Tetraspanins in digestive-system cancers: Expression, function and therapeutic potential (Review)

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Abstract. The tetraspanin family of membrane proteins is essential for controlling different biological processes such as cell migration, penetration, adhesion, growth, apoptosis, angiogenesis and metastasis. The present review summarized the current knowledge regarding the expression and roles of tetraspanins in different types of cancer of the digestive system, including gastric, liver, colorectal, pancreatic, esophageal and oral cancer. Depending on the type and context of cancer, tetraspanins can act as either tumor promoters or suppressors. In the present review, the importance of tetraspanins in serving as biomarkers and targets for different types of digestive system-related cancer was emphasized. Additionally, the molecular mechanisms underlying the involvement of tetraspanins in cancer progression and metastasis were explored. Furthermore, the current challenges are addressed and future research directions for advancing investigations related to tetraspanins in the context of digestive system malignancies are proposed.

Contents

1. Introduction

Tetraspanins, also termed TSPANs or the transmembrane 4 super-family proteins, are members of a protein family widely conserved across different species. These proteins are ubiquitously distributed within various organisms (1).

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Abbreviations: 5-FU, 5-Fluorouracil; ALCAM, activated leukocyte cell adhesion molecule; BMDCs, B cells and dendritic cells; CAR-T, chimeric antigen receptor T cells; CDDP, cisplatin; CDK4, cyclin-dependent kinase 4; CIC, cancer-initiating cells; DCs, dendritic cells; DFS, disease-free survival; EC2, one large extracellular loop; EMT, epithelial-mesenchymal transition; EpCAM, epithelial cell adhesion molecule; ESCC, esophageal squamous cell carcinoma; EVs, extracellular vesicles; FAK, focal adhesion kinase; FAM83A, family with sequence similarity 83 member A; GC, gastric cancer; GIST, gastrointestinal stromal tumor; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HIST1H2BK, H2B clustered histone 12; JNK, c-JUN N-terminal kinase; mAb, monoclonal antibodies; MHC, major histocompatibility complex; miR, microRNA; OSCC, oral squamous cell carcinoma; PDAC, pancreatic ductal adenocarcinoma; PVT-1, plasmacytoma variant translocation-1; RAS, rennin-angiotensin system; RNAi, RNA interference; siRNAs, small interfering RNAs; SOX9, SRY-box transcription factor 9; TCR, T cell receptors; TEMs, tetraspanin-enriched microdomains; TIMP-1, tissue inhibitor of metalloproteinase-1; TM, transmembrane; TNM, tumor node metastasis; TSPAN8-LEL, TSPAN8 extracellular large loop; uPA, urokinase plasminogen activator; uPAR, urokinase-type plasminogen activator receptor; UTR, untranslated region

Key words: biomarkers, clinical significance, digestive-system cancers, molecular mechanisms, tetraspanins

Tetraspanins participate in a broad spectrum of biological processes, such as regulating cell morphology, motility, invasion, fusion and signaling. Specifically, tetraspanins serve crucial roles in tumor metastasis, membrane dynamics, infection, synapse formation, platelet aggregation, fertilization and the immune response (1). Although tetraspanins have a small molecular size of 200-350 amino acids and only extend 3-5 nm above the cell membrane (2,3), their function is significant. Studies have emphasized their essential biological and physiological functions in promoting cell movement and growth by serving as coordinators of complex structures within cell membranes (1,4-7).

Tetraspanins, form a protein group consisting of 33 identified members in humans (8). Members of the tetraspanin family possess four transmembrane (TM) domains, conserved amino acids, a small extracellular loop, a larger extracellular loop (EC2 loop), a cytoplasmic loop and short N- and C-terminal cytoplasmic tails. The EC2 loop is divided into a constant region, with three α-helices, and a variable region, which houses most tetraspanin protein-protein interaction sites (Fig. 1A). Tetraspanins typically undergo post-translational palmitoylation at cysteine residues proximal to the membrane, which is key for their interaction with other TM proteins, cholesterol and gangliosides (1,4,6,8). This modification is necessary to create 'tetraspanin-enriched microdomains' (TEMs), which are distinct from lipid rafts and can be disrupted by Triton X-100 (9). Furthermore, tetraspanins undergo additional post-translational modifications at several highly conserved cysteine and lysine residues, including *N*-glycosylation (common in the EC2 structural domain) and ubiquitination (in the N-terminal structural domain) (10). The general structure of a typical tetraspanin protein is shown in Fig. 1A.

Globally, cancer (excluding nonmelanoma skin cancer), estimated to cause 250 million (95% UI, 235-264 million) in 2019, is the second most common cause of mortality, with digestive system-related cancer being the most widespread form of malignancy (11). In the context of digestive system cancer (Fig. 1B), tetraspanins have emerged as significant contributors to tumorigenesis and disease progression. Therefore, understanding the expression patterns and functional implications of tetraspanins within the intricate network of digestive system malignancies is imperative for developing targeted therapeutic interventions and diagnostic approaches. Over the last 10 years, studies have linked tetraspanins to different cancer-related traits, such as tissue specialization, cell growth, migration, attachment, mobility, apoptosis, angiogenesis, cellular pluripotency and metastasis (1,12-18). For instance, tetraspanins have been implicated in the regulation of tumor cell metastasis, migration and altered adhesion through integrin signaling (1,19). Tetraspanins also bind to peptidases, a disintegrin, ADAM metalloproteinases (particularly ADAM10) (20), matrix metalloproteinases (21) and the urokinase-type plasminogen activator receptor (22) to regulate cell invasiveness. Although tetraspanins share a highly conserved structure, they can either promote or inhibit tumor development. In the context of digestive system tumors, the precise function of tetraspanins warrants further research and exploration. The present review comprehensively explored the current understanding of the expression profiles and diverse functions of tetraspanins in different types of digestive system-related cancer (Table I)(23-67), shedding light on their potential as biomarkers and therapeutic targets for combating these challenging malignancies.

2. Tetraspanins and gastric cancer (GC)

In terms of worldwide prevalence, GC ranks fourth for men and fifth for women, and >1 million new cases are attributed to GC annually globally (68). Nevertheless, individuals diagnosed with late-stage GC generally face a poor outlook, experiencing a decreased survival rate; the 5-year survival rate is <10% (69). In recent years, a number of experiments have been conducted to explore the pathogenesis of GC, revealing a close association with tetraspanins. These diverse proteins serve critical roles in various biological functions within GC cells (70). In this section, the effect of specific tetraspanins on GC cell proliferation and invasion are summarized. Notably, TSPAN8, TSPAN24/CD151, TSPAN4, TSPAN1, TSPAN29/CD9 and TSPAN31 enhance these processes, while TSPAN28/CD81, TSPAN27/CD82, TSPAN5, TSPAN9 and TSPAN21 suppress the growth of GC cells (Fig. 2).

Tetraspanins that promote the progression of GC

TSPAN8. TSPAN8 is associated with numerous types of cancer, contributing to increased metastasis, proliferation, angiogenesis and thrombosis (71-75). Upregulated TSPAN8 is also recognized as a standalone predictor of outcomes for patients with GC. Knockdown of TSPAN8 has been shown to reduce the invasive ability of GC cells, but TSPAN8-containing exosomes restores this ability (76). Research has demonstrated that TSPAN8 functions as an oncogene in GC, contributing to the growth and metastasis of GC cells by activating the EGFR (33) and ERK/MAPK (34) pathways. In conclusion, TSPAN8 is involved in promoting the progression of GC.

TSPAN24/CD151. TSPAN24/CD151 creates TEMs by interacting with different TM proteins, which control integrin-dependent cell adhesion, shape and movement. TSPAN24 serves a crucial role as a binding partner to laminin-binding integrins (77,78). A study suggests that the complex interaction of TSPAN24 with integrin α3 in GC cells is correlated with increased invasiveness (45). Additionally, non-coding RNA plasmacytoma variant translocation (PVT)-1 enhances TSPAN24 expression by interacting with microRNA (miR)-152, promoting GC and highlighting PVT-1 as a potential therapeutic target (79).

TSPAN1. TSPAN1, also referred to as neuroepithelial transforming gene 1, functions as a guanine nucleotide exchange factor (80). TSPAN1 can enhance tumor growth across various types of cancer, contributing to metastases (81-84). Lu *et al* (23) observed a significant upregulation of TSPAN1 expression in GC tissues, identifying TSPAN1 as a potential oncogene that facilitates GC cell proliferation and invasion. Additionally, it was demonstrated that miR-573 hinders the growth and invasion of GC by directly targeting the 3'-untranslated region (UTR) of TSPAN1. This regulated axis offers a fresh insight into the mechanisms underlying GC (23).

TSPAN4. Previous research by Ma *et al* (85) have identified TSPAN4 as a key regulator of a novel organelle called the migrasome, closely associated with cellular functions such as migration and other biological activities (86-88). TSPAN4

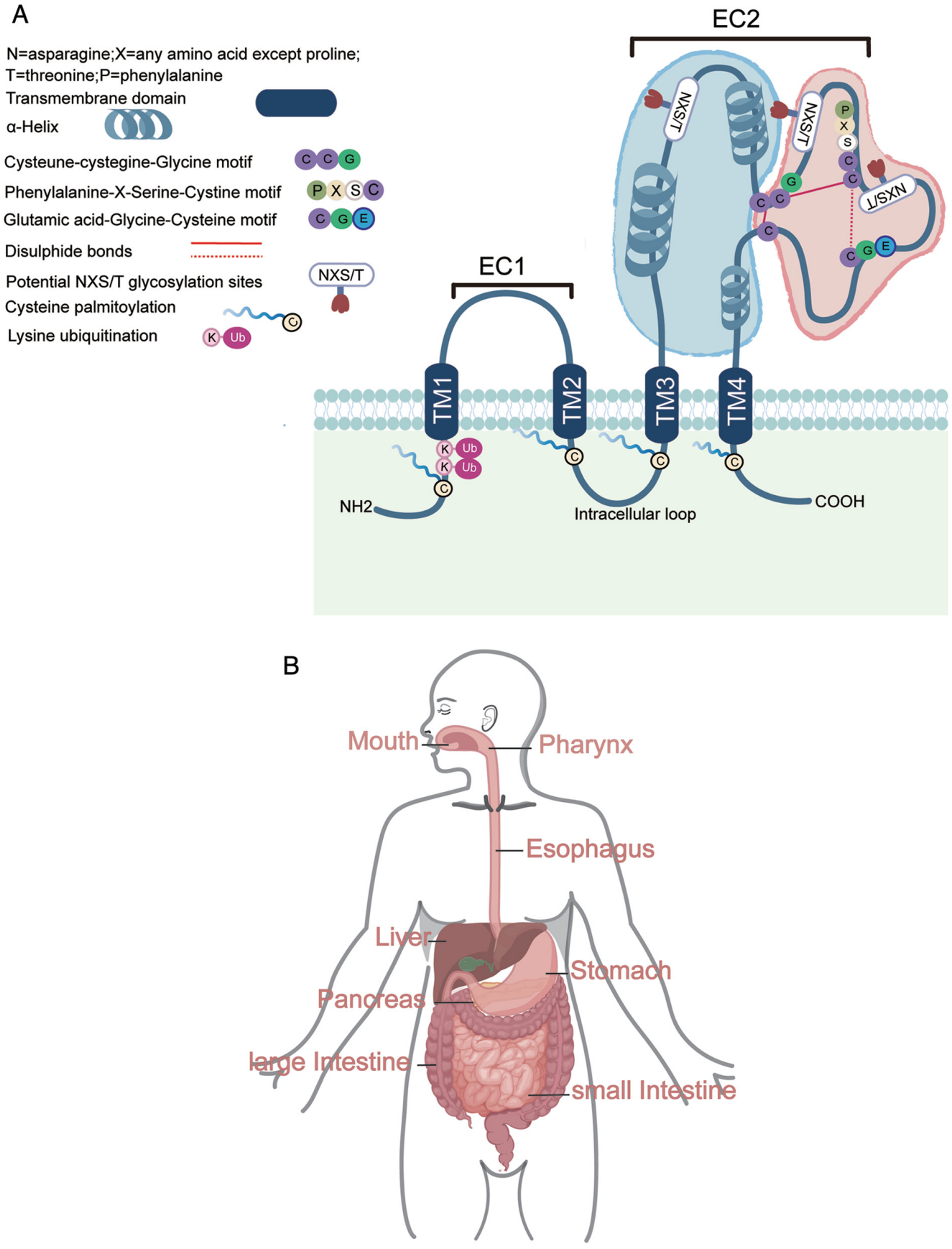

Figure 1. General structure of a tetraspanin protein and the human digestive system. (A) The tetraspanin protein structure. Tetraspanin proteins are characterized by four transmembrane domains, two cytoplasmic tails and two extracellular loops (EC1 and EC2). Disulfide bonds stabilize the EC2 loop, which is divided into constant (green) and variable (pink) regions and contains conserved cysteine residues, such as a CCG motif. The EC2 domain also contains conserved motifs such as PXSC and EGC, three α-helices and potential sites for palmitoylation, ubiquitination and glycosylation. (B) The digestive system anatomy. The mouth, pharynx, esophagus, liver, stomach, pancreas, large intestine and small intestine make up the human digestive system, organized in a top-to-bottom sequence. EC1, one small extracellular loop; EC2, one large extracellular loop.

Table I. Summary of tetraspanins aliases and their role in corresponding digestive-system cancers.

Tetraspanins	Alternative name	Digestive-system cancers	Effects in cancer progression	Specific roles	(Refs.)
TSPAN1	TSP-1, NET-1, TM4C, TM4SF, C4.8	Gastric cancer	Promotes	Proliferation, invasion	(23-26)
		Liver cancer	Promotes	Proliferation Proliferation,	
		Pancreatic cancer	Promotes	invasion, Migration	
		Colorectal cancer	Promotes	Proliferation, invasion	
		Esophageal cancer	Promotes		
TSPAN4	NAG-2, TSP-4, TM4SF7	Gastric cancer	Promotes	Proliferation	(27)
		Esophageal cancer	Promotes		
TSPAN5	NET-4, TSP-5, TM4SF9	Gastric cancer	Represses	Proliferation, colony	(28-30)
		Liver cancer	Promotes	formation, migration	
		Colorectal cancer	Promotes	Metastasis, epithelial-mesenchymal transition, proliferation, invasion, migration	
TSPAN6	TSP-6, T245, TM4SF6, UNQ767/PRO1560	Colorectal cancer	Represses	Growth	(31)
TSPAN7	A15, CCG-B7, CD231, DXS1692E, MRX58, MXS1, TALLA-1, TM4SF2-1, TM4SF2b, XLID58	Liver cancer	Represses	Proliferation	(32)
		Pancreatic cancer	Represses		
TSPAN8	CO-029, TM4SF3	Gastric cancer	Promotes	Proliferation, invasion	(33-38)
		Liver cancer	Promotes	Metastasis	
		Pancreatic cancer	Promotes	Invasion, metastasis	
		Colorectal cancer	Promotes	Migration	
		Esophageal cancer	Promotes	Invasion, migration	
TSPAN9	NET-5, PP1057	Gastric cancer	Represses	Proliferation, invasion,	(39,40)
		Colorectal cancer	Promotes	Migration, metastasis	
TSPAN12	EVR5, NET-2, TM4SF12, UNQ774/PRO1568	Colorectal cancer	Promotes	Proliferation, invasion, migration, growth	(41)
TSPAN15	2700063A19Rik, NET-7, TM4SF15, UNQ677/PRO1311	Liver cancer	Promotes	Proliferation	(42,43)
		Esophageal cancer	Promotes	Invasion, metastasis,	
		Oral cancer	Promotes	Migration	
TSPAN21	UPK1A, Uroplakin-1a, UP1a	Gastric cancer	Represses	Invasion, migration	(44)
TSPAN24	EBS7, MER2, RAPH, hemidesmosomal tetraspanin CD151, membrane glycoprotein SFA-1, platelet surface glycoprotein GP27, platelet-endothelial cell tetraspan antigen 3, PETA-3	Gastric cancer	Promotes	Invasion	(45-47)
		Liver cancer	Promotes	Angiogenesis, metastasis	
		Esophageal cancer	Promotes	Proliferation, invasion	
TSPAN27	4F9, C33, GR15, IA4, KAI1, R2, SAR2, ST6, CD82, metastasis suppressor Kangai-1	Gastric cancer	Represses	Invasion, metastasis	(48-55)
		Liver cancer	Represses	Invasion, metastasis	
		Pancreatic cancer	Represses	Metastasis	
		Colorectal cancer	Represses	Migration, invasion	
		Esophageal cancer	Represses	Proliferation, metastasis	
		Oral cancer	Represses		
TSPAN28	S5.7, CD81, CVID6, TAPA-1	Gastric cancer	Represses	Promotes apoptosis	(56,57)
		Liver cancer	Promotes	Metastasis	

Table I. Continued.

Tetraspanins	Alternative name	Digestive-system cancers	Effects in cancer progression	Specific roles	(Refs.)
TSPAN29	BTCC-1, DRAP-27, GIG2, MIC3, MRP-1, CD9,5H9, BA-2/p24 antigen, cell growth-inhibiting gene 2 protein, leukocyte antigen MIC3, MRP-1	Gastric cancer Liver cancer Pancreatic cancer Colorectal cancer Esophageal cancer Oral cancer	Promotes Represses Represses Represses Promotes Promotes	Proliferation, Angiogenesis Proliferation Proliferation, invasion, Migration Proliferation Metastasis	(58-64)
TSPAN30	CD63, melanoma 1 antigen, granulophysin, lysosomal-associated membrane protein 3, melanoma-associated antigen ME491, melanoma-associated antigen MLA1, ocular melanoma-associated antigen	Liver cancer	Promotes	Migration, survival	(65)
TSPAN31	Sarcoma amplified sequence, SAS	Gastric cancer Liver cancer	Promotes Promotes	Proliferation, invasion, migration, suppresses apoptosis, epithelial-mesenchymal transition Invasion and migration	(66,67)

TSPAN, tetraspanin; MRP-1, motility related protein-1; SAS, sarcoma amplified sequence.

upregulation in GC discovered through bioinformatics, is correlated with decreased survival rates. The downregulation of TSPAN4 significantly reduces GC cell proliferation, suggesting its potential as a therapeutic target as well as a biomarker (89).

TSPAN29/CD9. TSPAN29/CD9 expression is markedly elevated in primary GC tissues and becomes more prominent in advanced GC (90). Additionally, TSPAN29 expression is positively correlated with tumor status, including the extent of infiltration and metastasis of the lymph nodes (27). There is evidence for the co-expression of proHB-epidermal growth factor (EGF; the membrane-anchored form of HB-EGF) and TSPAN29 in GC, and one study has clearly demonstrated the presence of HB-EGF mRNA and EGF-receptor mRNA in GC tissues. These findings suggest that the direct interaction could play a role in GC development and tumor growth through paracrine, autocrine, and/or juxtacrine mechanisms (58). Nakamoto *et al* (59) successfully suppressed tumor progression by administering an anti-TSPAN29 antibody to mice bearing a human GC cell xenograft. Notably, TSPAN29 protein expression is low in metastatic gastrointestinal stromal tumors (GISTs), while low TSPAN29 expression in primary GIST is associated with poorer disease-free survival (DFS). However, TSPAN29 expression in intestinal stromal tumors is not significantly associated with the DFS of patients, suggesting that its role in regulating GIST metastasis may be related to organ type (91). Additionally, a study by Zhao *et al* (92) reveals that histone lysine-specific demethylase 1 promotes GC migration by decreasing miR-142-5p levels and increasing TSPAN29 expression.

TSPAN31. TSPAN31 has been extensively studied in human osteosarcoma (93); however, the relationship between TSPAN31 and GC has been rarely reported. Elevated levels of TSPAN31 in GC cell lines and tissues are associated with poor outcomes. Mechanistically, TSPAN31 promotes GC cell proliferation and migration while suppressing apoptosis via co-expression with methyltransferase like 1 and recombinant chaperonin containing tCP1, subunit 2 (94). Furthermore, TSPAN31 upregulation is linked to lymphatic and venous invasion, later pathological tumor and pathological node staging and higher recurrence rates. Conversely, silencing TSPAN31 expression suppresses the growth, movement and transition of GC cells through the PI3K-Akt pathway, promoting cell death regardless of the TP53 mutational status (66).

Tetraspanins that repress the progression of GC

TSPAN28/CD81. TSPAN28/CD81 was first identified as the binding site for an anti-growth antibody (95). Thus far, TSPAN28 has been shown to affect cell shape, adhesion and growth and the differentiation of B cells and T cells (96). In addition, Yoo *et al* (56) suggest that a reduction in TSPAN28 mRNA levels in GC tissues and GC cell lines is a result of abnormal CpG hypermethylation in its promoter region rather than genetic mutations. This decrease in TSPAN8 expression encourages the progression from the G_1 to the S phase of the cell cycle and reduces the cellular responses to different types of stress that

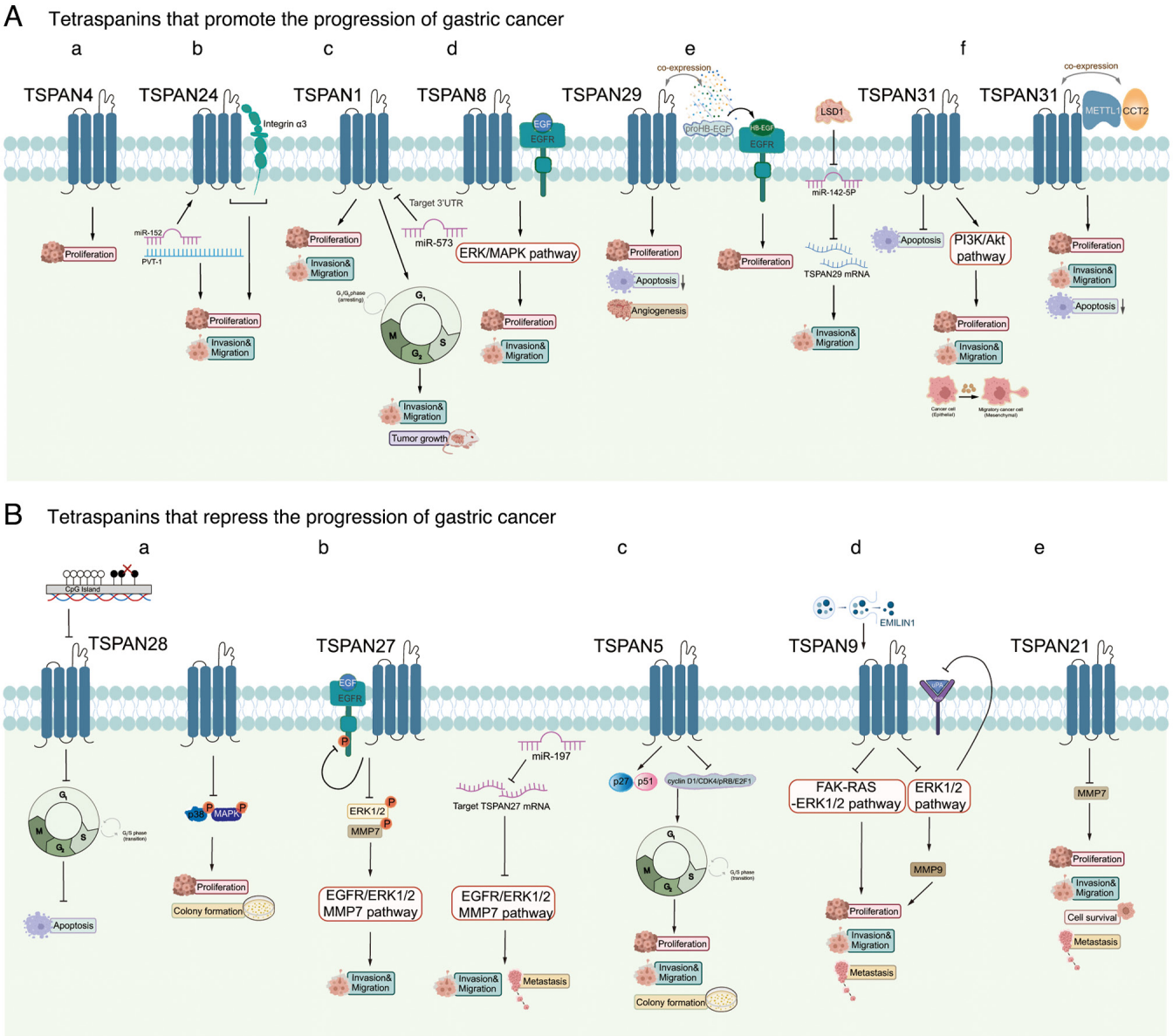

Figure 2. Functions of tetraspanins in GC. (A) Tetraspanins promoting GC progression: (a) Downregulation of TSPAN4 reduces GC cell proliferation. (b) In GC cells, TSPAN24/CD151 expression is positively associated with GC invasiveness due to the formation of a complex with integrin α3. PVT-1 increases TSPAN24 expression and inhibits miR-152 expression, promoting gastric carcinogenesis. (c) TSPAN1 enhances cell growth and infiltration in GC. miR-573 binds to the 3'UTR of TSPAN1, leading to cell cycle arrest in the G_1/G0 phase and suppression of GC growth and infiltration. (d) TSPAN8 enhances GC cell growth and migration by activating the EGFR pathway. (e) Co-expression of TSPAN29/CD9 and proHB-EGF may be involved in gastric carcinogenesis. LSD1 upregulates TSPAN29/CD9 by decreasing miR-142-5p levels, promoting GC migration. (f) TSPAN31 enhances the growth and movement of GC cells by suppressing cell death when METTL1 and CCT2 are co-expressed. (B) Tetraspanins suppressing GC progression: (a) Aberrant CpG hypermethylation of the TSPAN28/CD81 promoter reduces mRNA expression and impairs the ability of GC cells to form colonies. (b) TSPAN27/CD82 suppresses GC invasion by suppressing the activation of ERK1/2, EGFR and MMP7. (c) TSPAN5 inhibits GC cell proliferation, migration and colony formation by regulating the G_1 to S phase transition. (d) TSPAN9 inhibits the ERK1/2 pathway, leading to downregulation of MMP-9 and uPA. The extracellular secretory protein, EMILIN1, inhibits the FAK-RAS-ERK1/2 signaling pathway, resulting in increased TSPAN9 expression and inhibition of GC cell migration and invasion. TSPAN9 also interacts with PI3K to block PI3K-Akt-mTOR signaling, enhancing autophagy. (e) TSPAN21 inhibits MMP7, controlling cell metastasis, invasion and survival. GC, gastric cancer; TSPAN, tetraspanin; PVT-1, plasmacytoma variant translocation-1; miR, microRNA; UTR, untranslated region; LSD1, lysine-specific demethylase 1; METTL1, methyltransferase like 1; CCT2, recombinant chaperonin containing tCP1, subunit 2; MMP, matrix metalloproteinase; uPA, urokinase plasminogen activator; EMILIN1, elastin microfibril interface located protein 1; FAK, focal adhesion kinase; RAS, rennin-angiotensin system; mTOR, mammalian target of rapamycin.

can lead to cell death, including towards 5-fluorouracil (5-FU), etoposide, γ-irradiation, doxorubicin and hypoxia. In addition, TSPAN28 expression decreases the ability of GC cells to form colonies and hinders the activation of p38 MAPK phosphorylation (56).

TSPAN27/CD82. TSPAN27, also known as CD82 and KAI1, has been recognized as a gene that suppresses metastasis in various types of cancer (50,97). Furthermore, it has a strong connection to the invasion of GC cells. Xu *et al* (48) reveal that TSPAN27 hinders the infiltration of GC by reducing the phosphorylated (p-)EGFR, p-ERK1/2 and MMP7 levels. Meanwhile, the nuclear endonuclease RNase III enzyme, Drosha, facilitates the production of miR-197, and elevated miR-197 inhibits TSPAN27, leading to activation of the

EGFR-ERK1/2-MMP7 pathway and ultimately enhancing GC cell invasion and metastasis (48).

TSPAN5. TSPAN5 is essential for regulating brain function in mice (98). TSPAN5 expression is markedly decreased in GC and is negatively correlated with both tumor size and the tumor-node-metastasis (TNM) stage. Furthermore, TSPAN5 upregulates the levels of p27/p15 while downregulating cyclin-dependent kinase 1 (cyclin D1), cyclin-dependent kinase 4 (CDK4), retinoblastoma protein and recombinant E2F transcription factor 1, particularly cyclin D1/CDK4. This modulation indicates TSPAN5 as a tumor suppressor that regulates the cell cycle transition from the G_1 to S phase (28).

TSPAN9. Li *et al* (99) report that increased TSPAN9 levels suppresses the growth, movement and infiltration of human SGC7901 GC cells. Specifically, TSPAN9 inhibits the ERK1/2 signaling pathway, leading to the downregulation of proteins linked to cancer metastasis, such as MMP9 and urokinase plasminogen activator. Elastin microfibril interface located protein 1, a protein secreted outside the cell, exerts anticancer properties by increasing TSPAN9 levels and blocking the movement and penetration of GC cells through suppression of the focal adhesion kinase (FAK)-rennin-angiotensin system (RAS)-ERK1/2 pathway (39). TSPAN9 also blocks PI3K-Akt-mammalian target of rapamycin signaling by binding to PI3K, promoting autophagy and causing resistance to 5-FU in GC cells (100).

TSPAN21. Deng *et al* (70) discovered that TSPAN21 suppresses GC cell migration, infiltration and viability by reducing MMP7 levels. Additionally, TSPAN21 expression is notably decreased in GC tissues, with decreased expression correlating with an unfavorable prognosis. Furthermore, increased levels of TSPAN21 suppress the movement and spread of GC cell lines (44). This suggests that TSPAN21 may act as a tumor suppressor in GC, although further investigation is required to fully understand the mechanism.

In summary, certain tetraspanins can either promote or inhibit GC. Hence, investigating the internal molecular pathways involved in the progression of GC can lead to the discovery of improved treatment options and provide optimism for patients.

3. Tetraspanins and liver cancer

Hepatocellular carcinoma (HCC) is responsible for almost 80% of liver cancer cases, making it the sixth most prevalent cancer globally. HCC is known for its high occurrence, disease burden and mortality rate (101). At present, there is no effective remedy for advanced HCC (102). Tetraspanins have been linked to hepatitis B virus (HBV) infection, hepatitis C virus infection and cirrhosis and may therefore have a significant impact on the progression of pre-cancerous conditions resulting in HCC (103). For instance, TSPAN1 and TSPAN15 promote the proliferation of HCC, while TSPAN5, TSPAN8, TSPAN24/CD151, TSPAN28/CD81, TSPAN30/CD63 and TSPAN31 promote the metastasis of HCC. Conversely, TSPAN7/CD231, TSPAN27/CD82 and TSPAN29/CD9 inhibit the progression of HCC (Fig. 3).

Tetraspanins that promote the progression of HCC

TSPAN1. HCC tissues exhibit increased levels of TSPAN1 (104), which has been recognized as a stimulator of cell proliferation (105). TSPAN1 can control the proliferation of HCC cells by modulating the PI3K/Akt signaling pathway (24). Building on this, Wu *et al* (105,106) used specific nanobubbles to transport TSPAN1 small interfering RNA (siRNA) into HCC tissues in a mouse xenograft model. This method effectively decreases TSPAN1 expression in HCC tissues and extends the survival of the mouse model. This demonstrates that gene therapy can efficiently transport genes to cancer cells, potentially serving as a crucial treatment method for HCC and other tumor therapies.

TSPAN15. Heterogeneous TSPAN15 expression patterns have been observed in HCC patients with hepatitis C virus or HBV positive using bioinformatic analysis (42). In HCC (TSPAN15-high tumors), elevated TSPAN15 levels are positively correlated with cancer cell stemness and recurrence. TSPAN15 enhances the phosphorylation of ERK, which controls the expression and secretion of connective tissue growth factor, ultimately stimulating the proliferation of HCC cells. This pro-growth effect can also be associated with the ability of TSPAN15 to increase the release of ADAM10 to a certain degree, although the exact mechanism of this remains to be elucidated (42).

TSPAN31. Wang *et al* (67) demonstrate that TSPAN31 serves a role in transmitting signals related to cell survival and apoptosis within cells. TSPAN31 mRNA is complementary to CDK4, controls the levels of CDK4 mRNA and thus the production of CDK4 protein. Furthermore, miR-135b-induced silencing of TSPAN31 results in an increase in CDK4 protein levels. Silencing of TSPAN31 also reduces the p-Akt, p-GSK3β and β-catenin levels, proteins of the Akt signaling pathway. This silencing also blocks the translocation of β-catenin to the nucleus, consequently preventing the spread and movement of HCC cells (67).

TSPAN8. TSPAN8, which is correlated with tumor metastasis, is upregulated in a variety of tumor types (107). Fang *et al* (108) propose that TSPAN8 can potentially enhance metastasis in HCC cells through the activation of ADAM12. In the resting cells, the combination of TSPAN8 and integrin is positioned at the rear of cancer cells (109). This process could serve a role in the metastasis of HCC cells and establish a foundation for determining if TSPAN8 is a viable prognostic indicator for HCC. In addition, long non-coding RNA-TSPAN8 controls the TSPAN8 expression level (57), which is also influenced by astrocyte elevated gene-1 in HCC, a gene that is upregulated in different types of cancer. Therefore, TSPAN8 has a crucial role in promoting metastasis (35).

TSPAN24/CD151. TSPAN24/CD151, the first tetraspanin linked to metastasis, plays a metastasis-promoting role in a variety of types of cancer (110,111). TSPAN24 may promote metastasis by activating integrin β1 (112). Additionally, TSPAN24 is a distinct pro-angiogenic factor that is abundantly produced by HCC cells (113). TSPAN24 is able to initiate the PI3K/Akt/GSK-3β signaling pathway, leading to the upregulation of MMP9 and facilitating the breakdown of the extracellular matrix and movement of cancer cells, both of which play a role in angiogenesis and the invasion of HCC (46). Therefore, TSPAN24 may be a sensitive biomarker for HCC metastasis. Furthermore, the TSPAN24 expression level can be regulated by miR-199a-3p, miR-124 and miR-128. However, the specific crosstalk between TSPAN24 and its upstream effectors remains complicated (114-116).

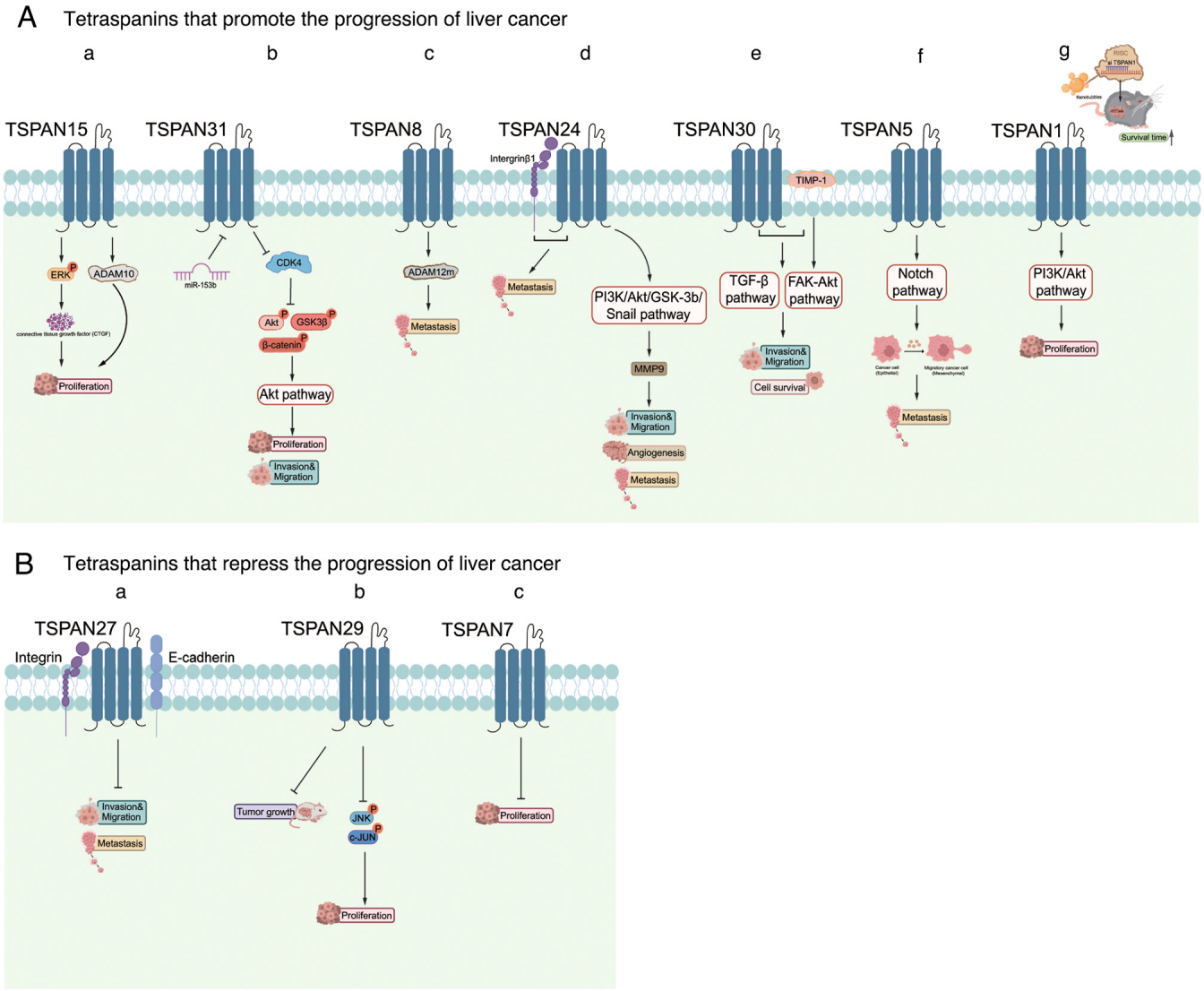

Figure 3. Functions of tetraspanins in liver cancer. (A) Tetraspanins promoting HCC progression: (a) TSPAN15 enhances ERK phosphorylation and ADAM10 secretion, controls CTGF expression and secretion and promotes HCC cell proliferation. (b) miR-135b targets TSPAN31, increasing CDK4 protein levels, which promotes HCC cell invasion and migration. (c) TSPAN8 promotes HCC cell metastasis by inducing ADAM12. (d) TSPAN24/CD151 induces metastasis through integrin β1, induces MMP9 expression, promotes cancer cell migration and contributes to angiogenesis and HCC metastasis. (e) TSPAN30/CD63 activates the TGF-β and FAK-Akt signaling pathways by binding to TIMP-1, promoting HCC cell migration and survival. (f) TSPAN5 activation of Notch signaling enhances EMT-promoted metastasis in tumor cells. (g) TSPAN1 regulates HCC cell proliferation by targeting the PI3K/Akt pathway. (B) Tetraspanins suppressing HCC progression: (a) TSPAN27 binds to integrins and E-cadherin, affecting the invasive and metastatic potential of HCC cells. (b) TSPAN29/CD9 blocks the activation of JNK and c-JUN, leading to the inhibition of HCC cell proliferation *in vitro*. (c) TSPAN7/CD231 upregulation suppresses the growth of HCC cells. HCC, hepatocellular carcinoma; TSPAN, tetraspanin; ADAM10/12, ADAM metalloproteinase 10/12; CTGF, connective tissue growth factor; miR, microRNA; CDK, cyclin-dependent kinase; MMP, matrix metalloproteinase; FAK, focal adhesion kinase; TIMP-1, tissue inhibitors of metalloproteinase-1; EMT, epithelial-mesenchymal transition; JNK, c-JUN N-terminal kinase.

TSPAN28/CD81. According to a study by Fang *et al*, TSPAN28/CD81 could be linked to metastasis to specific organs. Furthermore, TSPAN28 expression is reduced in HCC cell lines with elevated lymphatic metastatic capacity compared with those with lower lymphatic metastatic capacity, indicating that TSPAN28 could influence the progression of HCC (57).

TSPAN30/CD63. It is considered that TSPAN30/CD63 facilitates the TGF-β signaling pathway by interacting with tissue inhibitors of metalloproteinase-1 (TIMP-1), an important participant in the communication between hepatic stellate cells and HCC cells mediated by TGF-β. The FAK-Akt signaling pathway is triggered by TIMP-1, promoting the migration and survival of these cells (65).

TSPAN5. TSPAN5 has only been included in HCC research in the last few years and, as with most family members, serves a promotional role in HCC. Increased TSPAN5 levels have been confirmed to enhance the metastasis of cancer, vascular angiogenesis, clinical stage and overall survival in HCC (29). Additionally, validation of Notch signaling activation by TSPAN5 in clinical HCC samples leads to increased epithelial-mesenchymal transition (EMT) and actin rearrangement, as shown in mechanistic studies (29). Deletion of TSPAN5 is also shown to mediate the p16INK4a/pRb pathway, inducing oncogene-induced senescence. Specifically, the inhibition of TSPAN5 results in decreased actin polymerization, which consequently decreased the formation of the myocardin-related

transcription factor A (MRTF-A)-filamentosamine A complex. This leads to a decrease in the expression of MRTF/serum response factor-dependent target genes and the initiation of senescence both *in vitro* and *in vivo* (117).

Tetraspanins that repress the progression of HCC

TSPAN27/CD82. It has been reported that TSPAN27/CD82 and other members of the tetraspanin family can interact with each other, integrins and E-cadherin (49). Tetraspanins appear to facilitate cell-cell and cell-matrix interactions, which could affect the ability of cancer cells to invade and metastasize (49,50). Additionally, a reduction in TSPAN27 mRNA levels in HCC cells appears to affect their metastatic ability (118). HBx, a component of HBV, induces methylation of the TSPAN27 promoter and thus hinders TSPAN27 expression during transcription. Nevertheless, examination of clinical specimens did not reveal a significant disparity in TSPAN27 levels between samples that were positive or negative for HBV surface antigen (119).

TSPAN29/CD9. According to Li *et al* (60), a transcription factor of TSPAN29, Krüppel-like factor 4, significantly inhibits tumor growth in various types of cancer. The study demonstrates that TSPAN29 inhibits the phosphorylation and promoter activity of c-JUN N-terminal kinase (JNK) and c-JUN, thereby repressing HCC cell proliferation. Furthermore, knockdown of TSPAN29 enhances HCC tumorigenicity *in vivo*. Notably, reports suggest that TSPAN9 may also inhibit the apoptosis of HCC cells. Gilsanz *et al* (120) found that activated leukocyte cell adhesion molecule (ALCAM) and TSPAN29 are directly linked on the surface of leukocytes in protein complexes. Concurrently, in HCC, ALCAM can promote the transcription of an anti-apoptosis effector, yes-associated protein (121), through the activation of cAMP-response element-binding protein, ultimately supporting the survival of HCC cells (122). However, further research is needed to explore the role of tetraspanins in inhibiting the apoptosis or proliferation of HCC cells under various conditions.

TSPAN7/CD231. In Qi *et al* (32), a decrease in both the transcription and expression levels of TSPAN7 was discovered across various HCC cell lines. Furthermore, upregulation of TSPAN7 inhibited cell proliferation in nude tumor formation test *in vivo*. However, the specific mechanism by which TSPAN7 exerts its effects remains to be elucidated.

4. Tetraspanins and pancreatic cancer (PC)

PC is a highly aggressive tumor, with a 5-year survival rate of only 5%. Furthermore, ~90% of all PC cases are attributed to pancreatic ductal adenocarcinoma (PDAC) (123), which is known for its early metastasis and limited responsiveness to radiotherapy. Despite advances in diagnostic and surgical treatments aimed at prolonging survival and alleviating symptoms, few approaches have proven effective so far (124,125). Therefore, the early identification of specific therapeutic targets in PC is of paramount importance. This will not only allow for an earlier diagnosis of PC but will also facilitate more personalized treatments. In this section, the roles of five tetraspanins are summarized in the context of PC. TSPAN1 boosts the growth, movement and infiltration of PC cells, while TSPAN8 facilitates PC metastasis. Conversely, TSPAN7/CD231, TSPAN29/CD9 and TSPAN27/CD82 inhibit the progression of PC (Fig. 4).

Tetraspanins that promote the progression of PC

TSPAN1. A number of studies have established an intimate connection between TSPAN1 and PC (126-131). Zhou *et al* (127) found that depletion of TSPAN1 not only decreases PC cell proliferation *in vitro* and *in vivo*, but its expression is also linked to a poor survival rate among patients with PC. It was also discovered that TSPAN1 functions as an enhancer of macroautophagy/autophagy, with mutations in the LC3-interacting region pattern of TSPAN1 leading to the inability to trigger autophagy and support the growth of PC cells. Additionally, it shows that family with sequence similarity 83 member A (FAM83A) increases the expression of TSPAN1 via the Wnt-β-catenin signaling pathway and that miR-454 directly targets both TSPAN1 and FAM83A. These results indicate that elements of the miR454-FAM83A-TSPAN1 pathway can serve as important indicators for predicting outcomes or as targets for treatment in PC (127). In addition to miR-454, Wang *et al* (129) also found that miR-573 is downregulated and TSPAN1 is upregulated in PC tissues and cell lines. In addition, miR-573 suppresses the growth, movement and infiltration of PC cells through the regulation of TSPAN1. miR-216a is also found to be a controlling factor of TSPAN1, interacting with the 3'-UTR of TSPAN1 and affecting the levels of ten-eleven-translocation-2, methyltransferase 3B and DNA methyltransferase 1 to influence the expression of integrin α2 through epigenetic mechanisms. Silencing integrin α2 prevents the metastasis and growth of PC cells induced by elevated levels of TSPAN1. In summary, the newly discovered miR-216a-TSPAN1-integrin α2 pathway plays a role in controlling the advancement of PC and offers a fresh approach for the potential treatment of PC (131). Prior to this, Zhang *et al* (132) demonstrated that TSPAN1 siRNAs inhibits PC cell migration and infiltration and MMP2 mRNA expression by preventing the translocation and phosphorylation of phospholipase Cγ, which is crucial in human PC cell migration and invasion.

A previous study demonstrates that TSPAN1 positively transcriptionally regulates FAM110A, an oncogene that promotes tumorigenesis in PC cells (25). H2B clustered histone 12 (HIST1H2BK) is also recognized as a target of FAM110A, with its tumor-promoting ability potentially related to its regulation of G9a. The newly identified TSPAN1-FAM110A-HIST1H2BK-G9a pathway serves a role in controlling the advancement of PC and offers a fresh approach for predicting and treating PC outcomes (25). Mayado *et al* (133) found that linking antibodies to mucin16, TSPAN1 and epithelial cell adhesion molecule (EpCAM) can enhance the capturing efficiency of circulating tumor cells in the bloodstream of patients with PDAC, suggesting additional potential therapeutic implications of this tetraspanin.

TSPAN8. Prior research has established that TSPAN8 is a key player in the advancement of PC (134,135). TSPAN8 may enhance the movement of cancer cells via the recruitment and stimulation of the matrix metalloproteinases, MMP9 and MMP13 (135). Tetraspanins are also considered to be involved in exosome targeting. Tumor exosomes exhibiting TSPAN8 activity facilitate stromal degradation, reprogramme stromal and hematopoietic cells and induce a motile phenotype in a non-metastatic rat PC lineage harboring a TSPAN8 knockdown (136). A study revealed that in PDAC, increased TSPAN8 promoted metastasis both *in vivo* and *in vitro* (36). SRY-box

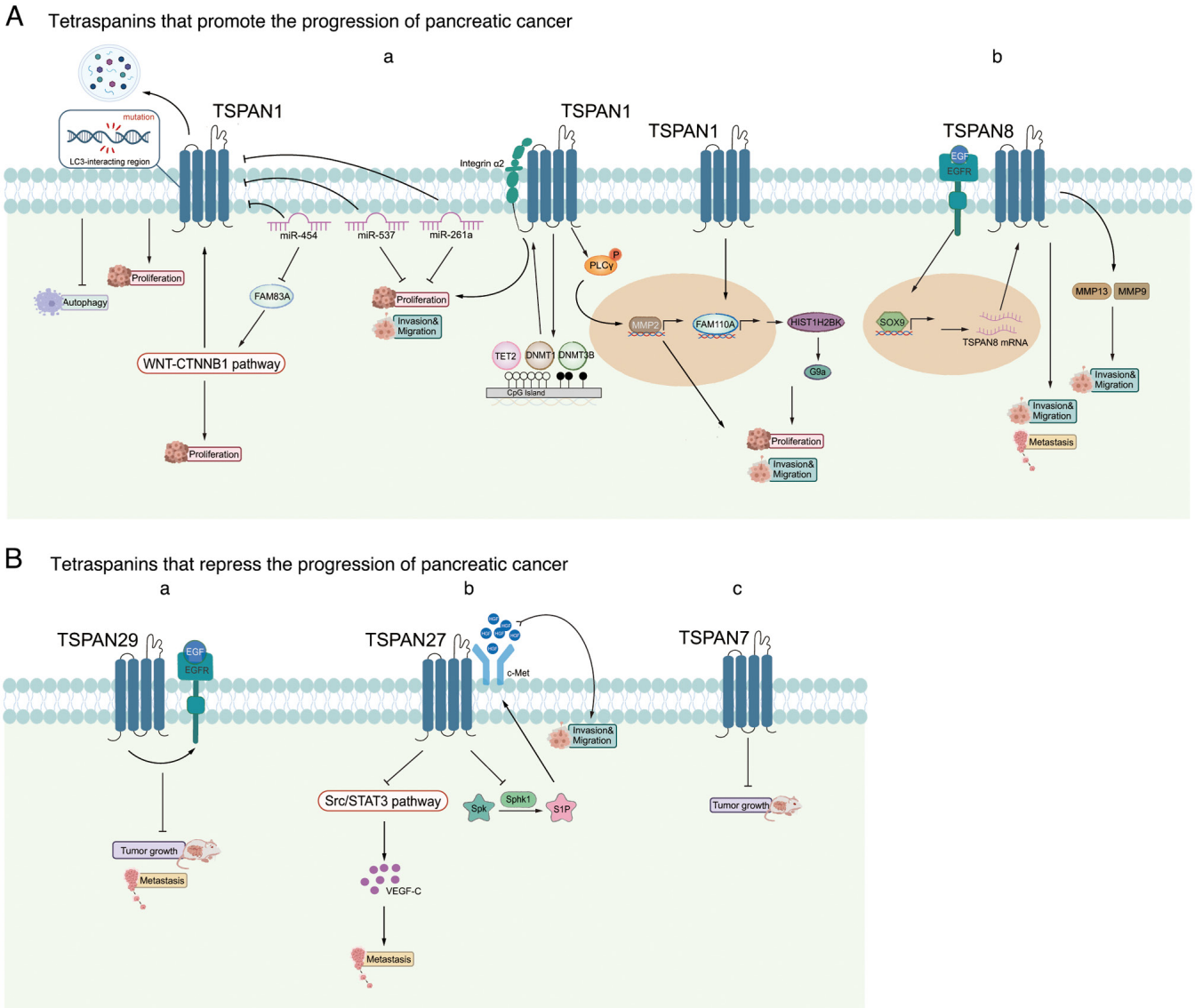

Figure 4. Functions of tetraspanins in PC. (A) Tetraspanins promoting PC progression: (a) LIR-mode mutations in TSPAN1 inhibit autophagy and promote PC cell proliferation. miR-454 targets TSPAN1 and FAM83A, promoting PC cell proliferation. miR-573 targets TSPAN1 to suppress the growth, movement and infiltration of PC cells. In addition, the proliferation and invasion of PC cells can be triggered by integrin α2 and TSPAN1, leading to the development of a miR-216a-TSPAN1-integrin α2 axis that has a role in controlling the progression of PC. TSPAN1 siRNAs hinder the migration and invasion of PC cells and suppress MMP2 mRNA expression, by preventing the translocation and phosphorylation of PLCγ. The TSPAN1-FAM110A-HIST1H2BK-G9a pathway plays a role in controlling the advancement of PC. (b) TSPAN8 recruits and activates MMP9 and MMP13 to promote PC cell migration. Under EGF stimulation, TSPAN8 expresses SOX9, which positively regulates the endogenous expression of TSPAN8, thereby increasing the metastatic and invasive ability of PC cells. (B) Tetraspanins suppressing PC progression: (a) TSPAN29/CD9 regulates EGFR, potentially inhibiting PC growth and metastasis. (b) TSPAN27/CD82 regulates c-Met expression and downregulates VEGF-C expression, inhibiting the HGF and Src/STAT3 signaling pathways respectively, and thus metastasis. (c) TSPAN7/CD231 is predicted to be a tumor suppressor in pancreatic ductal adenocarcinoma. PC, pancreatic cancer; LIR, LC3-interacting region; TSPAN, tetraspanin; miR, microRNA; FAM83A, family with sequence similarity 83 member A; siRNA, small interfering RNA; MMP, matrix metalloproteinase; PLCγ, phospholipase Cγ; HIST1H2BK, H2B clustered histone 12; EGF, epidermal growth factor; SOX9, SRY-box transcription factor 9; c-Met, cellular-mesenchymal epithelial transition factor; VEGF-C, vascular endothelial growth factor-C; HGF, hepatocyte growth factor.

transcription factor 9 (SOX9) enhances the production of TSPAN8 in response to EGF, which is associated with phenotypic changes including decreased adhesion to the extracellular matrix and heightened invasion capabilities. This research emphasizes the connection between the EGF-SOX9-TSPAN8 signaling pathway and the tumor stage, negative prognosis and decreased survival rate in patients with PDAC (36).

In the context of PC treatment, TSPAN8 serves as a potential target. One of the contributing factors to primary tumor growth and metastasis is the presence of cancer stem cells. These cells are characterized by a long life, self-renewal, differentiation, slow cell cycle progression and resistance to radiation and drugs (137,138). As TSPAN8 is an indicator of PC stem cells (139), it is plausible that it may facilitate cancer cell motility, penetration and homing through various mechanisms such as signaling, gene regulation and modulation of the tumor microenvironment (TME).

Tetraspanins that repress the progression of PC

TSPAN7/CD231. TSPAN7/CD231 is found to be downregulated in the majority of tumors. An analysis that combined a Gene Expression Omnibus dataset and the Human Cancer Metastasis

Database identified differentially expressed metastasis-related genes, among which TSPAN7 was included. The results predict that TSPAN7 may be downregulated in PDAC, identifying it as a tumor suppressor (140). Using bioinformatics methods involving differentially expressed genes, weighted gene co-expression network analysis and miRNA target genes linked to overall survival in patients with PDAC, Luo *et al* (141) also conclude that TSPAN7 could serve as a PDAC diagnostic marker.

TSPAN29/CD9. A notable inverse relationship is noted between the expression of TSPAN29 and the metastatic capabilities and survival rates of various types of tumors. In addition, TSPAN29 expression is shown to be reduced in PC cells compared with pancreatic tissues (142). Mechanistically, Tang *et al* (61) found that TSPAN29 inhibits the proliferation, migration and invasion of PC cells. Furthermore, TSPAN29 may suppress tumor growth and metastasis by moderating the endocytosis of EGFR.

TSPAN27/CD82. TSPAN27/CD82 is recognized as a broad-spectrum tumor metastasis suppressor (143,144), the inhibitory effect of which has been experimentally validated. It was found that TSPAN27 could control the presence of the cellular-mesenchymal epithelial transition factor on the surface of cells (145). The hepatocyte growth factor-induced invasion in PC is inhibited by sphingosine kinase deactivation and intracellular sphingosine-1-phosphate reduction (146). Furthermore, it was found that the STAT3 signaling pathways are implicated in TSPAN27-induced vascular endothelial growth factor-C downregulation. It was concluded that these pathways influence lymphatic metastasis in PC (51). Consequently, TSPAN27 has garnered notable attention for its potential to reduce the metastatic potential of cancer cells.

5. Tetraspanins and colorectal cancer (CRC)

CRC is a common type of cancer globally, ranked as the second highest contributor to cancer-related mortality and responsible for ~10% of all cancer fatalities (147,148). At present, the main treatment modality for CRC is surgical resection, supplemented by radiotherapy and chemotherapy, based on the stage and severity of the cancer (149). Recent data has indicated that the 5-year survival rate of CRC has risen by 15% in recent years, largely due to improvements in early detection, surgical methods and innovative treatments (149). In addition, the discovery of tetraspanins and the numerous studies on their roles and mechanisms in CRC have provided new directions for the treatment of this disease. In this section, several tetraspanins associated with CRC are summarized, including TSPAN1, TSPAN8, TSPAN9, TSPAN5 and TSPAN12 that promote CRC progression, and TSPAN6, TSPAN29/CD9 and TSPAN27/CD82 that inhibit CRC progression (Fig. 5).

Tetraspanins that promote the progression of CRC

TSPAN1. The role of TSPAN1 in CRC aligns with its function in other tumors as a promoter. Previous research has demonstrated that reducing TSPAN1 expression significantly suppresses the growth and infiltration of CRC cells (26). Additionally, a study using small extracellular vehicles (EVs) from CRC cell lines found that TSPAN1 is upregulated in EVs from CRC plasma compared with healthy controls. Previous research has also demonstrated that reducing TSPAN1 expression significantly suppresses the growth and metastasis of CRC (150). Guo *et al* (151) predicted and scored the infiltration characteristics, mutations and prognostic ability of CRC into immune cell infiltration (ICI) subtypes and ICI scores using a series of bioinformatics methods. In this study, TSPAN1 is identified as being closely associated with CRC.

TSPAN8. Tetraspanins are important for organizing multimolecular complexes in the plasma membrane. TSPAN8, found exclusively in epithelial cells, is associated with cell-cell junction proteins such as claudins and E-cadherin (152). It has been reported that TSPAN8, EpCAM, claudin-7 and CD44v6 are co-expressed and can form complexes in CRC liver metastases, as well as anaplastic colon and liver tissues. Although the co-expression of these proteins is not associated with tumor stage and grade in CRC, it is associated with DFS and a higher degree of anti-apoptotic properties (153). Cancer-initiating cells (CICs), which drive tumor progression, express markers that contribute to exon binding and uptake, promoting signaling cascade activation, transcription initiation and translational control (154). TSPAN8, EpCAM, claudin-7 and CD44v6 are among these markers and are highly expressed in CICs of the colon. These markers, along with other CIC markers, promote the development of CRC (155). Although co-expression in itself cannot be considered a prognostic marker for CRC, it does provide valuable insights. Guo *et al* (37) discovered that TSPAN8 acts as a controller of adhesion between cells and between cells and the extracellular matrix. Silencing TSPAN8 in CRC cells leads to increased laminin integrin α3β1 and fibronectin integrin α5β1 on the cell surface, and reduces CD44 levels. This alteration in cell-matrix adhesion significantly reduces cell migration. A further study demonstrating a direct interaction between E-cadherin and TSPAN8 reveals that TSPAN8 functions as a regulator of cancer cell motility. Therefore, targeting TSPAN8 may hinder tumor progression (156).

TSPAN9. A study of the ONCOMINE database demonstrated that TSPAN9 expression is reduced in patients with CRC (32). A research study that used targeted mass spectrometry to analyze EVs obtained from the supernatants of four CRC cell lines and plasma EVs from patients with CRC observed increased levels of TSPAN9, ADAM10 and CD59. Furthermore, elevated levels of TSPAN9 in EVs is significantly correlated with lymph node metastasis, distant metastasis upon diagnosis and advanced TNM stage. This suggests that TSPAN9 could serve as a novel biomarker for the detection of early CRC (40).

TSPAN5. Examination of the ONCOMINE database reveals that TSPAN5 is highly expressed in CRC (32), a result supported by the research conducted by Roh *et al* (30). This study found that inhibition of TSPAN5 expression suppresses the proliferation, migration and invasion of CRC cells. It was also discovered that TSPAN5 may promote CRC development by activating the Notch signaling pathway. This discovery of the promotional effect of TSPAN5 provides new insights for the treatment of CRC.

TSPAN12. In a study by Knoblich *et al* (157) on human breast cancer cells, it was found that Ablation of TSPAN12 inhibits the growth of primary tumors but promotes the metastasis of tumor cells *in vivo*. However, in the development of CRC, TSPAN12 promotes cell growth, migration and invasion (41).

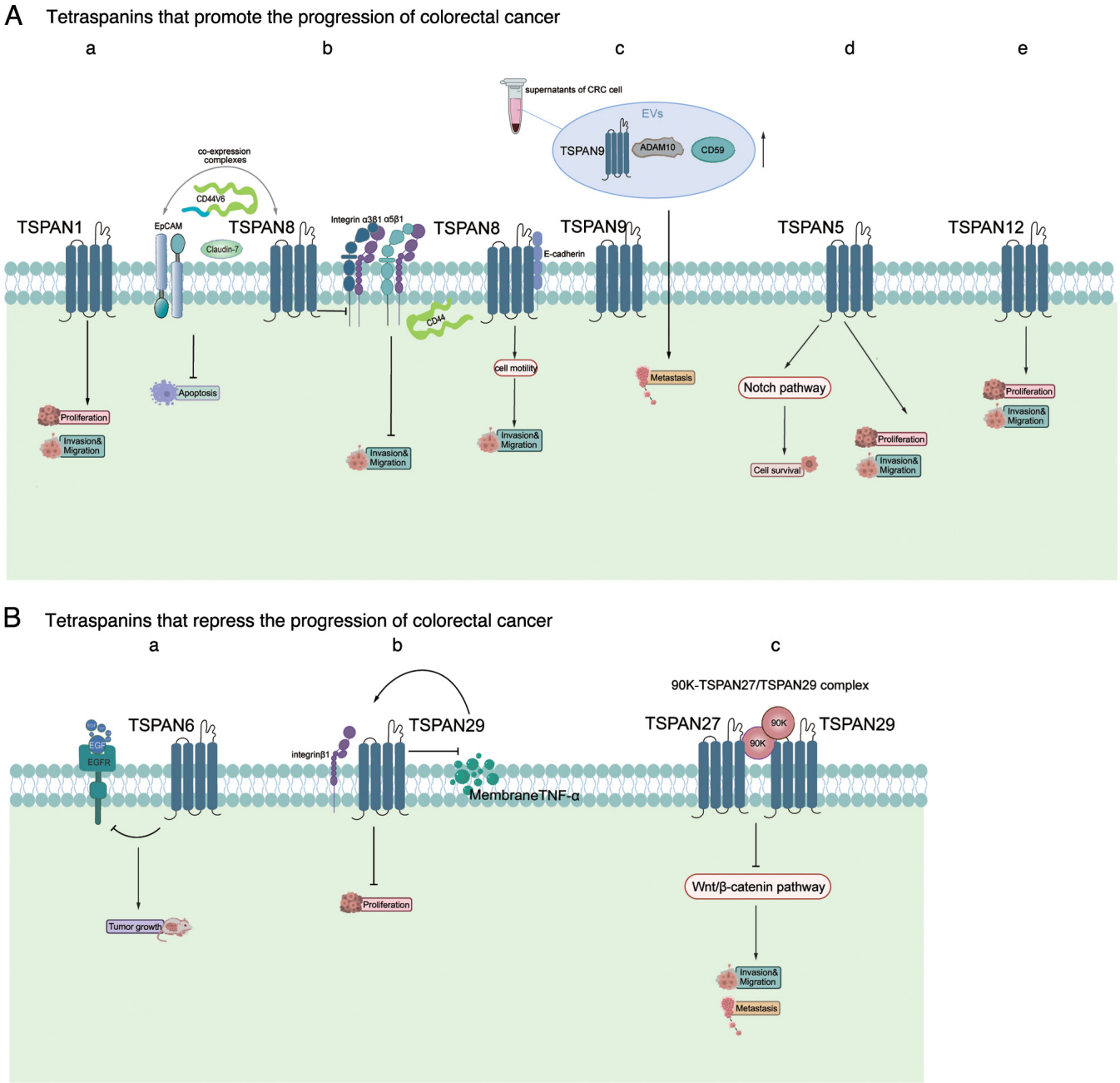

Figure 5. Functions of tetraspanins in CRC. (A) Tetraspanins promoting CRC progression: (a) RNAi-mediated suppression of TSPAN1 effectively hinders the growth and infiltration of colon cancer cells. (b) TSPAN8, EpCAM, claudin-7 and CD44v6 are co-expressed in CRC tissues, forming a complex that inhibits apoptosis. Silencing TSPAN8 strengthens the binding ability of integrin α3β1 and integrin α5β1, inhibits CD44 and reduces CRC cell migration. TSPAN8 directly interacts with E-cadherin and targeting this interaction may hinder tumor progression. (c) EVs isolated from the supernatants of CRC cell lines contain significantly elevated levels of TSPAN9, ADAM10 and CD59. Higher levels of EV TSPAN9 promote the metastasis of CRC cells. (d) TSPAN5 may promote the development of CRC by activating the Notch signaling pathway. The proliferation, migration and invasion of CRC cells are inhibited by siRNAs that suppress the expression of TSPAN5. (e) TSPAN12 promotes CRC cell growth, proliferation, migration and invasion. (B) Tetraspanins suppressing CRC progression: (a) Deletion of the TSPAN6 gene activates the EGF signaling pathway, leading to an increase in CRC tumor size. (b) Increased adhesion of TSPAN29 and integrin β1 to CRC cells and inhibition of TNFα expression contribute to the inhibition of cell proliferation. (c) The 90K-TSPAN27/TSPAN29 complex inhibits Wnt/β-catenin signaling in CRC, thereby suppressing CRC progression. CRC, colorectal cancer; RNAi, RNA interference; TSPAN, tetraspanin; EpCAM, epithelial cell adhesion molecule; EVs, extracellular vesicles; ADAM10, ADAM metalloproteinase 10; siRNAs, small interfering RNAs; EGF, epidermal growth factor.

Tetraspanins that repress the progression of CRC

TSPAN6. Relatively few studies have investigated the role of TSPAN6 in tumors. However, a study showed that the low survival rate of patients with CRC is due, at least in part, to the frequent reduction or loss of TSPAN6 expression, identifying TSPAN6 as a controller of CRC progression and a predictive biomarker for EGFR-targeted treatment in CRC, in addition to RAS pathway mutations (31). Additionally, deletion of TSPAN6 results in an increased incidence of adenomas and larger tumor sizes. This outcome is activated by an EGF-dependent signaling pathway. Furthermore, TSPAN6 expression is associated with an improved response

to EGFR-targeted therapies in patients with CRC, including cetuximab (31). However, there is little difference in the TSPAN6 levels in plasma from patients with CRC and plasma from healthy controls (158).

TSPAN29/CD9. A study by Hashida *et al* (159) discovered that patients with CRC and TSPAN29$^+$ tumors have a notably improved survival rate compared with those with TSPAN29$^-$ tumors. It was therefore concluded that decreased TSPAN29 expression is an indicator of poor prognosis. Building on this, Ovalle *et al* (62) further investigated the specific function of TSPAN29 in tumorigenesis and found that TSPAN29 expression in CRC cells enhances integrin β1-dependent adhesion and inhibits cell proliferation. The antiproliferative effects of TSPAN29 can also be mediated using a selective blocker of TNFα. Additional findings suggest that studies of multidrug resistance-associated protein 1/TSPAN29 expression could be useful in forecasting the outcomes of patients with CRC (160). In conclusion, TSPAN29 can inhibit the malignant transformation of CRC by affecting cell adhesion, morphology, proliferation and TNF-α expression.

TSPAN27/CD82. TSPAN27/CD82 is recognized as a biomarker for predicting metastatic potential due to its unique role as a well-defined suppressor of metastasis in various tumors that does not affect the growth of the original tumor (145). There is a wealth of research regarding TSPAN27 in CRC. In a study by Wu *et al* (161), the findings indicate that TSPAN27 gene expression is higher in CRC tissues than in normal colon epithelial tissues and lymphatic metastatic tissues. Notably, elevated expression of TSPAN27 is observed in early CRC, which decreases in the advanced stages and may be lost in metastasis. Certain research studies have demonstrated that TSPAN27 hinders the migration and penetration of CRC cells (52,53). Lee *et al* (162) found that a 90K-TSPAN27/TSPAN29 complex, which inhibits Wnt/β-catenin signaling in CRC, provides a useful treatment for inhibiting the progression of CRC. Downregulation of this complex may be a sign of poor prognosis in CRC.

6. Tetraspanins and other types of digestive system-related cancer

Compared with gastric, liver, pancreatic and colorectal cancer, the role of tetraspanins in esophageal and oral cancer has been less extensively studied. In this section, the latest findings on tetraspanins in these types of cancer are briefly summarized.

Globally, esophageal cancer ranks as the eighth most common type of cancer, contributing to 3% of all cancer diagnoses (163). The prognosis of esophageal cancer is poor, with one in every 18 cancer mortalities in 2020 (148). Furthermore, the occurrence of esophageal cancer is strongly associated with dietary and lifestyle factors (164). Several tetraspanins have been implicated in esophageal cancer pathogenesis. For instance, TSPAN1, TSPAN8 and TSPAN24/CD151 are upregulated in esophageal adenocarcinoma, whereas TSPAN29/CD9 is downregulated (165). Additionally, TSPAN4 expression is elevated in esophageal squamous cell carcinoma (ESCC), where it potentially enhances resistance to chemotherapy and suppresses apoptosis (166). Upregulation of TSPAN8 is associated with ESCC metastasis and drives invasion and migration *in vitro* (38). Upregulation of TSPAN15 in ESCC promotes cellular migration, infiltration and metastasis (43). TSPAN24/CD151 expression is correlated with proliferation, invasiveness and the survival of patients with esophageal cancer (47,167). Conversely, TSPAN27 expression has an inverse relationship with lymph node metastasis, distant metastasis and advanced stage in ESCC, and hinders the proliferation and migration of ESCC cells through the TGF-β1/Smad pathway (54,55).

With oral cancer, most cases comprise oral squamous cell carcinoma (OSCC), with 75% of cases linked to lifestyle factors (168-170). Increased expression of TSPAN15 in OSCC can promote the advancement and metastasis of tumors by activating ADAM10 (171). Additionally, while TSPAN25/CD53 and TSPAN29/CD9 are expressed in OSCC, TSPAN26/CD37, TSPAN28/CD81 and TSPAN30/CD63 are not (63,172). Furthermore, TSPAN29/CD9 expression is strongly associated with OSCC metastasis (63,64). As with esophageal cancer, TSPAN27/CD82 may have a role in oral cancer, but it may not be a reliable indicator of prognosis in OSCC due to the non-significant relationship between patient survival and expression of TSPAN27/CD82 by tumors; further studies still need in future to make this clear. (63,173,174).

In summary, several tetraspanins appear to act as oncogenes promoting proliferation, metastasis and chemotherapy resistance in esophageal and oral cancer, while TSPAN27/CD82 may act as a tumor suppressor gene. However, further research is warranted to clarify the pathogenic and prognostic utility of tetraspanins in these malignancies.

7. Therapeutic potential, challenges and perspectives

Therapeutic potential. It is essential to understand the biological and molecular processes involved in cancer advancement, specifically in metastasis, to develop improved treatment approaches. Tetraspanins are involved in numerous physiological and pathological processes, and both experimental and clinical studies in the field of cancer have reported a relationship between tetraspanin expression levels and metastasis. Each tetraspanin specifically binds to one or several other membrane proteins to form primary complexes, underscoring the role of tetraspanins as organizers of multimolecular complexes. TEMs, which are rich in tetraspanins, create a signaling platform that serves a role in a number of important cellular functions and cancer-related activities. Therefore, tetraspanins play a significant role in multiple stages of tumor formation and metastasis (175). As such, targeting tetraspanins for cancer treatment holds promising therapeutic potential. In this section, the potential clinical significance of tetraspanins in digestive system tumors is summarized (Table II).

Potential molecules used for targeted cancer therapies may include miRNA fragments (176,177), drugs (small molecule inhibitors), siRNA fragments, toxins, soluble proteins and monoclonal antibodies (mAb)(178). It is noteworthy that several antibodies targeting TSPAN8 have been indicated as potential candidates for the treatment of CRC and ovarian cancer. Notably, Kim *et al* (179) identify the extracellular large loop of TSPAN8 (TSPAN8-LEL) as a key domain for its antitumor effect. A new antibody directed at TSPAN8-LEL

was created through the use of phage display technology, potentially serving as an effective means to block the invasion of metastatic CRC. Additionally, antibodies targeting TSPAN8-LEL hinder the metastasis of ovarian cancer cells *in vivo* and *ex vivo* (180). TSPAN8 stands out as a potential target for therapy due to its reliable involvement and increased expression in HCC. Furthermore, according to prior research that demonstrated an interaction between TSPAN24/CD151 and integrin β1, Ke *et al* (181) produced a monoclonal antibody that identifies the integrin β1 binding region of TSPAN24/CD151. This monoclonal antibody (mAb) has broad potential for detecting CD151 antigen expression and localization in HCCs and could serve as an effective strategy to inhibit HCC progression.

Several antibodies targeting TSPAN26/CD37 have achieved significant results in treating malignant tumors. For instance, in 2011, it was announced that TRU-016 (otlertuzumab), a humanized anti-TSPAN26 fusion protein developed from SMIP-16 for B-cell malignancies treatment, had been approved by the U.S. Food and Drug Administration for the treatment of patients with chronic lymphocytic leukemia (182). Given that TSPAN26/CD37 expression is elevated in tumors of the gastrointestinal system, it is considered to be a valuable therapeutic target in these malignancies.

Inhibition of TSPAN1 expression through RNA interference (RNAi)-mediated or miRNA-targeted methods has been shown to suppress the growth and invasion of colon cancer and PC cells (26,129), suggesting a potential therapeutic strategy for these diseases. At present, approaches involving siRNA and antibodies have been utilized to target TSPAN29/CD9 in tumors (183,184). The connection between TSPAN29 and the motility and metastasis of digestive system-related cancer is significant, as it mainly inhibits the growth and tumorigenicity of CRC (62). As such, the prospect of utilizing TSPAN29 as a target to treat human cancer appears promising.

Furthermore, the importance of tumor immunotherapy in the treatment of cancer has grown significantly in the past few years. Immune cells penetrate the TME to control the advancement of cancer. In tumor immunology, the main focus is on studying T cells and antigen presentation is the most crucial step for T cell surveillance of cancer cells. Major histocompatibility complex (MHC) II proteins stimulate $CD4^+$ T lymphocytes, whereas MHC I proteins stimulate $CD8^+$ T lymphocytes. Monocytes, B cells and bone marrow-derived dendritic cells (BMDCs), which are specialized antigen-presenting cells, activate T cells that are specific to antigens by binding to MHC on T cell receptors (TCRs) (185). It has been noted that certain tetraspanins are key players in antigen presentation during immune responses, thereby influencing the TME. For instance, TSPAN29/CD9 is essential for facilitating the association of heterologous MHC II to enhance TCR stimulation by DCs (186). Additionally, knockout of TSPAN29/CD9 in mice has been shown to increase TNF-α levels and macrophage infiltration in lung cancer following lipopolysaccharide treatment (187). TSPAN29/CD9 can also induce the retention of MHC II by enhancing MHC II trafficking and decreasing MHC II recycling, expecting to enhance T cell receptor stimulation by DCs in tumor immunotherapy (188). TSPAN27/CD82 expression is enhanced following the activation of monocyte-derived DCs and BMDCs, promoting stable interactions between MHC II and T cells, making TSPAN27/CD82 a modulator to enhance Ag presentation machinery in tumor immunotherapy (189). Knocking out TSPAN26/CD37 also inhibits DC migration, potentially affecting immunity (190). Furthermore, TSPAN25/CD53 antibody ligation enhances natural killer (NK) cell adhesion and reduces NK cell degranulation in response to tumor target cells (191).

However, certain tetraspanins, such as TSPAN30/CD63 and TSPAN1/CD151, inhibit the activation of T cells. Specifically, knockdown of TSPAN30/CD6 in B lymphocytes activates $CD4^+$ T cells (192) and DCs lacking TSPAN1/CD15 stimulate T cells by co-stimulation (TCR activation and Ag presentation) (193). A recent study indicated that the clustering of MHC I by TSPAN5 is essential for effective $CD8^+$ T cell stimulation, potentially affecting TCR and CD8 clustering (194). Another study highlights TSPAN8 as a potential candidate for chimeric antigen receptor T (CAR-T) cells in combating PC. While TSPAN8-specific CAR-T cells notably decrease tumor formation in subcutaneous xenotransplantation models, the potential mechanisms still require further exploration (195). Despite a lack of direct evidence regarding their function in tumor immunology, particularly in digestive system-related cancer, immunotherapy based on tetraspanins still represents a promising strategy.

Challenges and perspectives. Although the tetraspanin family appears to have a notable effect on the treatment of cancer of the digestive system, there are still some obstacles to overcome in terms of chemoresistance and expression heterogeneity. First, tetraspanins, such as TSPAN29/CD9, TSPAN8, TSPAN4, TSPAN30/CD63, TSPAN12, TSPAN27/CD82, TSPAN28/CD81 and TSPAN1, are involved in cancer chemoresistance, which could be a challenge in cancer of the digestive system therapy. mAbs directed at TSPAN29/CD9 induce apoptosis in small cell lung cancer (SCLC) cells that are resistant to cisplatin (CDDP) and etoposide (196). Furthermore, TSPAN29 plays a crucial role in resistance to doxorubicin and 5-FU in breast cancer (197). However, TSPAN8 inhibition can suppress drug resistance in glioma and breast cancer (198,199). Additionally, ribophorin II knockdown reduces TSPAN30/CD63 glycosylation, leading to decreased chemoresistance and aggressiveness in breast cancer (200). TSPAN12 enhances chemoresistance in small cell lung cancer cells through miR-495 regulation (201). Enhanced expression of TSPAN27/CD82 leads to increased resistance to chemotherapy in acute myeloid leukemia through the activation of p38 MAPK via the PKCα and β1 integrin signaling pathways (202). Reduced TSPAN28/CD81 levels make acute lymphoblastic leukemia cells more responsive to chemotherapy and interferes with Bruton tyrosine kinase phosphorylation (203). *In vitro*, inhibition of TSPAN1 in head and neck squamous cell carcinoma cells resistant to cisplatin results in the suppression of resistance to chemotherapy, EMT, autophagy and proliferation, as well as the induction of apoptosis (84). Prior research in the field of gastrointestinal cancer has shown that TSPAN8 increases drug resistance and decreases cell mortality in stomach cancer cells by triggering the Wnt/β-catenin pathway through Notch2 interaction (204). High levels of TSPAN4 are observed in ESCC, leading to resistance to chemotherapy and suppression of apoptosis (166).

Table II. Treatment and clinical significance of tetraspanins in corresponding digestive-system cancers.

Tetraspanins	Expression in digestive-system cancer	Associated factors/proteins	Treatment and clinical significance	(Refs.)
TSPAN1	Gastric, liver, pancreatic, colorectal and esophageal	PI3K, Akt, TET2, DNMT3B, DNMT1, ITGA2, PLCγ, HIST1H2BK, G9a, MUC16, EpCAM	miRNA siRNA mAb *in vitro* experiments *in vitro* experiments and *in vivo* zebrafish models	(23,26,105, 133,127)
TSPAN5	Gastric, liver and colorectal	p27/p15, cyclin D1, CDK4, pRB, E2F1, Notch, p16INK4a/pRb, MRTF-A-FLNA, MRTF/SRF	Pathological analysis, *in vitro* and *in vivo* mouse models siRNA	(29,30,117)
TSPAN6	Colorectal	EGF, EGFR	*In vivo* mouse models	(31)
TSPAN7	Liver and pancreatic		*In vitro* experiments clinical trials	(32,141)
TSPAN8	Gastric, liver, pancreatic, colorectal and esophageal	ERK, MAPK, EGFR, ADAM12m, MMP9, MMP13, EpCAM, claudin-7, CD44v6, integrin α3β1, integrin α5β1, E-cadherin	clinical trials *in vitro* experiments siRNA miRNA *in vivo* mouse models	(33,34,136, 175,176)
TSPAN9	Gastric, liver and colorectal	ERK1/2, MMP-9, uPA, FAK, PI3K, Akt, mTOR, ADAM10, EVs, CD59	*In vitro* experiments clinical trials	(40,100)
TSPAN12	Colorectal	LRP5, Naked 1, Naked 2, DVL2, DVL3, Axin 1, GSK-3β	*In vitro* and *in vivo* mouse models	(157)
TSPAN15	Liver, esophageal and oral	ADAM10, CTGF, ERK	*In vitro* experiments	(42)
TSPAN21	Gastric	MMP7	Pathological analysis	(44)
TSPAN24	Gastric, liver and esophageal	Integrinα3, MMP9, PI3K, Akt, GSK-3β, Snail, integrin β1	Pathological analysis miRNA *In vivo* mouse models and *in vitro* experiments	(45,112-115,177)
TSPAN27	Gastric, liver, pancreatic, colorectal, esophageal and oral	EGFR, p-ERK1/2, MMP7, E-cadherin, SPK, c-Met, Src, STAT3, VEGFC, HGF, Wnt, β-catenin	miRNA Pathological analysis *In vitro* experiments and *in vivo* mouse models	(48,118,162)
TSPAN28	Gastric and liver	p38 MAPK	mAb Gene sequencing	(57,96)
TSPAN29	Gastric, liver, pancreatic, colorectal, esophageal and oral	HB-EGF, KLF4, JNK, c-JUN, ALCAM, EGFR, TNF-α, Integrinβ1, MRP1, TGF-β	Clinical trials mAb *in vitro* experiments and *in vivo* mouse models	(58-60)
TSPAN30	Liver	FAK, Akt, TGF-β, TIMP-1	*In vivo* mouse models	(65)
TSPAN31	Gastric and liver	METTL1, CCT2, PI3K, Akt, CDK4, p-GSK3β, β-catenin	*In vitro* experiments siRNA siRNA and miRNA	(66,67,94)

TET2, ten-eleven-translocation-2; DNMT3B, DNA methyltransferase 3B; DNMT1, DNA methyltransferase 1; ITGA2, integrin subunit α2; PLCγ, phospholipase Cγ; HIST1H2BK, H2B clustered histone 12; MUC16, mucin16; EpCAM, epithelial cell adhesion molecule; miRNA, microRNA; siRNA, small interfering RNA; mAb, monoclonal antibodies; pRB, retinoblastoma protein; E2F1, recombinant E2F transcription factor 1; MRTF-A-FLNA, actin-related transcription factor A-filamentosamine A; SRF, serum response factor; EGF, endothelial growth factor; ADAM12, ADAM metalloproteinase 12; MMPs, matrix metalloproteinases; uPA, urokinase plasminogen activator; FAK, focal adhesion kinase; LRP5, low-density lipoprotein receptor-related protein 5; GSK3-3β, glycogen synthase kinase 3β; CTGF, connective tissue growth factor; p-, phosphorylated; SPK, sphingosine kinase; c-Met, cellular-mesenchymal epithelial transition factor; Src, tyrosine protein kinase src-1; HGF, hepatocyte growth factor; HB-EGF, heparin-binding epidermal growth factor-like growth factor; KLF4, Kruppel-like factor 4; ALCAM, activated leukocyte cell adhesion molecule; MRP1, multidrug resistance-associated protein; TIMP-1, tissue inhibitor of metalloproteinase-1; METTL1, methyltransferase like 1; CCT2, recombinant chaperonin containing tCP1, subunit 2.

Overall, while targeting tetraspanins represents a promising strategy in cancer therapy, chemoresistance should be considered carefully during future research directions. When considering a specific type of cancer, it is important to examine the expression pattern of certain tetraspanins, as they may be related to chemoresistance. In such cases, combination therapy may be necessary to enhance the effectiveness of the treatment.

Tetraspanins exhibit extensive expression variations across various tissues and even expression heterogeneity between patients. For instance, the variable expression of TSPAN15 in HCC highlights the importance of evaluating TSPAN15 expression in these patients prior to treatment initiation (68). This variety could potentially affect the precision of targeted therapies. Therefore, researchers should gain a deeper understanding of the expression patterns of tetraspanins in diverse tissues, develop tissue-specific drug delivery systems (205) or focus on the functional characteristics of tetraspanins, which are often exerted through interactions with other proteins, to design more precise and specific drugs and minimize the effects on non-target tissues. A potential strategy to address this challenge is the development of more precise treatment methods, such as personalized therapies, based on individual suitability. By designing more specific RNAi sequences or small molecule inhibitors, it may become possible to selectively modulate the expression and functionality of particular tetraspanins, minimizing interference with normal cells and enhancing treatment specificity.

Although the proteins of the tetraspanin family have similar structures, the significant functional differences are observed in different digestive system-related types of cancer. Since stetraspanins can interact with numerous proteins, including those on the cell membrane, identifying proteins that interact with tetraspanins may help explain the mechanisms behind tetraspanin-induced resistance, expression differences and individual variability. Additionally, increasing evidence has confirmed that tetraspanin family proteins are involved in the formation of a new type of organelle termed migrasomes (206). Migrasomes are newly discovered organelles formed by migrating cells, first identified in 2015 (85), which have roles in cell communication, disposal of damaged organelles, the lateral transfer of mRNA and proteins and mitochondrial quality control (88,207,208) and have been reported to be associated with certain diseases such as stoke and podocyte injury (86,209). However, there is still limited research on the relationship between migrasomes and cancer, despite the presence of migrasomes in cancer cells (210). A previous report linked the development and prognosis of glioma to a key migrasome regulator TSPAN4, though the specific mechanisms remain unclear (211). Another study reported the role of TSPAN1/CD151 in migrasome formation in the invasiveness and angiogenesis of HCC (212). A pan-cancer analysis identified migrasome-related genes as a potential immunotherapeutic target among 22 tumors, including CRC (213). There have been a number of studies regarding tetraspanins, exosomes and types of cancer; therefore, it is worth investigating the impact of tetraspanins on cancer through migrasomes. Similarly, discovering the interactions between tetraspanins and other proteins or organelles may reveal new roles in cancer, potentially providing new strategies for treating digestive system-related and other types of cancer.

In conclusion, while the tetraspanin family holds notable potential in cancer therapy, overcoming challenges related to their widespread expression and achieving specificity in treatment remains critical. Future research efforts should focus on delving into the functionalities and interrelationships with proteins and organelles, chemoresistance, expression patterns and the structure of tetraspanin family members across different tissues and patients. Simultaneously, advances in personalized therapies and innovative treatment technologies, such as immunotherapy, are essential for providing more effective treatment options for patients with cancer.

8. Conclusions

Cancer presents a significant public health challenge due to treatment resistance and fatal metastases. Understanding the molecular mechanisms of cancer progression is crucial for developing effective therapies. Tetraspanins, integral membrane proteins, have a key role in cancer metastasis, particularly in digestive system-related types of cancer. Research on tetraspanins is therefore vital for cancer treatment and molecular biology advancement, as they regulate cancer initiation, progression and metastasis. Additionally, specific tetraspanins have both tumor-promoting and tumor-suppressive roles by influencing oncogenic pathways, cell motility and the TME. Identifying tetraspanin expression patterns as prognostic biomarkers in different digestive system-related types of cancer is a future focus for research. Furthermore, targeting dysregulated tetraspanins could halt tumor growth and progression. Advanced techniques such as super-resolution microscopy and single-cell sequencing may aid in understanding the complex roles of tetraspanins. Despite challenges in targeting tetraspanins, further research is needed before they are used as therapeutic targets and biomarkers for metastatic cancer. In conclusion, tetraspanins are crucial regulators of metastatic competence in different digestive system-related types of cancer, emphasizing the need for innovative diagnostic and therapeutic approaches based on their molecular functions to enhance clinical outcomes.

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Availability of data and materials

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Authors' contributions

KC wrote the original draft and edited the manuscript. QL was responsible for conceptualization, writing the original draft and reviewing and editing the manuscript. YL wrote the original draft and edited the manuscript. DJ was responsible for writing the original draft and reviewing and editing the manuscript LC and JJ reviewed and supervised the manuscript. SL wrote the original draft reviewed and supervised the manuscript. CZ was responsible for conceptualization, writing the original draft and reviewing and editing the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

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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