between S100A4 expression and tumor metastasis was initially reported in 1989.[28] Numerous studies confirmed that S100A4 has a close association with cancer progression and metastasis.[29,30] Besides, it has been commonly used as an effective marker of EMT.[30] In LADC, Matsubara D et al analyzed the expression of S100A4 in the tissues of 94 patients with ADC. Results indicated that only 20.2% (19) of patients showed a positive expression of S100A4 with vascular invasion; its expression was inversely correlated with positive P53 staining and considered a predictor of poor prognosis in patients with LADC.[18] This

proportion was similar to that reported in the study of Stewart RL et al (17/81, 21%).[31] Moreover, this proportion was slightly higher than the proportion reported in the study of Miyazaki N et al, which demonstrated a high expression of S100A4 in 12 of 92 patients (13.0%) with pulmonary ADC and the correlation between poor survival rate and high S100A4 expression.[32] By comparison, Mika Tsuna et al detected S100A4 expression in 175 patients with ADC. Furthermore, the study reported a detection rate of 53.14%, while no correlation was found between survival length and S100A4 positive staining in these patients.[33] This discrepancy may be attributed to the different detection rates of S100A4, and the latter may result from the different antibodies used in the experiments and different techniques used for evaluating and scoring the immunostaining results. Previous studies examining the mechanisms at the cellular level showed that S100A4 promotes cell invasiveness and motility in Lewis LADC. In A549 LADC cell line, S100A4 altered the mitochondria metabolism by controlling its complex I subunit nicotinamide adenine dinucleotide dehydrogenase (ubiquinone) Fe-S protein 2,[34] thereby promoting the invasion and metastatic capacity of cells. Moreover, S100A4 knockdown could inhibit the nuclear factor kappa B (NF-κB) activity and decrease tumor necrosis factor α-induced matrix metalloproteinase-9 expression, while S100A4 upregulation could inhibit starvation-induced autophagy and enhance cell proliferation via the Wnt/β-catenin signaling pathway.[31] Additionally, exosomes derived from NSCLC cells, including A549, could act as a promoter in cancer progression by transmitting S100A4 to activate the signal transducer and activator of transcription 3 (STAT3) pathway. In LADC cell line HCC4006, along with A549, the expression of S100A4 was regulated by a long noncoding RNA (linc01833) by adsorbing miR-519e-3p.[35]

S100A6

S100A6 (calcylin) is a small molecule, acidic, and stable protein with a nonspherical secondary structure. This protein has two domains and two calcium-binding regions.[36] S100A6 is present in the cell membrane, cytoplasm, and nuclear membrane. It could regulate cell cycle and differentiation, and mediate the intracellular calcium signals.[37] In the S100 protein family, S100A6 is the first member proven to play a role in tumor cell differentiation, migration, and invasion.[14] In NSCLC, the expression of S100A6 was examined in 141 patients and 150 normal controls; results demonstrated an increased expression of S100A6 in the serum samples of patients compared with those of controls. This difference was already apparent at the early stage of NSCLC (I and II stages). Further analysis indicated no significance between ADC and squamous cell carcinoma (SCC).[38] In another study, the expression of S100A6 was analyzed in the tissues of 92 patients with LADC. The results showed significantly higher S100A6 expression in ADC than in normal adjacent tissues. Moreover, S100A6 was predominantly expressed in the cytoplasm than in the nucleus.[39] In the study of De Petris L et al, the level of S100A6 was evaluated in the surgical specimens of 103 patients with stage I lung cancer. The findings revealed a significantly higher S100A6 level in LADC than in lung SCC (25/51 vs 1/52).[40] In the A549 LADC cell line, S100A6 was found to promote tumor cell invasion and migration through the acetylation of P53.[41] While S100A6 has been shown to promote tumor cell invasion and migration through P53 acetylation in lung adenocarcinoma, the detailed molecular interactions and downstream signaling pathways remain unclear. Future studies should focus on elucidating the specific targets of S100A6-mediated P53 acetylation and its impact on the tumor microenvironment. Another research demonstrated that the expression of S100A6 was increased in LADC cell lines, including Calu-3, NCI-H1395, NCI-H1975, and A549. This high expression was associated with enhanced cell growth and metastasis. Meanwhile, its transcription could be regulated by hypoxia-inducible factor-1α-mediated deoxyribonucleic acid methylation enzymes (TET2 and DNMT3a) under hypoxic conditions and methylation modifications.[42] Although S100A6 has been observed to be highly expressed in various stages of LADC and can promote its development, the precise regulatory mechanism remains unclear.

S100A7

Many previous studies investigating the role of S100A7 in NSCLC suggested that S100A7, also known as Psoriasin, is selectively expressed in SCC and large-cell carcinoma cells but not in LADC.[43] In the study conducted by Woo T et al, the expression level of S100A7 was evaluated by immunohistochemistry in 179 patients with primary LADC. Results showed that S100A6 was only expressed in a few ADC cells.[22] In LADC H292 cells, the levels of ADC markers, including TTF1 and NapsinA, showed significant upregulation following S100A7 depletion. Conversely, the

level of the SCC marker DNp63 was downregulated. These findings suggest that S100A7 promoted the trans-differentiation of LADC to SCC.[44] Further studies on the mechanism demonstrated that this process could be induced by the Hippo pathway, while nuclear YAP suppressed the S100A7 expression. Similar results were also obtained in the LADC A549 cells.[44] In another study, using A549 LADC cells, the S100A7-c-Jun activation domain-binding protein 1 pathway was confirmed to facilitate the cells' malignant biological behavior via the upregulation of TGF-β-induced long noncoding RNAs by binding to nuclear S100A7.[45] This mechanism was also observed in H226 SCC cells, suggesting its involvement in the co-regulation of different NSCLC pathological subtypes. In a recent study, nine genes, including S100A7, were identified for defining LUAD into four distinct metabolic subtypes and predicting patients' prognosis.[46]

S100A8/9

S100A8 (calgranulin A) and S100A9 (calgranulin B) play crucial roles in inflammation modulation and immune response. The coexpression of these two factors can form a heterodimer known as S100A8/A9.[47] In lung cancer, compared with normal controls, immunohistochemical staining and polymerase chain reaction analysis demonstrated an upregulation of S100A8/9 in malignant tissues (60 patients). A higher expression of S100A8/9 was detected in patients with LADC or stage IV lesion.[48] Another study suggested that S100A8 and S100A9 exhibited a noticeable positive expression (>70%) in both the cytoplasm and nucleus of NSCLC cells. Their positive expression was associated with the degree of tumor differentiation, but was not correlated with pathology type.[49] Additionally, the research findings of Arai K et al, which focused on the expression level of S100A9 in pulmonary ADC, showed a strong association between S100A9 expression and tumor differentiation.[50] Specifically, S100A9 immunopositivity was observed in 19/19 (100%), 12/30 (40%), and 0/21 (0%) patients with poorly, moderately, and well-differentiated ADC, respectively. Therefore, S100A9 may be closely related to the differentiation of carcinomas originating from glandular cells.[50] In A549 and secretory pathway Ca (2+) -ATPase pump type 1 LADC cells, S100A9 activated the P38 and REK1/2 kinases, while also slightly inducing the phosphorylation of the c-Jun NH 2-terminal kinase in the mitogen-activated protein kinase (MAPK) pathway. LINC00852 was able to positively regulate the progression and metastasis of cells by targeting S100A9.[51] As a major regulator in inflammation, S100A9 could affect the tumor microenvironment in various ways,[52,53] underscoring its potential as a cancer treatment target. In patients with LADC harboring epidermal growth factor receptor (EGFR) activating mutation treated with first-line EGFR tyrosine kinase inhibitors, the elevated blood levels of $S100A9^{+}$ monocytic myeloid-derived suppressor cell count (MDSC) was associated with poor therapeutic effect and shorter progression-free survival. This association was mediated by the tumor-associated macrophages (TAMs) derived from $S100A9^{+}$ MDSCs through the activation of noncanonical NF-κB RELB pathway.[54] Besides that, targeting TAM-secreted S100A9 enhances the tumor-suppressive effect of metformin, a classical hypoglycemia agent, in treating LADC.[55] $CD14^{+}$ $S100A9^{+}$ myeloid-derived suppressor cells could decrease the survival of patients with advanced lung cancer treated with chemotherapy, showing the potential value of S100A9 in cancer treatment.[56]

S100B

S100B, a significant marker of blood-brain barrier leakage, has a predictive value in cancer-related brain metastasis, including NSCLC.[57,58] In the study of Chen L et al, patients with stage IV NSCLC without brain metastasis (50 patients) were compared with those with benign cerebrovascular diseases (50 patients). Results showed that S100B was upregulated in the sera of patients with stage IV NSCLC with brain metastasis (100 patients).[59] In the PC14/B cell, which was constructed as a model of brain metastasis from LADC, S100B exhibited a higher expression compared with that in PC14 and A549 LADC cells. The knockdown of S100B in the PC14/B cell resulted in the cell's diminished propensity for migration, invasion, and proliferation. Additionally, the downregulation of Bcl-2 AND Bcl-xL expression in these cells enhanced their susceptibility to apoptosis.[60] Using Lewis LADC cells, Chiappalupi S et al investigated the involvement of S100B in cancer cachexia. The findings revealed that S100B, acting as a receptor for advanced glycation end product (RAGE) ligand and a molecular marker, activated the p38 MAPK/myogenin axis and STAT3-dependent myoblast determination protein 1 degradation, ultimately inducing muscle atrophy.[61]

S100P

S100P is involved in tumor growth, tumor metastasis, and drug resistance by binding to RAGE and activating cellular signaling.[62,63] Compared with other lung cancer subtypes, S100P is highly expressed in LUAD.[20,64] In the tissue (16 patients) and cellular levels (H538), S100P was upregulated. Detailed analyses revealed that this overexpression was highly related to stage T1, and S100P-overexpressing H358 LADC cells more frequently form tumor colonies in vitro. However, the number of H538 cells exhibiting S100P overexpression showed a reduction in migration and proliferation. Hence, S100P expression was a strong indicator of the early stages of LADC, while its downregulation during the advanced stages indicated tumor progression.[64] In recent years, relevant studies confirmed the role of S100P as an immune-related gene. It is also used to predict the need for immunotherapy, drug resistance, and the prognosis of LADC.[65–67] Mechanistically, RNA-binding motif, single-stranded interacting protein 1 interacts with YTH N6-methyladenosine RNA binding protein 1 and then facilitates the translation of S100P, thereby accelerating A549 LADC cell metastasis. In H1975 cells, through Wnt/β-catenin signaling, SIX homeobox 3 could inhibit cell metastasis and proliferation by inhibiting S100P.[68] Interestingly, the classic antioxidant stress pathway Keap1-Nrf2 interaction could also be involved in suppressing cell motility in LADC by targeting the S100P protein.[69] In vitro, S100P was found to enhance the secretion of chemokines on LUAD cells and polarizing factors by activating the PKA/c-Jun pathway, which was implicated in tumor-associated macrophages recruitment and polarization towards the M2 phenotype.[70]

Role of S100 Proteins in Lung Squamous Carcinoma

S100A2

Generally, S100A2 was expressed more frequently in SCC than in ADC. SL Smith et al conducted an immunohistochemistry to assess the expression of S100A2 in 48 tumor sections. Their findings revealed that squamous cell lesions were more likely to exhibit positivity for S100A2 (nuclear: 16/19, cytoplasmic: 16/19) compared with ADCs (nuclear: 9/24, cytoplasmic: 10/24).[19] In the study of Mojca Strazisar et al, the S100A2 gene was upregulated in 77.8% (26) of patients with SCC and downregulated in 87.5% (32) of patients with ADC. By contrast, S100A2 downregulation was more commonly observed in ADC than in SCC (87.5% vs 14.3%).[21] In stage I NSCLC, the expression of S100A2 was observed in the surgical specimens from 113 patients. S100A2 was highly expressed in SCC (30/42) than in ADC (41/62), although no statistical difference was found.[24] However, there have also been opposite research findings. Data from the research of G Feng et al reduced the expression of S100A2 in SCC cells, including H226 and H596 cell lines. Additionally, S100A2 was expressed in 83.3% (5/6) of normal lung tissues, but was only expressed in 9.1% (1/11) of SCC tissues.[17] Inconsistent findings regarding the expression of S100A2 in SCC highlight the importance of considering sample size, patient population, and experimental methods. Studies with larger cohorts and standardized protocols are needed to resolve these discrepancies. Besides, detailed research on its molecular mechanism of action in this subtype of lung cancer is also currently lacking.

S100A4

Studies on the role of S100A4 in LSCC remain insufficient, with inconsistent conclusions. Tsuna M et al investigated the expression of S100A4 in samples from 93 patients with LSCC. Results revealed a positive expression of S100A4 in 69.89% of the patients. Moreover, the rate of lymph node metastasis decreased, but the survival was relatively poor, suggesting S100A4 as a prognostic marker of SCC.[33] In a cohort of 204 patients with surgically resected LSCC, S100A4 was detected in 137 patients (67.2%) both in granular cytoplasm and cell nuclei. Moreover, significant correlations were observed between S100A4 expression and increased incidence of lymph node metastasis, recurrence, and poor overall survival.[71] However, in the study conducted by Bartling B et al, the S100A4 mRNA level was measured in lung cancer specimens, and results demonstrated a downregulation of S100A4 in both LADC and SCC compared with normal lung tissues.[20] The inconsistency may be due to the differences in the number and characteristics of studied populations. Moreover, the first two studies primarily comprised patients with early-stage LSCC, while the last one only included 15 patients with LSCC, of whom 6 had stage I disease. At present, most studies examining the role of S100A4 in NSCLC

development were performed using ADC or NSCLC cell lines; thus, further studies should examine the functions of S100A4 in this specific cancer subtype.

S100A6

Findings from the study of Bartling B et al indicated negative expressions of S100A6 in normal tissues and SCC/ADC tissues (15 patients, respectively), while S100A6 was particularly expressed in lung fibroblasts.[20] However, further evidence suggests that S100A6 expression is correlated directly with nonsquamous histology. In another study involving 177 patients with SCC, the expression of S100A6 and the correlation between its expression levels and certain clinicopathological factors were examined. In 177 patients, only 33.33% (58/177) of the patients exhibited a high expression of S100A6. More detailed analysis showed that the high expression of S100A6 was more prevalent in patients with poorer differentiation and lower 5-year survival rates. This finding indicates that S100A6 could act as an independent unfavorable prognostic factor for SCC.[72]

S100A7

Numerous studies have consistently reported higher expression of S100A7 in SCC than in other types of lung cancer. Liu G et al used immunohistochemistry to evaluate S100A6 expression in the tissues of 140 patients with SCC and 60 normal controls. Results revealed that S100A7 was overexpressed in SCC (87/140 vs 11/60), especially in the cytoplasm of tumor cells. Its positive expression was associated with advanced stage and poor prognosis of SCC.[73] In SCC cells (H520), the knockdown of S100A7 could suppress cell growth in part by attenuating NF-κB activity.[73] A recent study conducted in 2022 revealed that the upregulation of S100A7 could result in the resistance to immune checkpoint inhibitors by decreasing the programmed death-ligand 1 expression and $CD8^+$ tumor-infiltrating lymphocyte count through the p-AKT pathway and reducing the C-X-C motif chemokine 9 expression, thus remodeling the immunosuppressive tumor immune micro-environment in lung SCC.[74]

S100A8/9 and S100B

Due to limited research, we summarized the roles of these three molecules in SCC in this section. As indicated in the study findings mentioned above, the S100A8/9 proteins were positively expressed in SCC. In the study of Arai K et al, similar to poorly differentiated ADCs, conspicuous S100A9 immunopositivity was observed in pulmonary SCCs, regardless of the degree of differentiation, but not in adenomatous hyperplasia or normal surface epithelia.[50] In addition, S100B was not associated with different pathological subtypes of NSCLC, although a close correlation was found between S100B and NSCLC with brain metastasis.[57] With regard to the mechanism of S100A8/9 and S100B, studies examining their role in LSCC are limited.

S100P

In the study of Bartling B et al, S100P exhibited a strong expression in NSCLC (30 patients), while this upregulation was notably dependent on the histological subtype.[20] Although relatively less expressed than LADC, the mRNA level of S100P in SCC was still noticeably higher than that in normal lung tissues, fibroblasts, and tumor fibroblasts. Similar to LADC, the elevated level of S100P in SCC tended to occur in early tumor stages. However, further studies are needed to demonstrate the specific role of S100P in SCC.

S100 Proteins and Small-Cell Lung Cancer

In general, the S100 protein family is involved in the occurrence and progression of NSCLC. However, studies investigating the relationship between SCLC and S100 proteins are limited, often yielding negative conclusions for proteins such as S100A2, S100A6, S100A7, and S100P.[43,75–77] Meanwhile, a few studies investigated the functions of some S100 members in this highly malignant subtype. In SCLC cells (LK79 and SBC-3), S100A4 was overexpressed in LK79 and promoted the growth and motility of two types of cells.[78] In patients with lung cancer who developed bone metastasis, models constructed using SCLC cells (SBC3 and SBC5) demonstrated that osteolytic bone destruction could be enhanced by bone marrow adipocytes by activating S100A8/A9-interleukin 6 receptor-Toll-like receptor 4

Table 1 The Expression of S100 Proteins in Different Subtypes of Lung Cancer

S100 Proteins Pathological Subtypes	LADC	LSCC	SCLC	References
S100A2	↑ or ↓ Different according to stages	↑	No expression	[24,25]
S100A4	Positive expression rate 13.0%~53.14%	↑	↑	[25,31]
S100A6	↑	↓	No expression	[25,73]
S100A7	↓	↑	No expression	[25,74]
S100A8/9	↑	↑	–	[25,77]
S100B	↑ (with brain metastases)	↑ (with brain metastases)	↑ (with brain metastases)	[25,78]
S100P	↑	↓	No expression	[25,63,75]

Notes: ↑ upregulated, ↓ downregulated.
Abbreviations: LADC, lung adenocarcinoma; LSCC, lung squamous carcinoma; SCLC, small cell lung cancer.

pathways.[79] Meanwhile, S100B served as a serological marker and predictor of poor prognosis in patients with SCLC who developed brain metastases.[80]

Conclusion

Several members of the S100 protein family participate in tumor biological processes across various stages of lung cancer, particularly in NSCLC. Previous studies have predominantly focused on LADC, validating their significance in tumor promotion, diagnosis, prognosis, and drug resistance, as summarized in Table 1. However, research on the functions of S100 proteins in SCC and SCLC remains limited. Overall, various proteins in this family exhibit varying expressions across distinct subtypes of lung cancer, with their exact roles varying accordingly and further studies are warranted to elucidate the mechanisms of S100 proteins in lung cancer.

In addition, translating these findings into clinical practice, such as detection S100 proteins in clinical work or developing medicines against S100 proteins, requires addressing several challenges, including standardization of assays, determination of clinically relevant cut-off values, potential off-target effects and resistance mechanisms. Therefore, future research should also focus on developing robust, cost-effective assays, as well as identifying selective inhibitors. However, this review acknowledges potential limitations, including the possibility of publication bias and incomplete coverage of all relevant research, and we will consider conducting meta-analyses and including grey literature to provide a more comprehensive understanding of S100 proteins in lung cancer in future study.

Abbreviations

NSCLC, non-small cell lung cancer; SCLC, small-cell lung cancer; ADC, adenocarcinoma; LADC, lung adenocarcinoma; ERα, estrogen receptor alpha; Mrna, messenger ribonucleic acid; EGFR, epidermal growth factor receptor; MDSC, myeloid-derived suppressor cell count; SCC, squamous cell carcinoma; TAMs, tumor-associated macrophages.

Data Sharing Statement

All the data that support the findings of this study are openly available in PubMed at https://pubmed.ncbi.nlm.nih.gov/.

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Disclosure

No potential competing interest was reported by the authors.

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