The roles and functions of TMEM protein family members in cancers, cardiovascular and kidney diseases (Review)

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Abstract. Transmembrane protein (TMEM) is a type of membrane proteins, encoded by TMEM gene, also known as integral membrane protein. TMEM gene family contains various members and its encoded proteins have various functions and expressed in numerous organs. It has been proved to be widely involved in the formation of a lot of organelle membranes, enzymes, receptors and channels, mediating numerous normal physiological functions and regulating various disease processes. At present, accumulating evidences at home and abroad have shown that TMEM is involved in regulating the occurrence and development of different tumors, cardiovascular and kidney diseases. The improved understanding of molecular mechanisms of TMEM genes and proteins may provide new directions and ideas for the prevention, diagnosis and treatment of diseases. In the present review, the roles of TMEM and biological functions in various cancers, cardiovascular and kidney diseases were discussed.

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Abbreviations: TMEM, transmembrane; GC, gastric cancer; EMT, epithelial-mesenchymal transition; HCC, hepatocellular carcinoma; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1; CRC, colorectal cancer; KO, knockout; Tg, transgenic; PAH, pulmonary artery hypertension; PASMCs, pulmonary artery smooth muscle cells; VSMCs, vascular smooth muscle cells; ECs, endothelial cells; CKD, chronic kidney disease; ccRCC, clear cell renal cell carcinoma; FSGS, focal segmental glomerulosclerosis; PTE, proximal tubular epithelial cells; PKD, polycystic kidney disease; hPC, human podocytes; SNP, single nucleotide polymorphism; AD, Alzheimer's disease; FTLD, frontotemporal lobar degeneration; PD, Parkinson's disease; SLE, systemic lupus erythematosus; VCP, valosin-containing protein; DERL1, derlin 1; TNBC, triple-negative breast cancer; DN, diabetic nephropathy

Key words: transmembrane protein, cancer, cardiovascular diseases, kidney diseases

Contents

1. Introduction

Membrane proteins, ubiquitously distributed both on the cellular and organelle membranes across multiple cell types in the body, serve as pivotal mediators of information exchange, material transition, and signal transduction among cells and their interior milieu (1); thus, they are referred to as the principal custodians of biofilm function. The categorization of these proteins spans lipid-anchored membrane proteins, integrated membrane proteins and peripheral membrane proteins, based on the complexities inherent in their separation and their spatial localization within the membrane (2). Notably, integrated membrane proteins, also designated as transmembrane (TMEM) proteins, constitute a substantial majority (70-80%). TMEM proteins include extracellular region, transmembrane region and cytoplasmic region, with at least one or more hydrophobic transmembrane domains inserted into the lipid bilayer (3).

The TMEM gene family, along with its myriad encoded proteins, as validated by prior research, plays significant roles in formulating various organelle membranes, including mitochondria (4,5), endoplasmic reticulum (6,7), Golgi apparatus (8) and lysosomes (9,10). Therefore, TMEM proteins could exert various biological functions. As such, TMEM

proteins exhibit a broad spectrum of biological functionality including their roles as diverse receptors (11,12), enzymes (13) and channels (14). Furthermore, by activating or inhibiting various signaling pathways, TMEM proteins are found to be indispensable in physiological processes as well as in the initiation and progression of myriad diseases. Amongst the TMEM family, TMEM16A is the most extensively studied member, and correlations between TMEM and disease pathogenesis have been systematically and comprehensively examined in conditions such as tumors, cardiovascular disorders and kidney diseases. The present review aims to make a systematic and comprehensive summary of TMEM and the aforementioned three aspects.

2. TMEM and cancers

TMEM family members ubiquitously exist across different systems and tissues, and are closely related to various diseases. Their roles in the onset and progression of malignant tumors have been studied widely. Through the activation of diverse signaling pathways, TMEM family plays a critical role in pro-tumor, antitumor and the heterogeneity of tumors. Several recent investigations have elaborated the relationship between TMEM and cancers (Table I).

Wnt and RTK related signaling pathways. TMEM205 overexpresses in cisplatin-resistant gastric cancer (GC), which promotes proliferation, stemness, epithelial-mesenchymal transition (EMT), migration and angiogenesis of GC cells via activation of the Wnt/β-catenin signaling pathway (15). In colon cancer cells, the expression of TMEM8B decreases. TMEM8B could limit the translocation of beta-catenin from nucleus and cytoplasm to plasma membrane, and inhibit the adhesion and invasion of colon cancer cells by suppressing the transcription factor TCF-4 and downregulating the expression of downstream target genes c-Myc, cyclin D1 and COX-2 in the Wnt signaling pathway (16). The expression levels of TMEM196 are significantly decreased in lung cancer tissues and cells, and its low expression in clinical patients is associated with poor prognosis. TMEM196 can inhibit the Wnt signaling pathway and repress β-catenin promoter transcription *in vitro* and *in vivo*. TMEM196 silencing results in significant upregulation of the expression of downstream target genes MMP2 and MMP7, attenuating the anti-metastatic effect (17).

In chemoresistant hepatocellular carcinoma (HCC) cells, the silence/overexpression of TMEM98 would restore/reduce their chemosensitivity, in which forced overexpression of TMEM98 may inhibit the expression of p53 via activating the AKT signaling pathway, thereby fostering drug resistance in tumor cells. Therefore, TMEM98 functions as a chemoresistance-conferring gene in HCC (18). The expression levels of TMEM229A are significantly decreased in non-small cell lung cancer (NSCLC). Survival analysis identifies that low expression of TMEM229A was associated with a poor prognosis. TMEM229A overexpression would suppress the EMT effectively, increasing E-cadherin expression and reducing N-cadherin, Snail family transcriptional repressor 1 and MMP2 expression, thereby significantly inhibiting cell proliferation, migration and invasion. Additionally, TMEM229A overexpression reduces the expression levels of phosphorylated (p)-ERK and p-AKT, which can be partially suppressed by the specific ERK inhibitor PD98059 (19).

TMEM16J is highly expressed in pancreatic cancer, accompanied with the activation of the MAPK signaling pathway. TMEM16J forms a protein complex binding to EGFR, which will accelerate the proliferation of cancer cells, thereby deteriorating the patients' prognosis and survival rates. However, specific knockdown of TMEM16J could inhibit the phosphorylation of ERK1/2 and EGFR, and reduce the expression level of total protein, thereby inhibiting the proliferation activity of cancer cells, and enhancing the anticancer effect of drugs such as gemcitabine and erlotinib (20). Hence, TMEM16J appears to be a potential therapeutic target and clinically prognostic marker for pancreatic cancer.

Multiple signaling pathways. TMEM16A can affect the growth of different tumors by activating various signaling pathways, including MAPK or EGFR signaling in colorectal cancer (CRC) (21), HCC (22) and head and neck squamous cell carcinoma (23,24), EGFR and Wnt/CAMKII signaling in breast cancer (25), TGF-β signaling in GC (26) and NF-κB signaling in glioma (27). Furthermore, TMEM16A is also associated with lung cancer (28), pancreatic cancer (29), prostate cancer (30) and esophageal squamous cell carcinoma (31), but the specific mechanism require further elucidation.

The expression level of TMEM17 is upregulated in breast cancer tissues, which upregulates active β-catenin, Snail and downregulates E-cadherin through the AKT/GSK3β signaling pathway, enhancing the proliferation, invasion and migration of breast cancer cells. However, these effects reversed by AKT inhibitor LY294002 *in vitro* (32). YY1 (a well-recognized oncogenic transcription factor) increases the expression of TMEM17 in glioblastoma, which promotes the proliferation, migration and invasion of cancer cells through the AKT/PI3K pathway; and reduces apoptosis, ultimately leading to the high malignancy of glioblastoma (33). The PI3K activator 740Y-P can reverse the effects caused by TMEM17 knockdown. However, the expression level of TMEM17 in NSCLC is significantly lower than adjacent normal lung tissues. Overexpression of TMEM17 downregulates the levels of p-ERK and its downstream molecules p-P90RSK and Snail while the levels of Occludin and Zo-1 are upregulated, inhibiting the invasive and migratory ability of lung cancer cells. Therefore, TMEM17 could be a negative regulator in NSCLC (34).

Elevated expression of TMEM45A has been observed in liver cancer and breast cancer, and its overexpression will induce the chemoresistance of tumor cells under hypoxia. Thus, the availability of TMEM45A potentially renders it a biomarker of chemotherapy resistance (35). Notably, overexpression of TMEM45A not only features in liver and breast cancer, but also in ovarian cancer cells. Conversely, knockdown of TMEM45A can markedly downregulate the expression of TGF-β1, TGF-β2, RhoA and ROCK2 so as to markedly restrain tumor cell proliferation, adhesion and invasion. This discovery reveals that TMEM45A participates in regulating TGF-β and Wnt signaling pathways, offering insights towards potential therapeutic targets (36). TMEM45B is highly expressed in GC tissue cells in patients. Knockdown of TMEM45B can inhibit the proliferation, migration, invasion and EMT of GC

Table I. The roles and functions of TMEMs in various cancers.

First author/s, year	TMEM	Disease types	Associated tissues or cells	Alterations	Pathway	Associated targets	Function or mechanism	(Refs.)
Fu *et al*, 2024	TMEM205	GC	GES-1, SGC-7901	Upregulation	Wnt/β-catenin	c-myc	Promote proliferation, stemness, EMT, migration and angiogenesis	(15)
Guo *et al*, 2010	TMEM8B (NGX6)	Colon cancer	HT-29	Downregulation	Wnt/β-catenin	TCF-4, c-myc, cyclin D1 and COX-2	Inhibit cell invasion and adhesion	(16)
Chen *et al*, 2023; Liu *et al*, 2019; Liu *et al*, 2015	TMEM196	Lung cancer	HBE, 293T SPC-A-1, A549 and LTEP-a-2,	Downregulation	Wnt/β-catenin	MMP2 and MMP7; p21, Bax, cyclin D1, c-myc, CD44 and β-catenin	Inhibit metastasis and progression	(17,48,49)
Ng *et al*, 2014	TMEM98	HCC	MHCC97L, PLC, Hep3B	Upregulation	AKT	AKT, GSK3-β, BCL-XL, P53	Confer chemoresistance	(18)
Zhang *et al*, 2021	TMEM229A	NSCLC	BEAS-2B, A549, H23, H226, 95D, H1975, PC-9 and H1299	Downregulation	AKT/ERK	AKT, ERK, MMP2, Snail 1, E-cadherin, N-cadherin	Suppress cell EMT, proliferation, migration and invasion	(19)
Jun *et al*, 2017	TMEM16J (ANO9)	Pancreatic cancer	hTERT-HPNE, PANC-1, AsPC-1, BxPC-3 and Capan-2,	Upregulation	MAPK	ERK1/2, EGFR	Increase cell proliferation	(20)
Zhao *et al*, 2018	TMEM17	Breast cancer	MCF-10A, MCF-7, T47D, MDA-MB-231 and MDA-MB-468	Upregulation	AKT/GSK3β	β-catenin, Snail, c-myc and cyclin D1 and E-cadherin	Promote malignant progression	(32)
Wang *et al*, 2024		Glioblastoma	LN229 and U87MG	Upregulation	PI3K/AKT	YY1, PI3K, AKT	Promote cell proliferation, migration, and invasion, reduce apoptosis,	(33)
Zhang *et al*, 2017		NSCLC	HBE, A549, H292, H1299, Calu-1, SK-MES-1, SPC-A-1 and LK2	Downregulation	MAPK	ERK, P90RSK, Snail, Occludin and Zo-1	Inhibit cell invasion and migration	(34)
Flamant *et al*, 2012	TMEM45A	Breast and liver cancer	MDA-MB-231, HepG2	Upregulation	N/A	caspase 3	Promote hypoxia-induced chemoresistance	(35)

Table I. Continued.

First author/s, year	TMEM	Disease types	Associated tissues or cells	Alterations	Pathway	Associated targets	Function or mechanism	(Refs.)
Guo *et al*, 2015		Ovarian cancer	OVCAR3, A2780, HO-8910, CAOV3, SK-OV-3 and 293T	Upregulation	TGF-β, Wnt	TGF-β1, TGF-β2, RhoA and ROCK2	Promote cell proliferation, adhesion and invasion	(36)
Shen *et al*, 2018	TMEM45B	GC	BGC-823, MGC-803, SGC-7901 and HGC-27	Upregulation	JAK2/STAT3	JAK2, STAT3	Promote cell proliferation, migration and invasion	(37)
Li *et al*, 2017		Osteosarcoma	U2OS, SaOS2, MG-63 and hFOB1.19	Upregulation	Wnt/β-catenin	β-catenin, cyclin D1, and c-myc	Promote cell proliferation, migration, and invasion	(38)
Zhang *et al*, 2015	TMEM88	NSCLC	HBE, A549, H1299, H460, H292, SPC-A-1 (SPC), LTEP-A-2, PG-BE1 and PG-LH7	Upregulation	Wnt	DVLS, p38, GSK3β (Thr390), Snail, Zo-1, Occludin	Promote invasion and metastasis	(39)
Yu *et al*, 2015		Breast cancer	MCF-10A, MCF-7, HER18, MDA-MB-231, and MDA-MB-468	Upregulation	Wnt	DVLS, Snail, Zo-1, Occludin	Promote invasion and metastasis	(40)
De Leon *et al*, 2016		Ovarian cancer	A2780, CP70, PEO1 and PEO4	Upregulation	Wnt	PITX2, FOSL1, c-Myc, Cyclin D1	Promoter hypomethylation promote cancer cell platinum resistance	(41)
Cheng *et al*, 2015	TMEM158	Ovarian cancer	OVCAR3, A2780, HO-8910, CAOV3, SK-OV-3 and 293T	Upregulation	TGF-β	TGF-β1, BMP4, ICAM-1 and VCAM-1,	Promote cell proliferation, adhesion and invasion	(42)
Fu *et al*, 2020		Pancreatic cancer	SW1990, COLO357, MIAPACA-2, PANC-1, CFPAC-1, and BXPC-3	Upregulation	TGF-β and PI3K/ AKT	E-cadherin, Vimentin, N-cadherin, and α-SMA, MMP-2/9	Promote cell proliferation, migration, and invasion	(43)
Xu *et al*, 2014	TMEM97 (MAC30)	GC	BGC-823, AGS	Upregulation	AKT	cyclin B1 and WAVE2	Promote cell proliferation migration, and invasion	(44)

Table I. Continued.

First author/s, year	TMEM	Disease types	Associated tissues or cells	Alterations	Pathway	Associated targets	Function or mechanism	(Refs.)
Zhu *et al*, 2021		Breast cancer	MCF-10A, MCF7, BT549, Bcap37, and MDA-MB-231	Upregulation	Wnt/β-catenin and PI3K/Akt	E-cadherin, N-cadherin, vimentin, Slug, Snail, Twist, ZEB1 AKT, β-catenin, survivin, and cyclin D1	Promote cell invasion and EMT	(45)
Mao *et al*, 2022		Colorectal cancer	SW480, No. iCell-h204; SW620, No. iCell-h206; LoVo, No. iCell-h126; HCT116, No. iCell-h071 and DLD1, No. iCell-h053	Upregulation	GSK-3β/β-catenin	YY1, GSK-3β/β-catenin, PCNA, cleaved caspase 8/3/7 and cleaved PARP	Inhibit cell invasion migration, growth and enhance apoptosi	(46)
Xu *et al*, 2024		CRC	FHC, HCT15, HCT8, HCT116, and SW480	Upregulation	AKT/mTOR	ATP-binding cassette, E-cadherin, Vimentin, N-cadherin, P-glycoprotein, ABCC1, ABCC2	Promote 5-FU resistance	(47)

TMEM, transmembrane; NSCLC, non-small cell lung cancer; GC, gastric cancer; HBE cells, human normal bronchial epithelial cells; FHC, normal colorectal mucosa cells; CRC, colorectal cancer; N/A, not available.

cells via suppressing the expression of p-JAK2 and p-STAT3 through the JAK2/STAT3 signaling pathway in cancer cells. Therefore, TMEM45B may become a new therapeutic molecular target for GC (37). The expression of TMEM45B is obviously upregulated in human osteosarcoma U2OS cell lines, knockdown of TMEM45B can significantly suppress the expression of beta-catenin, cyclin D1 and c-Myc, and inhibit the proliferation, migration and invasion of U2OS cells (38).

TMEM88 is highly expressed in NSCLC (39) and triple negative breast cancer tissues (40). It enhances invasive and metastatic cell characters via promoting Snail expression and inhibiting Zo-1 and Occludin expression, which is associated to Dishevelled of the Wnt signaling pathway. In addition, the expression of TMEM88 is increased due to promoter hypomethylation in ovarian cancer, which is closely related to platinum resistance of tumor cells. However, knockdown of TMEM88 leads to notable upregulation of downstream genes c-Myc and cyclin-D1 of the Wnt signaling pathway, which can promote the proliferation and colony formation of cancer cells, and also re-sensitize cells to cisplatin (41).

The expression of TMEM158 in ovarian and pancreatic cancer is increased. Knockdown of TMEM158 would significantly inhibit the proliferation of ovarian cancer cells by curbing the TGF-β signaling pathway, and also obviously inhibit cell adhesion by downregulating the expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) (42). TMEM158 enhances the proliferation, migration and invasion of pancreatic cancer cells by activating TGF-β1 and PI3K/AKT signaling pathways to accelerate cell cycle, EMT and MMP-2/9 productions (43).

TMEM97 is a conserved integral membrane protein highly expressed in various human cancers including GC, breast cancer and CRC. Upregulation of TMEM97 has been associated with progression and poor outcome in cancers. Knockdown of TMEM97 in GC cells can restrain the degree of phosphorylation of AKT and reduce the expression level of cyclin B1 and WAVE2, leading to inhibit proliferation and mobility of GC cells (44). In breast cancer cells, TMEM97 deficiency attenuates the Wnt/β-catenin signaling cascade via regulating LRP6 phosphorylation, leading to a decrease in the expression of Wnt target genes AXIN2, LEF1 and survivin. Meanwhile, knockdown of TMEM97 suppresses cell viability, proliferation, colony formation, migration, invasion and stemness properties in breast cancer cells. Importantly, TMEM97 deficiency was revealed to suppress tumor growth through downregulating the Wnt/β-catenin signaling pathway in breast cancer xenograft mouse models (45). In CRC, TMEM97 is transcriptionally activated by YY1 and promotes CRC progression via the GSK-3β/β-catenin signaling pathway. The silencing of TMEM97 inhibits invasion and migration of CRC cells *in vitro* and leads to suppress growth and enhance apoptosis in cells and xenografts (46). Another study demonstrated that TMEM97 knockdown suppresses EMT, expression of ATP-binding cassette transporters via inactivating the AKT/mTOR pathway, thus attenuating 5-FU resistance in CRC cells (47). These findings demonstrate that TMEM97-targeted inhibition may be a promising therapeutic strategy for cancer.

There are numerous members in TMEM family, most of which are involved in the occurrence and development of various tumors, performing an indispensable role in the proliferation, migration and invasion of diverse tumor cells. Most of TMEM proteins are increased in tumors: TMEM17 in glioblastoma (33), TMEM45A in breast and liver cancer (35) and ovarian cancer (36); TMEM45B in GC (37) and osteosarcoma (38); TMEM88 in NSCLC (39), breast (40) and ovarian cancer (41); TMEM158 in ovarian (42) and pancreatic cancer (43); TMEM97 in GC (44), breast (45) and colon cancer (46). They promote proliferation, invasion and metastasis of tumor cells. Among these TMEM proteins whose expression is upregulated, TMEM98 (18), TMEM45A (35) and TMEM88 (41) promote chemotherapy resistance in different ways. If there are inhibitors targeting these TMEM proteins, it may restore chemotherapy sensitivity of cancer cells and improve patients' prognosis and survival time. On the contrary, a small amount of TMEM members, TMEM8B (16), TMEM196 (48) and TMEM229A (19), have inhibitory effects on the occurrence and development of tumors, and their expression levels are downregulated. Notably, the role of TMEM196 in lung cancer was demonstrated in genetic model animals. The hypermethylation and low expression level of TMEM196 are significantly associated with age, worse pathological type and poorer survival of patients, thus it is considered a biomarker of lung cancer in the clinic (48,49). The aforementioned study generated xenograft tumor metastasis mice and TMEM196 knockout (KO) mice, which strongly supports that TMEM196 can be used as prognostic markers in lung cancer and may represent potential targets for cancer treatment (17). Concurrently, TMEM17 is increased in breast cancer (32) and glioblastoma (33) but decreased in NSCLC (34), suggesting even the same TMEM protein may play different roles in different cancers. With further exploration and research, more different signaling pathways and molecules or unknown mechanisms will be revealed, potentially providing new directions or targets for the treatment of cancers.

3. TMEM and cardiovascular diseases

In recent years, the mechanism of TMEM in cardiovascular diseases has also attracted the attention of numerous researchers, especially its family member TMEM16A, whose role is mainly manifested in pulmonary artery hypertension (PAH) and hypertension (Table II).

TMEM16A and cardiovascular diseases. There is accumulating evidence suggesting that TMEM16A could be a positive regulator of disease progression in PAH. TMEM16A is highly expressed in pulmonary artery smooth muscle cells (PASMCs) of PAH with high pulmonary blood flow, which may activate PASMC and accelerate phosphorylation of EKR and AKT (50), or enhance the expression of cyclin D1 and cyclin E in PASMCs to facilitate the transition from of cell cycle from G1 to S phase (51), participating in pulmonary vascular remodeling and leading to PAH eventually.

Unlike PAH, TMEM16A exert a dual role in hypertension. Vascular smooth muscle cells (VSMCs)-specific TMEM16A transgenic (Tg) mice were generated, prevented from being affected by other cells in systemic TMEM16A Tg mice (52). It was demonstrated that TMEM16A may inhibit the RhoA/ROCK2/MLCP/MLC20 and integrinβ3/FAK signaling pathways via suppressing WNK1, so as to limit the migration

Table II. The roles and functions of TMEMs in in various heart diseases.

First author/s, year	TMEM	Disease types	Associated tissues or cells	Alterations	Pathway	Associated targets	Function or mechanism	(Refs.)
Liu *et al*, 2020	TMEM16A (ANO1)	PAH	Pulmonary ASMCs	Upregulation	p38MAPK/ERK	PCNA, p38 and ERK	Promote cell proliferation	(50)
Shang *et al*, 2020		PAH	Pulmonary ASMCs	Upregulation	N/A	cyclin E, cyclin D1	Accelerate cell cycle	(51)
Zheng *et al*, 2021		Vascular remodeling	Basilar ASMCs	N/A	RhoA/ROCK2 and integrinβ3/ FAK	RhoA/ROCK2/ MLCP/MLC20 and integrinβ3/ FAK	Limit cells migration, protect vascular remodeling	(52)
Lv *et al*, 2020		Aortic remodeling	ASMCs	Downregulation	N/A	p62, Bcl-2, Beclin-1, and VPS34	Prevents vascular autophagy and remodeling	(53)
Ma *et al*, 2017		Endothelial dysfunction and hypertension	HUVECs, aortic ECs and ASMCs	Upregulation	N/A	Nox2, p22phox, p47phox and p67phox	Induce endothelial dysfunction and hypertension	(54)
Li *et al*, 2020	TMEM106B	CAD	HCAECs	Upregulation	N/A	N/A	Increase cell adhesion and migration	(56)
Li *et al*, 2021	TMEM98	ECs and VSMCs dysfunction disease	HUVECs and VSMCs	Upregulation	ERK and AKT/ GSK3β	ICAM-1/ VCAM-1, cyclin D1 and β-catenin	Promote ECs adhesion, VSMCs proliferation and migration	(57)
Chen *et al*, 2023	TMEM11	Cardiac repair and regeneration	Cardiomyocytes	N/A	TMEM11-METTL1-ATF5-INCA1 axis	METTL1, ATF5, INCA1	Suppress cardiomyocyte proliferation	(58)

TMEM, transmembrane; PAH, pulmonary artery hypertension; CAD, coronary artery disease; VECs, vascular endothelial cells; VSMCs, vascular smooth muscle cells; ASMCs. artery smooth muscle cells; HCAECs, human coronary artery endothelial cells; HUVECs, human umbilical vein endothelial cells; N/A, not available.

of Ang II-induced basilar artery smooth muscle cells, thereby protecting cerebral vascular remodeling in Ang II-induced hypertension *in vivo* and *in vitro* studies (52). TMEM16A has the same effect in the aorta of hypertension mice. TMEM16A would downregulate the autophagy degree of VSMCs via regulating the four-way interaction, which inhibits p62/Bcl-2 binding and the formation of Beclin-1/VPS34 complex, thereby coordinately preventing vascular autophagy, inhibiting vascular remodeling and ultimately alleviating elevated blood pressure; this finding is also supported by a previous study using VSMCs-specific TMEM16A Tg mice (53). Conversely, TMEM16A can also promote the activation of NOX2 and add the production of ROS in vascular endothelial cells (ECs), leading to endothelial dysfunction and potentially hypertension. In particular, vascular endothelial-specific TMEM16A KO and-specific TMEM16A Tg mice were generated, respectively from *in vivo* and *in vitro* studies, as well as upregulation and downregulation of TMEM16A, comprehensively investigating the specific involvement of TMEM16A in regulating endothelial function, blood pressure and the underlying mechanism (54). Modification of TMEM16A may be a novel therapeutic strategy for endothelial dysfunction-associated diseases (54). Inhibition of the function of TMEM16A with specific TMEM16A inhibitor TMinh-23 can attenuate the vasoconstriction effect *in vitro* and reduce blood pressure in spontaneously hypertensive rats *in vivo* (55). Taken together, TMEM16A plays a dual role in some vascular-related diseases and potentially serves as a novel therapeutic target for hypertension, endothelial dysfunction and VSMCs' migration-related cardiovascular diseases such as vascular remodeling.

Other TMEM protein family members and cardiovascular diseases. ANRIL and TMEM106B are both coronary heart disease susceptibility genes, located on chromosome 9p21.3 and 7q21.11 respectively. Elevated expression of ANRIL appear to reduce the adhesion of monocytes to ECs and the trans-endothelial migration ability of monocytes, which plays an important role in limiting the progression of coronary artery disease (CAD), while high expression of TMEM106B can completely offset this effect of ANRIL (56). On the contrary, silencing of TMEM106B can significantly reduce the effect of promoting CAD caused by low expression of ANRIL. TMEM98 encodes a secreted protein that can be expressed and secreted with the induction of platelet-derived growth factor-BB. It can affect the adhesion between monocytes and ECs through regulating the expression of ICAM-1 and VCAM-1. Furthermore, TMEM98 can also trigger the proliferation and migration of VSMCs by influencing the expression of cyclin D1 and β-catenin and regulating the AKT/GSK-3β/Cyclin D1 signaling pathway (57). TMEM11 is located mainly in the mitochondria of heart muscle cells and directly interacts with METTL1 and enhances m(7)G methylation of ATF5 mRNA, thereby increasing ATF5 and INCA1 expression, which is involved in the regulation of cardiomyocyte proliferation via mediating TMEM11-METTL1-ATF5-INCA1 axis. This finding reveals that targeting this axis may serve as a novel therapeutic strategy for promoting cardiac repair and regeneration, supported by TMEM11 KO mice and TMEM11 Tg mice (58).

4. TMEM and kidney diseases

Although the aforementioned sections extensively discuss the relationship between the TMEM proteins family and both tumor and cardiovascular diseases, increasing attention from researchers has been directed towards understanding the association between TMEM and renal disorders. Numerous studies have been conducted to explore this domain (Table III).

TMEM and clear cell renal cell cancer. In clear cell renal cell carcinoma (ccRCC), TMEM22 and TMEM45A are found to be upregulated, whereas TMEM7, TMEM30B, TMEM45B, TMEM52B, TMEM61, TMEM72, TMEM116, TMEM207 and TMEM213 demonstrate a downregulated state (6). TMEM45A is the most upregulated and TMEM213 is the most downregulated among them. The TMEM72 protein has four transmembrane domains and a long c-terminal tail, located on the plasma membrane. It exerts a vital role in protein folding, assembly and transport in normal kidney development and the pathogenesis of membrane transport-related diseases, especially renal cancer (59). There exists an interaction between TMEM22 and Ras-related protein RAB-37, which highly expresses in renal cell carcinoma. Specific knockdown of TMEM22 by siRNA or downregulation of RAB-37 would significantly slow down the proliferation of cancer cells (60). Therefore, TMEM22 and TMEM72 may be involved in the development, progression and metastasis of renal cell carcinoma.

TMEM45A is upregulated in ccRCC, especially in high grade ccRCC (61), which may be involved in post-translational protein modification and transport. It can promote tumor cell proliferation, EMT and inflammatory response (62) and increase the resistance of RCC4 + pVHL cells to cisplatin by activating the UPR pathway (63). TMEM174 consists of 243 amino acids and contains two transmembrane helices, which determines its subcellular localization in the endoplasmic reticulum and affects its function. It is highly expressed in human normal renal tissues and occassioanlly in patients with renal cancer. Overexpression of TMEM174 can enhance the transcriptional activity of activator protein-1 and promote cell proliferation through the ERK pathway, thus TMEM174 has a potential influence in the normal physiological function and development of kidney and even the occurrence and development of renal carcinoma (64,65). TMEM106A serves as a potential tumor suppressor and is downregulated in renal cancer cells. Its inactivation accelerates proliferation and migration of tumor cells while inhibiting apoptosis (66).

TMEM and polycystic kidney disease. The expression product of TMEM67 is Meckelin protein, which is located on the cell membrane and primary cilia of renal proximal tubular epithelial cells (PTE), which is of great significance for their formation. The normal morphology and function of the cilia are particularly important for the physiological renal function (67,68). Missense mutations of TMEM67 have been detected in patients with cystic kidney disease, indicating that the potential role of Meckelin protein and primary cilia in the development of polycystic kidney disease (PKD) (69-71). Compared with control mice, accumulation of p-ERK, p-JNK, p-4E-BP1 and high level of overall phosphorylation (4G10)

Table III. The roles and functions of TMEMs in in various kidney diseases.

First author/s, year	TMEM	Disease types	Associated tissues or cells	Alterations	Associated targets	Function or mechanism	(Refs.)
Ding *et al*, 2023	TMEM72	ccRCC, CKD	293T, HeLa	Downregulation	COPII	Involved in protein synthesis	(59)
Sachiko *et al*, 2009	TMEM22 (SLC35G2)	Renal cell carcinoma	RCC13, RCC54	Upregulation	Ras-related protein Rab-37	Promote cancer cell growth	(60)
Thibodeau *et al*, 2016; Jiang *et al*, 2021; Schmit *et al*, 2019	TMEM45A	ccRCC	ACHN, RCC4	Upregulation	N/A	Promote the proliferation and migration and inhibit the apoptosis	(61-63)
Wang *et al*, 2010; Zhang *et al*, 2014	TMEM174	Renal development and carcinomas	293T	Upregulation	AP-1, ERK	Promote cell proliferation	(64,65)
Miyazaki-Anzai *et al*, 2022		CKD	PCS-400-010	Downregulation	NPT2A	Regulate the homeostasis of phosphorus	(80)
Wu *et al*, 2017	TMEM106A	Renal cancer	[a]786-O, 769-P, ACHN, A-498, A-794	Downregulation	JNK, caspase3	Attenuate cell proliferation, migration and enhance apoptosis	(66)
Du *et al*, 2013	TMEM67 (Meckelin)	PKD	293T	N/A	JNK, ERK, 4E-BP1	Aberrant TMEM67 expression results in abnormal cell proliferation and cyst formation	(72)
Zhu *et al*, 2021		PKD	N/A	Downregulation	mTOR	TMEM67 mutants aggravate renal cysts	(73)
Orphal *et al*, 2020	TMEM63C	EMT associated diseases	293T	Downregulation	TGF-β, α-SMA and E-cadherin	Maintain cell viability	(77)
Schulz *et al*, 2019		FSGS	Podocyte	Downregulation	Nephrin	Maintain cell viability and inhibit apoptosis	(76)
Faria *et al*, 2014	TMEM16A	Proximal tubular dysfunction	PTE	Downregulation	N/A	Reduce urinary protein excretion	(79)
Liu *et al*, 2021	TMEM30A	MN, MCD and FSGS	Podocyte	Downregulation	CHOP, PDI	Maintain podocyte survival and integrity of GFB	(81)

TMEM106: [a]Primary Renal Proximal Tubule Epithelial Cells, Primary Renal Cortical Epithelial Cells and renal cancer cells (786-O,769-P, ACHN, A-498, A-794). TMEM, transmembrane; CKD, chronic kidney disease; ccRCC, clear cell renal cell carcinoma; FSGS, focal segmental glomerulosclerosis; MN, membranous nephropathy; MCD, minimal change disease; PKD, polycystic kidney disease; EMT, epithelial-mesenchymal transition; α-SMA, α-smooth muscle actin; N/A, not available.

are observed in B6C3Fe a/a-*bpck* mice (with TMEM67 mutation, which displays a severe cystic kidney phenotype and enlarged kidney after birth quickly) in different weeks of age, consistent with the observations of 293T cells *in vitro*. This finding supports that TMEM67 also mediates PKD through the JNK/ERK signaling pathway (72). However, another group generates TMEM67 mutant zebrafish, which is the first adult zebrafish model of PKD (TMEM67 transcript levels are reduced). The present study has demonstrated that TMEM67 mutants have impaired ciliary function, resulting in abnormal cell structure and signaling, ultimately triggering kidney cysts. Furthermore, there is a hyperactive mTOR signal in the model, and inhibition of this pathway is beneficial to ameliorate PKD in both the embryonic and adult zebrafish models (73). In addition, TMEM107 also plays an important role in the formation and function of cilia, and may be related to PKD, though the underlying mechanisms involved are not yet understood (71,74).

TMEM and other kidney-related diseases. TMEM63 proteins include TMEM63A, TMEM63B and TMEM63C, which together constitute a hyperosmotic activated ion channel and may participate in the osmotic regulation of renal cells and even the whole body (75). TMEM63C may be associated with normal renal function and renal injury in rats and zebrafish (76). MicroRNA (miR)-564 can reduce the expression of TMEM63C in 293T cells and human podocytes (hPC), while TGF-β could add the expression of TMEM63C in a concentration-dependent manner in renal cells (77). In 293T cells, the downregulation of TMEM63C is related to the increase of a-SMA and E-cadherin ratio, which leads to the decreased cell viability (77). In hPC, Ang II may induce the expression of TMEM63C possibly through NF-κB-dependent mechanisms, and TMEM63C is related to the development of proteinuria (78). The decrease of TMEM63C is related to the lowered expression of nephrin, and its inhibition will also lead to impaired cell viability. For example, the downregulation of TMEM63C in patients' podocytes with focal segmental glomerulosclerosis (FSGS) (76). This finding indicates that TMEM63C is a potential hPC survival factor and contributed to maintaining the function of glomerular filtration barrier (77).

TMEM16A is dominantly expressed in human and mouse PTE, with minor expression in podocytes and other tubular segments. In a previous study, three gene models of TMEM16A were generated: systemic KO, podocyte-specific KO and PTE-specific KO mice, fully demonstrating that TMEM16A plays a vital role in PTE rather than podocyte (79). It is a calcium-activated chloride channel in PTE that controls H^+ transport by the V-ATPase and uptake of albumin, thereby mediating proton secretion and protein reabsorption. TMEM16A KO decreases urine electrolyte concentrations and increases urine protein excretion (79). TMEM174 is a specific gene expressed in PTC and its corresponding protein interacts with NPT2A in both human and mice, which is a major proximal-specific Pi cotransporter. TMEM174 regulates the homeostasis of Pi by reducing phosphorus uptake and maintaining function of NPT2A. TMEM174 KO mice were generated to demonstrate that NPT2A would be reduced when TMEM174 is deficient *in vivo*, leading to chronic kidney disease (CKD)-dependent complications such as hyperphosphatemia and vascular calcification (80). The level of TMEM30A is decreased in patients with podocytopathy, including minimal change disease and membranous nephropathy. Podocyte-specific TMEM30A KO mice are generated, which shows, podocyte foot process effacement, lack of a slit diaphragm and increases in the GBM, leading to a series of pathological phenotypic changes such as podocytes injury, proteinuria, mesangial cell proliferation and mesangial matrix accumulation, even glomerulosclerosis ultimately. Mechanistically, podocyte-specific TMEM30A KO may cause endoplasmic reticulum stress via interfering with protein modification and programmed cell death (81).

5. Discussion

In the summary of the association between TMEM proteins and other systemic diseases, it is apparent that the current studies are limited and lack systematic exploration. Concurrently, these studies involve a restricted number of TMEM proteins and a narrowly focused range of diseases. Therefore, the present review does not present a comprehensive summary or discussion concerning TMEM proteins and other systemic diseases. Nonetheless, it is warranting of additional attention that genomic mutations of TMEM genes have been identified, involving single nucleotide polymorphism (SNP) locus or allele point mutation. Predominantly, these mutations are associated with neurodegenerative and immune-related disorders.

The risk variations of TMEM106B are related to some neurodegenerative diseases, particularly SNP locus. Dementia risk allele SNP rs1990622-A predisposes to TMEM106B fibril formation in the hippocampus, and affects brain lipid homeostasis, particularly myelin lipids (82). The risk variation of SNP locus rs1990622 can contribute to Alzheimer's disease (AD) risk and is related to the pathological manifestations of AD, but its T allele is only related to the risk of women, whereas not in men (83). However, variant rs1990621 of TMEM106B may have a neuronal protection effect against general aging, independent of disease status (84). At the same time, the extensive accumulation of C-terminal immunoreactive material of TMEM106B in cases of frontotemporal lobar degeneration (FTLD) with TMEM106B progranulin gene mutations (85). These findings support the pathogenic effect of TMEM106B in a diverse range of neurodegenerative disorders. TMEM gene family is also related to Parkinson's disease (PD). A total of three rare Dmis variants of TMEM230, rare missense variants of TMEM59 in sporadic early onset PD or familial PD. Rare missense variants of TMEM108 appear in sporadic late-onset PD (86).

A total of three SNPs (the CT and CT + TT genotypes in rs12493175, the AC and AC + AA genotypes in rs13062955 and CGTA haplotype) are located in the TMEM39A gene, which is observed to significantly reduce the risk of systemic lupus erythematosus (SLE) in a Chinese Han population (87). A genome-wide association study of SLE susceptibility in European Americans showed that the TMEM39A SNP locus rs1132200 is a susceptibility gene for SLE (88). The major allele G of TMEM187 (rs13397) could be considered as a risk genetic allele for rheumatoid arthritis in Egyptian populations (89). These studies underscore the necessity for expanded investigation into the multifaceted

roles of the TMEM gene family across diverse pathological processes.

Some aforementioned studies were supported by genetic models *in vivo*: TMEM196 in lung cancer (17); TMEM11 in cardiac repair and regeneration (58), VSMC-TMEM16A in hypertension (52-54); PTE-TMEM16A in normal renal function (79), TMEM174 in Pi homeostasis (80) and podocyte-specific TMEM30A in podocytopathy (81). Among them, the results about TMEM proteins as therapeutic targets are limited. For example, targeting TMEM proteins themselves such as TMEM16A (55) and TMEM63C (77), or upstream/downstream molecules dependent on TMEM proteins, such as TMEM63A (90), TMEM229A (19), TMEM17 (32) and TMEM11 (58).

Inhibition of the function of TMEM16A with specific TMEM16A inhibitor TMinh-23 can attenuate the vasoconstriction effect *in vitro* and *in vivo* (55). MiR-564 can reduce the expression of TMEM63C in hPC and 293T cells, thereby decreasing cell viability and increasing EMT in renal cells (77). TMEM63A is localized in endoplasmic reticulum and lysosomal membrane, and interacts with valosin-containing protein (VCP) and its cofactor derlin 1 (DERL1). Pharmacological inhibition of VCP by CB-5083 or knockdown of DERL1 partially eliminated the carcinogenic effect of TMEM63A on triple-negative breast cancer (TNBC) progression *in vivo* and *in vitro* (90). TMEM229A is decreased in NSCLC and associated with a poor prognosis in patients. Overexpression of TMEM229A reduces the expression levels of p-ERK and p-AKT, which can be partially suppressed by the specific ERK inhibitor PD98059, suggesting that TMEM229A plays a favorable role in NSCLC via the downstream molecule ERK (19). TMEM17 can promote malignant progression of breast cancer cells by activating the AKT/GSK3β signaling pathway, and these effects reversed by AKT inhibitor LY294002. However, how TMEM17 affects p-AKT remains unclear, and the detailed mechanism should be elucidated in future studies (32). It is TMEM11-METTL1-ATF5-INCA1 axis in cardiomyocyte proliferation that reveals that targeting this axis may serve as a novel therapeutic strategy for promoting cardiac repair and regeneration (58).

In the present review, it was also discussed that some TMEM family members are involved in the occurrence and development of different diseases in multiple systems, such as TMEM63, TMEM98 and TMEM106. TMEM63 includes TMEM63A, TMEM63B and TMEM63C. TMEM63 localizes to lysosomes, mediate lysosomal mechano-sensitivity and modulate lysosomal morphology and function in drosophilae (91). TMEM63A promotes TNBC progression (90). TMEM63C maintains viability of 293T and podocyte and inhibits their apoptosis in EMT-associated diseases and FSGS (76-78). TMEM98 confers chemoresistance of HCC (18) and promotes adhesion of ECs and proliferation and migration of VSMCs in ECs and VSMCs dysfunction related-diseases (57). TMEM106 includes TMEM106A, TMEM106B and TMEM106C. Inactivation of TMEM106A accelerates proliferation and migration of tumor cells while inhibiting apoptosis in renal cancer cells (66). TMEM106B plays an unfavorable role in CAD by mediating another CAD susceptibility gene (56) and risk variations of SNP locus of TMEM106B are related to some neurodegenerative diseases such as AD (83) and FTLD (85). TMEM106C contributes to malignant characteristics and poor prognosis in HCC (92).

In conclusion, members of the TMEM family are diversely distributed across various systems and tissues. The localization and function of proteins encoded by them are also different considerably. They are involved in the normal physiological function of human and animal, and modulate disease onset or progression. For example, they exert their functions in promoting tumor, inhibiting tumor and heterogeneity in the development of neoplasms through different signaling pathways: TMEM17, TMEM45A, TMEM45B, TMEM88, TMEM158 and TMEM97 can mediate the proliferation, adhesion and invasion of various tumors, even affect the chemosensitivity. The TMEM protein family is also involved in the pathogenesis and progression of cardiovascular diseases.

Furthermore, the relationship between TMEM and renal disease has sparked great interest. There are TMEM family members related to the most common ccRCC in renal cancer, which need more comprehensive elaboration. However, the exploration of the relationship between TMEM and CKD such as diabetic nephropathy (DN) remains in its infancy, with few current studies and results available. TMEM256, a number of TMEM families, encodes a protein of ~11.7 kDa (https://www.genecards.org/cgi-bin/carddisp.pl?gene=TMEM256&keywords=TMEM256). TMEM256 is expressed in proximal renal tubular cells, and its subcellular localization is in exosomes. Nonetheless, its underlying structure and function remain uncertain. The role of TMEM256 in DN and how it mediates disease progression have not been studied and further studies are needed.

At present, results about TMEM proteins as therapeutic targets, even researches of drug and rescue, are still lacking either *in vivo* or *in vitro*. Especially the efficiency and results of clinical transformation are still few. Very few studies have been reported. For TMEM proteins, the following parameters should be investigated: the structural characteristics of transmembrane proteins, whether they have special roles in hydrophilic, hydrophobic or transmembrane regions, or whether there are specific post-translational modifications on certain amino acid sequences, which are closely related to their functions in the organism. In the future, genetic model animals should be added to studies that have been reported only *in vitro* to validate the accuracy of results *in vitro*, involving either Tg or KO animal, either systemic or even specific animal. Signaling pathways or downstream molecules being involved in the occurrence and development of diseases should be confirmed by transcriptomics, proteomics or other predictive methods and experimental verification. Only through such similar processes can corresponding purified proteins, recombinant proteins or agonist/inhibitors be designed to conduct drug intervention or rescue studies, in order to increase the efficiency of clinical transformation and make clinical practice become possible in the future.

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Availability of data and materials

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Authors' contributions

HX designed and wrote the major part of original manuscript. SY, PL, YZ and TZ prepared the tables and revised the manuscript. JLa, HJ, DW, JLi and XB participated in revising and reviewing the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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