Review Article

The emerging role of transmembrane proteins in tumorigenesis and therapy

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Abstract: Transmembrane proteins (TMEMs) are a kind of proteins that can cross the phospholipid bilayer one or multiple times and remain permanently anchored. They are involved in the regulation of many biological functions, and their dysregulation is associated with many human diseases and even cancer. Abnormal expression alterations of TMEMs widely exist in tumor tissues compared with paracancerous tissues. They are associated with the clinicopathological features of cancer patients by promoting or inhibiting the development of cancer, thus affecting survival. This review summarized the structure and physiological functions of TMEMs, as well as their roles in tumorigenesis, such as cell proliferation, apoptosis, autophagy, adhesion, metastasis, metabolism and drug resistance. In addition, we elaborated on the potentiality of TMEMs for tumor immunity. Moreover, the advances of TMEMs were subsequently retrospected in several common types of human cancers, including breast cancer, gastric cancer, and lung cancer. Subsequently, we outlined the targeted therapeutic strategies against TMEMs proposed based on existing studies. To date, there are still many TMEMs whose functions and mechanisms have not been well known due to their special structures. Since the important roles TMEMs plays in the development of human cancers, it is urgent to portray their structure and function in carcinogenesis, providing potential biomarkers for cancer patients in the future.

Keywords: Transmembrane proteins (TMEMs); tumorigenesis; metabolism; drug resistance; tumor immunity

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Introduction

Background

Transmembrane proteins (TMEMs) are integral membrane proteins that traverse the entire lipid bilayer either once or multiple times and remain permanently anchored to the membrane (1,2). TMEMs are usually present in cell membranes and organelle membranes, such as mitochondria (3), endoplasmic reticulum (4), lysosomes (5), and Golgi apparatus (6). Owing to the difficulty of extraction and purification, the biological functions of most TMEMs have not been well explored (4). Once the functions and structures of these proteins are further elucidated, they are renamed and classified into the corresponding categories. For example, TMEM16A has been confirmed as a selective anion channel, a Ca^{2+}-activated Cl^- channel, including ten transmembrane domains. Thus, TMEM16A is also known as anoctamin-1 (7). TMEM173 is named as stimulator of interferon genes (STING), which plays a crucial role in regulating type I interferon (IFN-I) signaling and innate immunity (8).

TMEMs classification

There are two common TMEMs classifications. To start with, TMEMs can be divided into two basic types according to their fundamental structures: α-helices and β-barrels (9). The α helix is arranged in side-by-side rings. The hydrophobic side chain is exposed to the lipid membrane, and the hydrophilic side chain forms the lining of the hydrophilic pore through the lipid bilayer; the β-barrel passes through the lipid double layer in the form of a β-folded sheet, which is bent into a cylindrical shape to form an open barrel-like structure (9). The proportion of TMEMs with α-helical is greater than that of β-folded (10,11). Moreover, TMEMs can be classified into single TMEMs and that cross the membrane protein multiple times (12,13). The fundamental structures of TMEMs are shown in *Figure 1*.

The function of TMEMs

TMEMs are widely expressed in cells and tissues, playing crucial roles in various biological behaviors, including cardiac function, angiogenesis, and ion transport (14-16). For example, TMEM11 interacts with methyltransferase like 1 (METTL1) to increase N7-methylguanosine (m7G) methylation of activating transcription factor 5 (ATF5) and upregulate its expression level, thereby inhibiting cell-cycle activity of cardiomyocytes. In response to myocardial injury, loss of *TMEM11* increases the proliferation of cardiomyocytes and restores cardiac function (14). TMEM100 contains two putative transmembrane domains and is a key factor in vascular system development and maintenance (15). TMEM100 is implicated in angiogenesis, blood vessel, integrity, and morphogenesis (17). And its overexpression in lung endothelium is essential for the regeneration and repair of the pulmonary vascular system. In contrast, the deletion of *TMEM100* results in impaired regenerative capacity in endothelial cells (15). TMEM16A is involved in smooth muscle contraction, olfactory, visual, and nociceptive transmission, as well as neuronal excitatory control and epithelial ion transport (13,16). TMEM120A, also referred to TACAN, can form symmetrical dimers, each of which is composed of six transmembrane domains. TMEM120A has been linked to the control of adipocytes and has structural homology with a lipid-modifying enzyme (18).

However, the dysfunction of TMEMs leads to many diseases and even cancer. For example, Golgi glycosylation deficiencies and poor glycosylation arise from the disruption of Golgi manganese (Mn^{2+}) homeostasis caused by TMEM165, which has been largely conserved throughout evolution (6). TMEM16B is expressed mainly in the central and lateral amygdala, composed of several γ-aminobutyric acid (GAGB) inhibitory neurons, suggesting that TMEM16B and abnormal GAGB neurotransmission are related to anxiety (19). Many typical human tissues, particularly epidermal keratinocytes, exhibit high expression levels of TMEM45A. Hayez *et al.* found that the expression of TMEM45A is elevated during epidermal differentiation, resulting in keratosis development (20). In addition, the abnormal expression of TMEM48 has been observed in both cervical cancer tissues and cell lines, and its depletion inhibits the Wnt/β-catenin pathway, thereby inhibiting cell proliferation, migration, and invasion and alleviating the development of cervical cancer (21). In prostate cancer, the overexpression of TMEM100 increases cell cycle arrest and exacerbates cell apoptosis (22). Therefore, it is of great importance to investigate the roles of TMEMs in tumorigenesis and cancer therapy.

Biological function of TMEMs in tumorigenesis

Cell proliferation

Unrestrained proliferation is a hallmark of cancer cells,

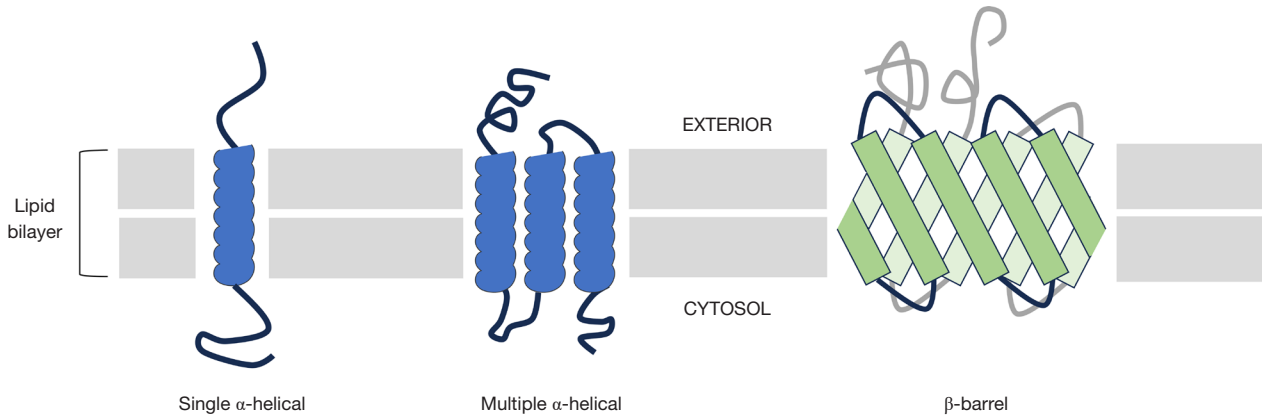

Figure 1 Structure of transmembrane proteins. Transmembrane proteins can cross the lipid bilayer singly, multiple times in an α-helix, or multiple times in a β-barrel folded structure.

driven by alterations at multiple cellular levels. This complexity underscores the involvement of numerous proteins in regulating these processes (23). Numerous studies have reported the dysregulation of TMEMs in multiple kinds of human cancers (24-27). On the one hand, many TMEMs were found to promote the proliferation of cancer cells. For example, TMEM9A, TMEM48, TMEM168, and TMEM97 influence cell proliferation via the Wnt/β-catenin signaling pathway (21,27-29). Specifically, TMEM9A stimulates cell proliferation, migration, and invasion by triggering the Wnt/β-catenin signaling pathway in breast cancer (27). TMEM48 is upregulated and strongly correlated with the cellular viability of cervical cancer and non-small cell lung cancer (NSCLC) (21,30). Knocking down *TMEM48* significantly reduces the expression levels of β-catenin, T cell factor 1 (TCF1), and axis formation inhibitor 2 (AXIN2), inhibiting the Wnt/β-catenin pathway to decelerate cellular proliferation of cervical cancer (21). In glioblastoma multiforme (GBM), the depletion of *TMEM168* causes G0/G1 phase arrest, decreases the levels of β-catenin, c-Myc, cyclin D1, and Survivin, and retards cell proliferation (28). Moreover, *TMEM97* deficiency restrains the viability of breast cancer cells (29). Similarly, downregulation of TMEM97 inhibits the G1/S transition and decelerates cell proliferation in glioma (31). The silencing of *TMEM45A* markedly downregulates transforming growth factor-β (TGF-β1, TGF-β2), Ras homolog family member A (RhoA), and Rho-associated kinase 2 (ROCK2) expression, increases the ratio of G1 phase cells, and subsequently inhibits the proliferation of ovarian cancer cells (32). The effect of TMEM45B on the proliferation of osteosarcoma cells is partially through the Wnt/β-catenin pathway (33). Knocking out *TMEM45B* inhibits the JAK2/STAT3 signaling pathway and partially suppresses proliferation, migration, and invasion in gastric cancer cells (34). TMEM16A is markedly upregulated across various human lung cancer cell lines, exerts oncogenic effects by driving cell proliferation, migration, and invasion (35).

On the other hand, some TMEMs exhibit suppressive roles in the regulation of cell proliferation in human cancers. For example, the knockdown of *TMEM17* results in the upregulation of phosphorylated (p)-AKT, p-GSK3β, β-catenin, and Snail levels, leading to accelerated proliferation, invasion, and migration of breast cancer cells (36). Moreover, a significant reduction of TMEM100 expression was observed in colorectal cancer (CRC), and the restoration of TMEM100 expression inactivates the TGF-β signaling pathway, leading to a marked suppression of cancer cell growth (37). Nevertheless, TMEM100 affects the proliferation, migration, and invasion of prostate cancer cells by inhibiting PI3K/AKT signaling pathway (22). TMEM176A was initially identified through the screening of tumor-associated antigens in hepatocellular carcinoma (HCC) (38). Subsequently, the downregulation of TMEM176A was observed in CRC, liver cancer, and esophageal cancer, and its inactivation is modulated by DNA methylation (39-41). The restoration of TMEM176A remarkably inhibits the proliferation, migration, and invasion of cancer cells (42). TMEM7 is also downregulated in liver cancer, and its restoration enhances tumor proliferation (43).

Apoptosis

Apoptosis, a main kind of programmed cell death, restricts cell growth to preserve tissue homeostasis and eradicate potentially hazardous cells (44). Accumulating evidence demonstrates that TMEMs are of great importance for the regulation of apoptosis. Ye *et al.* reported that the overexpression of TMEM100 leads to the increase of Bcl2-associated X (Bax) and caspase-3, and the decrease of B-cell lymphoma-2 (Bcl-2), thus inducing apoptosis (22). TMEM106A is significantly downregulated in NSCLC, and its restoration upregulates the levels of Bax and cleaved caspase-3, leading to the activation of apoptosis (45).

In contrast, some TMEMs were reported to play a suppressive role in apoptosis. For instance, TMEM48 localizes to the nuclear pore complex (NPC) and is associated with the nuclear envelope assembly process (46). TMEM48 is overexpressed in NSCLC cells, and its depletion stimulates cellular apoptosis (30). MicroRNA-421 suppresses the translation process of *TMEM48* and induces a decrease in mitochondrial membrane potential, resulting in the activation of apoptosis (47). Zhao *et al.* found that knocking down *TMEM45B* increases the rate of apoptotic cells, which can be reversed by the re-expression of *TMEM45B* in pancreatic cancer (48). Moreover, the knockdown of *TMEM97* increases the levels of proapoptotic proteins, such as cleaved caspase 8/3/7 and cleaved poly ADP-ribose polymerase (PARP), indicating that TMEM97 regulates apoptosis via the regulation of the caspase cascade in CRC cells (49). The deletion of *TMEM140* leads to the upregulation of Bax and cleaved caspase 3 as well as the downregulation of Bcl-2, promoting the apoptotic process in glioma cells (50). Furthermore, *TMEM168* mRNA is upregulated in GBM patients compared with healthy individuals (28). The silence of *TMEM168* leads to G0/G1 cell cycle arrest and triggers apoptosis by the decrease of Survivin and increase of Bax (28).

Autophagy

Autophagy is a highly regulated degradation pathway that is evolutionarily conserved and crucial for maintaining cellular homeostasis through the digestion of damaged cytoplasmic proteins, macromolecules, and organelles (51). Emerging evidence showed that TMEMs have been implicated in the modulation of cancer development via the autophagy pathway. He *et al.* found that upregulated TMEM100 leads to alterations in the expression of certain proteins essential for autophagy by inhibiting the PI3K/AKT signaling pathway (52). For example, the conversion of light chain 3 (LC3) I (a cytosolic form of LC3) to LC3 II (LC3-phosphatidylethanolamine conjugate) is significantly enhanced, and the p62 level is markedly reduced (53). TMEM164 is pivotal role in driving autophagy-dependent ferroptosis by promoting autophagy during lipid peroxidation. Unlike the classical autophagy pathway, TMEM164 selectively participates in the autophagy-related 5 (ATG5)-dependent autophagy assembly process during ferroptosis (54). TMEM74 anchors to lysosome and has been proven to affect Earle's balanced salt solution (EBSS)-induced autophagy (5). TMEM74 interacts with autophagy-related protein 16 like 1 (ATG16L1) and autophagy-related protein 9A (ATG9A) to induce autophagy flux in HCC cells (55,56).

Drug resistance

Drug resistance is responsible for most relapses of cancer, and remains a challenge in cancer treatment (57). Many proteins interfere with the action of drugs, thereby affecting the chemotherapeutics uptake of cancer cells (58). Up to now, many TMEMs have been reported to contribute to the modulation of drug sensitivity against chemotherapeutics. For example, TMEM25 expression is aberrantly upregulated in paclitaxel-resistant breast cancer cell lines (59). Down-regulation of TMEM25 expression reduces the expression of P-glycoprotein, drug resistance-related gene 1 (MDR1), multidrug resistance-related protein (MRP), and breast cancer resistance protein (BCRP), and makes the resistant cells more susceptible to paclitaxel (59). The silence of *TMEM88* increases the drug sensitivity of ovarian cancer cells to platinum (60). Moreover, TMEM98 is elevated to resistant cisplatin and doxorubicin in HCC (61) The overexpression of TMEM47 leads to tamoxifen-resistance in MCF-7 cells, whereas the knockout of *TMEM47* in tamoxifen-resistant MCF-7 cells restores tamoxifen sensitivity (62). NSCLC patients with higher TMEM97 expression levels have worse drug response to platinum-based chemotherapy (63). Patients receiving platinum-based chemotherapy with increased TMEM97 expression have shorter survival (64). TMEM205 is elevated in cisplatin-resistant cells and induces cisplatin resistance by increasing rejection or "secretion" to reduce cisplatin accumulation (65).

On the contrary, some TMEMs can increase the

sensitivity of cancer cells to chemotherapy. For example, TMEM100 increases the sensitivity of gastric cancer cells to 5-fluorouracil (5-FU), cisplatin, and other commonly used chemotherapy drugs (66). TMEM45A plays a dual role in regulating the drug sensitivity of different types of human cancers. TMEM45A expression is upregulated in patients with head and neck cancer and renal cancer. The knockdown of *TMEM45A* induces the activation of the unfolded protein response (UPR) pathway, leading to cisplatin resistance in renal cell carcinoma cells (67). However, TMEM45A inactivation increases the sensitivity to cisplatin by deactivating the response to cisplatin-induced DNA damage in head and neck squamous cell carcinoma cells (67). Moreover, TMEM45A expression is also associated with paclitaxel resistance (68). The combined action of paclitaxel and TMEM45A overexpression induces protection against apoptosis and cell death in MDA-MB-231 cells under hypoxic conditions, whereas the response is attenuated upon the silencing of *TMEM45A* (68).

Metabolism

Tumorigenesis relies on the reprogramming of cell metabolism. Cancer cells obtain the necessary elements from nutrient-poor environments to maintain viability (69). Accumulating evidence showed that TMEMs are important in the regulation of cell metabolism in different kinds of human cancers. For example, TMEM14A participates in glucose metabolism to accelerate energy metabolism, such as glycolysis and oxygen respiration, thereby promoting the progression of ovarian cancer (70). The silence of *TMEM14A* reduces the extracellular acidification rate (ECAR) and oxygen consumption rate (OCR) of ovarian cancer cells, and this alteration is amplified after treatment with 2-deoxyglucose (2-DG), a kind of glycolysis inhibitor (70). Additionally, TMEM180 increases the levels of glutaminase and nitric oxide synthase in the nitric oxide (NO) production pathway, indicating that it plays an important role in the metabolism of glucose and glutamine of cancer cells (71).

Cancer cells require large amounts of lipids for membrane construction, the synthesis of lipid-derived molecules, and the generation of metabolic energy to support their proliferation in the absence of other nutrients (72). To date, TMEMs have been confirmed to be involved in the metabolic reprogramming of cancer cells, including glycolysis and lipid metabolism. TMEM33 is a downstream effector of pyruvate kinase M2 (PKM2) that regulates the activation of sterol regulatory element binding proteins (SREBPs) and lipid metabolism (73). Loss of *PKM2* results in elevated levels of TMEM33, which induces the upregulation of ring finger protein 5 (RNF5), thereby promoting cleavage activation of SREBPs and accelerating fatty acid synthesis and cholesterol synthesis (73). Moreover, the silence of *TMEM97* suppresses the cellular uptake of cholesterol, attenuates its interaction with calcium release-activated calcium channel protein 1 (Orai1), inhibits the activation of store-operated calcium entry (SOCE), and consequently impedes the proliferation of breast cancer cells (74).

Cell adhesion

The capacity of a cell adhering to the extracellular matrix (ECM) or other cells is known as cell adhesion (75). Cell adhesion is often attenuated in cancer cells, leading to the breakdown of normal cellular behavior and the destruction of histological structure (76). In ovarian cancer, the knockdown of *TMEM158* renders the downregulation of intercellular adhesion molecule 1 (ICAM1) and vascular cell adhesion molecule 1 (VCAM1), causing the inhibition of cell adhesion (77). The depletion of *TMEM45A* decreases the expression levels of TGF-β1, TGF-β2, RhoA, and ROCK2, inhibiting cell adhesion and invasion of ovarian cancer cells (32). Similarly, the silence of *TMEM140* leads to the downregulation of ICAM1, VCAM1, and Syndecan, suppressing adhesion and metastasis and affecting the progression of glioma (50).

Metastasis

Metastasis is an evolutionary process essential for cancer development, including infiltration of tumor cells into the circulation, survival of circulating cells, dissemination of circulating cells to distant organs, and subsequent colonization (78). Many studies have identified epithelial-mesenchymal transition (EMT) as an important mediator of tumor metastasis, enabling cancer cells to acquire migratory and invasive properties (79-81). Increased TMEM16A channel activity is essential for the migration and invasion of breast cancer cells. TMEM16A promotes the expression of Rho-associated, coiled-coil containing protein kinase 1 (ROCK1) by activating EGFR/STAT3 signaling pathway (82). Subsequently, ROCK1 phosphorylates Moesin at T558 and increases the activity of TMEM16A channel, thereby synergistically promoting the migration,

invasion and metastasis of breast cancer cells (82). Moreover, targeting *TMEM116* by CRISPR-Cas9 technology can reduce the migration and invasion of lung cancer cells by PDK1/AKT/FOXO3A/TAp63 axis *in vitro* and *in vivo* (83). TMEM158 is highly expressed in gastric adenocarcinoma, glioma and breast cancer, and its expression level is closely related to the EMT process (81,84,85). The knockdown of *TMEM158* in breast cancer cells alters their morphology, with cells becoming shorter and rounder and exhibiting epithelioid features. However, the overexpression of TMEM158 alters their morphology, elongates the cells, and participates in the EMT process, thereby promoting tumor migration, invasion, and metastasis (81). In addition, TMEM158 regulates the EMT of glioma cells by activating the STAT3 signaling (84). In gastric adenocarcinoma, TMEM158 directly interacts with Twist-related protein 1 (TWIST1) to activate the PI3K/AKT signaling pathway, accelerating the progression of cell proliferation, migration and invasion (85). TWIST1 has been proven to induce EMT in different malignant cell lines, and enhance cancer stem cell-related traits (86).

Certainly, there are some TMEMs that have the effect of suppressive metastasis in cancers. The expression of TMEM196, both mRNA and protein levels, are significantly decreased in lung cancer tissues and cells, which is associated with poor prognosis (87). The silencing of *TMEM196* leads to the activation of the Wnt/β-catenin signaling pathways and the upregulation of its downstream target genes matrix metallopeptidase 2 (MMP2) and matrix metallopeptidase 7 (MMP7), eventually promoting tumor metastasis and progression *in vitro* and *in vivo* (87). Moreover, TMEM229A affects the migration and invasion by regulating the EMT phenotype of lung cancer cells (88). The overexpression of TMEM229A increases E-cadherin levels, decreases the levels of N-cadherin, Snail1 and MMP2, and also downregulates the levels of p-ERK and p-AKT, which partially inhibits the ERK pathway (88). Similarly, TMEM17 is downregulated in NSCLC, and its restoration inhibits cell invasion and metastasis by inactivating the ERK-P90RSK-Snail axis (89). A comprehensive overview of the TMEMs mentioned above is summarized in *Figure 2*.

TMEMs in immunity

Under normal circumstances, the immune system can identify and eliminate abnormal cells through the "immune surveillance" mechanism, but tumor cells can evade immune surveillance through a variety of mechanisms, thereby hindering the recognition and killing of T cells and promoting their own survival and spread (90). As a well-established TMEMs, TMEM173 (as known as STING) modulates the innate immune response through the cyclic GMP-AMP synthase (cGAS)-STING signaling pathway (91). Abnormal DNA contained in tumor cells can activate the cGAS-STING pathway, which promotes the production of cytokines and chemokines to recruit and activate immune cells in the tumor microenvironment (91). Activation of the cGAS-STING pathway in NSCLC is closely associated with elevated levels of endogenous DNA damage, enhanced immune checkpoint targeting, and increased production of chemokines in response to immunotherapy (92). Moreover, cisplatin treatment has been shown to activate the cGAS-STING pathway in multiple preclinical models of NSCLC (92). In gastric cancer, trastuzumab deruxtecan (T-DXd) treatment can induce DNA damage and apoptosis, activate the cGAS-STING pathway, and induce IFN-I responses in human epidermal growth factor receptor 2 (HER2)-positive gastric cancer cells, showing a potent antitumor effect (93). Furthermore, T-DXd treatment can activate dendritic cells through the intrinsic cGAS-STING-IFN axis of cancer cells and enhance peripheral blood mononuclear cell (PBMC)-mediated tumor cell killing by stimulating cluster of differentiation (CD)8^+ T cells (93).

In addition to innate immunity, TMEMs can also influence the function of immune cells in the tumor microenvironment. Patient-based RNA-seq and clinical data analysis suggest that TMEM205 inhibits M2 macrophage polarization, suppresses Treg recruitment, and promotes $CD8^+$ T cell infiltration into tumor tissue, thereby improving patient prognosis in HCC (94). However, in a study related to cisplatin resistance of gastric cancer, TMEM205 played an opposite role (95). TMEM205 decreases the cisplatin sensitivity by promoting the proliferation and stemness of gastric cancer cells (95). The combination treatment of TMEM205 knockdown and cisplatin renders the decrease of CD206, and the increase of CD86 and inducible nitric oxide synthase (iNOS), suggesting that TMEM205 modulates the cisplatin sensitivity of gastric cancer cells via the induction of tumor associated macrophages (TAMs)/M2 polarization (95). TMEM176B is an intracellular non-specific cation channel belonging to the membrane-spanning 4A (MS4A) family (96). In mouse models, the depletion of *TMEM176B* is associated with higher survival and reduced tumor progression in lymphoma, colon and

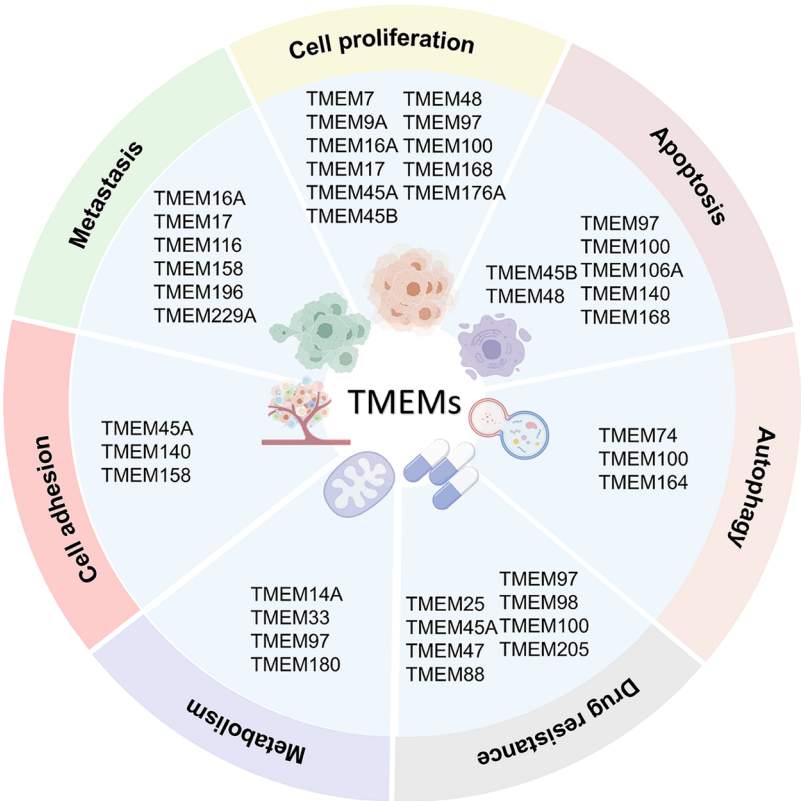

Figure 2 Roles of transmembrane proteins in cancer. Transmembrane proteins are involved in the processes of cell proliferation, apoptosis, autophagy, drug resistance, metabolism, cell adhesion and metastasis in cancer. Created with BioGDP.com; TMEMs, transmembrane proteins.

lung cancer (97). Inhibition of TMEM176B expression enhances $CD8^+$ T cell-dependent anti-tumor immunity by promoting the release of cytosolic Ca^{2+}, activating NOD-like receptor protein 3 (NLRP3) inflammasome and inducing IL-1β secretion (97,98). TMEM160 hinders ubiquitination-dependent programmed cell death 1 ligand 1 (PD-L1) degradation by competing with speckle-type POZ protein (SPOP) for PD-L1 binding in CRC cells. The up-regulation of TMEM160 stabilizes the expression of PD-L1, weakens the cytotoxic effect of $CD8^+$ T cells on tumor cells, and promotes tumor immune escape (99). Bioinformatics analysis of several studies showed that TMEMs were closely related to immune infiltration. $CD8^+$ T cells were significantly reduced in TMEM200A high expression group in gastric cancer (100). The infiltration of $CD4^+$ T cell subsets and the expression of T cell exhaustion immunosuppressive molecules were decreased in breast cancer tissues with high expression of TMEM178 (101). TMEM204 expression was positively correlated with prognosis and was associated with infiltration of $CD8^+$ and $CD4^+$ T cells, macrophages, neutrophils, and myeloid dendritic cells in HCC (102). The regulation of representative TMEMs for tumor immunity is described in *Figure 3*.

The roles of TMEMs in different types of human cancers

Lung cancer

Lung cancer, with five-year survival rates of less than 20%, ranks first in cancer incidence and mortality worldwide (103). Exploring new biomarkers and therapeutic targets is urgently needed to improve the survival rate of patients. Several key TMEMs have been proven as activators in the progression of lung cancer. In NSCLC, the receptor tyrosine kinase Anexelekto (AXL) acts as a potent activator of tumor progression and therapy resistance (104). AXL-silenced NSCLC cells are accompanied by the upregulation of TMEM14A, which is linked to a worse

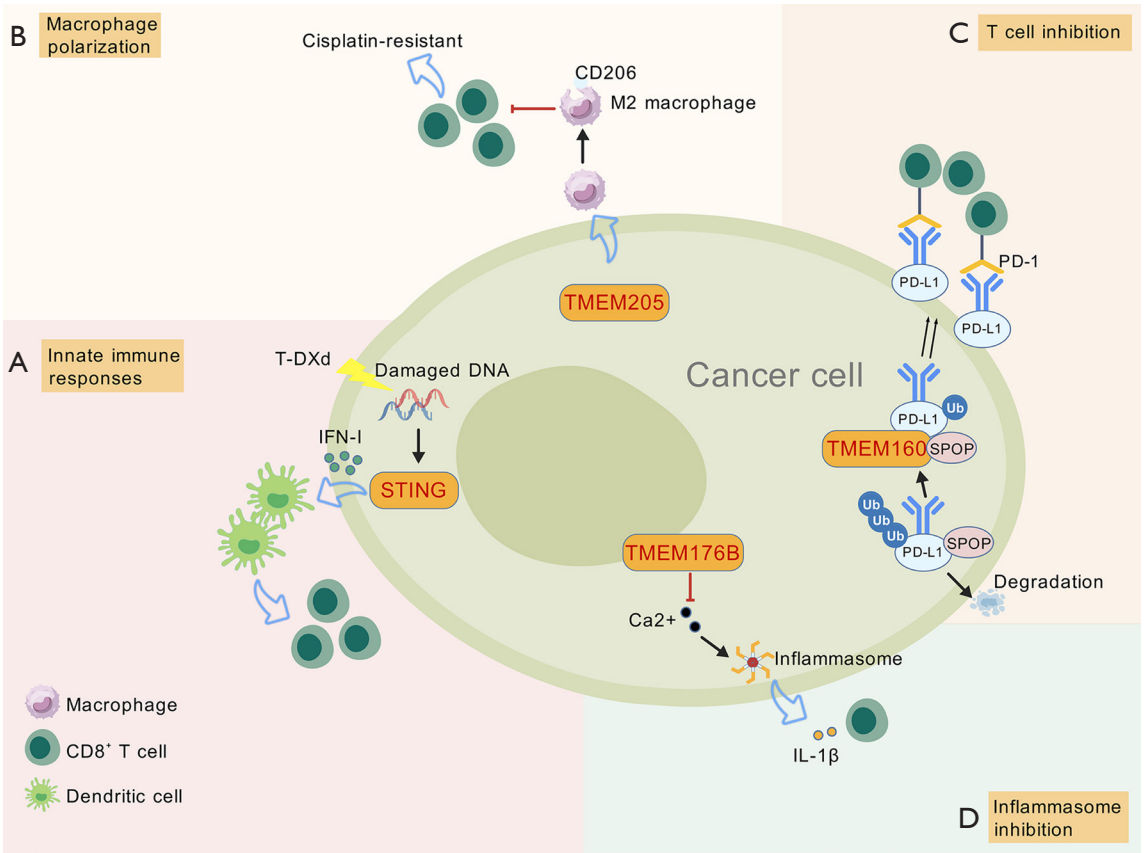

Figure 3 Transmembrane proteins are involved in tumor immunity. (A) T-DXd activates dendritic cells via the innate cGAS-STING-IFN axis of tumor cells and causes tumor cell killing by activating $CD8^+$ T cells. (B) TMEM205 induces TAMs/M2 polarization to promote cisplatin resistance. (C) TMEM160 competitively binds to PD-L1 with SPOP, stabilizes and increases the expression of PD-L1, inhibits $CD8^+$T cells, and promotes tumor immune escape. (D) TMEM176B inhibits CD8 T cell-dependent anti-tumor immunity by limiting cytosolic Ca^{2+} release, inhibiting inflammasome activity, IL-1β secretion. Created with BioGDP.com. T-DXd, trastuzumab deruxtecan; cGAS-STING, cyclic GMP–AMP synthase-stimulator of interferon genes; IFN-I, type I interferon; TAMs, tumor associated macrophages; PD-1, programmed cell death 1; PD-L1, programmed cell death 1 ligand 1; SPOP, speckle-type POZ protein; Ub, ubiquitination; TMEM, transmembrane protein.

overall survival rate of patients. *TMEM14A* knockdown reduces cell proliferation, underscoring its critical role in the progression of NSCLC (3). Moreover, TMEM116 is abundantly expressed in NSCLC tissues and cells, its depletion decreases the proliferation, migration, and invasion of cancer cells (83). *TMEM116* deficiency inhibits the PDK1-AKT-FOXO3A signaling pathway and leads to the accumulation of transactivation domain of tumor protein p63 (TAp63), and this phenomenon can be reversed by the activation of 3-phosphoinositide-dependent protein kinase 1 (PDK1) (83). A lung cancer cohort analysis, including 488 tumor tissue samples and 58 normal tissue samples, showed that the downregulation of TMEM45B decreases the levels of cell cycle-related proteins (cyclin-dependent kinase 2, cell division cycle 25 homolog A, and proliferating cell nuclear antigen) and transfer-related proteins (Matrix metallopeptidase 9, Twist, and Snail), and increases the levels of apoptosis-related proteins (Bax and cleaved caspase 3), eventually induces G1 phase arrest and apoptosis (105).

On the contrary, some TMEMs have been reported as suppressors in the development of lung cancer. TMEM196, which consists of four transmembrane domains, has been identified as a tumor suppressor gene for lung cancer (87). Silencing *TMEM196* inhibits the Wnt/β-catenin pathway, thereby reducing its anti-metastatic effect in

lung cancer cells (87). The abundance of TMEM106A is significantly decreased in human NSCLC tissues and cells, its overexpression impedes the EMT process through the PI3K/Akt/NF-κB signaling pathway (45). Low level of TMEM229A is linked to poor prognosis (88). The overexpression of TMEM229A restrains cell proliferation, migration, and invasion by inactivating the ERK signaling pathway, an effect can partially be rescued by the addition of the ERK inhibitor PD98059 (88). TMEM100 enhances the activity of caspase-3, upregulates Bcl-2 interacting mediator of cell death (Bim) levels, and facilitates the release of cytochrome C into cytoplasm to induce apoptosis of NSCLC cells (106).

Breast cancer

Breast cancer is the most prevalent malignancy in global women, ranking second in incidence and fourth in mortality worldwide (103). Some TMEMs are overexpressed and contribute to the progression of breast cancer. For example, TMEM9A is upregulated to strengthen the transcriptional levels of *cyclin D1* and *AXIN2* via the Wnt/β-catenin signaling pathway, thereby promoting tumor progression of breast cancer (27). Similarly, TMEM97 is significantly increased in breast cancer. Knockdown of *TMEM97* reduces the levels of β-catenin, Survivin, and cyclin D1 by restraining the Wnt/β-catenin and PI3K/AKT pathways (107). Moreover, TMEM16A promotes the invasion and migration of breast cancer cells through a mutual activation loop. Epidermal growth factor (EGF) can enhance the expression of TMEM16A by activating the EGFR/STAT3 signaling pathway. In turn, the overexpression of TMEM16A further activates EGFR/STAT3 signaling (108). In addition, *TMEM158* mRNA is maintained in relatively higher levels in tissues of triple-negative breast cancer (TNBC), compared to other subtypes of breast cancer (81). Silencing *TMEM158* decreases the levels of N-cadherin and Vimentin, and increases the levels of E-cadherin, ultimately facilitating the invasion and migration of breast cancer cells (81). TMEM47 was reported to induce tamoxifen resistance of MCF-7 cells by inhibiting apoptosis (62). Furthermore, TMEM97 enhances the transcriptional activity of estrogen receptor α (ERα), upregulates the expression of estrogen-responsive genes, and stimulates the mTOR/S6K1 signaling pathway to increase tamoxifen resistance of two ERα-positive breast cancer cell lines, MCF7 and T47D (26).

On the other hand, some TMEMs, like TMEM25 and TMEM178, were proven to inhibit the progression of breast cancer. TMEM25 was confirmed as an EGFR-binding protein, the EGFR monomer can phosphorylate STAT3 without the binding of TMEM25, increasing basal STAT3 activity and accelerating the development of TNBC (109). Moreover, TMEM178 is downregulated in breast cancer tissues, and its expression level is positively associated with the prognosis of breast cancer patients. Thus, TMEM178 can be used as a potential prognostic marker for breast cancer patients (101).

Gastric cancer

Gastric cancer ranks among the most prevalent cancers worldwide (103). Since the low likelihood of early detection, the majority of gastric cancer patients are detected at an advanced stage and get a dismal prognosis (110). Therefore, exploring new biomarkers or specific therapeutic targets is crucial to improve the treatment outcomes of gastric cancer patients. Studies showed many TMEMs, including TMEM16A (111,112), TMEM119 (113,114), and TMEM41A (115) are maintained in higher expression levels in gastric cancer tissues than those in paracancerous tissues, suggesting that they play oncogenic roles in the development and progression of gastric cancer. The expression of TMEM16A is negatively correlated with patient survival (111). The silence of *TMEM16A* decreases the calcium-activated chloride ion current, inhibits TGF-β secretion, and downregulates E-cadherin expression, thereby inhibiting the migration and invasion of gastric cancer cells (111). The expression of microRNA-381 (miR-381) is negatively correlated with the expression of TMEM16A in gastric cancer tissues, and miR-381 regulates the TGF-β pathway and the EMT process by directly targeting TMEM16A (112). Both of these two independent studies revealed that TMEM16A plays an oncogenic role in gastric cancer. Moreover, the downregulation of TMEM41A increases E-cadherin, and decreases N-cadherin, promoting the migration of gastric cancer cells (115). The inhibition of TMEM45B and TMEM132A partly reduces the invasion, migration, and proliferation of gastric cancer cells by inactivating the Wnt/β-catenin pathway and JAK2/STAT3 signaling pathway, respectively (34,116). Furthermore, TMEM119 stimulates the phosphorylation of STAT3 to promote invasion and migration of gastric cancer cells (114). The depletion of *TMEM119* induces apoptosis of gastric cancer cells by upregulating apoptotic proteins, including Bax and caspase-3 (113). TMEM200A level is positively correlated with the overall survival of gastric cancer patients

and serves as a valuable diagnostic marker for gastric cancer (100). TMEM205 stimulates the Wnt/β-catenin signaling pathway in cisplatin-resistant gastric cancer cells to promote angiogenesis, motility, stemness, and epithelial-mesenchymal transition (95). Moreover, TMEM205 accelerates the development of gastric cancer by inducing TAMs polarized to M2, suggesting that TMEM205 is a potential biomarker to predict drug sensitivity to cisplatin (95).

In contrast, the upregulation of TMEM100 suppresses cell migration and invasion but has no effects on the cell growth of gastric cancer (66). The susceptibility of gastric cancer cells to chemotherapeutics, like 5-FU and cisplatin, can be restored by the overexpression of TMEM100 (66).

Other cancers

Besides the three typical types of human cancers mentioned above, some TMEMs were reported to be abnormally expressed in kinds of human cancers. For example, *TMEM7*, an interferon-alpha response gene, is universally downregulated in HCC (43). Moreover, *TMEM237*, a new hypoxia response gene, is highly expressed in HCC, and associates with nephrocystin 1 to mediate the activation of the Pyk2/ERK1/2 axis, contributing to the development of hypoxia (117). TMEM100 acts as an anti-tumor factor in CRC (118). The overexpression of TMEM100 promotes the degradation of hypoxia-inducible factor-1 (HIF-1α) via the ubiquitination/protease pathway, thereby suppressing the proliferation and migration of CRC cells (118). Similarly, the overexpression of TMEM100 restrains the PI3K/AKT signaling pathway, hence impeding the growth of prostate cancer (22). TMEM64 activates the Wnt/β-catenin signaling pathway by accelerating the translocation of β-catenin from the cytoplasm to the nucleus, thus enhancing the malignant appearance of gliomas (119). In ovarian cancer, TMEM119 partially plays a carcinogenic role by upregulating platelet-derived growth factor receptor beta (PDGFRB) and activating the PI3K/AKT signaling pathway (120). Gene expression alteration is widely recognized as a key driver of carcinogenesis (121). Abnormal expression of TMEMs has been observed in various kinds of human cancers. The mechanisms mediated by TMEMs have also been gradually elucidated (*Table 1*). A comprehensive investigation of TMEMs holds great promise for identifying novel targets and devising innovative strategies for cancers therapy.

Application of TMEMs in cancer therapy

Many cancer patients were diagnosed at an advanced stage with an unfavorable outcome. Conventional treatment approaches, such as chemotherapy and radiation, result in unpleasant responses and side effects (13). Recent developments in molecular biology and genetics have revealed that malignant tumors possess complex biological defects, such as oncogene mutation and chromatin modification (13). Consequently, molecular targeted therapy is a promising treatment strategy. Many TMEMs mentioned previously are linked to early metastasis, prognosis, and the emergence of resistance to chemotherapy or radiotherapy, representing potential new targets for cancer therapy (2,130,131).

Currently, TMEMs, such as CD20, claudin 18.2, G protein-coupled receptors (GPCRs), are important targets in the development of tumor-specific drugs (132,133). With the function of TMEMs revealed, it is also gradually developed as new therapeutic targets for cancers. It was shown that individuals, who have highly metastatic prostate cancer with a bad prognosis, may benefit from therapy directed at the type I transmembrane glycoprotein podocalyxin-like (PODXL) (134). IFN-I signaling plays an important role in T cell infiltrating into tumors. In response to bacterial or viral infections, the cGAS-STING pathway can activate type I IFN and other inflammatory cytokines (135,136). In recent years, with the increasingly prominent role of cGAS-STING pathway in cancer immunotherapy, the use of STING agonists for immunotherapy is a very promising strategy (137). A variety of STING agonists have been reported, such as natural cyclic dinucleotide (CDN) agonists, synthetic CDN agonists, non-nucleotide and small molecule STING agonists (91,138). MK-1454, a novel modified CDN, can completely inhibit tumor growth and improve the efficacy of programmed death 1 (PD-1) antibody treatment in mouse models of colon adenocarcinoma and melanoma by intratumoral administration (139). In addition, to overcome the potential off-target inflammation or autoimmunity caused by the hydrophilicity and negative charge of STING agonists, a variety of biomaterials delivery systems offer many possibilities, such as nano-liposomes, polymers and inorganics (140-142).

TMEM63A, which contains ten transmembrane domains, is localized in the endoplasmic reticulum (ER) and lysosomal membrane (126). TMEM63A is degraded mainly through the toll-interacting protein (TOLLIP)-mediated

Table 1 Overview of the main features of TMEMs in cancer

TMEMs	Domains	Localization	Tumor types	Processes involved in cancer	Related signaling pathways	Ref
TMEM7	1	Unknown	Hepatocellular carcinoma	Proliferation, migration	–	(43)
TMEM9A	1	Late endosomes and lysosomes	Breast cancer	Proliferation, migration, apoptosis	Wnt/β-catenin	(27,122)
TMEM14A	3	Mitochondria	Ovarian cancer	Proliferation, apoptosis, energy metabolism	–	(3,70,123)
			Non-small-cell lung cancer	Proliferation	–	
TMEM16A (ANO1)	10	Plasma membrane	Lung cancer	Proliferation, migration, invasion	–	(7,35,82, 108,112)
			Breast cancer	Proliferation, migration, invasion, metastasis	EGFR/STAT3	
			Gastric cancer	Migration, invasion, EMT	TGF-β	
TMEM17	4	Plasma membrane	Breast cancer	Proliferation, invasion, migration	AKT/GSK3β	(36,89)
TMEM25	1	Plasma membrane	Breast cancer	Proliferation	EGFR/STAT3	(59,109)
TMEM33	3	ER	Breast cancer	Lipid homeostasis	–	(73,124)
TMEM41A	Unknown	Unknown	Gastric cancer	Migration, adhesion, EMT, autophagy	–	(115)
TMEM45A	7	ER, Golgi	Ovarian cancer	Proliferation, adhesion, invasion, cell cycle	–	(32,67,68)
			Renal cell carcinoma	Proliferation	–	
			Neck squamous cell carcinoma	Proliferation, drug resistance	–	
			Breast cancer	Apoptosis, drug resistance	–	
			Liver cancer	Apoptosis, drug resistance	–	
TMEM45B	7	ER	Gastric cancer	Proliferation, migration, invasion, EMT	JAK2/STAT3	(33,34,48,105)
			Pancreatic cancer	Proliferation, migration, invasion, apoptosis, cell cycle	–	
			Lung cancer	Proliferation, cell cycle, apoptosis, EMT	–	
			Osteosarcoma	Proliferation, migration, invasion	Wnt/β-catenin	
TMEM47 (TM4SF10)	4	ER	Breast cancer	Apoptosis, drug resistance	–	(62,125)
TMEM48 (NDC1)	6	Nuclear membrane	Cervical cancer	Proliferation, migration, invasion	Wnt/β-catenin	(21,30)
			Non-small cell lung carcinoma	Proliferation, cell cycle, adhesion, EMT, apoptosis	–	

Table 1 (*continued*)

Table 1 (*continued*)

TMEMs	Domains	Localization	Tumor types	Processes involved in cancer	Related signaling pathways	Ref
TMEM63A	10	ER and lysosome membranes	Triple-negative breast cancer	Proliferation, migration, invasion	–	(126)
TMEM64	7	ER	Glioma	Proliferation, apoptosis	Wnt/β-catenin	(119)
TMEM74	2	Lysosome and autophagosome	Liver cancer	Autophagy	–	(5,55)
			Lung cancer	Autophagy	–	
TMEM88	2	Plasma membrane	Ovarian cancer	Proliferation, cell cycle, drug resistance	Wnt	(60)
TMEM97 (Mac30)	4	ER, lysosomes and plasma membranes, lipid rafts	Glioma	Proliferation, EMT, cell cycle	–	(26,29,31,49,63, 64,74,107)
			Colorectal cancer	Proliferation, apoptosis, EMT	GSK-3β/β-catenin	
			Breast cancer	Proliferation, cell cycle, EMT, drug resistance	Wnt/β-catenin, PI3K/AKT, mTOR/ S6K1	
			Non-small cell lung cancer	Drug resistance	–	
TMEM98	1	ER, cytosol, nuclear membrane	Hepatocellular carcinoma	Proliferation, migration, drug resistance	–	(61)
TMEM100	2	Uncertain; plasma membrane, ER	Colorectal cancer	Proliferation, migration, invasion, EMT	TGF-β	(15,22,37,52, 66,106)
			Non-small cell lung cancer	Proliferation, apoptosis, autophagy	PI3K/AKT	
			Prostate cancer	Proliferation, migration, invasion, EMT, cell cycle, apoptosis	FAK/PI3K/AKT	
			Gastric cancer	Drug resistance, migration, invasion, EMT	–	
TMEM106A	1	Plasma membrane, mitochondria	Lung cancer	Proliferation, EMT, apoptosis	PI3K/AKT/NF-κB	(45,127)
			Gastric cancer	Proliferation, apoptosis	–	
TMEM116	6	ER	Lung cancer	Proliferation, EMT	PDK1-AKT-FOXO3A	(83)
TMEM119	1	Plasma membrane	Gastric cancer	Cell viability, apoptosis, migration, invasion	STAT3	(113,114,120)
			Ovarian cancer	Proliferation, EMT, invasion, migration	PDGFRβ/PI3K/ AKT	
TMEM132A	1	Plasma membrane, ER	Gastric cancer	Proliferation, migration, invasion	Wnt	(116,128)
TMEM140	4	Cytoplasm, nuclear membrane	Glioma	Proliferation, migration, invasion, cell cycle, apoptosis	–	(50,129)

Table 1 (*continued*)

Table 1 (*continued*)

TMEMs	Domains	Localization	Tumor types	Processes involved in cancer	Related signaling pathways	Ref
TMEM158	2	Plasma membrane	Ovarian cancer	Proliferation, invasion, adhesion, cell cycle	TGF-β	(77,81)
			Triple-negative breast cancer	Proliferation, EMT	TGF-β	
TMEM160	3	Mitochondrial membrane	Colorectal cancer	Proliferation, migration, invasion, metastasis immune	–	(99)
TMEM164	Unknown	Unknown	Pancreatic cancer	Autophagy	–	(54)
TMEM168	11	Membrane	Glioblastoma	Proliferation, cell cycle, apoptosis	Wnt/β-catenin	(28)
TMEM173	4	ER	Non-small cell lung cancer, gastric cancer	Immune	cGAS-STING	(92)
TMEM176A	4	Plasma membrane, mitochondria	Lung cancer	Proliferation, migration, invasion, apoptosis	–	(39-42)
			Colorectal cancer	Proliferation, apoptosis, migration, invasion	–	
			Esophageal squamous cell cancer	Cell growth, invasion, migration, apoptosis	–	
			Hepatocellular carcinoma	Proliferation, apoptosis, migration, invasion	ERK	
TMEM176B	4	Plasma membrane; Nuclear membrane	Colon cancer	Immune	–	(96-98)
			Lung cancer			
TMEM178	4	ER	Breast cancer	Drug resistance	–	(101)
TMEM180	12	Plasma membrane	Colorectal cancer	Proliferation, metabolism	–	(71)
TMEM196	4	Unknown	Lung cancer	EMT	Wnt/β-catenin	(87)
TMEM205	4	Plasma membrane or perinuclear	Liver cancer	Proliferation, stem-cell, EMT, migration	–	(65)
			Gastric cancer	Drug resistance	–	
TMEM229A	7	Unknown	Non-small cell lung cancer	Proliferation, migration, invasion, EMT	ERK	(88)
TMEM237	Unknown	Unknown	Hepatocellular carcinoma	Proliferation, migration, invasion, EMT	NPHP1/Pyk2/ERK	(117)

TMEMs, transmembrane proteins; EGFR, epidermal growth factor receptor; STAT3, signal transducer and activator of transcription 3; EMT, epithelial-mesenchymal transition; TGF-β, transforming growth factor beta; AKT, protein kinase B; ER, endoplasmic reticulum; JAK2, Janus kinase 2; NDC1, nuclear division cycle 1; Mac30, meningioma-associated protein 30; GSK-3β, glycogen synthase kinase-3β; PI3K, phosphatidylinositol 3-kinase; mTOR, mammalian target of rapamycin; S6K1, ribosomal protein S6 kinase beta-1; FAK, focal adhesion kinase; NF-κB, nuclear factor kappa-B; PDGFRβ, platelet-derived growth factor receptor beta; cGAS-STING, cyclic GMP–AMP synthase–stimulator of interferon genes; ERK, extracellular regulated protein kinases; NPHP1, nephrocystin 1; Pyk2, proline-rich tyrosine kinase.

autophagy-lysosome pathway, and valosin-containing protein (VCP) can block its degradation to stabilize oncoprotein derlin 1 (DERL1). Notably, after the treatment with the VCP inhibitor CB-5083, the interaction between TMEM63A and TOLLIP can be improved. The VCP inhibitors CB-5083 and CB-5339 have been developed to treat hematologic and solid tumors (143). Pharmacological inhibition of VCP eliminates the carcinogenic effects of TMEM63A on TNBC progression *in vitro* and *in vivo*, providing new clues for targeting TMEM63A-driven TNBC (126).

The first TMEM which was studied in detail is TMEM16A (7,144). A study has shown that ion channel is one of the most important drug targets and plays an essential role in cancer (145). Miner *et al.* highlighted the antiparasitic agents, niclosamide and nitazoxanide, as effective antagonists for TMEM16A to prevent the proliferation of colon cancer cells (146). It has also been demonstrated that small molecules, such as CaCCinh-A01, T16Ainh-A01, MONNA, and Ani9 have anticancer effects through the inhibition of TMEM16A (147,148). Understanding the structure of TMEM16A makes it possible to design or optimize antagonist compounds and develop therapy strategies for targeting TMEM16A (149,150). In addition, the strategy of quantitative structure-activity relationship (QSAR) prediction of target-compound interactions enables virtual screening of potent TMEM16A modulators (151). Shi *et al.* performed a virtual screen to target the putative inhibitor binding pocket and identified theaflavin, a highly potent TMEM16A inhibitor (152). Theaflavin inhibits cell proliferation and migration by targeting TMEM16A, and shows good therapeutic effects on lung adenocarcinoma (152).

However, the functions and mechanisms of many TMEMs have not yet been clarified; the full length, three-dimensional structure, and epitopes were not well investigated; and the studies related to the active sites and affinity are inadequate. Moreover, the hydrophobic and lipophilic features of the transmembrane regions of TMEMs make their extraction challenging. This challenge is exacerbated by an increased number of transmembrane regions, leading to lower expression levels in host cells and greater preparation difficulties. Based on the emerging investigations on the functions of TMEMs and various innovative delivery platforms, molecular targeted activators or inhibitors targeting specific TMEMs will be developed and applied in preclinical or clinical researches.

Conclusions

To date, the physiological functions and cancer correlations of TMEMs have been gradually characterized. Through the elucidation of their effects on cell proliferation, migration, invasion, adhesion, apoptosis, autophagy, metabolism, and drug resistance, a variety of TMEMs are linked to the emergence and progression of cancers as we described in this review. In addition, we also illustrated the potential of TMEMs in immunity and proposed the targeted therapeutic strategies for TMEMs based on existing studies. Indeed, there are still many TMEMs of which its functions and mechanisms have not yet been well studied. Exploring the specific functions and mechanisms of TMEMs will benefit the development of individualized therapeutic regimens for cancer patients, and provide new options for clinical treatment in the future.

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Footnote

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