Research progress on TMEM proteins in cancer progression and chemoresistance (Review)

JI SHI[1-4*], DUO ZHENG[5*], BING YAO[1-3], QIANG LIU[1-3], HUIZHE XU[6] and HAOZHE PIAO[1-3]

[1]Department of Neurosurgery, Liaoning Cancer Hospital and Institute, Shenyang, Liaoning 110042, P.R. China;
[2]Department of Neurosurgery, Cancer Hospital of Dalian University of Technology, Shenyang, Liaoning 110042, P.R. China;
[3]Department of Neurosurgery, Cancer Hospital of China Medical University, Shenyang, Liaoning 110042, P.R. China;
[4]Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing 100050, P.R. China;
[5]Department of Neurology, Shengjing Hospital of China Medical University, Shenyang, Liaoning 110042, P.R. China;
[6]Central Laboratory Department, Liaoning Cancer Hospital and Institute/Cancer Hospital of Dalian University of Technology/Cancer Hospital of China Medical University, Shenyang, Liaoning 110042, P.R. China

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Abstract. In cancer research, the transmembrane (TMEM) family of proteins has attracted considerable attention due to its role in tumor progression and chemoresistance. These membrane proteins are integral to cellular processes, including signal transduction, ion transport and cellular homeostasis, rendering them promising therapeutic targets. The TMEM proteins are implicated in several types of cancer, including breast, ovarian, lung and thyroid cancer, where they regulate numerous cellular processes, including proliferation, migration, invasion and survival. Notably, TMEM45A and TMEM158 contribute to resistance to platinum-based chemotherapy by increasing the expression of proteins associated with hypoxic conditions and multidrug resistance. Additionally, epigenetic regulation, particularly promoter methylation of TMEM88, is pivotal in regulating TMEM88 expression and function in chemoresistance. The present review presents a systematic and comprehensive overview of the structural features, biological functions and regulatory mechanisms of key TMEM proteins across various types of cancer. It also highlights emerging connections between TMEM proteins and the tumor microenvironment, emphasizing their potential as promising therapeutic targets. The novel findings underscore the key role of the TMEM protein family in overcoming chemoresistance and lay a foundation for the development of targeted therapeutic strategies in cancer treatment.

Correspondence to: Professor Haozhe Piao, Department of Neurosurgery, Liaoning Cancer Hospital and Institute, 44 Xiaoshizhi Street, Shenyang, Liaoning 110042, P.R. China
E-mail: piaohaozhe@cancerhosp-ln-cmu.com

Professor Huizhe Xu, Central Laboratory Department, Liaoning Cancer Hospital and Institute/Cancer Hospital of Dalian University of Technology/Cancer Hospital of China Medical University, 44 Xiaoshizhi Street, Shenyang, Liaoning 110042, P.R. China
E-mail: xuhuizhe@cancerhosp-ln-cmu.com

*Contributed equally

Abbreviations: CC, cervical cancer; CRC, colorectal cancer; ESCC, esophageal squamous cell carcinoma; GBM, glioblastoma; GC, gastric cancer; HCC, hepatocellular carcinoma; MDR, multidrug resistance; MPs, membrane proteins; NSCLC, non-small cell lung cancer; OC, ovarian cancer; OS, overall survival; PC, pancreatic cancer; RCC, renal cell carcinoma; TC, thyroid cancer; TME, tumor microenvironment; TMEM, transmembrane; TNBC, triple-negative breast cancer; TPs, transmembrane proteins; HNSCC, head and neck squamous cell carcinoma

Key words: TMEM proteins, tumorigenesis, chemoresistance, therapeutic targets, biomarker

Contents

1. Introduction

Membrane proteins (MPs) are proteins integrated into biological membranes, where they interact with lipid domains to execute a range of essential functions within living organisms (1). These proteins are key for maintaining the structural integrity and functional operation of cells, engaging in numerous processes such as ion transport, signal transduction and regulation of cellular homeostasis (2). MPs are central to the regulation of ion gradients across membranes, modulation

of cellular communication and responsiveness to extracellular signals (3). In addition to their physiological roles, MPs also carry out a pivotal role in the development of multidrug resistance (MDR), rendering them central to mechanisms of therapeutic resistance (2). Research has expanded the understanding of MPs, revealing that their functions extend beyond basic cellular roles to include key involvement in complex physiological processes and disease states, particularly in different types of cancer such as colorectal, ovarian, lung breast (1-5).

In the majority of mammalian cells, MPs assist in maintaining membrane structure, facilitate the transport of ions, nutrients and waste products or facilitate intercellular communication (3). They are integral to the formation of cellular microenvironments that enable efficient communication between cells, regulating processes such as immune responses, tissue remodeling and apoptosis (6). MPs are also involved in the establishment of the blood-brain barrier, the regulation of neurotransmitter transport and cellular metabolic processes (7). This array of functions underscores their key roles in maintaining cellular homeostasis and regulating the essential biological processes necessary for life.

Emerging research has emphasized the key role of MPs in the pathogenesis of cancer, including breast cancer, colorectal cancer, lung cancer, ovarian cancer and brain tumors (1,3-7). For example, subfamilies of tyrosine kinase receptors, including epidermal growth factor receptors (EGFRs) and fibroblast growth factor receptors (FGFRs), are key in signaling pathways that regulate cell proliferation, survival and migration, all important processes that drive tumorigenesis (8,9). These receptors become activated upon binding of ligands to their respective receptors, inducing conformational changes that initiate signal transduction to the cytoplasm via processes such as dimerization (10). Upon activation, receptors trigger downstream signaling cascades that regulate gene expression, cell cycle progression and metabolic reprogramming (11). In cancer cells, dysregulation of receptor signaling contributes to tumor growth, metastasis and resistance to chemotherapy, highlighting MPs as potential therapeutic targets for the management of cancer, including breast cancer and pancreatic cancer (12,13). MPs carry out a key role not only in maintaining normal cellular activities but also in cancer development and chemotherapy resistance (3-5). The tyrosine kinase receptor family, including EGFR and FGFR, has garnered increasing attention for its role in regulating cancer cell proliferation, survival and migration, particularly in the context of chemotherapy resistance (3-5,8,9). Cancer cells often exploit dysregulated membrane protein signaling pathways to drive tumor growth and metastasis, with resistance mechanisms frequently associated with alterations in membrane protein function (13-15). For example, discoidin domain receptor 2 interactions with collagen type I promote breast cancer cell proliferation and enhance resistance to chemotherapy, highlighting its potential role in chemoresistance in breast cancer (13-15). Moreover, transmembrane proteins (TPs) such as transmembrane (TMEM) 45A, TMEM158, TMEM88, TMEM205 and TMEM16A have been identified as key mediators of chemoresistance in several types of cancer (4,5,13,14). These proteins regulate cell proliferation, inhibit apoptosis or modulate the tumor microenvironment (TME) to increase resistance of cancer cells to chemotherapeutic agents (1,4-6,13,14). Therefore, MPs not only serve as key targets in cancer therapy but can also help in understanding and addressing chemotherapy resistance mechanisms.

The complexity of the nexus of signal transduction mediated by MPs presents substantial challenges in elucidating their precise roles in cellular processes and disease mechanisms (16). One of the primary challenges in research on MPs lies in establishing the structure-function relationship that governs ligand activation and enzyme activity specificity (17). Structural studies of MPs have been hindered by their amphipathic nature, which complicates their isolation and analysis *in vitro* (1,3-5,18). However, recent advances in cryo-electron microscopy (cryo-EM) and other high-resolution imaging techniques have enabled the structural elucidation of key MPs, offering insights into their functional mechanisms at the atomic level (19). These technological advances have markedly improved the ability to study MPs in their natural environments, thus facilitating the development of targeted drugs with high specificity and efficacy (19,20).

MPs are not only essential for cellular function but also act as key therapeutic targets, making them central to drug discovery efforts (21). They are involved in a range of physiological processes, many of which can be modulated by therapeutic agents targeting MPs to achieve clinical effects. Drug discovery efforts have concentrated on identifying small molecules, large molecules, peptides, polysaccharides and antibodies, particularly those that can specifically interact with MPs to regulate their activity (22). For example, monoclonal antibodies targeting EGFR and human epidermal growth factor receptor 2 (HER2) have been developed successfully and are now used in the treatment of several types of cancer, including glioma and breast cancer (22,23). Large molecule drugs, including polysaccharides and peptides, are seen as promising alternatives to traditional small molecule drugs, offering various therapeutic benefits such as reduced toxicity and enhanced efficacy when used in combination with conventional chemotherapy. For example, polysaccharides derived from medicinal plants such as *Anemarrhena asphodeloides* and *Houttuynia cordata* have demonstrated notable bioactivities, including immune modulation and anti-inflammatory effects, which can enhance the effectiveness of cancer treatments, including lung cancer and liver cancer (24,25). Furthermore, recent studies have highlighted the ability of peptides to target specific cancer cell pathways, enhancing treatment outcomes in several types of cancer, including pancreatic cancer (PC) (14,26). These findings underscore the potential of utilizing large-molecule drugs in cancer therapies, particularly in addressing the challenge of chemoresistance. Furthermore, several PMPs, including ion channels, transporters and G protein-coupled receptors (GPCRs), are well-established therapeutic targets for diseases ranging from cardiovascular disorders to neurological conditions (27-29). Given the key role of MPs in the pathophysiology of numerous diseases, understanding their structural and functional properties is essential for the development of novel drugs and therapies.

Biological processes, particularly those involving MPs, constitute a complex, interconnected network within the cell. Certain MPs can modulate interactions between various

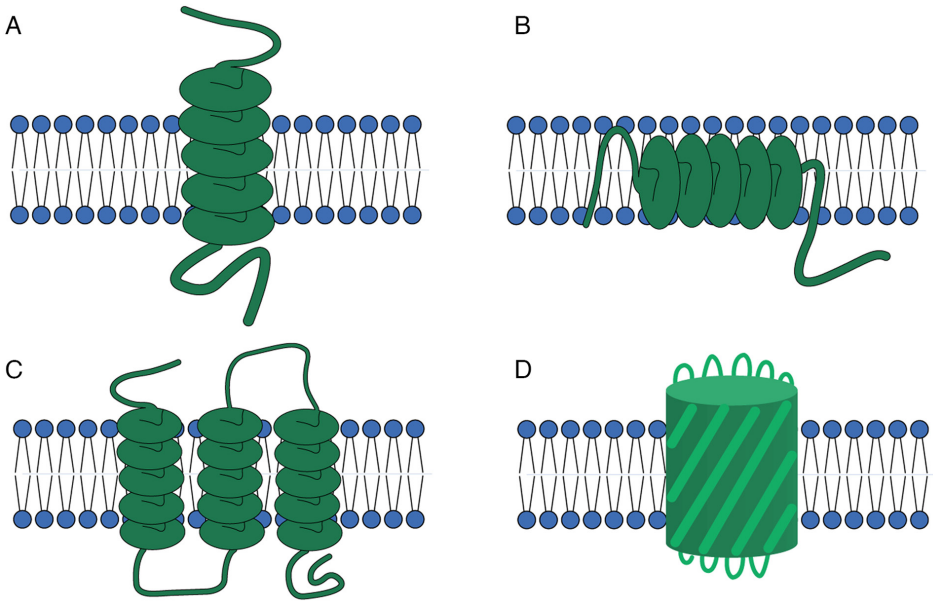

Figure 1. Classification of transmembrane protein structures. (A) Single-pass membrane protein, the lipid bilayer is traversed by the polypeptide chain via a single α-helix. (B) A number of transmembrane proteins are predominantly situated on the cytoplasmic side of the lipid bilayer. (C) Multi-membrane protein, the lipid bilayer is traversed by the polypeptide chain via two or more α-helix. (D) Some transmembrane proteins form large ion channels by transversing the plasma membrane with multiple β-folded sheets.

signaling pathways that govern fundamental cellular processes, such as metabolism, apoptosis and immune responses (30,31). The cyclic nature of these networks is particularly key for understanding how drugs influence cellular processes. The majority of therapeutic agents exert their effects by binding to MPs, thereby modulating signaling pathways essential for disease progression (32). Therefore, MPs serve as promising targets for novel therapeutic strategies targeting specific disease mechanisms at the molecular level. The expanding body of research on MPs and their interactions with drugs continues to reveal novel opportunities for drug development and personalized therapies (21,33).

MPs are essential to cellular function and disease pathogenesis (34). The study of MPs is essential for advancing the understanding of both normal physiology and disease mechanisms. Given their roles in signaling, cellular maintenance and disease progression, MPs serve as key targets for therapeutic intervention (7,12). Ongoing advancements in structural biology, coupled with novel drug discovery technologies, highlight novel opportunities for exploiting MPs as drug targets. Research on MPs holds potential for developing innovative treatments for a range of diseases, including cancer, cardiovascular disorders and neurological conditions (35-37).

2. Structure and function of the TMEM proteins

MPs are classified according to their interactions with membranes, which are categorized into peripheral MPs, integral MPs and lipid-anchored MPs (38). Integral MPs contain ≥1 transmembrane segment, commonly referred to as a TP (4). TMEM proteins represent a subgroup of integral MPs, defined by their ability to traverse the lipid bilayer, thus establishing stable anchors within the membrane. These proteins are essential in the transport of molecules across the cellular membrane (5,39). A protein is classified as a member of the TMEM family if it contains at least one predicted transmembrane domain that spans the biological membrane, either partially (in monomeric form) or fully (in multimeric form) (4).

Due to their amphipathic nature, members of the TMEM protein family adopt specific secondary structures when incorporation into the membrane (40,41). Based on their different structures, TMEMs can be divided into two categories: α-helical proteins and β-barrel proteins (Fig. 1). These two structures are the dominant structures of all transmembrane proteins, with α-helical proteins being mostly found in the cytoplasm and subcellular septum (Fig. 1A-C), while β-barrel proteins are mostly found in chloroplasts, bacteria and mitochondrial membranes (Fig. 1D) (40,41). These structural features allow TMEM proteins to modulate essential processes, including nutrient transport, waste removal and signal transduction (40,41).

TMEM proteins exhibit considerable functional diversity. These proteins are classified into distinct functional groups, including GPCRs, ion channels, transporters, carriers and other receptors (Fig. 2). GPCRs, one of the largest and most versatile classes of TMEM proteins, are involved in a range of signaling pathways that regulate essential physiological processes, including sensory perception, immune responses and cellular communication (42). Notably, TMEM proteins, including GPCRs (Fig. 2A), carry out key roles in cancer cell signaling, influencing tumor progression and metastasis (43). Ion channels (Fig. 2B) are TPs that form pores, allowing ions (such as Na^+, K^+, Ca^{2+} and Cl^-) to passively flow across the membrane. This movement is vital for processes such as nerve signal transmission, muscle contraction and maintaining cellular ion balance (44). Transporter proteins (Fig. 2C) facilitate the movement of molecules across the lipid bilayer, typically against their concentration gradients. This process requires energy and carries out a key role in nutrient uptake, waste removal and the maintenance of cellular homeostasis (43,44). Dysfunction of

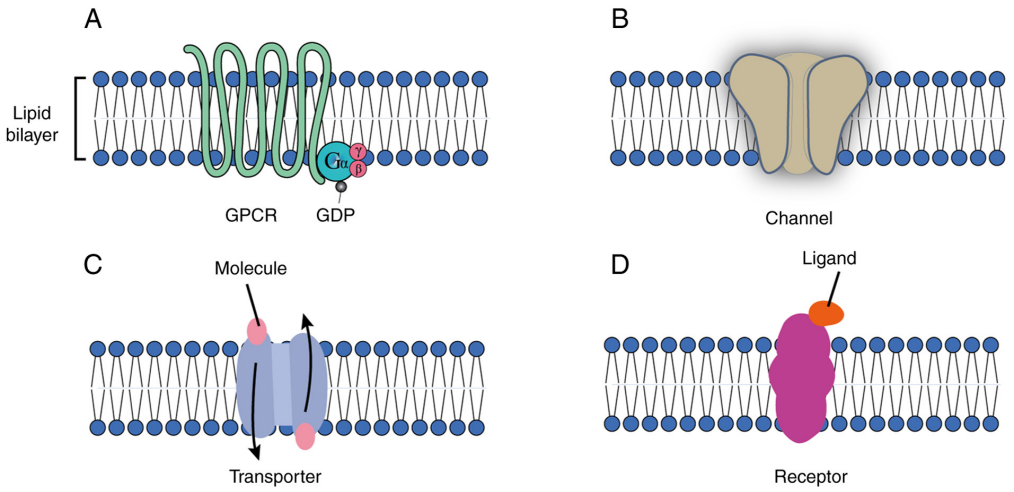

Figure 2. Classification of transmembrane family functions. (A) GPCRs mediate cellular responses by activating intracellular signaling pathways through G-proteins upon ligand binding. (B) Ion channels allow the passive flow of ions across the membrane, essential for processes such as nerve transmission and muscle contraction. (C) Transporter proteins actively move molecules across the membrane, often against concentration gradients, to maintain cellular homeostasis. (D) Receptors bind specific molecules to initiate cellular responses, influencing processes such as immune function, cell growth and metabolism. GPCR, G protein-coupled receptor.

these proteins is implicated in a variety of diseases, including neurological and cardiovascular disorders (43,44). TMEM proteins also function as transmembrane receptors (Fig. 2D), such as the well-known EGFR, which is involved in regulating cell growth, differentiation and survival. Dysregulation of these transmembrane receptors is frequently associated with the development and progression of various types of cancer, including breast, lung, ovarian, cervical, bladder, esophageal, brain, and head and neck cancer (45,46).

Previous studies have underscored the role of TMEM proteins in various disease mechanisms, which highlights their potential as therapeutic targets for drug development (47,48). For example, mutations in TMEM proteins have been associated with several genetic disorders, including cystic fibrosis, leading to defects in ion channels and disruption of chloride transport (47,48). Moreover, TMEM proteins, such as glucose transporters (GLUTs), carry out a pivotal role in cancer metabolism by facilitating glucose uptake, therefore promoting tumor growth, especially under nutrient-limited conditions (49). This highlights the potential of targeting TMEM proteins for therapeutic interventions in a range of diseases.

The increasing understanding of the structural and functional properties of TMEM proteins offers potential for drug development. Their involvement in cellular signaling and molecular transport makes them strong candidates for targeted therapies (50). Advances in structural biology, particularly the application of cryo-EM, have facilitated the determination of the atomic structures of key TMEM proteins, offering valuable insights into their functional mechanisms (51-53). The TMEM family proteins are essential components of the cellular membrane system, carrying out key roles in cellular signaling and the transport of ions and small molecules (39). Specific TMEM proteins interact with hormone or neurotransmitter receptors, inducing structural changes that initiate signaling cascades important for cellular function. These proteins mediate the selective transfer of ions or molecules across biological membranes, thereby establishing concentration gradients essential for cellular homeostasis and function (54). TMEM proteins are essential not only to the plasma membrane but also to the membranes of various intracellular organelles, including mitochondria, the endoplasmic reticulum (ER), lysosomes and the Golgi apparatus, where they participate in key biological processes (55). These processes carry out a key role in an array of physiological functions and diseases, including immune response regulation and tumorigenesis. Examples of key TMEM proteins include TMEM45A in epidermal keratinization (56), TMEM16 in smooth muscle contraction (57), TMEM165 in protein glycosylation (58) and TMEM9B in immune response modulation (59).

TMEM proteins are key contributors to cancer biology, carrying out key roles in tumor initiation, progression and metastasis. Their differential expression in various types of cancer not only serves as biomarkers but also offers new targets for therapeutic intervention (4,60). Furthermore, alterations in TMEM protein expression levels or function are closely associated with tumor progression, metastasis and drug resistance (60). Recent studies have emphasized the vital role of TMEM proteins in cancer cell survival and proliferation under harsh conditions, such as hypoxia or nutrient deprivation, which are commonly associated with the TME (4,5,12-16,60,61). For example, TMEM16, an ion channel, has been shown to regulate chloride and calcium ion flux, thereby influencing cell proliferation and migration in cancer cells (62). Likewise, TMEM65 has been implicated in regulating autophagy, an essential process for maintaining cellular homeostasis and promoting cancer cell survival (63). Given their upregulated expression in various types of cancer, targeting specific TMEM proteins presents a viable strategy for therapeutic intervention. Therapeutic strategies may include the development of small-molecule inhibitors or monoclonal antibodies that selectively target these proteins, thereby inhibiting their function and disrupting the signaling pathways they regulate (64). These approaches may address certain limitations of conventional cancer therapies, such as drug resistance and off-target effects, offering a more personalized and effective treatment regimen (65).

The TMEM protein family is important for maintaining cellular homeostasis and regulating various physiological processes. Their involvement in the pathogenesis of cancer and other diseases makes them potential candidates for targeted therapies. Ongoing research into the molecular mechanisms of TMEM proteins and their roles in disease progression is likely to lead to novel therapeutic strategies, particularly for several types of cancer and other disorders associated with abnormal TMEM protein activity.

3. Research on the correlation between TMEM proteins and cancer

TMEM family members as tumor suppressor genes

TMEM7. Multiple regions on chromosome 3p are commonly affected by loss of heterozygosity in several types of cancer (66). TMEM7 is a candidate tumor suppressor gene located at the 3p21.3 region of the human genome. It is a 232-amino acid, single-pass membrane protein, primarily expressed in the liver (67) and is integral to liver carcinogenesis (Fig. 3). It shares considerable sequence homology with the 28 kDa interferon-α (IFN-α)-responsive protein, suggesting a potential role in immune response modulation (67). TMEM7 has been implicated as a candidate tumor suppressor gene due to its frequent downregulation or inactivation in several types of cancer. Zhou *et al* (67) examined primary hepatocellular carcinoma (HCC) tissues and HCC cell lines, and found that TMEM7 mRNA expression was downregulated or silenced in 85% of primary HCC samples and 33% of HCC cell lines. This recurrent loss of function suggests that TMEM7 carries out a key role in suppressing hepatocarcinogenesis (67). Mechanistically, the downregulation of TMEM7 is primarily driven by epigenetic modifications such as DNA methylation and histone deacetylation, rather than by genomic deletions or mutations (67-69). To the best of our knowledge, no homozygous deletions or mutations of TMEM7 have been identified in HCC tissues or cell lines.

Zhou *et al* (67) demonstrated that treatment with DNA methylation inhibitors (such as 5-aza-2'-deoxycytidine) and histone deacetylase inhibitors (such as trichostatin A) can restore TMEM7 expression in knockdown cell lines, confirming the role of epigenetic alterations in its silencing. Through the ectopic expression of TMEM7 in two HCC cell lines with TMEM7 knockdown, cell proliferation, colony formation and cell migration were inhibited, and tumor formation in nude mice was reduced. After 7 days of IFN-α treatment in two highly invasive HCC cell lines, TMEM7 expression was markedly increased and cell migration was inhibited, further establishing the role of TMEM7 in liver cancer metastasis (67). These findings also suggest that modulating TMEM7 expression via IFN-α may have therapeutic potential for certain patients with HCC. While the role of TMEM7 in HCC is well-documented, its interaction with other genes on chromosome 3p further expands its roles. In a study by Kholodnyuk *et al* (68) involving human chromosome 3-mouse fibrosarcoma hybrids, the transcription of TMEM7 and its neighboring genes (such as LTF and SLC38A3) was found to be impaired in renal cell carcinoma (RCC) cell lines, suggesting a broader tumor-suppressive role across multiple cancer types (68).

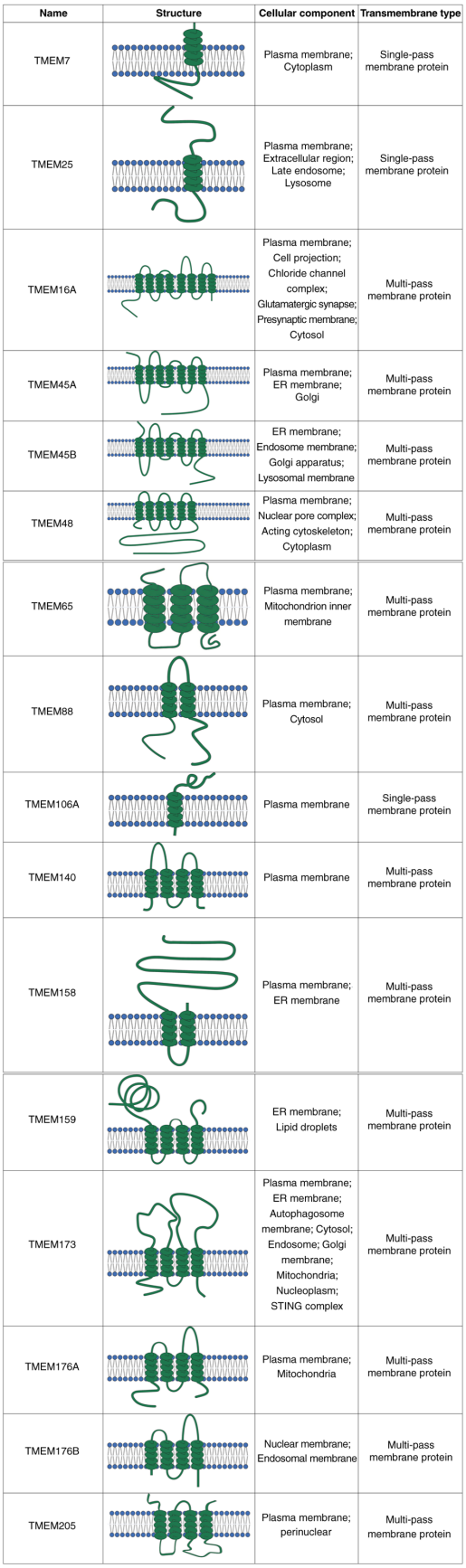

Figure 3. List of TMEM protein structures. Representative schematic diagrams of 16 TMEM proteins, TMEM7, TMEM25, TMEM16A, TMEM45A, TMEM45B, TMEM48, TMEM65, TMEM88, TMEM106A, TMEM140, TMEM158, TMEM159, TMEM173, TMEM176A, TMEM176B and TMEM205, illustrating their predicted transmembrane structures, subcellular localization and classification as single-pass or multi-pass membrane proteins. TMEM, transmembrane.

The epigenetic silencing of TMEM7 during hepatocarcinogenesis highlights the functional loss of TMEM7 as a key factor in liver cancer development, while its restoration or upregulation (by IFN-α, for example) offers potential therapeutic benefits (67-69). Understanding the precise role of TMEM7 in liver cancer progression may pave the way for targeted therapies aimed at improving outcomes for patients with this aggressive malignancy.

TMEM25. TMEM25, a member of the immunoglobulin superfamily, carries out a role in various cellular processes, including immune responses, growth factor signaling and cell adhesion (70,71). Its expression is markedly altered in several types of cancer, particularly in triple-negative breast cancer (TNBC), colorectal cancer (CRC) and clear cell RCC (ccRCC), making it a promising biomarker for diagnosis, prognosis and therapeutic targeting. The functional importance of TMEM25 in cancer is underscored by a study demonstrating its epigenetic regulation, particularly through DNA methylation and histone modifications, which affect its expression and role in tumorigenesis (71).

In colon adenocarcinoma, Hrašovec *et al* (70) observed a marked downregulation of TMEM25 mRNA in 68% of tumor tissues from patients with primary colon cancer. This downregulation was linked to hypermethylation of a specific CpG site within the 5' untranslated region of the TMEM25 gene, suggesting that epigenetic silencing through DNA methylation is a key mechanism responsible for the decreased expression of TMEM25 in colon adenocarcinoma. The inverse relationship between TMEM25 hypermethylation and its expression levels underscores the key role of epigenetic regulation in modulating TMEM25 expression during colon carcinogenesis (70). In breast cancer, the expression of TMEM25 is reduced in 50% of tumor samples compared with normal tissues, as reported by Doolan *et al* (72). Increased TMEM25 expression levels were associated with improved clinical outcomes, particularly in patients undergoing adjuvant chemotherapy, where it was associated with prolonged survival (72). By contrast, TMEM25 expression was often undetectable in TNBC, a subtype of breast cancer that is difficult to treat and associated with poor prognosis (70-72). In TNBC, TMEM25 acts as a suppressor of tumor progression by inhibiting the activation of the STAT3 signaling pathway. Specifically, TMEM25 physically interacts with the EGFR monomer, preventing EGFR-mediated STAT3 phosphorylation. This interaction sequesters unphosphorylated STAT3 in the cytoplasm, thereby inhibiting its nuclear translocation and subsequent tumor-promoting gene transcription (12,71,72). However, in TMEM25-deficient TNBC cells, EGFR monomers can phosphorylate STAT3 independently of ligand binding, leading to basal STAT3 activation and tumor progression. Restoring TMEM25 expression through adeno-associated virus delivery has been revealed to suppress STAT3 activation and TNBC progression in preclinical models, highlighting its potential as a therapeutic target (12,71,72). These findings indicate that TMEM25 may act as a valuable prognostic marker in breast cancer, particularly in predicting patient response to chemotherapy and providing insights into the molecular mechanisms underlying chemotherapy resistance. Growing evidence also indicates that TMEM25 carries out a tumor-suppressive role in ccRCC, a subtype of kidney cancer with limited therapeutic options (73). In ccRCC tissues, elevated DNA methylation of TMEM25 has been observed, suggesting epigenetic silencing in this type of cancer. Moreover, mutations in TMEM25 have been revealed to notably impact patient prognosis, with reduced TMEM25 expression associating with a more aggressive disease phenotype. Notably, the expression of TMEM25 in ccRCC is strongly associated with several immune-related factors, including immune checkpoint molecules, immune suppressive markers and major histocompatibility complex molecules, implying that TMEM25 may be involved in modulating the immune landscape of ccRCC (73). This interaction between TMEM25 and immune-related factors further underscores its role in immune evasion within the TME.

TMEM25 has been identified as a promising prognostic biomarker in colon cancer, breast cancer and ccRCC (70-72). Its expression is regulated epigenetically, primarily through DNA methylation and histone modifications, which suggests that reversing its epigenetic silencing could offer a promising therapeutic approach. Furthermore, the involvement of TMEM25 in immune modulation, especially through its interactions with immune checkpoint molecules, presents considerable promise for immunotherapeutic interventions. This establishes TMEM25 as a key therapeutic target in several types of cancer where its expression is reduced or absent. Given its pivotal role in cancer progression and immune regulation, TMEM25 may serve as a promising therapeutic target. Future research should focus on elucidating the molecular pathways through which TMEM25 influences tumor progression and immune responses. Restoring or enhancing TMEM25 expression could considerably improve treatment outcomes in colon cancer, breast cancer, and ccRCC, thereby positioning it as a promising target in future cancer therapies (70-72).

TMEM88. TMEM88 is a dual-transmembrane protein that participates in several key biological processes, particularly the regulation of human stem cell differentiation and embryonic development (74,75). Previous studies have indicated that TMEM88 carries out a key role in tumorigenesis, with its expression being altered in several types of cancer (74,75). Notably, TMEM88 binds to Dishevelled (DVL), preventing its interaction with LRP5/6 and inhibiting the canonical Wnt pathway. This leads to decreased β-catenin activity and downregulation of Wnt target genes, including c-Myc and cyclin D1 (75). While TMEM88 is widely expressed in various types of tumors, it is typically downregulated in the majority of tumor cells, suggesting its role as a potential tumor suppressor (76).

The expression of TMEM88 is also markedly decreased in thyroid cancer (TC) tissues and cell lines (75-77). Studies have revealed that TMEM88 inhibits the proliferation, colony formation and invasion of TC cancer cells, primarily through binding to DVL (75-77). In both *in vitro* and *in vivo* models, overexpression of TMEM88 has been shown to suppress tumorigenic properties, further supporting the role of TMEM88 as a tumor suppressor in TC. These findings suggest that restoring TMEM88 expression or inhibiting its methylation may offer a promising therapeutic strategy for treating TC. The involvement of TMEM88 in bladder cancer has been further emphasized instudies (78,79). Upregulation of TMEM88 in bladder cancer leads to a marked reduction in cellular proliferation and invasion (78,79). Bioinformatic

analysis revealed that TMEM88 expression was considerably reduced in bladder cancer tissues compared with normal tissues (79). Zhao *et al* (79) provided evidence that loss of TMEM88 expression in bladder cancer cells enhances invasive and proliferative capacities, while re-expression of TMEM88 effectively reverses these phenotypes (79). Additionally, overexpression of TMEM88 in bladder cancer xenograft models inhibited tumor growth (79), indicating that TMEM88 acts as a tumor suppressor gene in bladder cancer as well.

The biological role of TMEM88 depends on its subcellular localization. Membrane-localized TMEM88 inhibits Wnt signaling, while cytosolic TMEM88 promotes tumor progression through alternative pathways. Zhang *et al* (80) reported that cytosolic localization of TMEM88 in non-small cell lung cancer (NSCLC) is associated with poor differentiation, a high TNM stage, lymph node metastasis and worse overall survival (OS). TMEM88 was shown to promote invasion and metastasis by activating the p38-GSK3 β-Snail signaling pathway. Overexpression of TMEM88 in NSCLC cells inhibited excessive cell proliferation, invasion and migration, leading to the prevention of tumor growth in xenograft models (80). Furthermore, hypermethylation of the TMEM88 promoter has been observed in NSCLC tissues, which is associated with a worse prognosis. Demethylation of TMEM88 resulted in the inhibition of cell proliferation, migration and invasion, suggesting that TMEM88 expression and its epigenetic regulation carry out a key role in NSCLC progression (81). In TNBC, TMEM88 overexpression in the cytosol stimulated invasion and metastasis by interacting with DVL proteins and promoting Snail expression while inhibiting tight junction proteins, such as zonula occludens-1 and occluding (82). Thus, increased TMEM88 expression was associated with improved prognosis in HCC and bladder cancer, while its cytosolic localization was predictive of a worse outcome in NSCLC and TNBC.

TMEM88 carries out a key role in regulating cell proliferation, migration and invasion, and has demonstrated notable potential as both a diagnostic biomarker and therapeutic target across various types of cancer (79-82). Its expression is frequently downregulated in tumors, and promoter hypermethylation of TMEM88 is associated with a worse prognosis in NSCLC (80,81). These findings highlight TMEM88 as a potential marker for disease progression and survival prediction. The epigenetic regulation of TMEM88, particularly through DNA methylation, offers a novel therapeutic avenue. Demethylating agents can restore TMEM88 expression (81), thereby suppressing tumor cell growth and metastasis. As a negative regulator of the Wnt/β-catenin signaling pathway, TMEM88 exhibits tumor-suppressive activity in NSCLC, TC and bladder cancer. Therapeutic strategies aimed at restoring or enhancing TMEM88 expression could thus represent a viable approach for cancer treatment. Ongoing research into the molecular mechanisms of TMEM88 is expected to further clarify its value as both a therapeutic target and a prognostic biomarker in clinical oncology.

TMEM106A. TMEM106A is located on chromosome 17 and consists of 262 amino acids. TMEM106A is a conserved type II TP that has been implicated in suppressing tumorigenesis across multiple types of cancer (83,84). TMEM106A is typically expressed in normal gastric tissue and is often downregulated or silenced in gastric cancer (GC), due to methylation of the promoter region, and its methylation is associated with smoking and tumor metastasis (83,84). Frequent methylation of TMEM106A in GC tissues highlights its potential role as a tumor suppressor. Xu *et al* (84) demonstrated that overexpression of TMEM106A markedly inhibited GC cell proliferation and induced apoptosis, while also delaying tumor growth in xenograft models (84). Mechanistic studies suggested that these effects were closely associated with the activation of caspase-2, caspase-9 and caspase-3, as well as the inactivation of poly(ADP-ribose) polymerase (PARP) (84). Thus, TMEM106A has emerged as a functional tumor suppressor in the pathogenesis of GC.

Methylation of TMEM106A is generally associated with its reduced expression and the promoter region methylation serves as a key regulatory mechanism in GC. The downregulation of TMEM106A expression in patients with GC is associated with a worse prognosis, emphasizing its clinical relevance as a prognostic biomarker (85). In renal cancer, TMEM106A expression is markedly reduced, and its restoration in cancer cells leads to attenuated proliferation, reduced migration and enhanced caspase-3-dependent apoptosis (86). Similarly, the expression of TMEM106A in HCC tissues is notably reduced compared with normal liver tissue, accompanied by frequent promoter methylation in HCC tissues, further reinforcing its potential as a tumor suppressor (87). Treatment with 5-Aza-2'-deoxycytidine in HCC cells with high methylation restored TMEM106A expression and markedly suppressed the malignant behaviors of these cells, including reduced cell migration, invasion and lung metastasis (87). *In vivo* experiments demonstrated that overexpression of TMEM106A in HCC cells resulted in considerable tumor suppression, and this was associated with the suppression of epithelial-mesenchymal transition (EMT) and the inactivation of the ERK1/2/Slug signaling pathway (87). Moreover, in NSCLC, TMEM106A expression was revealed to be markedly decreased in tumor tissues. Overexpression of TMEM106A in NSCLC cells reduced proliferation, migration and invasion, while inducing apoptosis. It also repressed EMT by modulating E-cadherin, N-cadherin and vimentin expression, and inhibited the PI3K/Akt/NF-κB signaling pathway (88). In urothelial carcinoma, TMEM106A was identified as a novel biomarker, with its methylation levels in urine samples revealing high diagnostic accuracy for early detection (89).

TMEM106A also exhibits antiviral activity, specifically in the IFN-mediated antiviral immune response. TMEM106A was revealed to interact with the receptor SCARB2 of EV-A71 and CV-A16, thus disrupting viral binding to host cells and preventing viral infection (90). This finding not only highlights a novel mechanism of TMEM106A in antiviral immunity but also proposes a potential therapeutic target for antiviral strategies. In addition to its antiviral function, TMEM106A regulates macrophage activation and immune responses, especially in bacterial infection-induced inflammation. Its downregulation enhanced M1 macrophage polarization and exacerbated the LPS-induced inflammatory response through the MAPK and NF-κB signaling pathways, underscoring the key role of TMEM106A in immune homeostasis (91).

TMEM106A carries out a key tumor-suppressive role in various types of cancer, such as gastrointestinal tumors,

liver cancer and NSCLC, with its dysregulated expression, including methylation, potentially serving as a valuable clinical prognostic biomarker (84,86-91). Furthermore, the diverse functions of TMEM106A in immune responses and antiviral defense establish it as a potential target for future cancer treatments and immune modulation strategies. Further research should prioritize elucidating the specific mechanisms by which TMEM106A operates in various types of cancer and exploring its clinical applications.

TMEM173. TMEM173, also known as stimulator of interferon genes (STING), is a key TP located on the outer membrane of the ER and carries out a key role in cancer immunology and immunotherapy. It is essential in innate immunity and is primarily expressed in hematopoietic cells and immune organs such as the thymus and spleen (92,93). Composed of four transmembrane domains, TMEM173 forms dimers that allow ligand binding and activation of immune responses, in addition to mediating reactions to cytosolic DNA, which can result from infections, cellular stress or genomic instability (94). TMEM173 carries out a key role in host defense against pathogenic infections by regulating type I IFN (IFN-I) signaling, pro-inflammatory cytokines and innate immunity (95). In addition to its role in innate immunity, TMEM173 also contributes to autoimmune inflammation, oxidative stress and autophagy (96).

While TMEM173 has demonstrated tumor-suppressive functions in various cancer types, including CRC, prostate cancer and melanoma (92); it is important to note that TMEM173 activation can act as a double-edged sword in cancer. It promotes antitumor immunity by enhancing dendritic cell (DC) maturation, T cell activation and macrophage polarization toward an M1 phenotype, which supports tumor elimination (97-99). T cell infiltration into tumors is largely dependent on IFN-I signaling, and activation of TMEM173 enhances immune surveillance against tumors. For example, TMEM173 agonists have been revealed to amplify the cGAS-STING pathway, leading to increased IFN-β secretion and T cell-mediated immune responses in colorectal and breast cancer models (97). Additionally, TMEM173 activation can reprogram tumor-associated macrophages (TAMs) from an immunosuppressive M2 phenotype to an immunostimulatory M1 phenotype, further enhancing antitumor immunity (97,100). TMEM173 expression is downregulated in various types of cancer, including GC and HCC, and this downregulation associates with tumor size, invasiveness and lymph node metastasis. *In vitro* experiments have revealed that knockout of TMEM173 promotes clonal formation, migration and invasion of GC cells, whereas its activation induces apoptosis and autophagy in malignant cells, inhibiting tumor growth (101). However, STING signaling can also promote immune evasion and tumor progression. For example, TMEM173 activation in tumor monocytes induces programmed death (PD)-ligand 1 expression, which suppresses T cell activity and contributes to resistance against TMEM173 agonist therapy (102). Similarly, TMEM173 signaling can expand regulatory B cells that produce IL-35, which attenuates natural killer (NK) cell function and compromises antitumor immunity (103). TMEM173 may carry out a key role in metastasis formation. Activation of TMEM173 promotes metastatic tumor formation and spread, partly through the production of TNF-α and other cytokines (104). For example, Bu *et al* (105) reported that, in clinical samples from patients with hepatitis B virus (HBV)-induced liver cancer, TMEM173 downregulation may contribute to immune evasion and subsequently facilitate tumor progression.

TMEM173 is not only a key regulator of tumor immunity but also holds substantial therapeutic potential within cancer immunotherapy. Targeting TMEM173, either by modulating its upstream or downstream signaling pathways, may provide novel therapeutic strategies to enhance cancer treatment outcomes, particularly when combined with immune checkpoint blockade therapies (106). Therefore, TMEM173 agonists are emerging as promising candidates for cancer immunotherapy. Nanoparticle-based delivery systems have been developed to enhance the spatiotemporal activation of TMEM173, improving its therapeutic efficacy while minimizing off-target effects (107). For example, TME-responsive nanoparticles have been designed to simultaneously activate TMEM173 and TLR4, leading to enhanced IFN-β production and T cell responses in colorectal and metastatic breast cancer models (97). Additionally, combining TMEM173 agonists with immune checkpoint inhibitors, such as anti-PD-1 antibodies, has shown synergistic effects in preclinical models (97,100). However, challenges remain in translating TMEM173 agonists to clinical practice. Issues such as poor drug stability, limited tumor targeting and immune-related adverse events need to be addressed (103,108). Nanomedicine approaches, including the use of radiosensitizers and targeted delivery systems, are being explored to overcome these limitations.

TMEM173 is a central player in cancer immunology, with its activation driving both antitumor immunity and immune evasion. While TMEM173 agonists hold potential for cancer immunotherapy, their clinical translation requires careful consideration of the TME and potential off-target effects. Future research should focus on developing targeted delivery systems and combination therapies to maximize the therapeutic potential of TMEM173 activation in cancer treatment.

TMEM176A/TMEM176B. TMEM176A and TMEM176B, both belonging to the membrane-spanning 4-domains family, have emerged as key regulators of immune responses and cancer progression. TMEM176A is localized on chromosome 7q36.1 and has been identified as a potential tumor suppressor in various types of cancer, including esophageal squamous cell carcinoma (ESCC) and CRC (109). In addition, TMEM176B, also known as tolerance-related and induced, carries out a key role in immune modulation and cancer progression (110).

TMEM176A has been revealed to suppress the growth of ESCC cells both *in vitro* and *in vivo* (110-112), suggesting its potential as a diagnostic and prognostic biomarker for ESCC. In ESCC, the loss of TMEM176A expression is associated with promoter hypermethylation (111). TMEM176A promoter methylation occurs in ~66% of primary ESCC tumors, which associates with its reduced expression, poor tumor differentiation, reduced survival rates and aggressive cancer phenotypes (111). The restoration of TMEM176A expression using demethylation agents, such as 5'-aza-2'-deoxycytidine, inhibits cell migration and invasion, thereby promoting apoptosis in ESCC cells and suppressing cancer progression. Additionally, in CRC, TMEM176A promoter methylation is observed in nearly half of the primary tumors,

with TMEM176A overexpression resulting in suppressed cell proliferation, migration, invasion and induced apoptosis (112). Notably, TMEM176A is also involved in regulating glioma cell cycles through pathways such as ERK1/2, further validating its role as a tumor suppressor (112). Collectively, these findings establish TMEM176A as a potential tumor suppressor gene, with its expression levels serving as valuable prognostic indicators across multiple cancer types (113).

TMEM176B has been extensively studied in various types of cancer, where it often promotes tumor progression. In CRC, TMEM176B inhibits the NOD-, LRR-, and pyrin domain-containing protein 3 inflammasome, thereby suppressing NK cell activity and promoting EMT, a key process in metastasis. Silencing TMEM176B reduces tumor growth, metastasis and EMT while enhancing apoptosis and immune activation (114). In GC, TMEM176B overexpression drives tumor progression by regulating the PI3K-Akt-mTOR signaling pathway and amino acid metabolism. Its knockdown inhibits cell proliferation, migration and invasion, while promoting apoptosis. Clinically, TMEM176B expression is associated with a worse prognosis, making it a potential prognostic marker (115). TMEM176B also carries out a role in ovarian cancer (OC), where it acts as a tumor suppressor. Its downregulation is associated with increased EMT, proliferation and metastasis, mediated through the Wnt/β-catenin signaling pathway. Restoring TMEM176B expression inhibits these processes, highlighting its therapeutic potential (116).

TMEM176B also carries out a key role in regulating immune responses, especially in DCs (117). TMEM176B is recognized as a key modulator of allograft tolerance and immune system function (117). A study involving autologous tolerogenic DCs (ATDCs) demonstrated that TMEM176B expression in ATDCs was essential for inducing donor-specific immune tolerance and prolonging graft survival (118). TMEM176B-deficient ATDCs failed to cross-present antigens effectively, impairing their ability to induce regulatory CD^{8+} T cells and hindering allograft tolerance (118). TMEM176B inhibits inflammasome activation, which dampens anti-tumor immunity. Targeting TMEM176B unleashes inflammasome activity, increasing $CD8^{+}$ T cell-mediated tumor control and enhancing the effects of anti-CTLA-4 and anti-PD-1 therapies (119). These findings underscore the importance of TMEM176B in modulating immune responses, particularly through its influence on antigen cross-presentation and regulation of phagosomal pH, both of which are important for immune tolerance (120). Additionally, TMEM176B has been implicated in regulating immune checkpoint responses, particularly in the context of PD-1 blockade therapy. Elevated TMEM176B expression in tumor stromal cells is associated with a worse prognosis, suggesting that it may act as a negative modulator of anti-tumor immunity (121). Its role in immune evasion has prompted investigations into its potential as a biomarker for predicting patient response to immune checkpoint inhibitors, including anti-PD-1 therapies. TMEM176B negatively regulated the antitumor activity of $CD146^{+}$ TAMs. Inhibition of TMEM176B enhanced TAM-mediated anti-tumor immunity, highlighting a potential immunotherapeutic strategy (122). Thus, as an immune-regulating cation channel, TMEM176B modulates immune cell trafficking and function, further highlighting its potential as a therapeutic target (123).

TMEM176A and TMEM176B are known to physically interact and co-localize at both the plasma membrane and vesicular compartments within immune cells (124). In lymphoma, overexpression of both proteins has been associated with immune evasion, enabling cancer cells to evade immune surveillance and develop resistance to chemotherapy (124,125). This interaction suggested that the two proteins may function synergistically to regulate immune responses and contribute to tumor progression. Both TMEM176A and TMEM176B are downregulated during DC maturation, with their overexpression inhibiting this process and suggesting a role in maintaining an immature state that facilitates immune tolerance (123).

TMEM176A and TMEM176B have emerged as key factors in cancer biology, particularly in immune regulation and tumor suppression. Their roles in immune modulation, especially through the regulation of DC function and antigen cross-presentation, position them as promising targets for novel therapeutic strategies aimed at enhancing immune checkpoint blockade efficacy and improving cancer immunotherapy outcomes. Future research should focus on more comprehensively elucidating the precise molecular mechanisms by which TMEM176A and TMEM176B regulate immune responses and tumor progression. Clinical trials targeting these proteins, either alone or in combination with existing immune checkpoint inhibitors, may provide key insights into their therapeutic potential.

TMEM family members as oncogenes

TMEM16A. TMEM16 proteins, also known as anoctamins, are a family of ten MPs with various tissue expression and subcellular localization. TMEM16A, also referred to as anoctamin 1 (ANO1), is a calcium-activated chloride channel (CaCC) mapped to chromosome 11q13. It contains eight transmembrane domains and a highly conserved, functionally undefined domain (DUF590), with its expression predominantly observed in secretory epithelial cells, smooth muscle tissue and sensory neurons (126). TMEM16A is acknowledged as a key modulator of tumor progression. It is frequently amplified in a variety of malignancies, including breast cancer, esophageal cancer and head and neck squamous cell carcinomas (HNSCCs), where its expression is associated with a poor prognosis, increased tumor size and advanced clinical stages (127).

TMEM16A carries out a key role in tumorigenesis by activating key signaling pathways, including the EGFR and calcium/calmodulin-dependent protein kinase pathways (128). Silencing of TMEM16A has been revealed to inhibit the proliferation of esophageal and HNSCC cells and induce apoptosis through the MAPK and AKT signaling pathways. TMEM16A is involved in EMT, a key process in cancer metastasis, by regulating the transition from an epithelial to a mesenchymal state, thus enhancing cell migration and invasion (129). In CRC, TMEM16A carries out a key role in disease progression by promoting cell migration and invasion. It activates the Wnt/β-catenin signaling pathway by upregulating key components such as Frizzled protein 1 and β-catenin, while downregulating GSK3β (129,130). The overexpression of TMEM16A is notably elevated in HNSCC, esophageal and prostate cancer, where it is associated with distant metastasis and a poor prognosis (131).

The molecular mechanisms underlying these effects include a role independent of its channel function in promoting

cell proliferation. Research suggests that TMEM16A regulates cancer cell growth by interacting with other MPs rather than exclusively through its chloride conductance (131). For example, TMEM16A has been revealed to interact with EGFR, thereby potentiating EGFR signaling in HNSCC cells (128). This interaction not only stabilizes EGFR but also increases TMEM16A protein expression, thereby establishing a feedback loop between TMEM16A and EGFR signaling pathways, which likely contributes to enhanced cancer cell proliferation and survival. Knockdown of TMEM16A has been revealed to reduce myeloid cell leukemia 1 expression and promote the perinuclear redistribution of $p27^{Kip1}$, thereby inducing cell cycle arrest, suppressing tumor proliferation and promoting apoptosis (132). However, Shiwarski *et al* (133) reported that stable reduction of TMEM16A expression enhanced the motility of HNSCC cells and facilitated metastasis, independent of 11q13 amplification. Additionally, TMEM16A overexpression is associated with increased Erk1/2 activity, reduced Bim expression and decreased apoptotic activity, contributing to tumor progression and cisplatin resistance (134). These conflicting findings underscore the multifaceted role of TMEM16A in HNSCC progression. Further studies revealed that TMEM16A expression is associated with tumor subtype: In general, in HNSCC, elevated TMEM16A levels associate with shorter survival and increased risk of distant metastasis (135,136), whereas in human papilloma virus (HPV)-positive HNSCC, its expression was not associated with prognostic significance (136). This suggests that TMEM16A-targeted therapies may be inappropriate for HPV-positive patients. Collectively, these findings indicate that the function of TMEM16A is context-dependent, shaped by the TME and specific cellular subtypes. Continued clinical and molecular investigations are required to clarify its precise role in cancer progression.

TMEM16A has emerged as a potential biomarker for several types of cancer, including esophageal and gastrointestinal squamous cell carcinoma (127). Its expression is associated with clinical staging and disease progression, making it a valuable prognostic indicator. Moreover, TMEM16A functions as a predictor of therapeutic response to EGFR-targeted therapies, particularly in HNSCC, where TMEM16A overexpression may mediate resistance to EGFR inhibitors (137). Given its key role in tumor progression and interaction with EGFR signaling, TMEM16A represents a compelling therapeutic target. Targeting TMEM16A in conjunction with EGFR may offer a strategy to bypass resistance mechanisms and enhance the efficacy of existing EGFR-targeted therapies in cancer treatment (128).

Amplification of chromosome 11q13, where TMEM16A (ANO1) is located, is associated with a poor prognosis in patients with breast cancer. TMEM16A amplification and overexpression are associated with a higher tumor grade and worse outcomes, primarily through activation of EGFR and CaMKII signaling pathways to promote cell proliferation (138). TMEM16A expression also associates with immunohistochemical markers such as β-catenin, cyclin D1 and E-cadherin, and has been identified as an independent prognostic marker (139). Functional studies revealed that TMEM16A inhibition induced G0/G1 cell cycle arrest and reduced the invasiveness of breast cancer cells, underscoring its potential as a therapeutic target (139,140). However, conflicting data regarding its association with hormone receptors (HER2, ER and PR) suggested that the role of TMEM16A may vary across molecular subtypes and cellular contexts (140). Upregulation of TMEM16A is notably associated with CRC progression and higher TNM staging (141). Sui *et al* (142) confirmed that TMEM16A knockout inhibited the growth, migration and invasion of CRC cells by suppressing the MAPK/ERK signaling pathway. It has been reported that endogenous TMEM16A knockout suppressed CRC cell proliferation and induced apoptosis by inactivating the downstream Wnt/β-catenin signaling pathway (142). Li *et al* (143) proposed that TMEM16A mRNA expression was associated with lymph node metastasis in CRC and may thus serve as an independent predictive marker for lymphatic involvement. These findings establish the key role of TMEM16A in CRC progression and metastasis. Overexpression of TMEM16A is associated with TNM staging and Gleason scoring in prostate cancer, carrying out a key role in tumor growth, progression and metastasis (144).

Silencing or inhibiting endogenous TMEM16A has been revealed to suppress prostate cancer growth, induce apoptosis and increase TNF-α expression levels (145). Notably, natural products such as resveratrol and luteolin serve both as TMEM16A inhibitors and antitumor agents, effectively reducing prostate cancer cell proliferation and migration (146,147). These findings highlight the therapeutic potential of targeting TMEM16A in prostate cancer treatment. TMEM16A is considerably upregulated in epithelial OC cells, and its upregulation is associated with increased staging and lower differentiation (148). Downregulation of TMEM16A suppressed OC cell growth by reducing PI3K/Akt phosphorylation and disrupting the PI3K/Akt signaling pathway (148). These findings highlight the key role of TMEM16A in OC progression, with its expression associated with advanced disease and a poor prognosis. Given its role in cancer progression, TMEM16A has emerged as a promising therapeutic target. Inhibition of TMEM16A suppresses tumor growth, induces apoptosis and enhances the efficacy of existing therapies (144-149). For example, allicin, a natural compound from garlic, was shown to inhibit the chloride ion current through the TMEM16A channel and exhibit synergistic anticancer effects with cisplatin in lung cancer (149). Similarly, idebenone, a novel TMEM16A inhibitor, can block chloride channel activity and was shown to induce apoptosis in normal prostate and PC cells (150). Furthermore, TMEM16A inhibitors such as T16Ainh-A01 and CaCCinh-A01 have demonstrated efficacy in reducing tumor growth and invasiveness in prostate cancer (144).

TMEM16A, as a CaCC, carries out a key role in calcium-activated chloride secretion, which is involved in the pathogenesis of secretory diarrhea. Yin *et al* (151) revealed in rotavirus-induced diarrhea that viral enterotoxin NSP4 enhanced intracellular calcium levels, activating TMEM16A-mediated chloride secretion, which, in-turn, contributed to fluid loss and diarrhea. Given that chemotherapy-induced diarrhea in patients with cancer often involves dysregulated epithelial ion transport, TMEM16A may similarly contribute to this adverse effect. Thus, TMEM16A may serve as a mechanistic link between increased chloride secretion and diarrhea in both infectious and iatrogenic contexts.

TMEM16A, through its dual function as both a chloride channel and a signaling modulator, carries out a pivotal role in tumor biology. The regulation of cell proliferation, migration and metastasis by TMEM16A, in addition to its association with EGFR signaling, highlights its potential as both a prognostic biomarker and a therapeutic target for various malignancies.

TMEM45A. TMEM45A consists of 275 amino acids, composed of 5-7 transmembrane domains and is primarily localized in the Golgi apparatus (4). It is highly expressed in the skin, where it carries out a key role in epidermal differentiation and keratinization, processes essential for preserving the structural integrity of the skin and barrier function (152). Beyond its role in normal cellular functions, TMEM45A is involved in the pathogenesis of various types of cancer, including gliomas, breast cancer, HCC, RCC and OC, where it is commonly upregulated (153).

TGF-β is a key factor regulating various cellular processes such as proliferation, migration and invasion. In OC, the expression of TMEM45A is closely associated with the activation of the TGF-β signaling pathway. Silencing TMEM45A not only reduced cell proliferation, adhesion and invasion, but also downregulated cancer-promoting factors such as TGF-β1, TGF-β2, RhoA and ROCK2 (154). This association has been revealed to contribute to tumor progression and metastasis and a similar mechanism has been identified in glioma cell lines, providing further evidence for the oncogenic potential of TMEM45A in these cancer types (152,153). Notably, increased TMEM45A expression in breast cancer and cervical cancer (CC) has been associated with poor OS, indicating that TMEM45A could function as an important prognostic biomarker for these malignancies (155).

TMEM45A short hairpin RNA inhibited the proliferation of CC cells, arrested the cell cycle at the S phase and promoted apoptosis. It also suppressed EMT by downregulating Vimentin and N-cadherin, and upregulating E-cadherin, thereby reducing the invasive and migratory ability of the cells. The expression of TMEM45A in cisplatin-resistant cell lines SiHa/DDP and HeLa/DDP was revealed to be increased compared with their parental cells, and inhibiting TMEM45A markedly reduced the IC_{50} of these resistant cells to cisplatin. Silencing TMEM45A inhibited the proliferation, invasion, migration and EMT of HPV-positive CC cells, regulated cell cycle distribution and promoted apoptosis (156). Sun *et al* (153) revealed that TMEM45A was overexpressed in glioma tissues compared with non-tumorous brain tissues. TMEM45A mRNA levels progressively increased with higher histological grades of glioma and were associated with shorter survival times of patients. Knockout of TMEM45A in glioma cell lines markedly inhibited cell proliferation and induced G1 phase arrest, and reduced the migratory and invasive abilities of glioma cells. Notably, treatment with TMEM45A small interfering (si)RNA downregulated key proteins involved in cell cycle progression (Cyclin D1, CDK4 and proliferating cell nuclear antigen) as well as invasion-related proteins (MMP-2 and MMP-9), providing a potential mechanistic explanation for its role in glioma.

TMEM45A is closely associated with intratumoral heterogeneity, a major challenge in cancer treatment. In lung adenocarcinoma, TMEM45A was revealed to be overexpressed in tumor tissues compared with healthy tissues, and its expression was associated with markers such as GLUT1, MCT4 and CA9, which are associated with a hypoxic microenvironment and altered metabolism (157). Similarly, in ccRCC, TMEM45A upregulation associated with poor OS, disease-free survival and advanced clinicopathological features such as higher histological grade and TNM stage (158).

TMEM45A is a multifunctional protein associated with tumorigenesis, chemotherapy resistance and fibrosis. Its ability to modulate key signaling pathways, including TGF-β and Notch, positions it as a promising candidate for therapeutic targeting. In GC, increased TMEM45A expression was associated with poor prognosis and immune cell infiltration, making it a potential independent prognostic marker (159). In breast cancer, TMEM45A expression is associated with poor survival and resistance to CDK4/6 inhibitors such as palbociclib, further underscoring its prognostic value (160). Furthermore, the association of TMEM45A with a poor prognosis in various types of cancer and its involvement in MDR highlights its potential as a biomarker for cancer progression and therapeutic resistance (155,161,162). In breast cancer, engineered exosomes loaded with siRNA targeting TMEM45A restored sensitivity to palbociclib and suppressed tumor growth (160). Similarly, in CC, TMEM45A knockdown reversed cisplatin resistance and inhibited proliferation, migration and EMT in HPV-positive cell lines (156). Future research focusing on the molecular mechanisms underlying the functions of TMEM45A in these contexts are essential for the development of targeted therapies aimed at overcoming resistance and improving patient outcomes.

TMEM45B. TMEM45B has attracted considerable attention due to its involvement in various types of cancer, including lung cancer, PC and GC (163). Okada *et al* (163) have highlighted that TMEM45B as an oncogene that plays a pivotal role in cancer pathogenesis by regulating essential cellular processes, including proliferation, invasion, migration, and apoptosis.

In lung cancer, TMEM45B overexpression is associated with poor patient survival. Knockdown of TMEM45B reduced cell proliferation, induced cell cycle arrest and apoptosis, and inhibited cell migration and invasion. These effects were mediated through the regulation of cell cycle-related proteins (CDK2 and CDC25A), apoptosis-related proteins (Bcl2 and Bax) and metastasis-related proteins (MMP-9, Twist and Snail). TMEM45B may thus serve as a potential prognostic marker and therapeutic target in lung cancer (164). TMEM45B is highly expressed in PC tissues and cell lines. Its knockdown inhibited cell proliferation, invasion and migration while inducing cell cycle arrest and apoptosis. Conversely, TMEM45B overexpression promoted these processes and inhibited apoptosis. Gene set enrichment analysis revealed that TMEM45B regulated genes that are involved in the cell cycle and metastasis pathways, further supporting its oncogenic role in PC (165). Shen *et al* (166) also demonstrated that in GC, TMEM45B was overexpressed in both tissues and cell lines. Silencing TMEM45B inhibited cell proliferation, migration, invasion and EMT. This suppression was mediated through the inhibition of the JAK2/STAT3 signaling pathway, as evidenced by reduced levels of phosphorylated JAK2 and STAT3 upon TMEM45B knockdown (166).

Moreover, in osteosarcoma, Li *et al* (167) verified the upregulation of TMEM45B expression and revealed that its

knockdown in U2OS cells effectively suppressed proliferation, migration and invasion *in vitro*, and inhibited tumor growth in xenograft models. This effect was associated with the downregulation of key proteins such as β-catenin, cyclin D1 and c-Myc, which are important for cancer cell proliferation and metastasis (167). These findings collectively indicate that TMEM45B is a potent regulator of tumorigenesis across various cancer types. Its dysregulated expression may act as a potential prognostic biomarker for cancer progression and it holds promise as a therapeutic target. Furthermore, previous studies have demonstrated that the regulatory effects of TMEM45B extend to modulating the TME, influencing immune responses and potentially modulating the response to chemotherapeutic agents (167,168). Similarly, TMEM45B has been identified as a novel predictive biomarker for prostate cancer progression and metastasis. Its expression is notably increased in tumor cell lines with high metastatic potential and is associated with biochemical recurrence, distant metastasis and a poor OS. Multivariate analysis confirmed that TMEM45B was an independent risk factor for metastasis, making it a promising prognostic marker for patients with prostate cancer (169).

TMEM45B exerts its oncogenic effects through multiple signaling pathways, including Wnt/β-catenin, JAK2/STAT3 and TGF-β. It regulates key cellular processes such as proliferation, apoptosis, migration and invasion by modulating the expression of downstream target genes and proteins. Additionally, the involvement of TMEM45B in EMT and chemotherapy resistance further underscores its role in cancer progression. Given its central role in regulating key pathways involved in cancer progression, TMEM45B may be developed as a targeted therapy, thereby improving patient outcomes.

TMEM48. TMEM48 is a member of the nuclear pore complex (NPC) family of proteins and is essential for maintaining nuclear membrane integrity and enabling nuclear transport (170). The protein consists of six transmembrane domains and is vital for NPC assembly, which is important for regulating several cellular processes, including chromosome segregation, gene transcription, DNA replication, DNA damage repair and apoptosis (170,171). Alterations in the expression of NPC proteins, including TMEM48, have been associated with the onset and progression of various malignancies, such as breast, melanoma, pancreatic, colon, gastric, prostate, esophageal, lung cancer and lymphoma (170-172).

Previous studies have highlighted the involvement of TMEM48 in NSCLC (170-173). Qiao *et al* (173) demonstrated that TMEM48 expression was markedly increased in NSCLC tissues compared with adjacent normal tissues. This overexpression was associated with a poor prognosis, including reduced survival times, increased tumor size and lymph node metastasis. TMEM48 regulates essential cellular processes, such as proliferation, migration and invasion, by regulating genes involved in the cell cycle and DNA replication. Knockdown of TMEM48 in NSCLC cell lines led to reduced cell proliferation, induction of G1 phase cell cycle arrest and inhibition of migration and invasion. Furthermore, silencing of TMEM48 triggered apoptosis in NSCLC cells. In an *in vivo* study, silencing TMEM48 led to a notable reduction in tumor weight in xenograft models (173).

Moreover, the study by Akkafa *et al* (6) suggests that microRNA (miR)-421, an miR targeting TMEM48, potentiates apoptotic signaling pathways in NSCLC. Suppression of TMEM48 by miR-421 upregulated the expression of apoptosis-related proteins, such as caspase-3, PTEN and p53, which collectively promote cell death. This indicated that targeting TMEM48 may serve as a therapeutic strategy for improving the efficacy of treatments in NSCLC. TMEM48 has been identified in other types of cancer, such as CC (174). In CC, TMEM48 is overexpressed and its knockdown inhibited cell proliferation, migration and invasion both *in vitro* and *in vivo* (174). Jiang *et al* (174) indicated that TMEM48 promotes CC progression by activating the Wnt/β-catenin signaling pathway, as evidenced by the reduced expression of β-catenin, TCF1 and AXIN2 following TMEM48 knockdown. This suggested that TMEM48 is important in tumorigenesis by modulating key signaling pathways involved in cancer progression.

TMEM48 is a promising prognostic marker and therapeutic target. Given its central role in regulating cellular functions key for tumor progression, TMEM48 represents a valuable target for future therapeutic strategies focused on inhibiting cancer growth and metastasis. Further research is needed to explore the therapeutic potential of TMEM48 in various malignancies, including its modulation by miRNAs.

TMEM65. TMEM65 is a mitochondrial inner membrane protein whose deficiency has been implicated in a mitochondrial disorder characterized by a complex encephalomyopathic phenotype (175,176). Clinical manifestations include microcephaly, craniofacial dysmorphism, psychomotor regression, generalized hypotonia, growth retardation, lactic acidosis, intractable seizures and dyskinetic movements, notably in the absence of cardiomyopathy (175). Previously, TMEM65 has emerged as a pivotal factor in cancer biology, with its involvement reported across various malignancies, including CRC, TNBC, GC and HCC (175-180). TMEM65 carries out a multifaceted role in tumorigenesis by modulating mitochondrial dynamics, driving metabolic reprogramming and regulating signaling pathways associated with cancer progression and therapeutic resistance. This contrast between its role in congenital mitochondrial disease and acquired malignancies underscores its biological value and potential as a therapeutic target.

In CRC, TMEM65 is transcriptionally regulated by the CHD6-TCF4 axis, which is activated by both EGF and Wnt signaling pathways. CHD6, a chromatin remodeler, binds to Wnt signaling transcription factor TCF4 to facilitate TMEM65 expression. This axis promotes mitochondrial dynamics and ATP production, essential for cancer cell proliferation, migration and invasion. Targeting the CHD6-TMEM65 axis with Wnt inhibitors and anti-EGFR therapies showed promise in restricting CRC growth (176). TMEM65 acts as an oncogene in TNBC, where it was revealed to be upregulated by the transcription factor MYC and DNA demethylase TET3. TMEM65 enhanced mitochondrial oxidative phosphorylation and reactive oxygen species production, which, in turn, activates hypoxia inducible factor (HIF)-1α and SERPINB3 and promotes cancer stemness, progression, and cisplatin resistance. Inhibition of MYC and TET3 attenuated TMEM65-driven TNBC progression, highlighting its potential as a therapeutic target (177). TMEM65 amplification and overexpression are common in GC and are associated with a poor

prognosis. TMEM65 promoted tumorigenesis by activating the PI3K-Akt-mTOR signaling pathway through its interaction with YWHAZ, a protein that inhibits ubiquitin-mediated degradation. Silencing TMEM65 suppresses tumor growth and metastasis, making it a promising therapeutic target in GC (163). In HBV-related HCC, TMEM65 amplification was driven by HBV integration-induced genomic rearrangements. TMEM65 contributes to tumorigenesis by promoting mitochondrial function and metabolic reprogramming, which are key for cancer cell survival and proliferation (178).

TMEM65 expression is associated with tumor immune infiltration, particularly $CD8^+$ T effector cells and immune checkpoint markers. Its role in modulating the TME and immune response makes it a potential biomarker for predicting prognosis and the efficacy of immunotherapy (179). TMEM65 may serve as a target for chimeric antigen receptor T-cell therapies and antibody-drug conjugates. Its overexpression in cancer tissues and low expression in normal tissues make it an attractive candidate for immune-based interventions (180). TMEM65 is a pivotal oncogene that drives cancer progression through its roles in mitochondrial dynamics, metabolic reprogramming and signaling pathway activation. Its overexpression is associated with poor prognosis across multiple cancer types, making it a promising biomarker and therapeutic target. Future research should focus on developing targeted therapies that exploit the oncogenic function of TMEM65 while minimizing off-target effects.

TMEM140. TMEM140, also known as FLJ11000, is a TP encoded by a gene located on chromosome 7q33, consisting of 185 amino acids (181). Although initially identified for its role in supporting hematopoietic stem cells *in vitro* (181-183), TMEM140 has since been associated with various biological processes, including tumorigenesis and viral infection (182). Guan *et al* (183) have highlighted the dual functions of TMEM140 as both a prognostic biomarker and a potential therapeutic target in cancer and its role in inhibiting herpes simplex virus 1 (HSV-1) replication. TMEM140 has emerged as a key player in various types of cancer, including gliomas and GC. Gliomas are among the most common and aggressive primary brain tumors, characterized by a poor prognosis and limited treatment options. TMEM140 is overexpressed in gliomas compared with normal brain tissues and its high expression is associated with a larger tumor size, higher histologic grade and shorter OS (181). An *In vitro* study using glioma cell lines have revealed that silencing TMEM140 inhibited cell proliferation, migration and invasion, with concurrent arrest in the G1 phase of the cell cycle and activation of apoptotic pathways (181). It regulates cell cycle progression by shortening the cell cycle and reducing apoptosis, thereby promoting tumor cell proliferation. Additionally, TMEM140 enhanced tumor cell adhesion and survival by modulating the expression of adhesion and anti-apoptotic proteins (181-183). *In vivo* silencing of TMEM140 led to a marked reduction in tumor volume and weight (183), highlighting its pivotal role in tumor growth. These findings identify TMEM140 as a novel prognostic biomarker and therapeutic target for gliomas, underscoring its potential for clinical application in glioma treatment. Beyond gliomas, TMEM140 has been implicated in other cancer types through its co-expression with long-chain acyl-coenzyme A synthetase 5 and this was predictive of improved prognosis in breast, ovarian and lung cancer (184). This suggests that TMEM140 may carry out a context-dependent role in cancer progression, potentially acting as a tumor suppressor in certain malignancies (184). Furthermore, TMEM140 has been identified as a candidate gene in HTLV-1-infected cancer cells, indicating its broader relevance in cancer biology (185).

TMEM140 is a multifunctional protein that is involved in several processes in cancer biology, autoimmune diseases and viral infections. In systemic sclerosis, the involvement of TMEM140 in DNA methylation changes indicates a potential key role in disease pathogenesis, particularly in fibroblast function (186). Additionally, its role in inhibiting HSV-1 replication highlights its promise as an antiviral target. Given its diverse functions, TMEM140 may serve as a compelling candidate for further investigation, with implications for therapeutic strategies across a variety of diseases.

TMEM158. TMEM158, located on chromosome 3p21.3, also known as BBP, Ras-induced senescence 1 protein, p40BBP and HBB, was initially recognized as an upregulated potential tumor suppressor gene in the context of Ras V12 lentiviral infection-induced senescence in fibroblasts (187). Li *et al* (188) have highlighted its key role in the development of various types of cancer. Importantly, TMEM158 is overexpressed in Wilms tumor (nephroblastoma), with somatic mutations in the β-catenin gene, indicating a connection between Ras and Wnt signaling pathways (189). In lung cancer, TMEM158 is highly expressed in advanced-stage tumors and is associated with poor OS (61). It promotes EMT and enhanced cell migration, contributing to aggressive tumor behavior (61). Additionally, TMEM158 expression is induced under hypoxic conditions in a HIF-1α-dependent manner, associating it with tumor hypoxia, a hallmark of cancer progression (61). Moreover, TMEM158 has emerged as a potential biomarker for predicting the efficacy of cisplatin-based therapy in NSCLC, with its expression correlating with improved therapeutic outcomes (61,190).

In PC, TMEM158 overexpression promotes cell proliferation, migration and invasion through the activation of the TGFβ1 and PI3K/AKT signaling pathways, highlighting its oncogenic potential (191). TMEM158 is amplified in GC tissues and is associated with poor prognosis (192). In GC, it was revealed to accelerate GC cell proliferation by activating the PI3K/AKT signaling pathway and its knockdown inhibited tumor growth, suggesting its potential as a biomarker and therapeutic target (192). In CRC, downregulation of TMEM158 expression notably impairs tumor cell proliferation, migration and MDR, highlighting its value in both tumor progression and chemoresistance (193). Furthermore, TMEM158 is involved in regulating EMT in various types of cancer, enhancing metastasis and aggressiveness. In OC, TMEM158 expression was shown to be considerably upregulated, thereby promoting tumorigenic properties, including cell proliferation, invasion, adhesion and migration (194). Silencing TMEM158 resulted in downregulation of intercellular adhesion molecules (ICAM1 and VCAM1) and disruption of the TGF-β signaling pathway, further emphasizing its role as an oncogene (194). It also contributed to doxorubicin resistance by upregulating ABCG2, a drug efflux transporter (195). TMEM158 is highly expressed in TNBC and was shown to be associated with poor clinical outcomes and to drive EMT and tumor metastasis via

activation of the TGF-β signaling pathway, highlighting it as a potential therapeutic target for this aggressive breast cancer subtype (196).

In glioblastoma (GBM), overexpression of TMEM158 was associated with a poor prognosis, whereas silencing it suppressed cell migration and invasion by interfering with STAT3 signaling pathways (188). Unlike its oncogenic role in other types of cancer, TMEM158 is downregulated in prostate cancer and is associated with advanced disease features and poor survival. Its expression is negatively regulated by androgen receptor signaling, and it may carry out a tumor-suppressive role in this context (197,198). Additionally, TMEM158 was shown to be involved in immune modulation, correlating with tumor mutational burden, microsatellite instability and immune cell infiltration in the TME (190,197,198).

In NSCLC, TMEM158 is considered to modulate immune checkpoints, thereby enhancing the therapeutic efficacy of immune checkpoint inhibitors such as anti-PD-1 and anti-CTLA-4 (190,197,198). This emerging role in immuno-oncology highlights a promising avenue for therapeutic interventions targeting TMEM158. Additionally, pan-cancer analyses demonstrated that TMEM158 is upregulated in a range of cancer types, including melanoma and HCC, where its elevated expression is associated with tumor aggressiveness and poor prognosis (197). In these contexts, TMEM158 has been implicated in hypoxia-induced pathways, thus facilitating tumor growth in hypoxic conditions. These findings collectively highlight the key role of TMEM158 in regulating tumor progression, metastasis, immune evasion and chemoresistance across various cancer types. Its involvement in signaling pathways, including TGFβ, PI3K/AKT, STAT3 and Wnt, as well as its potential in immune modulation, establishes TMEM158 as both a prognostic biomarker and a promising therapeutic target in oncology.

TMEM159. TMEM159, also known as promethin, is a small TP consisting of 161 amino acids with four adjacent transmembrane helices forming two helical hairpins (199). It carries out a key role in lipid droplet (LD) biogenesis through its interaction with Seipin, a key regulator of lipid storage in the ER (200). The TMEM159-Seipin complex co-purified with triacylglycerol and facilitated the initiation of LD formation. Upon maturation of LD, TMEM159 dissociated and relocated to the LD surface, thereby participating in the maintenance of lipid homeostasis (200).

Although extensively studied in the context of lipid metabolism, TMEM159 has recently gained attention for its potential involvement in cancer progression (199-202). Notably, in GBM, enhanced LD formation, which is associated with a poor prognosis under metabolic stress, has been associated with altered TMEM159 expression (201). TMEM159 may contribute to glioma malignancy by modulating EGFR signaling pathways, which are important for cancer cell proliferation, migration and survival (201). These findings suggest that TMEM159 could serve as both a molecular biomarker and therapeutic target in lipid-associated malignancies such as GBM (201,202).

Beyond cancer, TMEM159 has also been associated with neuropsychiatric disorders through genome-wide association studies (199-205), but its mechanistic involvement in tumorigenesis, particularly through pathways associated with lipid regulation and oncogenic signaling, may represent promising directions for future cancer-focused research. Continued investigation is warranted to fully elucidate the multifaceted role of TMEM159 in lipid metabolism and cancer biology (203-205).

TMEM205. TMEM205 is a TP encoded by a gene located on chromosome 19p13.2, and is formed of 189 amino acids. TMEM205 has emerged as a notable player in cancer biology, particularly in the context of drug resistance, tumor progression and immune modulation. TMEM205 has shown promise as a biomarker for chemoresistance and prognosis. In high-grade serous OC, TMEM205 was found to be differentially expressed in extracellular vesicles derived from platinum-resistant patients with OC, demonstrating high diagnostic accuracy for platinum resistance (206). In HCC, low TMEM205 expression was independently associated with poor OS and disease-specific survival, highlighting it as a potential prognostic marker (207). TMEM205 is associated with chemoresistance, particularly to platinum-based therapies such as cisplatin (208). Moreover, TMEM205 was also shown to carry out a role in tumor progression and immune evasion (208). Targeting TMEM205 may offer a novel strategy to overcome chemoresistance and improve treatment outcomes. In ovarian clear cell carcinoma, the combination of oncolytic viruses and cisplatin reduced TMEM205 expression and sensitized cells to chemotherapy (208). Similarly, small molecule inhibitors such as L-2663 have shown efficacy in enhancing platinum sensitivity in OC (209). These findings underscore the potential of TMEM205 as a therapeutic target in combination therapies.

TMEM205 is a multifaceted protein involved in chemoresistance, tumor progression and immune modulation across various types of cancer. Its upregulation is associated with poor treatment outcomes, while its inhibition enhances chemotherapy efficacy. As a biomarker, TMEM205 may serve as a diagnostic and prognostic value, particularly in various types of platinum-resistant cancer (206-209). Future research should focus on developing targeted therapies to modulate TMEM205 activity, potentially improving patient outcomes in various types of resistant cancer.

TMEM proteins involved in TME. The TME, composed of immune cells, stromal components, extracellular matrix and soluble factors, carries out a pivotal role in cancer progression, immune evasion and therapy response. Growing evidence shows that TPs not only regulate tumor cell behavior but also engage in bidirectional crosstalk with the TME, contributing to its remodeling and tumor development (4,5).

Several TMEM proteins have been shown to regulate tumor-immune interactions. For example, TMEM173 carries out a key role in the activation of innate immune responses and can modulate T-cell infiltration and antitumor immunity within the TME (210-212). Evidence from several types of cancer, including SCLC, TNBC, CC and GBM, demonstrates that activation of the cGAS-STING pathway can reshape the TME by promoting chemokine production (such as CXCL10 and CCL5), increasing $CD8^+$ T cell infiltration and potentiating antitumor immunity (210,212-214). Microbiota-derived STING agonists can reprogram monocytes and DC in the TME, enhancing IFN-I production and improving the efficacy of immune checkpoint blockade (215). Moreover, STING

signaling can be triggered not only by endogenous cytosolic DNA but also by tumor-derived exosomes, indicating a dynamic extracellular-intracellular feedback loop that facilitates immune regulation (213). STING was also shown to contribute to immunosuppression in certain contexts, such as by promoting regulatory T cell (Treg) differentiation or inducing ER stress and T cell apoptosis through non-canonical pathways (213,216). Senescent tumor cells release mitochondrial DNA that activates the cGAS-STING pathway in myeloid-derived suppressor cells, promoting immunosuppression and tumor progression (107). These multifaceted roles highlight TMEM173 as a key modulator of immune surveillance and tumor progression, reflecting the complex bidirectional communication between TMEM proteins and the TME.

TMEM205 carries out a key role in modulating TME and influencing cancer progression. In HCC, TMEM205 expression was shown to be associated with the immune landscape of the tumor, where low TMEM205 expression was associated with a poor prognosis and survival outcomes (207,209). TMEM205 interacted with various immune cell populations in the TME, particularly macrophages and Tregs (207,209). The expression of TMEM205 was positively associated with the proportion of macrophages, including M1 macrophages, while it was negatively associated with immunosuppressive M2 macrophage markers and Treg markers. This suggested that TMEM205 may exert its antitumor effects by reducing the levels of immunosuppressive cells such as M2 macrophages and Tregs, while promoting the infiltration of cytotoxic $CD8^+$ T cells into the TME. Therefore, extracellular feedback through TMEM205 may regulate immune cell infiltration, enhancing antitumor immunity and potentially improving therapeutic responses, especially in combination therapies targeting immune checkpoints (207,209).

TMEM16A also carries out a key role in shaping the TME. In PC, high TMEM16A expression is associated with an immunosuppressive TME, characterized by increased cancer-associated fibroblasts (CAFs) and reduced $CD8^+$ T cell infiltration (217). Similarly, in gastrointestinal cancer, TMEM16A contributed to immunotherapy resistance by inhibiting cancer ferroptosis and recruiting CAFs, thereby impairing $CD8^+$ T cell-mediated anti-tumor immunity (218). TMEM101 also carried out a key role in modulating the HCC TME and influencing HCC progression. In HCC, TMEM101 expression was markedly upregulated, and was associated with a poor prognosis and advanced tumor grade and stage (219). TMEM101 was shown to interact with various immune cell populations within the TME, particularly influencing macrophage infiltration and T cell activity. High TMEM101 expression is associated with increased M0 macrophage infiltration, which are pro-tumorigenic and decreased infiltration of anti-tumor immune cells such as M1 macrophages and resting memory $CD4^+$ T cells. This shift in immune cell populations suggests that TMEM101 promotes tumor progression by modifying the immune landscape in favor of tumor growth. Furthermore, intracellular feedback regulation by TMEM101 was shown to impact pathways related to cell cycle, DNA replication and repair, facilitating tumor proliferation and survival (219). Thus, TMEM101 not only serves as a diagnostic and prognostic biomarker for HCC but also acts as an oncogene that influences the TME, contributing to HCC initiation and progression (219).

TMEM proteins also mediate extracellular and intracellular feedback regulation. Extracellularly, they can interact with cytokines, growth factors and adhesion molecules, modulating upstream signaling events. TMEM52B is a novel regulator that modulates the activity of both E-cadherin and EGFR, exhibiting tumor suppressor-like functions. Lee *et al* (220) revealed that peptides derived from the extracellular domain (ECD) of TMEM52B considerably inhibit cancer cell survival, invasion and anchorage-independent growth, while reducing the phosphorylation of ERK1/2 and AKT. These peptides stabilize E-cadherin at cell-cell junctions, leading to decreased β-catenin activity, and directly bind to the E-cadherin ECD to block the interaction between soluble E-cadherin and EGFR, thereby suppressing EGFR activation. These findings suggest that TMEM52B ECD-derived peptides not only possess strong anti-cancer potential but also serve as valuable tools for investigating the regulatory role of TMEM52B in the crosstalk between E-cadherin and EGFR (220). Intracellularly, TMEM proteins often participate in key oncogenic pathways such as MAPK, PI3K/AKT and Wnt, forming regulatory loops that either amplify or attenuate cellular responses to environmental cues. These feedback mechanisms may affect cell proliferation, apoptosis, migration and ultimately, cancer progression (4,5,220).

Collectively, the bidirectional interaction between TMEM proteins and the TME contributes to tumor plasticity, immune evasion and chemoresistance. Although this area remains underexplored, it represents a promising direction for future research. An improved understanding of how TMEM proteins influence the TME may lead to the identification of novel therapeutic targets and strategies to modulate tumor-host interactions.

4. TMEM proteins in tumor chemoresistance

TMEM45A. Hypoxia is a defining characteristic of solid tumors, markedly contributing to resistance to both radiotherapy and chemotherapy, which increases the likelihood of tumor recurrence (221,222). This phenomenon is particularly prominent in liver and breast cancer, where the hypoxic TME provides a protective effect against chemotherapy-induced cell death. In these conditions, TMEM45A has been shown to serve as a key mediator of tumor progression and resistance to chemotherapeutic agents under hypoxic conditions (156-161,221,222). Previous studies have demonstrated an upregulation of TMEM45A in hypoxic tumor cells, such as HepG2 and MDA-MB-231 cells, exposed to chemotherapeutic agents such as Taxol or etoposide. Under these conditions, TMEM45A protects against apoptosis, a key mechanism that drives chemotherapy resistance (156-161,221,222). Specifically, silencing TMEM45A using siRNA alleviated the protective effect of hypoxia and sensitized the cells to chemotherapy-induced cell death. This indicates that TMEM45A carries out a key role in sustaining chemoresistance under hypoxic stress (156-161,221,222). The role of TMEM45A in modulating chemosensitivity depends on the cancer type, with its activation potentially acting as either a pro-apoptotic or anti-apoptotic factor.

In HNSCC and RCC, TMEM45A is upregulated, and its upregulation is associated with a poorer prognosis. In these types of cancer, silencing TMEM45A enhanced sensitivity to cisplatin, a commonly used chemotherapeutic agent, by modulating DNA damage repair mechanisms and the unfolded protein response pathway (156-161,221,222). Conversely, in breast and liver cancer cells, TMEM45A contributed to chemoresistance by inhibiting apoptotic pathways, thus preventing cell death induced by Taxol and etoposide (156-161,221,222). Further investigation into the mechanisms by which TMEM45A regulates chemoresistance uncovered its involvement in regulating the EMT, a process associated with enhanced tumor invasion and metastasis (156-161,221,222). In CC, silencing TMEM45A downregulated EMT markers such as Vimentin and N-cadherin and increased the expression of the epithelial marker E-cadherin. This indicated that TMEM45A not only influenced chemoresistance but also promoted tumor progression through EMT, thereby enhancing the invasive potential of cancer cells (156-161,221,222). The association between TMEM45A expression and chemotherapy resistance has been demonstrated in HPV-positive CC cells. In this context, TMEM45A was highly expressed in SiHa and HeLa cells and silencing TMEM45A notably reduced cisplatin resistance, as evidenced by a decrease in the IC_{50} values of cisplatin-treated SiHa/DDP and HeLa/DDP cells. This finding highlights the potential of TMEM45A as a therapeutic target for overcoming chemoresistance in HPV-positive CC (156-161,221,222).

TMEM45A expression is upregulated in Palbociclib-resistant HR^+ breast cancer cells and is associated with accelerated tumor progression and increased glycolysis (156-161,221,222). Its overexpression drove Palbociclib resistance, while silencing TMEM45A enhanced sensitivity to the drug, induced cell cycle arrest and apoptosis, and inhibited cancer cell proliferation. Mechanistic analysis revealed that TMEM45A downregulated EMT markers and glycolysis-related proteins, and this reduced tumor invasiveness. By activating the AKT/mTOR pathway, TMEM45A regulated the cell cycle and glycolysis (4,5,156-161,221,222). In mouse models, TMEM45A knockdown restored Palbociclib sensitivity and inhibited tumor growth (156-161,221,222). Exosome-mediated delivery of TMEM45A-targeting siRNA in patient-derived xenografts enhanced sensitivity to CDK4/6 inhibitors without toxicity (160).

Furthermore, TMEM45A carries out a key role in MDR, especially in CRC. Studies have shown that TMEM45A expression is upregulated in 5-fluorouracil (5-FU)-resistant CRC cells (155-162). Knockdown of TMEM45A increased the sensitivity of these cells to 5-FU, induced apoptosis and increased the intracellular accumulation of drugs. Additionally, inhibition of TMEM45A suppressed cell migration and invasion and reduced the activation of the TGF-β signaling pathway, which is known to promote EMT and contribute to drug resistance in cancer (155-162). These findings underscore the potential of TMEM45A as a target for overcoming MDR in CRC.

In conclusion, TMEM45A is a key regulator of chemoresistance in various types of cancer, particularly when a hypoxic environment is present. Its dual role in promoting either pro-apoptotic or anti-apoptotic pathways, which varies depending on the cancer type, highlights its complexity as a therapeutic target. Targeting TMEM45A may, therefore, serve as a promising strategy to enhance the efficacy of chemotherapy, especially in hypoxic tumors prone to resistance. Further studies are needed to fully elucidate the molecular pathways through which TMEM45A exerts its effects on tumor progression and drug resistance, offering key insights into the development of novel therapeutic strategies (156-162,221,222).

TMEM158. TMEM158 carries out a key role in mediating chemoresistance in several types of cancer, including CRC. Overexpression of TMEM158 increases resistance to cisplatin and 5-FU by upregulating MDR-related proteins such as MDR1, MRP1 and Bcl-2, thereby enhancing drug efflux and inhibiting apoptosis (188,190-194). Silencing TMEM158 decreased the levels of these MDR proteins, restoring drug sensitivity. Conversely, its overexpression in drug-resistant CRC cells increased the IC_{50} values for cisplatin and 5-FU, highlighting its role in chemoresistance (188,190-194). Modulation of the intrinsic apoptotic pathway by TMEM158 further contributed to its impact on tumor survival and drug resistance (193). In cisplatin-resistant NSCLC PC-9/CDDP cell lines, knockdown of TMEM158 enhanced the sensitivity of the cells to cisplatin, demonstrating that TMEM158 carries out a key role in the development of chemoresistance (194). Moreover, TMEM158 expression is not only associated with resistance to cisplatin in NSCLC but also acts as a predictive biomarker for treatment response. Given its role in regulating tumor progression and drug resistance, TMEM158 may serve as a potential biomarker for predicting treatment response and as a potential therapeutic target for overcoming chemoresistance.

TMEM88. TMEM88 is a dual-transmembrane protein implicated in several types of cancer, including breast, ovarian, lung and testicular cancer. Research suggests that TMEM88 carries out a key role in mediating tumor progression and is notably associated with chemoresistance. TMEM88 modulates essential cellular processes, including cell proliferation, differentiation and apoptosis, by regulating the Wnt signaling pathway (74-77,223,224).

In OC, TMEM88 expression is associated with cisplatin resistance, a commonly used chemotherapeutic agent. Studies revealed that in cisplatin-resistant OC cells, the promoter methylation of TMEM88 was markedly reduced, leading to its overexpression (223). TMEM88 inhibited the canonical Wnt signaling pathway and its overexpression or knockdown affected tumor cell sensitivity to chemotherapy. Silencing TMEM88 in resistant cells enhanced sensitivity to cisplatin and increased the expression of Wnt target genes, such as cyclin D1 and c-Myc, further confirming its role in modulating Wnt signaling (75,223). Treatment with DNA methyltransferase inhibitors, such as SGI-110, restored TMEM88 expression, reversing chemoresistance and increasing cellular sensitivity to cisplatin (223,224). TMEM88 inhibited canonical Wnt signaling by interacting with DVL, a key mediator in the pathway. This inhibition carries out a dual role, suppressing tumor progression and influencing chemoresistance by modulating the TME.

TMEM88 has emerged as a promising therapeutic target for overcoming chemoresistance across several types of cancer. Targeting TMEM88 through epigenetic modulation or gene therapy may reverse chemoresistance and enhance

chemotherapy efficacy. The role of TMEM88 in the Wnt signaling pathway offers a molecular basis for its involvement in tumor progression and drug resistance, highlighting novel avenues for therapeutic strategies in the management of cancer. Further studies are required to fully elucidate the mechanisms underlying the role of TMEM88 in tumor progression and chemoresistance, which may lead to the development of novel therapeutic interventions to restore chemotherapy sensitivity (74-,82,223,224).

TMEM205. TMEM205 has been identified as a key player in cisplatin resistance across several types of cancer, including OC and GC (207-209). It mediates resistance through various mechanisms, particularly by enhancing drug efflux via the exosomal pathway. TMEM205 has been associated with increased exosome release, which can expel cisplatin from cancer cells, reducing its intracellular accumulation and thus contributing to resistance (209,225,226).

In OC, TMEM205 was revealed to be upregulated in cisplatin-resistant cell lines, and its inhibition using specific small molecules or genetic knockdown notably increased cisplatin accumulation in these cells, enhancing their sensitivity to the drug (208,227). Additionally, TMEM205 was shown to co-localize with RAB8, a protein involved in vesicular trafficking, further suggesting its role in the regulation of exosome-mediated drug efflux (208,227). Combining TMEM205 inhibition with cisplatin or oncolytic virus therapy was found to restore chemosensitivity and inhibit tumor growth (209,226).

In GC, TMEM205 also carries out a key role in promoting cisplatin resistance by inducing M2 polarization of TAMs, which enhanced cancer cell stemness, migration and EMT. These processes contribute to the malignant progression of the disease (208,225). The modulation of TMEM205 expression can alter the immune environment of the tumor, further influencing chemoresistance (227).

Overall, TMEM205 represents a potential therapeutic target to overcome cisplatin resistance, and strategies such as its inhibition, combined with other treatments, may improve the efficacy of chemotherapy in different types of resistant cancer.

TMEM16A. Recent research has highlighted the key role of TMEM16A in mediating chemoresistance, particularly to platinum-based therapies in HNSCC (228). TMEM16A overexpression has been revealed to increase oxidative stress, which upregulates ATP7B, a copper-transporting ATPase that facilitates lysosomal sequestration of platinum compounds, such as cisplatin, thereby diminishing their cytoplasmic efficacy. This mechanism underpins a novel resistance pathway, as demonstrated by a positive association between TMEM16A and ATP7B mRNA levels in squamous cell carcinoma of the head and neck tumor specimens (133). Notably, interventions with copper chelators (such as cuprizone and bathocuproine disulfonic acid) and antioxidants (for example, N-acetylcysteine) effectively reversed ATP7B induction and restored cisplatin sensitivity, especially in TMEM16A-overexpressing cells (229). These findings suggest that TMEM16A contributes to a copper-dependent resistance mechanism, offering potential therapeutic implications. Additionally, TMEM16A expression may serve as a biomarker to guide the selection of chemotherapy. For example, patients with cisplatin-resistant oral squamous cell carcinoma in high-risk groups showed enhanced sensitivity to docetaxel and shikonin, indicating the potential of TMEM16A in risk stratification and treatment optimization (229).

5. Discussion

The present review discusses the roles of various TMEM proteins in tumorigenesis and their potential contributions to chemoresistance, providing insights into their mechanisms and potential therapeutic implications (Table I). TMEM proteins have been implicated in multiple types of cancer, in which they regulate fundamental cellular processes such as proliferation, invasion, migration and apoptosis. The ability of TMEM proteins to influence tumor progression and resistance to therapy highlights their potential as targets for cancer treatment (Fig. 4). TMEM proteins carry out a key role in regulating cancer cell proliferation, migration and invasion through various molecular mechanisms and signaling pathways, which can be categorized into four key aspects (Table I and Fig. 4).

Epigenetic modifications and DNA methylation. TMEM proteins are frequently regulated at the gene level by epigenetic modifications, such as DNA methylation and histone modifications (67-69). For example, TMEM7 and TMEM106A expression in HCC and GC is silenced by promoter methylation, which is associated with a poor prognosis (67-69,83,84). Studies have revealed that the downregulation of these TMEM proteins can be reversed through DNA demethylation, leading to the restoration of their tumor-suppressive functions (67-69,83,84). Similarly, TMEM25 in colon cancer and TMEM176A in esophageal cancer exhibit hypermethylation at their promoters, which suppresses their expression and promotes tumor progression (70,71,111,112). A common theme across these studies is that epigenetic changes, especially promoter methylation, not only regulate the expression and function of TMEM proteins but also influence treatment responses (112). For example, TMEM88 in OC has been associated with the differential sensitivity to chemotherapy based on its methylation status (223). Moreover, TMEM proteins such as TMEM173 and TMEM176B are involved in immune regulation, suggesting that reversing epigenetic silencing of TMEMs could offer dual therapeutic benefits: Restoring tumor suppressor activity and enhancing anti-tumor immune responses (97,100,101,119-121). Epigenetic silencing of TMEM proteins thus represents a notable mechanism of tumorigenesis and a promising target for therapeutic intervention.

Pathway level, EGFR and other signaling pathways. TMEM proteins are involved in the modulation of key signaling pathways that regulate cancer cell behaviors. For example, TMEM16A interacts with the EGFR in HNSCC and colon cancer, enhancing EGFR signaling and contributing to cancer cell proliferation, migration and survival (128). TMEM16A stabilizes EGFR and forms a positive feedback loop that potentiates cancer progression (128). Additionally, TMEM45A is associated with the TGF-β signaling pathway in OC, where it regulates proliferation and migration (154). TMEM158 has been implicated in modulating the Wnt/β-catenin signaling

Table I. List of TMEM proteins involved in cancer.

Name	Amino acids	Location	Involvement in cancer	Main function	Mechanism	(Refs.)
TMEM7	232	Chromosome 3p21.3	Tumor suppressor; involved in liver cancer.	Inhibits the proliferation, migration, and carcinogenesis of HCC cells.	Mediates epigenetic silencing through DNA methylation and histone deacetylation.	(66-69)
TMEM16A	986	Chromosome 11q13.3	Oncogene; involved in breast, esophageal, head and neck cancers.	Chloride channel; regulates cell proliferation, migration and EMT.	Interacts with EGFR signaling pathways; involved in the activation of EGFR and CAMK pathways, promoting metastasis through EMT.	(126-151, 217,218, 228,229)
TMEM25	366	Chromosome 11q23.3	Tumor suppressor, involved in colon, breast, and renal cell carcinoma.	Modulates immune response; regulates growth factor signaling; affects cell adhesion; suppresses tumor progression.	Mediates epigenetic silencing through DNA methylation and histone deacetylation; inhibits EGFR-mediated STAT3 activation; facilitates immune evasion.	(12,70-73)
TMEM45A	275	Chromosome 3q12.1	Oncogene; involved in gliomas, breast, liver, renal, ovarian cancer.	Mediator of chemoresistance under hypoxic and drug-stressed conditions; involved in epidermal differentiation and keratinization.	Activates the TGF-β pathway; enhances chemoresistance in hypoxic conditions and metabolic adaptation; promotes EMT; regulates the cell cycle and apoptosis.	(4,152-162,221, 222)
TMEM45B	275	Chromosome 11q24.3	Oncogene; involved in lung, pancreatic, gastric cancer.	Promotes cell proliferation, migration, invasion; inhibits apoptosis.	Regulates STAT3/JAK2 pathways; modulates tumor microenvironment by influencing immune responses and hypoxic adaptation.	(163-169)
TMEM48	674	Chromosome 1p32.3	Oncogene; involved in NSCLC, cervical cancer.	Regulates nuclear transport and membrane integrity; promotes tumor cell proliferation, migration, and invasion.	Activates the Wnt/β-catenin signaling pathway; regulates the cell cycle and apoptosis.	(170-174)
TMEM65	240	Chromosome 8q24.1	Oncogene; involved in TNBC, HCC, CRC and GC	Regulates mitochondrial dynamics and OXPHOS; promotes cell proliferation and stemness; modulates immune response and tumor microenvironment.	Transcriptionally activated by CHD6-TCF4 in CRC, by MYC and TET3 in TNBC; Activates PI3K-Akt-mTOR pathway via interaction with YWHAZ in GC; enhances ROS-HIF-1α-SERPINB3 axis to promote stemness and cisplatin resistance in TNBC.	(175-180)
TMEM88	159	Chromosome 17p13.1	Tumor suppressor; involved in breast, ovarian, lung, thyroid cancer.	Inhibits Wnt signaling and regulates chemoresistance; involved in cardiomyocyte differentiation.	Epigenetic modulation; inhibits the Wnt pathway by directly interacting with DVL; subcellular localization-dependent functional switch.	(74-82, 223,224)

Table I. Continued.

Name	Amino acids	Location	Involvement in cancer	Main function	Mechanism	(Refs.)
TMEM106A	262	Chromosome 17q21.3	Tumor suppressor; involved in gastric and liver cancer.	Immune modulation; induces apoptosis, delays tumor growth, activates the caspase pathway.	Promoter methylation; caspase activation; inhibition of EMT; inactivation of the ERK1/2/Slug pathway; regulation of macrophage activation and inflammatory responses.	(83-91)
TMEM140	185	Chromosome 7q33	Oncogene; involved in gliomas, gastric cancer.	Supports glioma cell proliferation, migration and invasion; enhances tumor cell adhesion and survival.	Promotes tumor aggressiveness and metastasis by regulating the cell cycle (G1 arrest) and inhibiting apoptosis, enhances expression of adhesion and anti-apoptotic proteins.	(181-186)
TMEM158	300	Chromosome 3p21.3	Oncogene; involved in NSCLC, pancreatic, colorectal, ovarian cancer.	Promotes cell proliferation and survival; regulates EMT.	Activation of TGF-β, PI3K/AKT and STAT3 pathways; implicated in Ras signaling and involved in tumor progression; regulates immune responses.	(61,187-198)
TMEM159	161	Chromosome 16p12.3	Oncogene; involved in glioblastoma	Regulates lipid droplet biogenesis, associated wth lipid metabolism; promotes cell proliferation and survival.	Interacts with Seipin; modulates lipid metabolism; implicated in psychiatric disorders; affects EGFR pathways.	(199-205)
TMEM173	379	Chromosome 5q31.2	Tumor suppressor; involved in various types of cancer including gastric and liver cancer.	Regulates type I interferon signaling, innate immunity, antitumor immunity.	Modulates autophagy and oxidative stress response; involved in T cell activation, immune checkpoint modulation, and macrophage polarization.	(92-108, 210-216)
TMEM176A	235	Chromosome 7q36.1	Tumor suppressor; involved in different types of cancer such as ESCC and CRC, linked with promoter methylation.	Suppresses tumor growth, regulates immune responses.	Acts through promoter methylation; inhibits ERK1/2 pathways; modulates immune responses.	(111-113)
TMEM176B	270	Chromosome 7q36.1	Tumor suppressor; involved in lung adenocarcinoma and GC progression.	Modulates immune tolerance and antigen cross-presentation; regulates immune checkpoint responses.	Regulates phagosomal pH, induces $CD8^+$ T cell activation, interacts with immune checkpoints, and may serve as a predictor of immune checkpoint inhibitor response; facilitates immune evasion; involves tumor-associated macrophages.	(114-123)

Table I. Continued.

Name	Amino acids	Location	Involvement in cancer	Main function	Mechanism	(Refs.)
TMEM205	189	Chromosome 19p13.2	Oncogene; involved in GC, OC and HCC.	Mediates chemoresistance, tumor growth, and immune modulation.	Involves the exosomal pathway and drug efflux; modulates macrophage polarization and immune evasion; promotes immune cell infiltration and cytotoxic T cell activity.	(206-209, 225-227)

CAMK, Calcium/calmodulin-dependent protein kinase; CHD6, chromodomain helicase DNA binding protein 6; CRC, colorectal cancer; DVL, Dishevelled; EGFR, epidermal growth factor receptors; EMT, epithelial-mesenchymal transition; ERK, extracellular regulated protein kinases; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; HCC, hepatocellular carcinoma; HIF1α, hypoxia inducible factor-1α; NSCLC, non-small cell lung cancer; OC, ovarian cancer; OXPHOS, oxidative phosphorylation; ROS, Reactive Oxygen Species; SERPINB3, Serine Protease Inhibitor B3; TCF4, Transcription factor 4; TET3, Methyl cytosine dioxygenase 3; TMEM, transmembrane; TNBC, triple-negative breast cancer; YWHAZ, Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta polypeptide.

pathway in various types of cancer, facilitating tumor progression and metastasis (189). These interactions with key oncogenic pathways highlight the importance of TMEM proteins in driving cancer development and their potential as therapeutic targets.

Functional mechanisms, regulation of the cell cycle and apoptosis. TMEM proteins also directly influence cancer cell function, particularly in terms of regulating the cell cycle and apoptosis. For example, TMEM106A and TMEM158 have been shown to induce apoptosis in cancer cells by activating caspases and inactivating PARPs, which are involved in DNA damage repair (83,84,193,194). Additionally, TMEM45A regulates cell cycle progression and promotes cell proliferation by modulating the TGF-β and Notch pathways, which are central to tumor growth and invasion (157-160).

TME, hypoxia and immune regulation. TMEM proteins also interact with the TME, influencing cancer cell behavior and immune responses. TMEM173 (STING) carries out a key role in modulating immune responses within the TME by regulating innate immunity and immune surveillance (210-212). The activation of STING signaling enhances T cell infiltration into tumors, thereby potentiating antitumor immunity (210,212-214). However, in certain contexts, TMEM173 can contribute to immune suppression by promoting the differentiation of Tregs or inducing ER stress (213,216). TMEM158, another key protein, is involved in immune evasion by regulating immune checkpoints such as PD-1 and CTLA-4, thereby enhancing the ability of tumors to resist immune system attacks (190,197,198). Furthermore, TMEM proteins, such as TMEM205, might improve the prognosis of HCC patients by reducing the levels of immunosuppressive cells (M2 macrophages and Tregs) and facilitating the infiltration of cytotoxic T cells into the TME (207). These interactions with the TME contribute to tumor plasticity, immune evasion and resistance to chemotherapy. TMEM proteins influence cancer cell proliferation, migration and invasion through a combination of epigenetic regulation, modulation of key signaling pathways (such as EGFR, TGF-β and Wnt), functional mechanisms related to cell cycle regulation and apoptosis, and interactions with the TME. Their complex roles in cancer progression make them promising therapeutic targets, and further research into their molecular mechanisms could pave the way for novel cancer therapies.

The TMEM family of proteins carries out pivotal roles in mediating tumor chemoresistance through a range of mechanisms across multiple cancer types. TMEM45A is upregulated under hypoxic conditions and contributes to chemoresistance by inhibiting apoptosis and promoting EMT, with its effects varying by cancer type (156-161,221,222). TMEM158 enhances resistance by upregulating MDR proteins and suppressing apoptosis, particularly in colorectal and lung cancer (193,194). TMEM88 regulates the Wnt signaling pathway and is epigenetically modulated, with its overexpression associated with cisplatin resistance in OC (75,223). TMEM205 promotes cisplatin resistance via exosome-mediated drug efflux and by shaping the tumor immune microenvironment, particularly through macrophage polarization in GC (209,225-227). Collectively, these TMEM proteins are key regulators of drug resistance, making them promising targets for overcoming chemoresistance and improving the efficacy of chemotherapy. TMEM16A mediates platinum-based chemotherapy resistance in HNSCC by increasing oxidative stress and upregulating ATP7B, which facilitates lysosomal sequestration of platinum compounds and may serve as a biomarker to guide chemotherapy selection (229).

However, there are limitations to the current body of knowledge regarding the roles of TMEM proteins in cancer. Variations in study design, population demographics and methodological approaches introduce inconsistencies, leading to challenges in generalizing findings across different cancer types. Further research should address these limitations by employing standardized methods and exploring longitudinal analyses to improve the definition of the causal relationships between TMEM protein expression with tumor progression

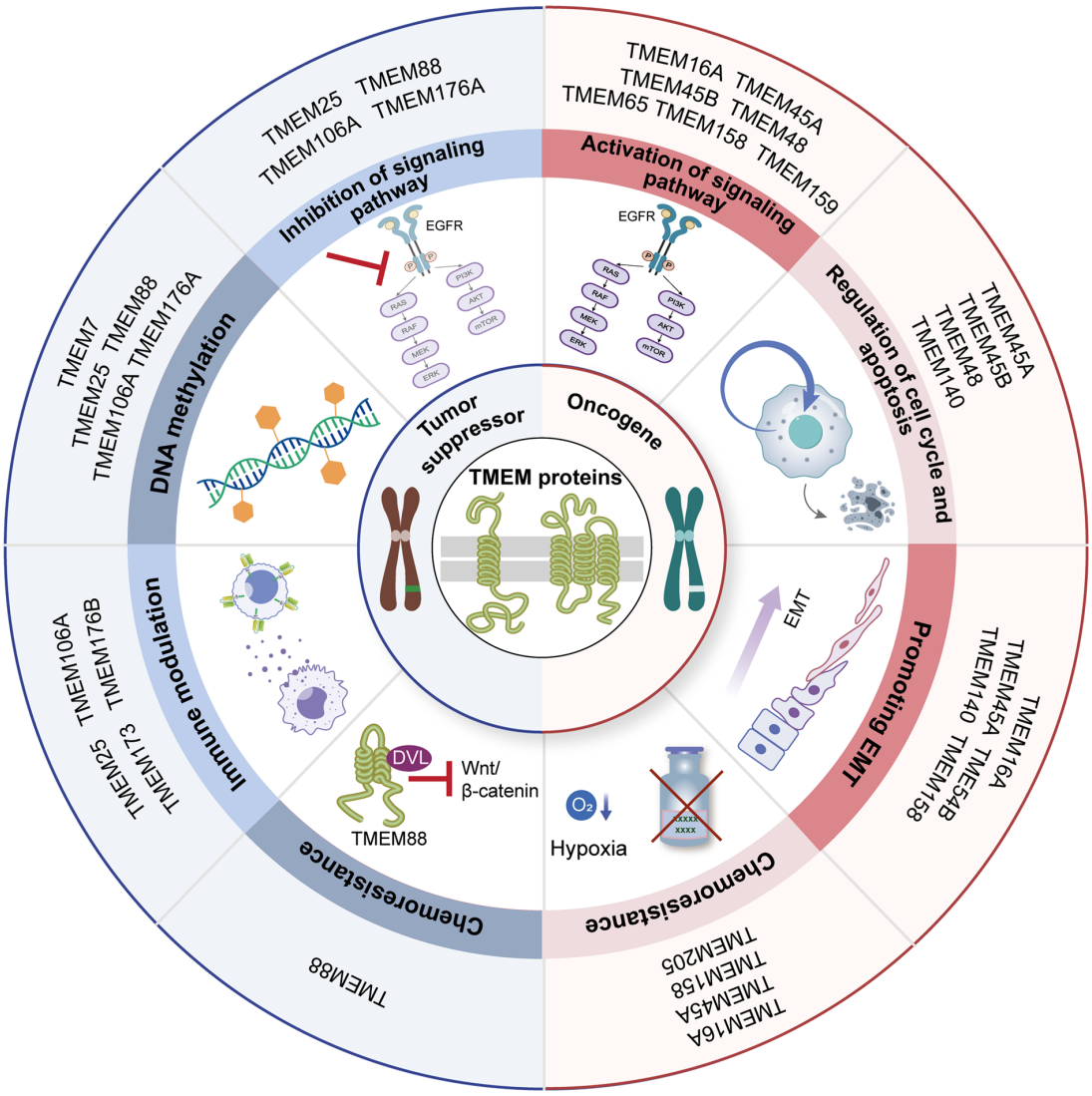

Figure 4. Roles and functions of TMEMs in cancer development, immune response and cellular regulation, providing a view of their functions across different pathways. TMEM, transmembrane; EMT, epithelial-mesenchymal transition; DVL, Dishevelled.

and chemoresistance. Future directions for research should focus on mechanistic studies to elucidate the molecular pathways through which TMEM proteins exert their effects on tumor biology and therapy resistance. With advancements in cryo-EM technology, researchers have overcome challenges such as low expression levels, hydrophobicity and conformational instability, enabling the high-resolution determination of several MP structures. Additionally, cryo-EM allows for the visualization of TPs at near-atomic resolution, providing detailed insights into their conformational states, ligand-binding sites and interactions with other proteins. This capability has greatly enhanced the understanding of TMEM protein structures and their roles in cellular signaling and chemotherapy resistance (20,230-232).

Chang *et al* (233) used cryo-EM to resolve the structure of a previously unsolved amyloid fibril composed of a 135-amino acid C-terminal fragment of TMEM106B, which is a common finding in various human neurodegenerative diseases. Cryo-EM allowed the determination of the TMEM106B fibril structure at a resolution of 2.7 Å from postmortem human brain tissue. The prevalence of amyloid fibrils made of TMEM106B across a range of debilitating human disorders suggests a shared fibrillization pathway that could initiate or accelerate neurodegeneration. Yuan *et al* (234) employed cryo-EM to analyze the structures of human GLUT4 bound to the small molecule inhibitor cytochalasin B, revealing an inward-open conformation at a resolution of 3.3 Å. Despite the nearly identical transmembrane domain conformation to GLUT1, the cryo-EM structure of GLUT4 reveals an extracellular glycosylation site and an intracellular helix that is invisible in the GLUT1 crystal structure. This structural study using cryo-EM lays the foundation for understanding the regulatory mechanisms of GLUT4 transport, and the methods developed for analyzing TMEMs will facilitate the structural determination of other small solute carrier. Shang *et al* (235) used cryo-EM to reveal the structural transitions of full-length STING/TMEM173 from both chicken and human. The structure was solved in its inactive dimeric state and in the dimeric and tetrameric states upon binding with cGAMP. These structural studies demonstrate how the transmembrane and cytoplasmic regions interact to form a domain-swapped dimeric assembly. Additionally, the closure of the ligand-binding domain, induced by cGAMP,

triggers a conformational change in STING, ultimately facilitating the formation and activation of the STING oligomer. Zhang *et al* (236) reported four distinct cryo-EM structures revealing the apo states of IGF1R, a single transmembrane protein with a flexible structure. IGF1R carries out a key role in regulating cellular metabolism and growth. These conformations were classified as 'Resting states' and 'Active states', based on the orientation of α-CT helices and structural symmetry. Moreover, a 'Ligand-pocket' formed in the active conformations, providing a new perspective on the conformational changes of apo-IGF1R.

The structural insights gained from cryo-EM have considerable implications for drug screening and discovery, particularly in the identification of novel drug targets. For instance, cryo-EM structures of GPCRs and ion channels have unveiled detailed molecular interactions with drugs, enabling the rational design of therapeutics with improved specificity and efficacy (237-239). Cryo-EM has also facilitated the study of drug-target complexes, such as the interaction between statins and the liver transporter OATP1B1, offering a mechanistic understanding of drug transport and inhibition (240). High-resolution cryo-EM structures provide a solid foundation for structure-based drug design, enabling the rational development of small molecules, peptides and biologics that modulate membrane protein function. For example, the identification of ligand-binding sites and allosteric pockets in cryo-EM structures has guided the design of inhibitors and activators with enhanced specificity and potency (241,242). Moreover, cryo-EM studies of drug-resistant MPs, such as efflux transporters, have revealed the structural basis of resistance mechanisms. These insights can inform the development of next-generation therapeutics that overcome resistance by targeting alternative binding sites or modulating protein dynamics (243). Additionally, interventional studies focused on TMEM-targeted therapies, including epigenetic modulation and immune checkpoint inhibition, are essential to validate their therapeutic potential. Expanding on these findings with multi-omics approaches, such as genomics and proteomics, may uncover new interactions between TMEM proteins and the TME, thereby enhancing therapeutic efficacy.

6. Conclusions

The present review provides a timely and comprehensive synthesis of the roles that TMEM proteins carry out in cancer pathogenesis and therapy resistance, emphasizing their emerging potential as targets for diagnosis, prognosis and therapeutic intervention. Although individual TMEM family members have been studied, an integrative analysis of their structural features, physiological functions and regulatory mechanisms, particularly their dual roles in tumor progression and chemoresistance, has been lacking. The present review fills that gap through a systematic and multi-dimensional analysis across various types of cancer.

The involvement of TMEM proteins in tumorigenesis, the TME and drug resistance was discussed, with Table I and Fig. 4 offering summaries of their functional roles. Furthermore, the regulation of TMEM proteins via epigenetic modifications, their participation in key signaling pathways and their influence on cell cycle control, apoptosis, and immune regulation provide further insight into their multifaceted contributions to cancer biology.

Importantly, the present review highlights emerging TMEM proteins with clinical relevance and discuss how targeting these molecules could offer promising strategies to overcome therapeutic resistance, particularly in hypoxic tumors. These findings support the continued investigation of TMEM proteins as diagnostic biomarkers and therapeutic targets. Personalized treatment strategies based on TMEM expression profiles may improve therapeutic efficacy while minimizing adverse effects. Ultimately, advancing research on TMEM proteins could lead to innovative diagnostic tools and targeted therapies, improving clinical outcomes for patients with different types of cancer.

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Availability of data and materials

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Authors' contributions

JS, DZ, BY, QL, HX and HP were responsible for the overall conceptualization and writing of the present review. JI, DZ, BY, QL, HX and HP contributed to drafting key content. HX and HP oversaw the critical review of key content and coordinated the review. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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