Review

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Deciphering Tetraspanins: Dual Roles in Cancer Progression and Therapeutic Implications

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Tetraspanins, characterized by their four transmembrane domains, function as versatile platforms for interactions with a wide range of molecules. Recent research has increasingly focused on the utility of tetraspanins as potential prognostic markers and indicators of metastatic likelihood, varying according to the type of cancer. This review comprehensively examines the multifaceted functions of tetraspanins, highlighting their dual roles as enhancers and inhibitors in cancer development. Furthermore, it provides a detailed exploration of the signaling pathways and interactions associated with tetraspanins that could significantly impact the course and treatment of cancer.

Keywords: tetraspanin; cancer metastasis; signaling pathway

Introduction

Cancer, as of today, remains a major global health concern and a leading cause of death [1]. Many cancers are already advanced by the time they are detected, significantly reducing the quality of life of patients and increasing the financial burden on families and society [2]. Consequently, it is vital specific markers are identified in the early stages of cancer, which may provide an opportunity for an early diagnosis, treatment, and management of the disease.

Tetraspanins (TSPANs) are a superfamily of four transmembrane proteins (TM4SF), which play crucial roles in both physiological and pathological processes [3]. Several researchers reported that TSPANs regulate cancer growth, survival, stemness, metastasis, and drug resistance [4]. Most TSPANs are associated with promoting tumor activity (Table 1, Ref. [3,5–104]). TSPANs play an important role in tumor biology and influence cancer progression via involvement in the biogenesis of extracellular vesicles and the immunomicroenvironment [105].

Interestingly, TSPANs exhibit a paradoxical nature in tumor development, functioning as a "double-edged sword". As complex and dynamic as plasma membrane organization is, the functions of TSPANs are complex and even contradictory. By modulating immune cell functions, they influence the tumor microenvironment and immune surveillance to achieve an anti-tumor effect [106]. Certain TSPANs play a crucial role in inhibiting the growth and proliferation of tumor cells [107]. Additionally, they contribute to diminishing the stemness characteristics of cancer cells and counteracting drug resistance [108], highlighting their potential as therapeutic targets in cancer treatment strategies.

This dual functionality of TSPANs in promoting and inhibiting tumor growth illustrates their complex role in cancer biology. Thus, understanding their context-dependent dual roles in cancer is crucial for formulating effective targeted cancer treatments. Therefore, we take into consideration the complex, dual nature of TSPANs in tumor biology and the need for targeted therapeutic approaches according to their multifaceted functions in different cancer types. This review summarizes TSPANs' complex roles as promoters and suppressors, underscoring their significance in cancer. It also provides an overview of their activity or interactions that could influence cancer progression and treatment.

TSPANs Composition

TSPANs are small membrane proteins characterized by four transmembrane domains, with 65 to 95% of amino acids being highly conserved [109,110]. TSPANs consist of four transmembrane proteins that are folded into a tight rod-like structure, as well as extracellular loops (1 small extracellular loop, which is short as Small Extracellular Loop (SEL), also known as Extracellular Loop1 (ECL1), and one large extracellular loop, which is short as Large Extracellular Loop (LEL), also known as Extracellular Loop2 (ECL2)), transmembrane (TM) domains and C- and N-terminal tails [111] (Fig. 1, Ref. [112]). As a family of proteins characterized by their unique structure, TSPANs facilitate interaction with other proteins [113]. The majority of protein-protein interaction sites are located within TSPAN extracellular loops (ECLs), resulting in two ECLs

Table 1. The role of TSPAN family members in cancer progression.

Common name	TSPAN member	Alternative name	Cancer progression	Cancer type
TSPAN1	TSPAN1	TSP-1, TSPAN-1, NET1, NET-1, TM4C, TM4-C, C4.8	Promote	BC1 [5]; CC1 [3]; CCA [18]; CC2 [19]; GC [20]; HNSCC [21]; OC [22]; PC1 [23]; PC2 [24]
TSPAN2	TSPAN2	TSP-2, TSPAN-2, TSN2, NET3, NET-3, FLJ12082	Promote	LC [6]
TSPAN3	TSPAN3	TSP-3, TSPAN-3, TM4-A, TM4SF8	Promote	AML [7]
TSPAN4	TSPAN4	TSP-4, TSPAN-4, NAG-2, TM4SF7	Promote	GC [8]; GBM [25]
TSPAN5	TSPAN5	TSP-5, TSPAN-5, NET4, NET-4, TM4SF9	Inhibit/Promote	Inhibit GC [26]; Inhibit TNBC [27] Promote HCC [28]
TSPAN6	TSPAN6	TSP-6, TSPAN-6, T245, TM4SF6	Inhibit	CRC [29]; LC and PC1 [30]
TSPAN7	TSPAN7	A15, CCG-B7, CD231, DXS1692E, MRX58, MXS1, TALLA-1, TM4SF2, TM4SF2b, XLID58	Promote/Inhibit	Promote RCC [31]; Promote LC [32]; Promote OS [33] Inhibit MM [34]; Inhibit BC2 [35]; Inhibit Glioma [36]
TSPAN8	TSPAN8	CO-029, TM4SF3	Promote	BC1 [9]; LC [37]; Melanoma [38]; HCC [39]; PC1 [40,41]; OC [42]; GC [43]; ESCC [44]; CRC [45]
TSPAN9	TSPAN9	NET5, NET-5, PP1057	Inhibit	GC [46,47]
TSPAN10	TSPAN10	Oculospanin/OCSP	Promote	Melanoma [10]
TSPAN11	TSPAN11	VSSW1971	Inhibit	NSCLC [48]
TSPAN12	TSPAN12	EVR5, NET2, NET-2, TM4SF12	Promote/Inhibit	Promote primary tumor growth, while inhibit BC1 metastasis [49]; Promote CRC [50]; Promote SCLC [51]; Promote NSCLC cell growth [52], while inhibit NSCLC proliferation, migration and tumor growth [53]; Promote OC [54]; Promote HCC [55]
TSPAN13	TSPAN13	NET6, NET-6, TM4SF13	Promote	BC1 [11,56]; OS [57]
TSPAN14	TSPAN14	TM4SF14, TSPAN14, DC-TM4F2, MGC11352	Inhibit	NSCLC [58]
TSPAN15	TSPAN15	NET7, NET-7, TM4SF15, 2700063A19Rik	Promote	ESCC [12]; HCC [59]; OSCC [60]
TSPAN16	TSPAN16	TM-8, TM4-B, TM4SF16	N/A	N/A
TSPAN17	TSPAN17	FBX23, FBXO23, TM4SF17	Promote	GBM [13]

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Table 1. Continued.

Common name	TSPAN member	Alternative name	Cancer progression	Cancer type
TSPAN18	TSPAN18	N/A	N/A	N/A
TSPAN19	TSPAN19	N/A	N/A	N/A
TSPAN20	TSPAN20	UPK1B, UPK1	Promote	BC2 [14]; RCC [61]
TSPAN21	TSPAN21	UP1A, UPK1A, UPIA, UPKA	Inhibit	GC [62]; ESCC [63]
TSPAN22	TSPAN22	AOFMD, AVMD, CACD2, DS, MDBS1, PRPH, RDS, RP7, rd2	N/A	N/A
TSPAN23	TSPAN23	ROM, ROM1, ROSP1, RP7	Inhibit	LC [64]
CD151	TSPAN24	PETA-3, RAPH, SFA-1, EBS7, GP27, MER2	Promote	BC1 (contain TNBC) [15,65]; GC [66]; GSCC [67]; HCC [68]; NSCLC [69]; PC1 [70]; PC2 [71]
CD53	TSPAN25	MOX44	N/A	N/A
CD37	TSPAN26	GP52-40	Inhibit/Promote	Promote AML [72]; Inhibit BCL [73,74]; Promote CLL [75]
CD82	TSPAN27	4F9, C33, GR15, IA4, KAI1, R2, SAR2, ST6	Inhibit/Promote	Promote AML [76]; Inhibit BC1 [77,78]; Inhibit ESCC [79]; Inhibit GC [80]
CD81	TSPAN28	TAPA-1, TAPA1, CVID6, S5.7	Promote/Inhibit	Promote ALL [81]; Promote GBM [82]; Promote HCC [83]; Promote OS [84]; Promote TNBC [85]; Inhibit GC [86]; Inhibit NSCLC [87]
CD9	TSPAN29	BTCC-1, DRAP-27, MIC3, MRP-1, TSPAN-29, GIG2, P24	Promote	AML [16]; ALL [88]; BC1 [89]; CRC [90]; GC [91]; Glioma [92]; HCC [93]; LC [94]; Melanoma [95,96]; OC [97]; PC1 [98]
CD63	TSPAN30	ME491, MLA1; AD1, HOP-26, OMA81H, Pltgp40, LAMP-3, LIMP1	Promote/Inhibit	Promote BC1 [99]; Inhibit Melanoma [100,101]
TSPAN31	TSPAN31	SAS	Inhibit/Promote	Inhibit CC1 [102]; Promote GC [103]; Promote HCC [104]
TSPAN32	TSPAN32	TSSC6, ART1, PHMX, PHEMX	N/A	N/A
TSPAN33	TSPAN33	MGC50844, Penumbra, PEN	Promote	BCL [17]

Abbreviation: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BC1, breast cancer; BC2, bladder cancer; BCL, B-cell lymphoma; CC1, cervical cancer; CC2, colon cancer; CCA, cholangiocarcinoma; CLL, chronic lymphocytic leukemia; CRC, colorectal cancer; ESCC, esophageal squamous cell carcinoma; GBM, glioblastoma multiforme; GC, gastric cancer; GSCC, gingival squamous cell carcinoma; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; LC, lung cancer; MM, Multiple myeloma; NSCLC, non-small cell lung cancer; OC, ovarian carcinoma; OSCC, oral squamous cell carcinoma; PC1, pancreatic cancer; PC2, prostate cancer; RCC, renal cell carcinoma; SCLC, small cell lung cancer; TNBC, triple-negative breast cancer; CCG, Cys-Cys-Gly amino acid motif; TSPAN, tetraspanin.

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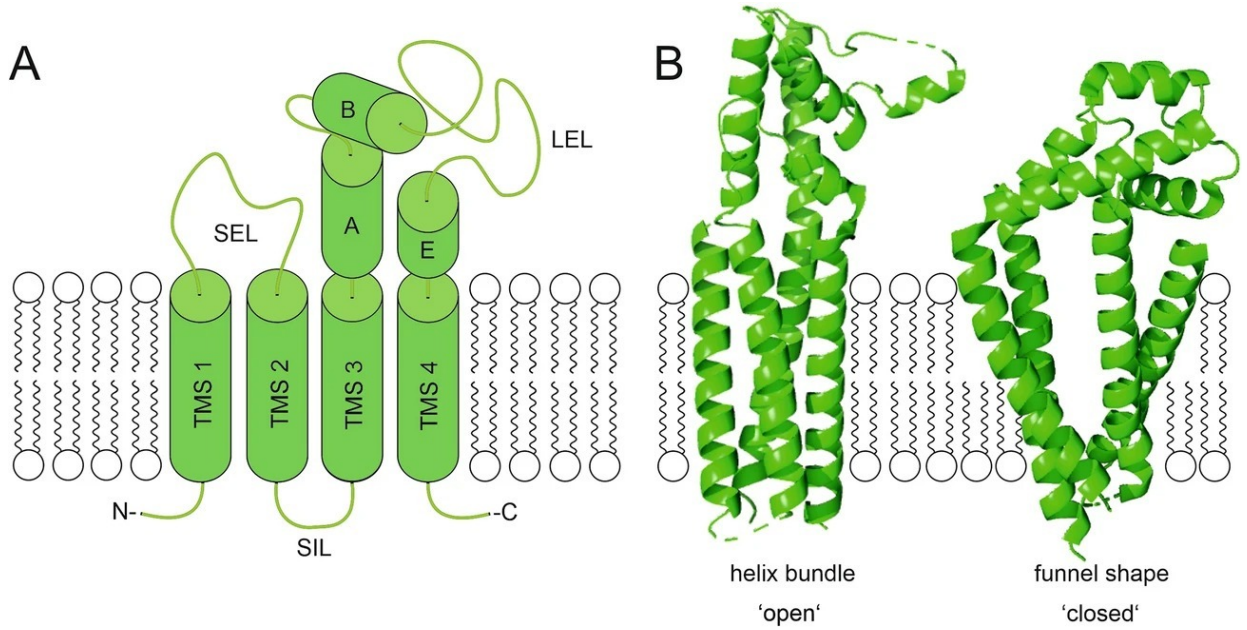

Fig. 1. Structure of a typical TSPAN. (A) A typical TSPAN has four TM helices, two extracellular loop regions, a short C-terminal tail, a small inner loop, and an N-terminal tail. (B) Proposed conformations for CD81, known as the helix bundle or 'open' and the funnel shape or 'closed'. TM, transmembrane; TMS, transmembrane segments; SEL, Small Extracellular Loop; LEL, Large Extracellular Loop. Reproduced with permission from Reppert N, Lang T, Scientific Reports; published by Springer Nature, 2022 [112].

of TSPANs. These domains form a compact structure within the cell membrane, crucial for protein interactions and their function [111,114]. Notably, the two extracellular loops (SEL and LEL) and an intracellular loop are central to TSPAN's functionality [112,115]. A particular significance is attributed to LEL, which contains most protein-protein interaction sites, such as Cys-Cys-Gly amino acid motif (CCG, the CCG motif is a characteristic sequence of two cysteine residues followed by a glycine), which is essential for protein-protein interaction [116]. While the functions of SEL and the intracellular loop are not fully understood, LCL's dual domain structure, consisting of a conserved domain for TSPAN interaction and a variable domain for non-TSPAN protein interactions, is crucial for understanding its function. The intracellular regions typically include short N- and C-terminal tails and sometimes contain a palmitoylation site, aiding their association with lipid rafts in the cell membrane, allowing for intricate engagements with other membrane proteins crucial for diverse cellular functions [117,118]. Recent research has revealed more about their crystal structure, like the reversed cone-like shape of CD9, which informs their role in membrane curvature and remodeling [119]. This structural organization enables TSPANs to interact with other membrane proteins, playing a crucial role in various cellular processes.

The Function of TSPANs

TSPANs in Cellular Functions and Cancer

In 1990, a tetraspanin (TSPAN) was found on the surface of leukocytes for the first time in humans [120]. Subsequently, TSPANs were identified across various cell types, underscoring their ubiquitous presence and functional significance in cellular biology [121]. The expression of TSPANs shows considerable variation among family members and is distinctly influenced by cell type. Most TSPANs, like CD81, CD9, and CD63, exhibit a broad expression profile, being present in various cancer types [84,122]. In contrast, a few individual TSPANs, such as CD37 and CD53, are uniquely expressed within the immune system cells [123].

Thirty-three members of TSPANs in humans were found, and their ability to integrate various cell surface receptors into functional clusters impacts essential cellular processes [124]. TSPANs are integral membrane proteins instrumental in normal cell physiology, including cell survival, proliferation, adhesion, motility, protein trafficking, and signaling [125,126]. TSPANs contribute to cell migration via mediating migrasome formation [127] and are involved in the invasion and dissemination of cancer cells. These processes involve several TSPANs, including TSPAN1, TSPAN8, and CD151 [4,128]. They interact with other cellular components, such as integrins, to influence pathways crucial for cancer progression, like PI3K/AKT (PI3K stands for Phosphoinositide 3-kinases, and AKT is a protein kinase, also known as Protein Kinase

B (PKB). In cancer, the PI3K/AKT signaling pathway activates PI3K and AKT, leading to cell growth, proliferation, and survival and causing oncogenesis when dysregulated) [5,129]. These interactions facilitate critical processes like the epithelial-mesenchymal transitions (EMT), enhancing the ability of cancer cells to migrate and invade [3,122].

TSPANs and Extracellular Vesicles (EVs)

TSPANs are recognized as critical organizers of microdomains in the cell membrane. This organization is pivotal in various cell functions, establishing a close relationship between TSPANs and extracellular vesicles (EVs). EVs are tiny, membrane-bound particles released by cells into the surrounding environment, playing key roles in intercellular communication. They range in size from about 30 nm to several micrometers and are categorized into various types, including exosomes, microvesicles, and apoptotic bodies, based on their size, origin, and biogenesis pathways. They carry diverse biomolecules, including proteins, lipids, and nucleic acids, facilitating a wide range of physiological and pathological processes [130].

The involvement of TSPANs and EVs in essential biological mechanisms also underscores their critical role in tumor development, where they facilitate malignancy by supporting various aspects of tumor progression and intercellular communication. TSPANs also play a role in exosome biogenesis, further emphasizing their role in cancer biology. TSPANs, including CD81, CD9, CD63, and others, are enriched on the membrane of EVs, particularly exosomes [131,132]. These proteins are critical for the formation, release, and function of EVs. TSPANs organize the membrane's molecular architecture, facilitating cargo sorting into EVs and mediating their interactions with recipient cells. The presence of TSPANs on EVs influences their uptake by target cells and signal transfer efficiency, impacting various biological responses [133]. In cancer, for example, TSPANs-enriched EVs can promote tumor progression by enhancing angiogenesis, metastasis, and immune evasion [134,135]. Similarly, in the context of immune responses, EVs bearing TSPANs can modulate the function of immune cells, influencing inflammation and immune surveillance [136]. The study of the interplay between EVs and TSPANs is thus crucial for understanding the mechanisms of EV-mediated communication and its implications for disease progression and therapy.

Role of TSPANs in Various Biological Systems

TSPANs are vital to the epithelial system, genitourinary system, hematopoietic system, immune system, reproductive system, and visual system, according to knockout and mutagenesis studies in animal experiments. A study reported that a reduction in long-term hematopoietic stem and progenitor cells (LT-HSPCs) in $CD82^{-/-}$ mice results from heightened HSPC activation coupled with a reduction in quiescent cells, which underscores the importance of CD82 in the maintenance and regeneration of HSPCs, particularly in their quiescence and response to hematopoietic stress [137]. TSPANs like CD81 are essential for immune responses, as their deficiency can lead to impaired antibody responses [138,139]. Likewise, CD37, prominently expressed in a range of mature B-cell lymphoma (BCL), including chronic lymphocytic leukemia (CLL), has emerged as a central target in the formulation of therapeutic agents to treat B-cell lymphomas and leukemias [74,140]. Additionally, CD53, another member of the TSPAN family, is vital for immune function, as its deficiency has been linked to increased susceptibility to infections [141,142]. These findings underscore the significant impact of TSPANs on various aspects of immune system function, from antibody production to the prevention of lymphoma and infection resistance. In mammals, TSPANs such as CD9, CD151, CD81, and CD63, which are present in spermatozoa, oocytes, and embryos, are crucial contributors to reproductive processes [143]. CD151 plays a vital role in the formation of human basement membranes within the genitourinary system, especially in the structural development of basement membranes in the kidney and skin [144,145]. Targeting the CD9 gene in parietal epithelial cells has been shown to prevent glomerular defect in crescentic glomerulonephritis (CGN) and focal segmental glomerulosclerosis (FSGS) mouse models by inhibiting cell migration and proliferation [146]. Migrasomes, marked by TSPAN4 expression in retinal pigment epithelium cells, play a significant role in the pathogenesis of proliferative vitreoretinopathy [147].

TSPANs are ubiquitous across various cell types and play critical roles in numerous biological systems. Their wide-ranging presence and functionality highlight their importance in cellular processes across different systems in the body.

TSPANs' Multifaceted Role in Cell Biology and Cancer Progression

TSPANs play a multifaceted role in cell biology, influencing various cellular processes. First, they are integral to the organization of the cell membrane, forming specialized microdomains known as tetraspanin-enriched microdomains (TEMs) through interactions with other proteins like integrins and growth factor receptors. These domains integrate membrane receptors, adhesion proteins, and signaling molecules, thereby influencing various signaling pathways [148]. TSPANs align laterally with multiple membrane proteins, leading to the formation of TEMs. These structures influence cellular processes, including cell adhesion, movement, invasion, and survival, triggering subsequent signaling pathways [113,149]. These interactions are key in organizing the plasma membrane and mediating cellular processes such as signal transduction, adhesion, and migration. TSPANs influence cell response by transmitting external signals, regulating cell adhesion, and are involved in cell fusion and shape maintenance. Their

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roles in immune cell function and disease pathogenesis, including cancer and infectious diseases, make them targets for therapeutic interventions.

Additionally, TSPANs regulate proteins essential for every facet of cell migration, encompassing interactions between cells, adherence to the extracellular matrix (ECM), cytoskeletal rearrangements, and ECM proteolysis [115, 150]. Distinct from typical adhesion molecules, TSPANs control the functions of their target molecules in a cis manner, indicating their expression within the same cell. They impact cell migration and adhesion by interacting with growth factors, growth factor receptors, and metalloproteases [150,151] (Fig. 2, Ref. [152]). Moreover, in the immune system, TSPANs control multiple functions of antigen-presenting cells, such as cell migration, the absorption of pathogens, the transport of MHC molecules, the formation of immunological synapses, and the presentation of antigens [149,153]. They organize specialized membrane platforms, integrating membrane receptors, adhesion proteins, and signaling molecules. Insufficiencies in certain TSPANs can lead to disruptions in immune synapse formation, hinder lymphocyte proliferation, diminish antibody production, and affect migration [149]. Furthermore, TSPANs play a significant part in mammalian reproductive processes, particularly influencing the role of EVs in gamete maturation, fertilization, and embryonic development. They contribute to cell contact and communication in the reproductive system, emphasizing their importance in reproductive biology [154]. Apart from their engagement in cell migration, signaling, and internal cellular transport, TSPANs are also manipulated by pathogens as a means of infection. They are pivotal at various stages of the viral life cycle, involving interactions with membrane receptors, proteins of the cytoskeleton, and molecules responsible for signaling. Certain TSPANs are implicated in the disease mechanisms of several viruses, including human immunodeficiency virus (HIV), human papillomavirus (HPV), influenza, and Zika virus [155,156]. Furthermore, TSPANs play a regulatory role in a series of cancer-related processes, sequentially affecting cancer cell proliferation, metastatic potential, stem cell-like characteristics, resistance to pharmacological treatments, and the formation of EVs. They act as markers for stem and tumor-initiating cells, determining cell fate. Some TSPANs are upregulated in certain cancer types, playing a role in cancer progression and serving as prognostic markers [152,157,158].

In summary, TSPANs are versatile proteins essential in various cell functions, including signaling, adhesion, migration, immune response, fertilization, and disease pathogenesis. Their extensive interactions and functions highlight their significance in basic cell biology and therapeutic strategy development for various diseases.

Promotive Role in Tumor Development

Through various complex mechanisms, TSPANs have emerged as key players in tumor progression and metastasis. A wide array of TSPANs, including TSPAN1, TSPAN2, TSPAN3, TSPAN4, TSPAN8, TSPAN13, TSPAN15, TSPAN17, TSPAN20, CD151, and CD9, have been recognized for their role in promoting the process of cancer metastasis (Table 1). Their role has been elucidated through extensive research, highlighting their involvement in various stages of the metastatic cascade, including cell migration, adhesion, and angiogenesis.

TSPANs and Immune System Modulation

TSPANs, recognized as membrane proteins, promote tumor development, dissemination, and metastasis. Their contribution is systematically organized, first by supporting cellular processes including proliferation, adhesion, and migration, followed by differentiation, activation, and signal transduction. These proteins are pivotal in structuring cell membrane assemblies termed TEMs, which incorporate crucial immune system components such as CD19 in B cells and CD4 in T cells [158].

Studies have shown that specific TSPANs, such as CD81, play a crucial role in modulating the functions of regulatory T cells (Treg) and myeloid-derived suppressor cells (MDSCs), both of which are integral to the immune system's reaction to tumors [159,160]. The absence of CD81 has been correlated with a decrease in tumor development and metastatic spread across multiple genetic mouse models, highlighting its pivotal role in the advancement of cancer [161]. Notably, while CD81 is not essential for the typical development of Treg and MDSCs, it is crucial for their ability to perform immunosuppressive functions [158]. Moreover, CD53 plays a crucial and irreplaceable role in modulating immune responses, which is unique to the immune system [142]. CD9 plays an important role in regulating cell adhesion within the immune system, affecting processes such as hemopoiesis, blood coagulation, and the body's ability to resist viral and bacterial infection [162]. In light of these functions, the TSPANs play a vital role in the immune system's ability to respond to pathogens.

Diversity of TSPAN Functions in Cancer

TSPANs are crucial membrane proteins that significantly impact cancer development through various stages of cancer progression, including invasion, migration, and angiogenesis, influencing cancer stemness and contributing to drug resistance. Their roles span from traditional tumor growth facilitation and metastasis to nuanced functions in cellular communication and immunology within cancer [110,163,164].

Key TSPANs such as TSPAN1, TSPAN8, and CD151 are particularly noted for their roles in metastasis [110]. TSPAN1 is linked to tumor growth and metastasis in can-

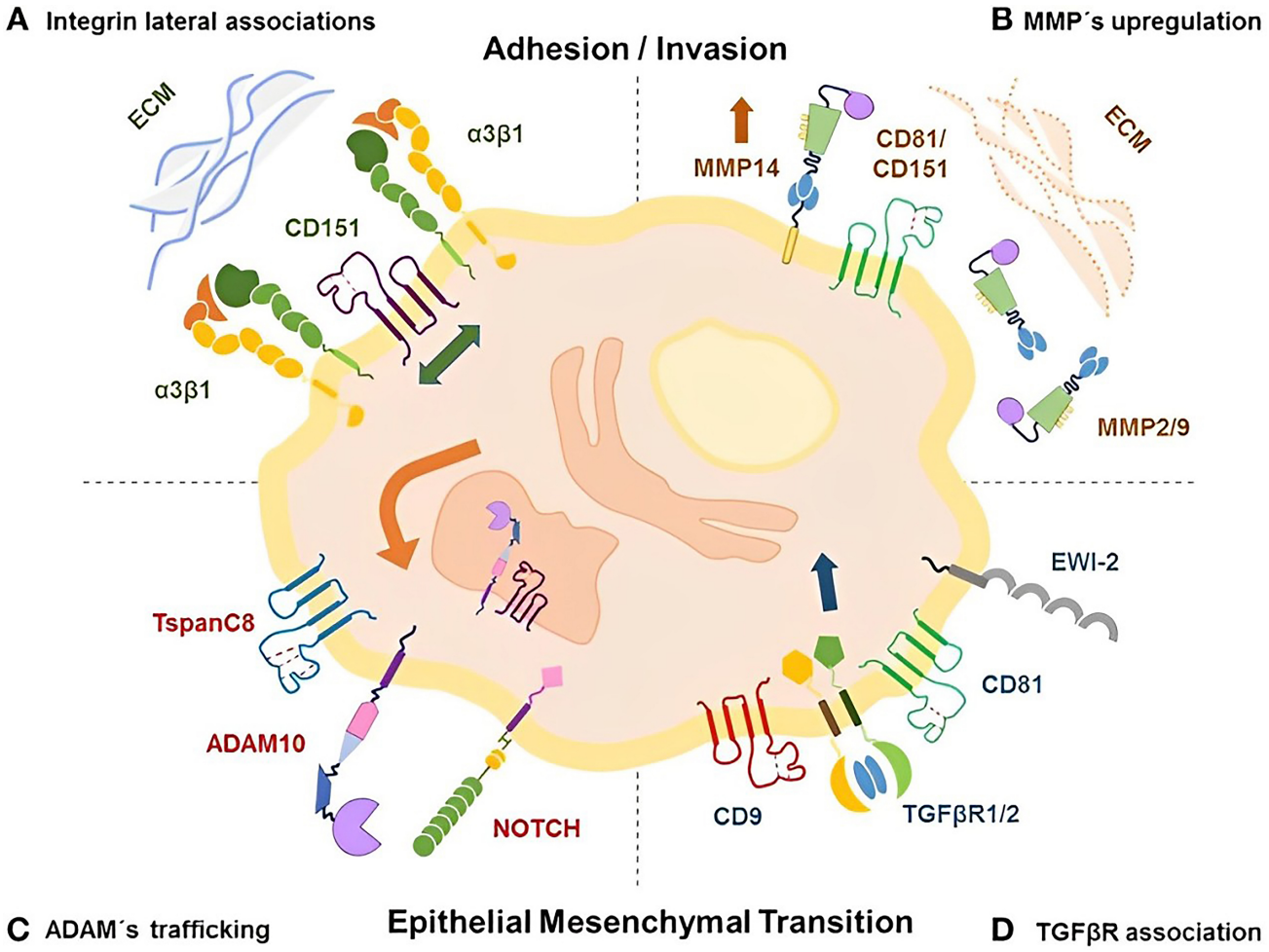

Fig. 2. The function of TSPANs in cancer. (A,B) TSPANs interact closely with integrins within TEMs, enhancing cellular processes like adhesion, spreading, and movement through the ECM. (C,D) Certain TSPANs enhance the trafficking and cellular positioning of a disintegrin and metalloproteinase (ADAM) family members, affecting EMT and, consequently, the invasion and metastasis of cancer cells. TSPANs, tetraspanins; TEMs, tetraspanin-enriched microdomains; ECM, extracellular matrix; EMT, epithelial-mesenchymal transitions; MMP, matrix metalloproteinase. Reproduced with permission from Vences-Catalán F, Levy S, Frontiers in Immunology; published by Frontiers, 2018 [152].

cers like cholangiocarcinoma and gastric cancer (GC), primarily through enhancing critical signaling pathways [3]. CD151 and TSPAN8, known markers of poor prognosis, are associated with the advancement and spread of tumors [122]. TSPAN8 is associated with the progression of colorectal and pancreatic cancers, aiding the EMT and improving cell-cell adhesion [165]. In mice lacking CD151, the development of metastases is reduced compared to normal, genetically unaltered mice in different cancer models, confirming the involvement of CD151 in tumor development [158]. Moreover, CD151 is known for its poor prognosis correlation and pivotal role in tumor cell migration, invasion, and interaction with the extracellular matrix, primarily through its relationships with integrins and matrix metalloproteinases (MMPs) [69,166].

Besides directly promoting tumor cell behaviors, TSPANs significantly influence the tumor microenvironment, affecting cancer stemness, drug resistance, and immune responses [152,167]. Their involvement in exosome biogenesis and migrasome formation underscores their extensive role in cancer biology [168,169]. The exploration into TSPANs' roles in cancer underscores their potential as therapeutic targets, suggesting strategies to inhibit their tumor-promoting activities while leveraging their beneficial functions for cancer treatment. Continuous research is crucial to unravel TSPANs' specific mechanisms in cancer, highlighting their importance in the complex cancer progression and metastasis network and paving the way for advancements in cancer therapy strategies.

CD151, Key Driver in Cancer Metastasis

CD151 is a prototypical member of the TSPANs and plays a pivotal role in cancer progression through its involvement in several key biological processes [170]. Research has extensively documented CD151's contribution to cancer metastasis, primarily via its regulation of cell mi-

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gration, interaction with MMPs, and association with integrins [171]. The mechanism by which CD151 influences cancer progression begins with its impact on cell migration [170,171]. CD151's absence significantly reduces integrin-mediated cell migration, spreading, and invasion, a process that is mediated by signaling pathways involving focal adhesion kinase (FAK, a cytoplasmic protein tyrosine kinase that functions as a pivotal enzyme in the signal transduction pathways that mediate cellular processes such as adhesion, migration, and proliferation by relaying cues from integrins and various receptors) and Rac1 (a GTPase within the Rho family, plays a significant role in modulating the organization of the actin cytoskeleton, thereby influencing cell morphology, motility, and growth) [172]. This reduction in cell mobility is crucial because it directly affects the cancer's ability to spread and form metastases. Further complicating its role in cancer, CD151's expression levels correlate with worse outcomes in various cancers, such as breast, pancreatic, colorectal, and non-small cell lung cancer (NSCLC) [69]. Notably, CD151's expression in prostate cancer is a more accurate prognostic indicator than traditional histological grading, underlining its significance in cancer biology [145].

A critical function of CD151 in tumor progression is its relationship with MMPs, specifically MMP7 and MMP9 [173,174]. CD151 facilitates the activation of these enzymes, which are vital for the degradation of the extracellular matrix (ECM), a necessary step for tumor invasion and metastasis [174]. This interaction is highlighted by the ability of anti-CD151 antibodies to inhibit MMP7 activation, thereby impeding cancer cell invasion [166]. The interaction between CD151 and integrins, particularly $\alpha 3\beta 1$ and $\alpha 6\beta 4$, is fundamental to its role in cancer. These integrins are crucial for tumor cell-stromal cell interactions, affecting their localization and functionality and influencing tumor growth and metastasis [128]. The co-internalization of CD151 with $\alpha 3\beta 1$ integrin, for example, enhances cell migration and invasion under conducive conditions [175].

In vivo and *in vitro* studies complement these findings by illustrating CD151's role in metastasis [128,176]. Although not essential for cell migration, CD151 facilitates the detachment of the cell's rear end from the ECM, suggesting a mechanism where CD151 might recruit molecules necessary for this detachment [171]. This indicates a potential compensatory mechanism that allows for effective cell migration without CD151. Beyond its role in tumor cells, CD151 is also significantly expressed in endothelial cells and is implicated in pathological angiogenesis [145]. Mice deficient in CD151 display angiogenesis abnormalities, emphasizing CD151's importance in initiating adhesion-related signaling on laminin substrates and suggesting its broader role in facilitating endothelial cell function [177].

In summary, CD151 accelerates tumor progression through its multifaceted roles, including regulating cell migration, MMP interaction, and integrin association. These mechanisms deepen our understanding of the molecular processes driving cancer metastasis and suggest potential therapeutic targets. The diverse functions of TSPANs, particularly CD151, underscore their importance in cancer biology and the development of strategies to combat tumor growth, invasion, and metastasis.

Signaling Pathway and Mechanism of TSPANs Promoting Tumor Progression

The signaling pathways and molecular mechanisms by which TSPANs promote cancer progression involve complex interactions within the cellular membrane. TSPANs cross the membrane four times and are implicated in the formation of TEMs. TEMs serve as crucial platforms for signaling, distinct from lipid rafts, facilitating interactions with a diverse set of proteins, including integrins, growth factor receptors, and various cytosolic signal transduction molecules. Such interactions are fundamental for processes critical to cancer progression, such as cell migration, invasion, and adhesion [4]. TSPANs, through their formation of TEMs, affect cellular physiology by organizing other membrane proteins laterally. This organization influences cancer cell growth, metastasis, and other aspects like stemness, drug resistance, and interactions with the immune microenvironment. The interaction of TSPANs with integrins is particularly notable, affecting downstream signaling pathways such as Extracellular Signal-Regulated Kinase (ERK)1/2, Notch, PI3K/AKT, Src, STAT3/5, and Wnt/β-catenin. For instance, CD151 (TSPAN24) activates PI3K or PI4K signaling pathways by forming complexes with integrin $\alpha 3\beta 1$, enhancing cancer cell migration and promoting matrix metalloproteinase (MMP) secretion.

TSPANs are also involved in various cancer types, including breast, cervical, and pancreatic cancers, among others, promoting invasion and metastasis. They interact with other molecules like growth factor receptors (epidermal growth factor receptor (EGFR), mtTGF-β), transporters (ASCT2, FATP1, MDR1), and membrane-linked kinases (BTRC, SOCSS3, ATXN3), undergoing post-translational modifications such as N-glycosylation, palmitoylation, and ubiquitination. These modifications are crucial for protein-protein interactions and the activation of subsequent downstream pathways, significantly influencing cancer cell behavior.

TSPAN1 has been identified as a facilitator of breast cancer (BC) and cholangiocarcinoma progression through the activation of the PI3K/AKT pathway [5,18]. It has been implicated in advancing head and neck squamous cell carcinoma through the induction of EMT and the activation of SRC signaling pathways [21]. TSPAN8 enhances stemness and drug resistance through the Hedgehog signaling pathway and facilitates invasion and metastasis via STAT3 signaling in BC [9,178]. TSPAN15 has been identified as a facilitator of hepatocellular carcinoma (HCC) proliferation through its role in activating the Mitogen-

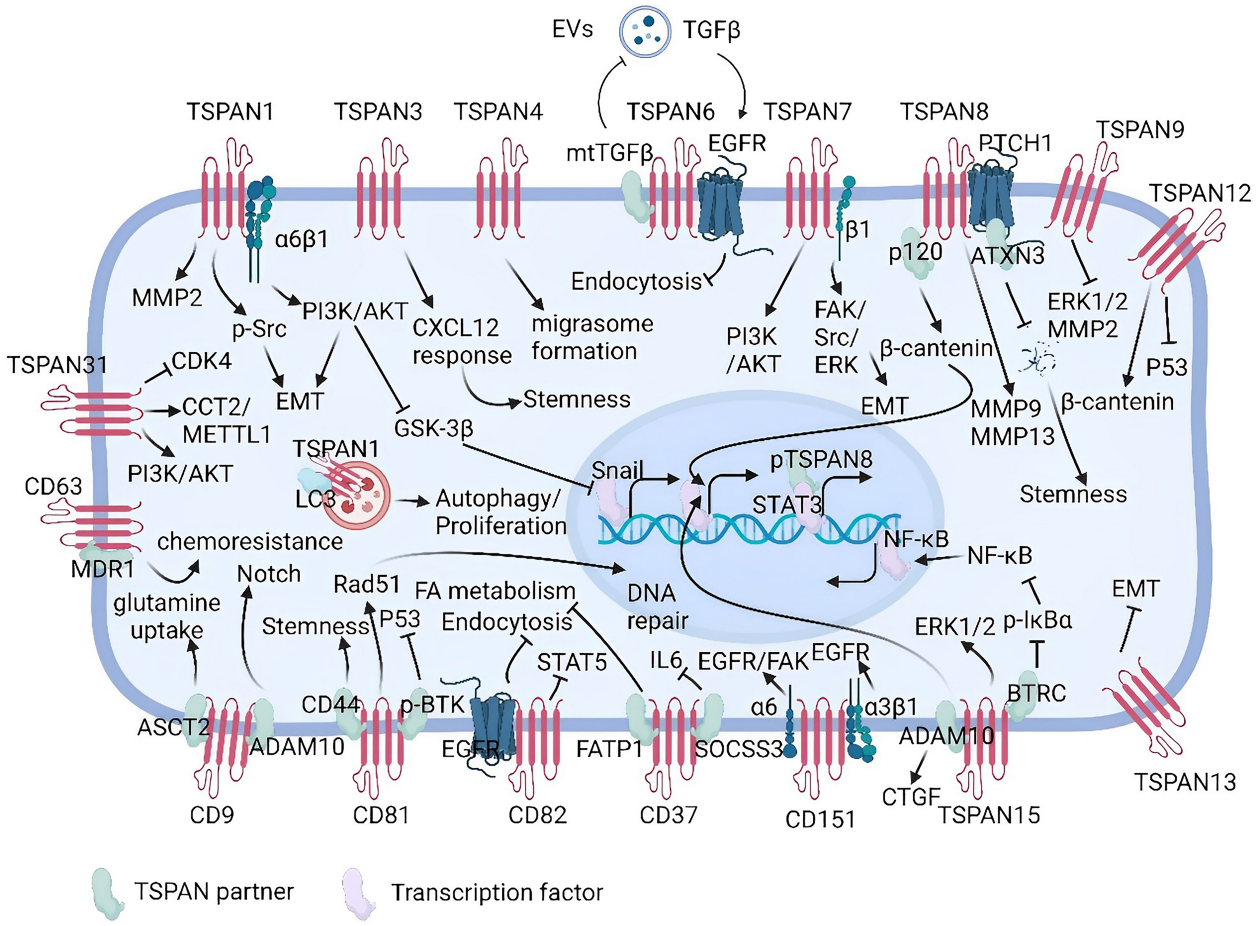

Fig. 3. Signaling of TSPANs in cancer and their partners and transcription factors. The internal signaling mechanisms of TSPANs in cancer predominantly involve their interactions with various partner molecules, leading to the formation of TEMs, which then influence diverse biological processes. Reproduced with permission from Zhou Z, Yang Z, Zhou L, Yang M, He S, Cell & Bioscience; published by BMC (Part of Springer Nature), 2023 [4].

Activated Protein Kinase/Extracellular Signal-Regulated Kinase (MAPK/ERK) signaling pathway, specifically by enhancing the secretion of ERK1/2 and Connective Tissue Growth Factor (CTGF) [59]. CD151 enhances migration and invasion in NSCLC by facilitating the interaction between EGFR and integrin $\alpha 3\beta 1$ [69]. CD81 facilitates the enhancement of chemoresistance in acute lymphoblastic leukemia (ALL) via the activation of Bruton's tyrosine kinase (BTK, a pivotal pathway in B-cell receptor-mediated regulation of B-cell development, activation, and survival, with its dysregulation implicated in various hematological malignancies) signaling pathway [81]. CD9 amplifies its oncogenic activity in colorectal cancer (CRC) by activating the Notch signaling pathway [90]. Consequently, TSPANs are implicated in modulating several signaling pathways, encompassing ERK1/2, Notch, PI3K/AKT, SRC, EGFR, and BTK signaling pathways (Fig. 3, Ref. [4]). Overall, TSPANs exhibit a multifaceted role in tumor development, affecting various biological processes and signaling pathways, thus highlighting their potential as therapeutic targets in cancer treatment.

TSPANs and the Metastasis Suppression Role

Metastasis, the dissemination of cancer from its initial site to distant organs, encompasses multiple critical phases: departure from the primary tumor, infiltration, and emergence from the blood circulation (intravasation and extravasation), culminating in the establishment and proliferation at new sites. This process is complex and involves a variety of cellular mechanisms and molecular players. One of the initiating events in metastasis is the EMT, where epithelial cells acquire mesenchymal characteristics, enabling them to invade and migrate. This transition is facilitated by a range of molecules, including cell adhesion molecules, enzymes that degrade the ECM, chemokine receptors, genes conferring resistance to apoptosis, and factors promoting angiogenesis. Within this context, TSPANs emerge as significant players that play a critical role in the complex process of cancer progression. Depending on the situation, their functions can be both pro- and anti-tumor. The preceding description has outlined the tumor-promoting effects of TSPANs. Equally critical is their role in tumor suppression, which will be elaborated on in the following section.

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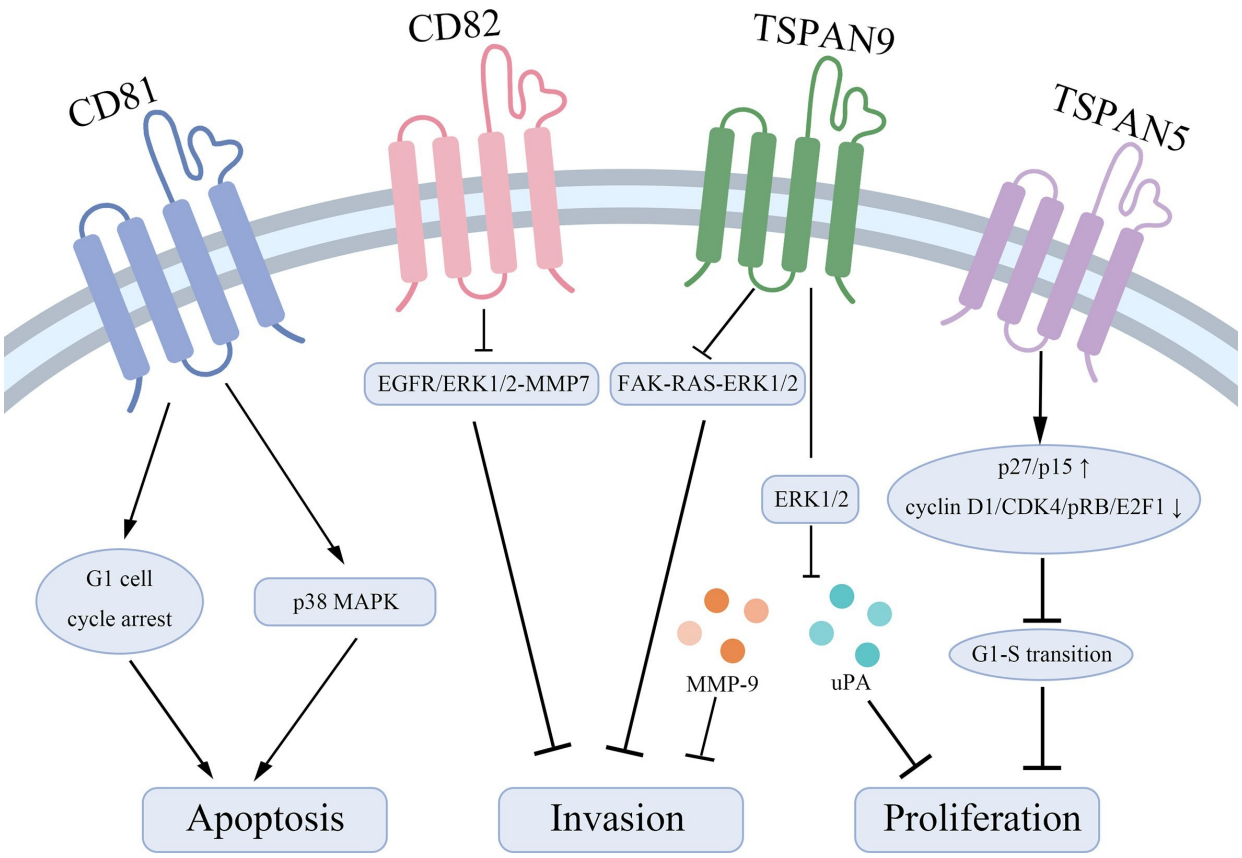

Fig. 4. TSPANs suppress gastric cancer. TSPAN5, TSPAN9, CD82, and CD81 are reported to inhibit gastric cancer by influencing tumor cell apoptosis, invasion, and proliferation. EGFR, epidermal growth factor receptor; ERK, Extracellular Signal-Regulated Kinase; FAK, focal adhesion kinase. Lines with arrows represent promoting effects, while lines with flat ends represent inhibiting effects. Reproduced with permission from Deng Y, Cai S, Shen J, Peng H, Frontiers in Oncology; published by Frontiers, 2021 [86].

Subsequently, TSPANs will be elucidated as a critical regulatory nexus in suppressing cancer metastasis. Several TSPANs, like TSAN6, TSPAN9, and TSPAN21, are reported to suppress metastasis (Table 1). TSPAN9 has been recognized as an inhibitor of tumor proliferation and dissemination in GC [47]. In addition to TSPAN9, CD82, TSPAN5, and CD81 have been identified as playing a significant role in the suppression of GC (Fig. 4, Ref. [86]). Furthermore, CD82's role in curbing tumor migration has been substantiated by findings in references [78,179]. CD37 has been reported to obstruct tumor advancement through IL-6 mediated pathways in BCL [74]. TSPANs exert their metastasis-suppressive effects through various mechanisms:

Regulation of Cell Motility and Invasion

Key members of the TSPAN family, like CD82, suppress cell motility, a crucial aspect of cancer metastasis [180]. Besides CD82, CD63 has been shown to inhibit cell motility and invasion, which are crucial steps in metastatic spread [181]. They achieve this by modulating the activity of integrins and other adhesion molecules, thereby affecting the adhesive properties of cancer cells and their interaction with the ECM.

Alteration of the Tumor Microenvironment

TSPANs significantly contribute to the alteration of the tumor microenvironment, a critical factor in metastasis development. Through their influence on the infiltration of immune cells, TSPANs create conditions that are less conducive to the spread of cancer [121]. The expression of TSPANs correlates with genes that are differentially expressed within the tumor microenvironment, affecting the presence and activity of immune cells. This interaction, in turn, directly impacts the tumor's progression and its response to therapeutic interventions.

Epithelial-Mesenchymal Transitions (EMT)

EMT is a critical process in cancer metastasis, where epithelial cells acquire mesenchymal characteristics to become more motile and invasive. TSPANs have been implicated in the regulation of EMT, with some members capable of suppressing this transition, thereby hindering the metastatic capability of cancer cells [182].

Influence on Signaling Pathways

TSPANs regulate several signaling pathways that control cell proliferation, survival, and migration. For instance,

they can inhibit the ERK1/2 and Wnt signaling, suppressing cancer cells' proliferative and invasive capabilities [46,49].

Understanding TSPANs' role in suppressing metastasis opens up new avenues for cancer therapy. The involvement of TSPANs in cancer development highlights the possibility of treatments targeting these proteins. By comprehending and influencing the behavior of TSPANs and associated proteins, there is an opportunity to interrupt the metastatic process at multiple points, presenting an encouraging strategy for cancer therapy.

Clinical Significance of the Duality of TSPANs

The clinical significance of the duality of TSPANs in cancer lies in their complex roles as both promoters and suppressors of tumor progression [110,183]. This duality presents unique opportunities and challenges for cancer therapy. On one hand, TSPANs like CD151 promote cancer growth and metastasis, making them targets for therapies by inhibiting their function. On the other hand, TSPANs like TSPAN9 and CD82 suppress tumor progression, suggesting their potential as biomarkers for prognosis or targets for enhancing tumor suppression. Understanding this dual nature is crucial for developing more effective, targeted cancer treatments.

The Potential of TSPANs as Tumor Markers

TSPANs, a varied group of proteins, hold substantial importance in the study of cancer biology. Engaged in a range of cellular activities such as cell survival, adhesion, migration, invasion, and signal transduction, they present themselves as potential focal points for cancer treatment strategies [159,184]. They are involved in cancer initiation and progression, performing tumor-promoting or tumor-suppressing activities depending on the circumstance. Numerous TSPANs, such as TSPAN1, TSPAN2, TSPAN3, TSPAN4, TSPAN8, TSPAN13, TSPAN15, TSPAN17, TSPAN20, CD151, and CD9, have been identified as facilitators of cancer metastasis (Table 1). For instance, TSPAN1 increases expression in various cancers, contributing to the EMT and tumor progression [5]. On the other hand, some TSPAN members like TSPAN6, TSPAN9, and CD82 display characteristics of tumor suppression (Table 1). They inhibit tumor progression, such as cell migration and metastasis. The role of TSPANs in cancer is highly context-dependent. For example, TSPAN12 exhibits varying effects across different cancer types, promoting proliferation in colorectal cancer, hepatocellular carcinoma, ovarian carcinoma, and small-cell lung cancer while inhibiting breast cancer metastasis (Table 1). TSPANs, including TSPAN8, CD81, CD9, and TSPAN31, contribute to increased drug resistance to cancer treatments, presenting a significant challenge in cancer therapy [81,103,178,185]. In conclusion, TSPANs demonstrate a complex and context-dependent role in cancer, affecting various aspects from invasion and metastasis to therapy resistance. Their diverse functions in cancer biology underscore their potential as novel therapeutic targets and tumor markers.

Potential Therapeutic Strategies Targeting TSPANs

TSPANs are a family of proteins that have become significant targets for therapeutic strategies due to their role in various cellular processes and their involvement in pathological conditions. Based on the information found in recent literature, here are some potential therapeutic strategies targeting TSPANs.

Monoclonal Antibodies

These target specific TSPANs, potentially inhibiting their function in cell migration, angiogenesis, invasion, and metastasis [186,187].

RNA Interference (RNAi) Technology

This approach combined RNA molecules was used to inhibit the expression of specific TSPANs, thereby modulating their role in various cellular processes [122].

Small-Molecule Mimetics and Small Interfering RNA (siRNA)

These are designed to mimic or interfere with the function of TSPANs, which could be useful in treating infections and other diseases where TSPANs play a crucial role [110].

Recombinant Soluble LEL/EC2 Domains

Recombinant domains of the proteins can interact with TSPANs, affecting their function and potentially offering therapeutic benefits [109,184].

These approaches underscore the escalating focus on TSPANs as potential therapeutic targets in cancer. The effectiveness of these approaches is subject to ongoing research and development.

Discussion

TSPANs represent a paradox in cancer biology due to their dual roles in promoting and inhibiting tumor progression. Some members of the TSPAN family exhibit protumorigenic, and some exhibit anti-tumorigenic effects, illustrating their varied functions in cancer biology.

Several TSPANs have been shown to exhibit both protumorigenic and antitumorigenic effects, acting as facilitators for the development of specific cancer types and inhibiting the progression of others (Table 1). TSPAN5 has been identified as a suppressor of GC and triple-negative breast cancer (TNBC) [26,27], yet it appears to enhance hepatocellular carcinoma (HCC) progression [28]. Conversely, TSPAN7 plays a dual role by facilitating the progression of renal cell carcinoma, lung cancer, and osteosarcoma (OS) [31–33], while it acts as a suppressor in multiple myeloma, bladder cancer, and glioma [34–36]. CD37 has been associated with promoting acute myeloid leukemia

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(AML) and chronic lymphocytic leukemia, but it exhibits inhibitory effects in B-cell lymphoma [72–75]. CD81 can advance the development of acute lymphoblastic leukemia, glioblastoma multiforme, HCC, OS, and TNBC [81–85], yet it inhibits GC and NSCLC [87,159]. CD63 has been shown to encourage breast cancer proliferation but inhibits melanoma growth [99–101]. TSPAN31 is known to enhance the malignancy of GC and HCC [103,104]. In contrast, it suppresses cervical cancer progression [102], illustrating these proteins' nuanced and context-dependent roles in cancer biology. Furthermore, CD82 is generally regarded as a cancer suppressor; however, it has been observed to have a promoting effect in AML cases [76].

Astonishingly, some TSPANs have been found to both promote and inhibit tumor growth, even within the same tumor type. For instance, research indicates that TSPAN12 not only enhances the growth of primary tumors but also plays a role in suppressing metastasis in breast cancer [49]. Concurrently, evidence suggests that while TSPAN12 contributes to the proliferation of NSCLC cells, it also can restrict their proliferation, migration, and overall tumor expansion [52,53], illustrating its multifaceted impact on cancer dynamics.

Their dual functionality underscores the potential of TSPANs as biomarkers and therapeutic targets in cancer treatment. Continued investigation is essential to unravel the nuanced roles of TSPANs in different cancer types and stages and to harness their dual nature to develop more effective and targeted cancer therapies. Understanding this balance between their pro-cancer and anti-cancer roles will be crucial in translating TSPAN research into clinical applications.

Conclusion

In the complex landscape of cancer biology, TSPANs have emerged as multifaceted players, exhibiting both tumor-promoting and suppressing roles. This duality presents a unique challenge in understanding and targeting these proteins in cancer therapy. On one side of the spectrum, certain TSPANs like TSPAN1, TSPAN2, TSPAN3, TSPAN4, TSPAN8, TSPAN13, TSPAN15, TSPAN17, TSPAN20, CD151, and CD9 have been well-documented for their role in enhancing tumor metastasis. Conversely, other TSPANs, such as TSPAN6, TSPAN9, TSPAN14, TSPAN21, and CD82, have been identified as tumor suppressors. Understanding the dual role of TSPANs in cancer progression is crucial for developing effective therapeutic strategies to exploit their tumor-suppressive properties while mitigating their tumor-promoting effects.

Research on TSPANs faces challenges due to their complex and context-dependent roles in cancer, their varied interactions, post-translational modifications, and the inconsistent effects they have on cancer progression, stemness, and treatment resistance. The dynamic nature of TEMs, which varies based on the cell's activation status and the presence of binding partners, adds to these challenges. Yet, the inherent biocompatibility, stability, and low immunogenicity of TSPAN-enriched exosomes underscore the potential of tumor-targeted therapies. Precision targeting specific cancer cells by TSPAN-targeted therapies could diminish side effects by preserving healthy tissues. Future research directions involve delving deeper into the molecular mechanisms of TSPANs in cancer, particularly their role in cancer metastasis and interaction with other cellular components like integrins. Understanding these interactions could reveal new therapeutic targets and strategies for treating various cancers. In summary, TSPAN research in cancer is marked by the complexity of these proteins' functions across different cancer types and stages. Further investigation is needed to fully understand their roles and develop effective therapeutic strategies.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Author Contributions

KZ, proposed conceptions, reviewed literature, and prepared the original draft. The author gave final approval for the version to be published. The author has participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The author declares no conflict of interest.

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