S100 protein family: Emerging role and mechanism in digestive tract cancer (Review)

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Abstract. Digestive tract cancer is one of the most common types of cancers globally, with ~4.8 million new cases and 3.4 million cancer-associated deaths in 2018, accounting for 26% of cancer incidence and 35% of cancer-related deaths worldwide. S100 protein family is involved in regulating cancer cell proliferation, angiogenesis, epithelial-mesenchymal transition (EMT), metastasis, metabolism and immune microenvironment homeostasis. The critical role of S100 protein family in digestive tract cancer involves complicated mechanisms, such as cancer stemness remodeling, anaerobic glycolysis regulation, tumor-associated macrophage differentiation and EMT. The present study systematically reviewed published studies on the compositions, function and the underlying molecular mechanisms of the S100 family, as well as guidance for diagnosis, treatment and prognosis of digestive tract cancer. Systematic review of the roles and underlying molecular mechanisms of S100 protein family may provide new insight into exploring potential cancer biomarkers and the optimized therapeutic strategies for digestive tract cancer.

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Contents

1. Introduction

Digestive tract cancer is one of the most common types of malignant tumors worldwide and primarily includes esophageal cancer (EC), gastric cancer (GC), pancreatic cancer (PC), liver cancer (LC) and colorectal cancer (CRC). According to the World Health Organization, digestive tract cancer accounts for more than a quarter (26%) of global cancer incidence, and more than a third (35%) of all cancer-associated deaths across the world (1). Therefore, it is urgent to identify early screening methods for digestive tract cancer, as well as improved approaches for prognosis of patients with advanced disease. Improving the prognosis of patients with digestive tract cancer, particularly those with advanced disease, is an urgent issue. Accordingly, it is key to identify new targets for the early diagnosis and treatment of digestive tract cancer to improve disease survival and overall quality of life.

S100 proteins belong to a polygenic calcium-binding family composed of small acidic proteins. S100 proteins are widely expressed with high tissue- and cell-specificity and were firstly extracted from bovine brain tissues by Moore in 1965 (2). S100 proteins dissolve in saturated ammonium sulfate solution at neutral pH (3). In human, the S100 protein family consists

of 20 members (4), 16 of which are located on chromosome 1q21 and known as group A S100 proteins (5) (Table I). The corresponding genes are highly conserved and encode small proteins with ~100 amino acids in size. S100 proteins have a highly similar calcium binding protein sequence, known as the elongation factor (EF hand). When calcium ion binds the EF hand, S100 proteins bind to the corresponding receptors and participate in various cellular processes, including proliferation, differentiation and apoptosis (6). Increasing evidence has demonstrated that the S100 protein family is associated with pathogenesis of digestive tract cancer, including LC (7-10). The aberrant expression of specific S100 isoforms drives LC, such as S100A4, S100A6, S100A8, S100A9 and S100A11 (7). The present review aimed to summarize studies on the role of S100 protein family in digestive tract cancer. Elucidating the effects and underlying mechanisms of S100 proteins may provide insight into the pathogenesis of digestive tract cancer. In particular, S100 inhibitors for cancer treatment may have significance, given the pivotal role of S100 signaling in tumorigenesis and tumor biology (4).

2. Composition and structure of the S100 protein family

S100 protein family consists of 25 members, characterized by low molecular weight and a symmetrical dimeric structure. S100 proteins exhibit notable homology with both calmodulin and calcium-binding proteins (11). The conformation of S100 protein changes when bound to Ca^{2+}, exposing hydrophobic amino acids in the first helix and hinge regions of the C-terminal EF hand (12). S100 protein members serve as intracellular $Ca2^{+}$ sensors during carcinogenesis via the regulation of $Ca2^{+}$/S100A4/myosin-IIA complex and other mechanisms (13,14).

3. Biological function of the S100 family proteins

S100 proteins serve a key role in regulating cell proliferation, differentiation, and apoptosis by interacting with enzymes, cytoskeletal subunits, receptors, transcriptional factors and nucleic acids (15). S100 proteins exert biological effects in either an autocrine or paracrine manner (16). S100 proteins are implicated in inflammation, tissue repair and resistance to pathogens by binding to various receptors, including G protein-coupled receptor, scavenger receptor and receptor for advanced glycation end products (RAGE), and activating mTOR, Src/annexin A2 (ANXA2)/AKT and PI3K signaling pathways (17,18). Besides, S100 family members participate in regulating neuroinflammation in astrocytes and microglia and may serve as diagnostic and therapeutic targets (for instance, S100A8/A9) (19). The expression of S100 protein members is specific in different types of cancer. Dysregulation of S100 family proteins occurs in most types of cancers, suggesting their key roles in tumorigenesis. S100P is upregulated in multiple cancers, such as lung cancer, CRC, and PC (20). S100A4 is an important regulator of immunosuppressive T cells in human glioma, affecting immune microenvironment balance and survival (21). S100A7 is significantly associated with the prognosis of head and neck squamous carcinoma (22). S100A6 regulates cancer cell proliferation, apoptosis, migration and invasion, which is also associated with poor prognosis (4,23). S100A10, also known as p11, is found to mediate the conversion of plasminogen to plasmin primarily by binding to ANXA2 (24). This interaction results in degradation of the extracellular matrix, facilitating the dissemination of cancer cells through the bloodstream. In breast cancer, S100A14 enhances the phosphorylation of HER2 and the activation of AKT/ERK signaling pathway, thereby promoting the development of breast cancer (25). Taken together, the aforementioned studies have suggested key roles of S100 family members (including S100P, S100A4, S100A6, S100A7, S100A10, and S100A14) in the development and progression of various types of cancers. The present study summarizes the role of S100 family in digestive tract cancers to provide insights into cancer pathogenesis and novel therapeutic strategies.

4. Expression, biological effects and molecular mechanisms of S100 family proteins in digestive tract cancer

GC. GC is one of the most common types of malignant tumors across the world. The majority of patients with GC are diagnosed at advanced stage with poor prognosis. Therefore, it is necessary to explore more effective strategies for the early diagnosis of GC. A previous study demonstrated that S100A4 promotes proliferation and migration of GC cells by regulating a downstream effector family with sequence similarity 107 member B via the PI3K signaling (Fig. 1) (26). Another study found that S100A4 increases the stemness of cancer cells via upregulating NANOG and SOX2, thereby promoting gastric carcinogenesis (27). Bian *et al* (28) reported that silencing S100A4 using small interfering RNA inhibited the proliferation and migration of GC cells. Furthermore, this effect is enhanced by microRNA (miRNA or miR)-3189-3p mimics, which targeting cofilin-2 and further inhibiting GC cell proliferation and migration (28). Accordingly, S100A4 may serve as a promising biomarker and treatment target for GC due to its key effects in regulating the biological behavior of cancer cells (Table II).

Another well-established S100 family member is S100A9, the expression and function of which exhibit variability across types of cancer (29-31). Enhanced expression of S100A9 has been observed in GC and promotes the proliferation and migration of cancer cells (30). S100A9 plays dual roles, acting both as a pro- and anti-tumor factor independently and forming heterodimers with S100A8 (S100A8/A9) during gastric carcinogenesis (31). It is involved in inflammation in GC. At low concentrations, S100A8/A9 promotes cancer cell proliferation and migration by activating NF-κB-, RAGE- and MAP kinase-dependent signaling pathways (32). Conversely, at high concentrations, S100A8/A9 exhibits cytotoxic (33) and pro-apoptosis effects on GC cells by regulating Bax/Bcl-2 expression and activation of ERK (34). Positive association between S100A9 expression and the overall survival of patients with GC has been demonstrated (35), suggesting the protective role of S100A9 at high concentration against GC. It has also been well documented that endogenous S100A8/A9 inhibits migration and invasion of GC cells, whereas exogenous S100A8/A9 functions as a heterodimer to activate NF-κB signaling, thereby promoting the development of GC (32,36). This discrepancy may be attributed to differences in cancer microenvironment (37). Given the complicated effects of S100A9 under varying concentrations and cellular locations,

Table I. S100 proteins in humans.

Protein	Chromosome location	Site of function	Function
S100A1	1q21	Intracellular	Associated with heart contraction and calcium ion storage activity; regulates carbon monoxide synthase activity; involved in intra-signal signaling
S100A2	1q21	Intracellular	Associated with endothelial cell migration and calcium ion storage activity; involved in intra-signal signaling
S100A3	1q21	Intracellular	Associated with wound healing and calcium ion storage activity
S100A4	1q21	Intracellular/ extracellular	Associated with angiogenesis and calcium ion storage activity; involved in intra-signal signaling
S100A5	1q21	Intracellular	Involved in intra-signal signaling; associated with calcium ion storage activity
S100A6	1q21	Intracellular/ extracellular	Associated with transmembrane transport of monatomic ions and calcium ion storage activity; regulates fibroblast proliferation; involved in intra-signal signaling
S100A7	1q21	Intracellular/ extracellular	Associated with angiogenesis and calcium ion storage activity, regulation of the immune response; involved in intra-signal signaling
S100A7L2	1q21	Extracellular	Associated with calcium ion storage activity
S100A8	1q21	Intracellular/ extracellular	Associated with inflammatory and immune response, apoptotic processes and calcium ion storage activity; regulates cell proliferation; involved in intra-signal signaling
S100A9	1q21	Intracellular/ extracellular	Serves as a chemotactic molecule during inflammation; associated with apoptotic processes, autocrine signaling, inflammatory and immune response and calcium ion storage activity; involved in intra-signal signaling
S100A10	1q21	Intracellular/ extracellular	Associated with plasminogen activation, neurogenesis, vesiculogenesis and calcium ion storage activity
S100A11	1q21	Intracellular/ extracellular	Associated with cell adhesion and proliferation and calcium ion storage activity; involved in intra-signal signaling
S100A12	1q21	Intracellular/ extracellular	Associated with inflammatory and immune response, xenobiotic metabolic processes and calcium ion storage activity; involved in intra-signal signaling
S100A13	1q21	Intracellular/ extracellular	Associated with immune response, cell proliferation and calcium ion storage activity; involved in intra-signal signaling
S100A14	1q21	Extracellular	Associated with apoptotic processes, immune response and calcium ion storage activity; involved in intra-signal signaling
S100A16	1q21	Intracellular/ extracellular	Involved in intra-signal signaling; associated with calcium ion storage activity
S100B	21q22	Extracellular	Binds Cu^{2+} to exert a neuroprotective effect; associated with cell adhesion and proliferation, central nervous system development and calcium ion storage activity; involved in intra-signal signaling
S100P	4p16	Intracellular/ extracellular	Associated with endothelial cell migration and calcium ion storage activity
S100Z	5q13	Intracellular	Associated with immune regulation and calcium ion storage activity
S100G	Xp22	Intracellular/ extracellular	Associated with calcium ion storage activity

it is key to elucidate the precise molecular mechanisms of S100A9 in regulating GC.

S100A10, a key member of the S100 family, is upregulated in some malignant tumors, including lung cancer (38) and LC (39). Similarly, increased expression of S100A10 has been found in GC (40). S100A10 can promote gastric carcinogenesis by enhancing GC cell proliferation and the consumption of glucose via the Src/ANXA2/AKT/mTOR signaling pathway (40). Besides, enhanced succinylation of S100A10 promotes GC invasion and metastasis depending on the activity of carnitine palmitoyltransferase 1A (41). Taken together, S100A10 emerges as a promising therapeutic target due to its key role in regulating the growth, invasion and metastasis of GC.

Other S100 family members involved in GC pathogenesis include S100A11 (42) and S100A16 (8). Koh and Lee (42)

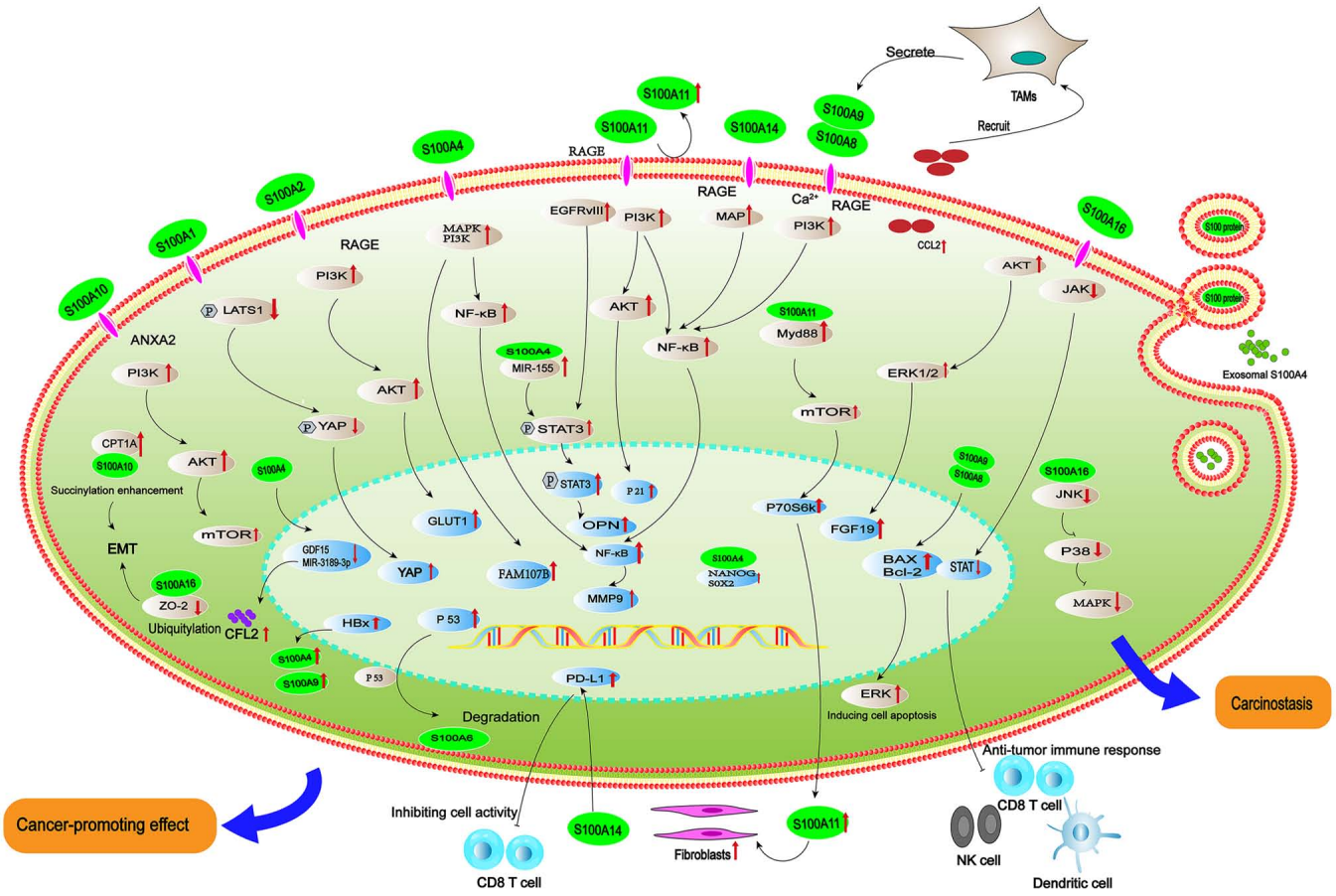

Figure 1. Mechanism of S100 family members in digestive tract cancer. S100 family members, primarily including S100A1, S100A2, S100A4, S100A6,S100A8/9, S100A11, S100A14, and S100A16, hold great potentials for the molecular diagnosis, progression monitoring and prognostic prediction of digestive tract cancers through signaling pathways of MAPK, MyD88/NF-Kb, PI3K/AKT, mTOR, JAK/STAT, p53. CPT1A, carnitine palmitoyltransferase 1A; PI3K, phosphoinositide-3 kinase (PI3K; LATS1, large tumor suppressor kinase 1(LATS1), Yes-associated protein (YAP), zonula occludens 2 (ZO-2), Annexin A2 (ANXA2), Receptor of Advanced Glycation End products (RAGE; miR, microRNA; EGFRvIII, epidermal growth factor receptor variant III (EGFRvIII; Myd88, Myeloid Differentiation Factor 88 (Myd88), growth differentiation factor 15 (GDF15; HBx, hepatitis B virus X (HBx; GLUT1, glucose transporter 1 (GLUT1), family with sequence similarity 107 member B (FAM107B), osteopontin (OPN; PD-L1, programmed cell death 1 ligand 1 (PD-L1; P70S6K, 70 kDa Ribosomal Protein S6 Kinase 2 (P70S6K), fibroblast growth factor 19 (FGF19; TAM, tumor-associated Macrophages (TAMs), small inducible cytokine subfamily A (Cys-Cys), member 2 (CCL2), cofilin-2 (CFL2), natural killing cell (NK cell), epithelial-mesenchymal transition (EMT).

reported that S100A11 inhibits the epithelial phenotype and promotes interstitial transformation by regulating MMP9 through the PI3K/NF-κB signaling pathway in GC. It is well-established that elevated expression of S100A11 is an independent prognosis-associated factor for GC (42,43). S100A11 is not only associated with tumor progression but affects the sensitivity and cytotoxicity of chemotherapy drugs (43). As a tumor regulator protein, zona occludens (ZO)-2 is a cytoplasmic protein of tight junctions. A recent study by You *et al* (8) demonstrated that S100A16 promotes the epithelial-mesenchymal transition (EMT) by promoting the ubiquitination and degradation of ZO-2, thus leading to GC cell invasion and migration. Apart from this, S100A16 can be targeted by a disintegrin and metalloproteinase with thrombospondin motifs 19 via the NF-κB pathway, resulting in the inhibition of cell migration and invasion (44). S100A16 is a biomarker predicting prognosis of GC (45). Therefore, S100 family proteins serve vital roles in the development, progression and prognosis of GC. However, their potential for predicting cancer prognosis warrants more high-quality studies. It is key to elucidate the effects and mechanisms of S100 family members in the pathogenesis of GC, particularly focusing on S100A4, S100A8/A9, S100A10 and S100A11, which may serve as novel makers for the diagnosis and prognosis of GC.

Hepatocellular carcinoma (HCC). Liver is one of the most important digestive organs responsible for the metabolisms of lipid, fatty acid and other substances by regulating various active factors, such as growth factors and cytokines (46,47). Effective therapeutic strategies for HCC include surgery, chemotherapy, targeted therapy and liver transplantation. However, the prognosis of HCC remains poor (48). Therefore, it is necessary to explore more effective strategies to achieve early intervention and treatment of HCC. Increasing studies have demonstrated that S100 proteins play important roles in HCC and may serve as useful diagnostic and prognostic markers (49-52). Increased expression of S100A1 is observed in HCC tissue and is positively related to tumor and tumor grade and survival rate (53). Moreover, S100A1 contributes to HCC by inhibiting phosphorylation of LATS1 and yes-associated protein via the Hippo pathway (53). S100A4 is a risk factor for GC (26). Zhai *et al* (50) reported that S100A4 is involved in HCC

Table II. Expression, effects and the underlying mechanisms of S100 protein family members in digestive tract cancer.

Cancer	Protein	Differential expression	Expressed cell	Biological effect	Molecular mechanism	Prognostic association	(Refs.)
GC	S100A4	Up	GC	Promotes proliferation, invasion, and metastasis; increases the stemness of and induces tumorigenesis	Downregulates FAM07B and miR-3189-3; enhances expression of NANOG and SOX2	Negative	(26-28)
	S100A9	Up	GC cell	Promotes cancer cell proliferation, invasion and metastasis; induces cancer cell apoptosis	Forms a heterodimer with S100A8; regulates NF-κB, RAGE and MAPK signaling pathways and Bcl-2	Negative	(29-37)
	S100A10	Up	GC cell	Enhances GC cell proliferation, invasion, and metastasis; promotes anaerobic glycolysis	Activates Src/ANXA2/AKT/mTOR signaling; induces succinylation of CTP1	Negative	(38-41)
	S100A11			Enhances proliferation, invasion and metastasis; promotes EMT	Regulates expression of MMP; activates PI3K/NF-κB signaling	Negative	(42,43)
	S100A16	Up	GC cell	Promotes cancer cell proliferation, invasion, and metastasis, leading to carcinogenesis and EMT	Promotes ubiquitination and degradation of ZO-2	Negative	(8,45)
HCC	S100A1	Up	HCC	Increases HCC cell proliferation; decreases tumor differentiation grade	Decreases phosphorylation of LATS1 by inhibiting activation of Hippo signaling; inhibits the phosphorylation of YAP	Negative	(53)
	S100A4	Up	HCC	Promotes HCC cell proliferation, invasion and metastasis; enhances EMT	Upregulates expression of miR-155, OPN and MMP-9; promotes the phosphorylation of STAT3 and activation of NF-κB signaling; upregulates expression of OPN and S100A4 induced by HBx.	Negative	(26,49-52, 54-58)
	S100A6	Up	HCC	Enhances HCC cell proliferation and invasion	Promotes p53 ubiquitin-dependent proteasome degradation	Negative	(59,64)
	S100A9	Up	HCC	Promotes proliferation, invasion and metastasis of HCC; increases stemness of HCC; promotes HCC progression; recruits tumor-associated macrophages and aggravates inflammation	Regulates tumor-associated macrophages via CCL2; interacts with Ca^{2+}; activates NF-κB signaling pathway via RAGE; regulated by HBx	Negative	(60,65-67)
	S100A10	Up	HCC	Promotes HCC growth and metastasis; enhances inflammation and fibrosis; promotes cancer progression	Regulated by LINC00174; increases growth and metastasis of HCC; promotes HCC initiation and progression by regulating translocation in extracellular vesicles and regulating protein loading; promotes carcinogenesis via EGFRvIII/STAT3 signaling	Negative	(39,122,123)

Table II. Continued.

Cancer	Protein	Differential expression	Expressed cell	Biological effect	Molecular mechanism	Prognostic association	(Refs.)
	S100A11	Up	HCC	Promotes HCC growth and metastasis; . enhances inflammation and fibrosis; promotes cancer progression, inflammation and fibrosis	Regulated by LPCAT1; inhibits activation of AKT and ERK signaling pathways	Negative	(62,68, 69,124)
PC	S100A2	Up	PC	Induces tumorigenesis; negatively associated with prognosis of PC	Regulates $CD8^+$ T cells; promotes infiltration of NK cells	Negative	(9,71,72)
	S100A4	Up	PC	Promotes PC cell proliferation, invasion and metastasis; induces angiogenesis	Unknown	Negative	(71,73,74)
	S100A10	UP	PC	Promotes PC cell proliferation, migration and adhesion	Activates LAMB3/LAMC2 via the JNK pathway	Negative	(125)
	S100A11	Up	PC	Increases PC growth and progression; inhibits cancer cell apoptosis; promotes G0/G1 transition; increases proliferation of fibroblasts	Induces high phosphorylation of AKT; activates PI3K/AKT and RAGE/MyD88/mTOR/p70 S6 signaling pathways; upregulates P21	Negative	(76-81)
	S100A14	Up	PC cell	Promotes PC cell proliferation, invasion and metastasis; enhances cancer cell stemness, leading to PC progression; decreases response rate of cancer immunotherapy	Activates Ras signaling; inhibits infiltration and activity of $CD8^+$T cells; enhances expression of PD-L1	Negative	(82-85)
	S100A16	Up	PC	Enhances cancer cell proliferation, invasion and metastasis; inhibits anti-tumor immunity; enhances EMT	Upregulates FGF19 via AKT/ERK1/2 signaling pathway; inhibits function of DC, NK and $CD8^+$T cells via JAK-STAT signaling; enhances TWIST expression; activates STAT3 signaling pathway	Negative	(86-90)
CRC	S100A2	Up	CRC cell	Enhances CRC cell proliferation; promotes glycolysis	Induces activation of PI3K/AKT signaling pathway; upregulates GLUT	Negative	(10,98,99)
	S100A4	Up	CRC	Promotes CRC cell proliferation, invasion and metastasis; induces angiogenesis; promotes cancer progression	Upregulates MMP-13; activates PI3K/Akt signaling pathway	Negative	(56,100-103)
	S100A8	Up	CRC	Inhibits CRC metastasis; Increases cancer cell apoptosis; improves cancer prognosis	Binds USF2; inhibits TGF-β/USF2 signaling	Negative	(108-110)
	S100A14	Down	CRC cell	Promotes CRC metastasis; associated with poor prognosis	Unknown	Positive	(111)
	S100A16	Down	CRC cell	Inhibits CRC cell proliferation, invasion and metastasis and	Inhibits JNK/p38 MAPK signaling; regulated by circ-FADS2 via the AKT signaling pathway	Positive	(112,113, 118)

Table II. Continued.

Cancer	Protein	Differential expression	Expressed cell	Biological effect	Molecular mechanism	Prognostic association	(Refs.)
Oral and EC	S100A7	Up	Oral squamous carcinoma	Increased expression of S100A7; serves as diagnostic marker	Unknown	Negative	(114)
	S100A8/A9	Up	Esophageal squamous carcinoma cell	Promotes ESCC cell invasion and metastasis	Forms S100A8/A9 dimer; activates the Akt/p38 MAPK signaling pathway	Negative	(115)
	S100A14	Down	Esophageal squamous carcinoma cell	Enhances ESCC cell proliferation and survival	Activates RAGE/MAPK/NF-κB signaling. pathway	Positive	(25)

FAM107B, family with sequence similarity 107 member B; miR, microRNA Receptor of Advanced glycation End products (RAGE), ANXA2, annexin A2 (ANXA2; CTP1, Src carnitine palmitoyltransferase 1; ZO-2, zonula occludens 2 (ZO-2, large tumor suppressor kinase 1 (LATS1), Yes associated protein (YAP), epithelial-mesenchymal transition (EMT), OPN, osteopontin; HBx, hepatitis B virus X (HBx), phosphorylated protein-53 (p53; DC, dendritic cell; CCL2, small inducible cytokine subfamily A (Cys-Cys), member 2 (CCL2), epidermal growth factor receptor variant III (EGFRvIII), LPCAT1, lysophosphatidylcholine acyltransferase 1; LAMC2, Laminin subunit gamma-2 (LAMC2), PI3K, phosphoinositide-3 kinase; Myd88, myeloid Differentiation Factor 88; PD-L1, Programmed cell death 1 ligand 1 (PD-L1), fibroblast growth factor 19 (FGF19; NK, natural killer; USF2, upstream transcription factor 2 (USF2), fatty acid desaturase 2 (FADS2).

pathogenesis by promoting EMT and upregulating MMP-9 via the NF-κB pathway (51,52). In HCC, Hepatitis B virus X (HBx) protein can enhance the expression of S100A4, thus promoting the proliferation of HCC cells (54). Exosome-derived S100A4 can induce the metastasis of HCC by regulating cell adhesion and remodeling of extracellular matrix (55,56). Furthermore, S100A4 is highly expressed in hypermetastatic HCC cells, which can promote invasion and metastasis by upregulating miR-155 and activating STAT3 (57,58). In addition, high expression of S100A4 predicts poor prognosis of HCC (49). Accordingly, S100A4 is a key regulator in HCC. Exosomal S100A4 may serve as a promising marker for HCC progression and prognosis. Other S100 proteins are involved in the pathogenesis of HCC, such as S100A6 (59), S100A9 (60), S100A10 (61), S100A11 (62) and S10013 (63). Among them, increased expression of S100A6 leads to HCC cell proliferation and invasion by enhancing degradation of p53 (64). In addition to cancer cell proliferation and invasion, high expression of S100A9 is associated with poor differentiation and increased malignancy of HCC (65). S100A9 secreted by tumor-associated macrophages functions as a cancer promoter by recruiting more macrophages and other inflammatory cells via chemokine ligand 2, thereby establishing a positive feedback loop that leads to increased production of S100A9 within the tumor microenvironment (66). Similar to S100A4, HBx protein can elevate the expression of S100A9 via the NF-κB pathway, which thus promotes hepatitis B virus-associated HCC occurrence and metastasis (67). In addition, increased expression of S100A11 occurs in HCC, contributing to the invasion and migration of HCC cells (68). It also enhances inflammation and fibrosis via epidermal growth factor receptor variant III/STAT3 signaling (68), ultimately leading to poor prognosis of HCC (62). A recent study confirmed that S100A11 is superior to alpha fetoprotein antibody in predicting haematogenous metastasis in patients with HCC (69). Certain S100 proteins and the key signaling molecules can serve as promising targets for the treatment of HCC in future, although more high-quality studies are warranted to determine the precise molecular mechanisms.

PC. PC is a highly malignant tumor. The survival rate of patients with PC is <10%. (70). Despite progress surgery and chemoradiotherapy, the prognosis of PC remains poor. Therefore, it is pivotal to identify novel strategies for early diagnosis and effective treatment of PC in future.

There are increasing studies supporting the key role of S100 protein members in PC (9,71,72). Bachet *et al* (71) demonstrated that S100A2 predicts longer disease-free and overall survival in patients with pancreatic adenocarcinoma, suggesting a predictive benefit of S100A2 in the adjuvant therapy of pancreatic adenocarcinoma. By contrast, another study (9) has implicated that elevated expression of S100A2 is related to progression and poor prognosis of patients with PC. Moreover, a recent study has shown that S100A2 serves as a predictive biomarker of $CD8^+$ T and activated natural killer (NK) cell infiltration in PC, suggesting a prognostic factor for predicting the response to immunotherapy response in patients with PC (72). The expression of S100A2 is positively associated with PD-L1 and infiltration of M0 macrophages in the immune microenvironment (72). Accordingly, more

studies are warranted to elucidate the effect and mechanism of S100A2 in regulating PC. Che *et al* (73) demonstrated that the expression of S100A4 is positively associated with the differentiation grade and metastasis of PC (71) and promoted the PC cell proliferation, angiogenesis, invasion, and progression. High expression of S100A4 leads to poor differentiation of PC by inducing hypomethylation of the corresponding intron (74). In addition, expression of S100A4 is positively associated with the serum levels of CA19.9, an important prognostic factor for PC (75). Accordingly, S100A4 is a tumor promoter in PC but its precise molecular mechanism remains unclear. It has been well documented that the expression of S100A11 is increased in multiple types of cancers, including lung (76) and thyroid cancer (77). A previous study demonstrated elevated expression of S100A11 in PC, which also predicts poor cancer prognosis (78). Similar findings have also been demonstrated in subsequent studies (79-81). S100A11 promotes pancreatic carcinogenesis by enhancing expression, phosphorylation and activation of AKT, upregulating P21 and facilitating the transition of G0/G1 cell cycle through the PI3K/AKT signaling pathway in cancer cells (80). Moreover, S100A11 can also function as a PC promoter by facilitating the spread of fibroblast population and promoting cancer progression via the RAGE/MyD88/mTOR/p70 signaling pathway (81). As a result, S100A11 may serve as a promising therapeutic target due to the key modifying effects in regulating PC. Increasing evidence has demonstrated the altered expression of S100A14 in multiple malignant tumors, such as LC, breast cancer and CRC (82-85). Elevated expression of S100A14 has also been reported in several publications (83-85). Zhuang *et al* (84) demonstrated that the overexpression of S100A14 promotes the proliferation, migration and invasion of PC cells by adhering to Ras and inhibiting $CD8^+$ T cell infiltration and cytolytic activity. S100A14 is found to inhibit the activation of $CD8^+$T cells by enhancing the expression of PD-L1, which affects the immunotherapy response of patients with PC (85). Accordingly, S100A14 is also a PC promoter and prognostic predictor. Fang *et al* (86) demonstrated that S100A16 promotes PC progression by enhancing the expression of FGF19 via the AKT/ERK1/2 signaling pathway. Besides, S100A16 plays a critical role in regulating cancer immunity in PC, affecting the function of $CD8^+$ T, dendritic and NK cells by inhibiting the activation of JAK/STAT signaling (87). S100A16 induces EMT by enhancing TWIST expression and activating the STAT3 signaling pathway (87). Moreover, the anti-tumor effect of gemcitabine is augmented following inhibition of S100A16 (88). Therefore, elevated expression of S100A16 predicts poor overall survival of patients with PC (89,90). Taken together, S100 family members are potential biomarkers for PC diagnosis, treatment and prognosis, particularly S100A4, S100A11, S100A14 and S100A16. Nonetheless, the underlying mechanisms of S100 family in PC warrant more studies with high quality.

CRC. CRC is one of the most common types of gastrointestinal cancer and has unclear etiology and pathogenesis (91). It is the fourth most common cause of cancer-related death worldwide after lung cancer, LC and GC (92). It is urgent to identify novel strategies for the early diagnosis and treatment of CRC.

Perineural invasion (PNI) is a well-established prognostic factor for CRC (93-95). A recent study by Fukuda *et al* (93) demonstrated that S100-stained PNI (S100-PNI) is correlated with worse prognosis of patients with stage I/II CRC. Significantly reduced stromal lymphocytic reaction is found in S100-PNI-positive compared with S100-PNI-negative tumors in stage I/II CRC, suggesting an underlying association between S100-PNI and immunosuppression in CRC (93). Accordingly, S100 protein family serves a pivotal role in the progression of CRC. A number of studies have investigated the role of S100 proteins in colorectal carcinogenesis (10,96,97). However, the effects of S100 proteins are different and exhibit complicated mechanisms. It has been shown that S100A2 expression is increased in CRC tissue and serves plays a crucial role in regulating tumor immunity of CRC (10,96). Sinapine thiocyanate inhibits expression of S100A2, thereby inhibiting the invasion and migration of CRC cells (97). Tumor-specific metabolism leads to dysregulated pH in tumor microenvironment, which might serve as an effective therapeutic target for malignancy (98). Another key S100 family member associated with CRC is S100A2, which promotes the proliferation of CRC cells by upregulating the key enzyme glucose transporter 1, which is involved in glycolysis, and activating PI3K/AKT signaling (99). S100A4 is upregulated in CRC compared with adjacent tissues (100). Dahlmann *et al* (101) demonstrated that S100A4 promotes colon cancer growth, invasion and metastasis by interacting with RAGE via MAPK and NF-κB pathways. MMPs are associated with the behavior of cancer cells (56). Extracellular S100A4 contributes to angiogenesis, thereby promoting the migration of CRC via upregulation of MMP-13 (56). Similar to S100A2, S100A4 also contributes to the progression of CRC via PI3K/Akt signaling (102). The expression of S100A4 in CRC tissue is associated with poor prognosis (102). It is well-documented that CRC cells with high expression of S100A4 are more sensitive to ingenol mebutate (103-106). Cantharidin and norcantharidin inhibit the expression of S100A4 and metastasis-associated with colon cancer protein 1, thus inhibiting the growth and metastasis of CRC (107). Therefore, S100A4 exerts key effects on CRC by regulating cancer cell proliferation, invasion and migration. S100A8 plays dual roles in cancer development and progression (108). Li *et al* (109) demonstrated that extracellular S100A8 is associated with good prognosis and inhibited the aggressiveness of colorectal carcinoma by regulating EMT and cancer cell apoptosis. Conversely, intracellular S100A8 is demonstrated to promote EMT and metastasis in CRC via the TGF-β/upstream transcription factor 2 (USF2) axis, while USF2 is an essential switch in the intracellular and extracellular S100A8 feedback loop (110). High expression of extracellular S100A8 affects the EMT via the TGF-β/USF2 axis in CRC. The molecular mechanism underlying the switch of intracellular and extracellular S100A8 in regulating CRC requires validation. S100A14 affects CRC progression by enhancing E-cadherin expression but decreasing the ability of SW480 CRC cells to form colonies in soft agar (111). S100A14 may serve as a prognostic marker for CRC (111). However, little is known about potential molecular mechanism of S100A14 in regulating

colorectal carcinogenesis and progression. According to localization, there are three types of S100A16, including membrane, cytoplasm and nucleus. A previous study has provided the evidence that patients with CRC with low expression of membrane S100A16 have shorter overall survival, while no significant association has been demonstrated between the expression of cytoplasmic/nuclear S100A16 and overall survival, suggesting the prognostic value of S100A16 in CRC (112). Ou *et al* (113) demonstrated lower expression of S100A16 in CRC (113). S100A16 suppresses the proliferation, migration and invasion of CRC cells via the JNK/p38 MAPK pathway (113). Accordingly, S100A16 may be a promising prognostic marker and therapeutic target for CRC.

Taken together, S100 family members are involved in the pathogenesis of CRC, particularly S100A2, S100A4, S100A8, S100A14 and S100A16. They may serve as useful therapeutic targets for CRC but the underlying mechanisms need to be elucidated in future.

Oral and EC. S100A7 is an ideal diagnostic marker for oral potentially malignant disorders (OPMDs) and oral squamous cell carcinoma (OSCC) (114). The disease-free survival of patients with esophageal squamous cell carcinoma (ESCC) with higher expression of S100A8/A9 is shorter (115). Besides, S100A8/A9 promotes migration and invasion of ESCC cells via Akt/p38 signaling (115), suggesting a pivotal role of S100A8/A9 in ESCC progression and prognosis. Moreover, extracellular S100A14 enhances the proliferation and survival of ESCC cells via interacting with RAGE and activating MAP and NF-κB pathways (25). Accordingly, S100 family members S100A7, S100A8/A9 and S100A14 may serve as useful markers for the diagnosis and treatment of oral cancer and EC.

5. Conclusion

To date, there is no effective strategy for the early diagnosis of most types of cancer. It is urgent to identify novel makers for early screening and effective treatment of digestive tract cancers due to the rising incidence and cancer-associated mortality. Tumor-targeted therapy, which selectively kills cancer cells while sparing healthy cells, has garnered significant attention in recent years (103,116). Molecular targeted therapy, also known as a 'biological missile', has emerged as a key focus in cancer research. The S100 protein has been identified as a highly promising biological target in recent studies (88,117). S100 protein family has been demonstrated to participate in regulating inflammation, immunity, tissue repair and tumorigenesis. Most importantly, certain S100 family members (such as S100A4, S100A8/9, S100A11, S100A14, and S100A16) have shown potential for the molecular diagnosis, progression monitoring and prognostic prediction of digestive tract cancer. These proteins are involved in regulating tumor proliferation, metastasis, angiogenesis and immune evasion, although the precise mechanisms are elusive (118-121). Thus, elucidating the effects and potential mechanisms of S100 proteins in digestive tract cancer may facilitate the identification of novel targets for targeted therapy. Future studies should focus on validation of cancer-specific S100 proteins as biomarkers for early detection, anti-tumor targets and prognostic prediction. S100 family members hold promise as potential targets for the diagnosis and targeted therapy of digestive tract cancer.

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Authors' contributions

ML, DX and SY wrote and revised the manuscript. SJ, BC, PC, WD, HZ, SY, DX and YS collected the data and constructed tables and figures. ML and SY confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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