

Research Progress of TMEM2 in Extracellular Matrix Remodeling and Tumor Microenvironment Regulation

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Abstract: Remodeling of the extracellular matrix (ECM) and regulation of the tumor microenvironment (TME) are essential processes in tumorigenesis and tumor progression. Transmembrane protein 2 (TMEM2), a recently identified cell surface hyaluronidase, participates in various physiological and pathological processes by degrading hyaluronan (HA) in the ECM. This review summarizes the molecular structure and enzymatic properties of TMEM2, the current evidence and controversy regarding its intrinsic catalytic activity, and the mechanisms by which TMEM2 mediates ECM remodeling. Emphasis is placed on recent advances in TMEM2 research in a variety of solid tumors, including its roles in tumor cell proliferation and migration, epithelial-mesenchymal transition, chemoresistance, and regulation of the tumor microenvironment through HA metabolism. Current evidence is mainly derived from bioinformatics analyses, cell-based experiments, and limited animal studies, and further prospective validation is still needed. The potential of TMEM2 as a prognostic biomarker and therapeutic target is also discussed, together with current limitations and future directions, with the goal of providing a reference for basic research and clinical translation in this field.

Keywords: TMEM2; Hyaluronidase; Hyaluronan; Extracellular Matrix; Tumor Microenvironment

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1. Introduction

The tumor microenvironment (TME) plays an important role in tumor initiation, progression, invasion, and drug resistance. As an important component of the TME, the extracellular matrix (ECM) directly influences the biological behavior of tumor cells through changes in its composition and mechanical properties^[1,2]. Hyaluronan (HA) is one of the most abundant glycosaminoglycans in the ECM; it is synthesized on the inner side of the plasma membrane by hyaluronan synthases 1-3 (HAS1-3) and directly extruded into the extracellular space, forming a highly hydrated gel-like matrix that participates in key processes such as cell proliferation, migration, differentiation, and signal transduction^[3,4]. In a variety of solid tumors, abnormal accumulation of HA is

closely associated with tumor progression, therapeutic resistance, and poor prognosis ^[5,6].

The metabolic balance of HA is jointly maintained by hyaluronan synthases (HASs) and hyaluronidases (HYALs). Traditionally, the hyaluronidase family members HYAL1 and HYAL2 are considered primarily responsible for HA catabolism: HYAL2 cleaves high-molecular-weight HA (HMW-HA) into intermediate fragments of approximately 20 kDa, which are then further degraded by HYAL1 into small oligosaccharides ^[7]. However, this classical model cannot fully account for all features of HA turnover *in vivo*; in particular, the mechanism underlying local HA degradation at the cell surface long remained elusive. In 2017, Yamamoto et al. ^[8] identified TMEM2 (transmembrane protein 2, also known as CEMIP2) as a novel cell-surface hyaluronidase, filling a knowledge gap in the field of HA metabolism and providing a new perspective for understanding cell-surface HA degradation and its role in tumors ^[9,10].

In recent years, research on TMEM2 has advanced rapidly, revealing that it not only plays an important role in physiological HA metabolism but also participates in tumor initiation and progression. By degrading cell-surface HA, TMEM2 regulates cell adhesion and migration ^[11,12], promotes epithelial-mesenchymal transition (EMT) ^[13], mediates chemoresistance ^[13], and remodels the mechanical properties of the ECM to alter drug delivery efficiency ^[5,6]; it may exert tumor-promoting effects in various malignancies, including breast cancer ^[11,14], pancreatic cancer ^[12,32], and glioblastoma (GBM) ^[13]. However, several issues still require systematic review and in-depth discussion, including the controversy over species differences in the catalytic activity of TMEM2 ^[16,17,18], its differential mechanisms of action across tumor types, and its feasibility as a therapeutic target. This review focuses on three main themes: (1) whether TMEM2 is a bona fide hyaluronidase: current evidence and controversy; (2) how TMEM2 affects tumor biological behavior and the tumor microenvironment through HA metabolism and ECM remodeling; and (3) whether TMEM2 can serve as a prognostic biomarker or therapeutic target for tumors. On this basis, the limitations of existing research and future directions are discussed.

2. Molecular structure and biological functions of TMEM2

2.1. Gene and protein structure

The TMEM2 gene is located on human chromosome 9q21.13 and encodes a type II transmembrane protein with a relative molecular mass of approximately 154 kDa; its gene symbol is CEMIP2 (cell migration-inducing hyaluronidase 2) ^[8,15]. Its ectodomain contains a conserved β -helix fold domain together with SD1 and SD2 domains, which are closely related to the recognition and binding of polysaccharide substrates ^[15,36]. In 2023, Niu et al. ^[36] resolved its high-resolution three-dimensional structure by cryo-electron microscopy, laying a structural foundation for understanding its catalytic mechanism.

The TMEM2 orthologs of humans, mice, and naked mole-rats share high sequence similarity, but their catalytic activities differ markedly: mouse TMEM2 exhibits strong HA-degrading activity, whereas naked mole-rat TMEM2, whose sequence features are closer to those of humans, has almost no physiological HA-degrading function ^[18]. These species differences provide important clues for understanding the functional adaptation of TMEM2.

2.2. Research progress and controversy regarding the hyaluronidase activity of TMEM2

Evidence supporting the HA-degrading enzymatic activity of TMEM2 mainly comes from classic functional studies. In the initial report in 2017, Yamamoto et al. ^[8] demonstrated through *in vitro* and *in vivo* experiments

that TMEM2 possesses HA-degrading activity, preliminarily establishing the research foundation of this field. In 2023, Narita et al. ^[17] provided further evidence through recombinant protein experiments, concluding that TMEM2 is a bona fide hyaluronidase with intrinsic catalytic activity that degrades HA via a catalytic mechanism distinct from that of traditional HYAL family enzymes. In addition, using conditional knockout mouse models, Tobisawa et al. ^[19] found that systemic knockout of TMEM2 increased serum HA levels by approximately 40-fold, and that TMEM2 deficiency led to substantial accumulation of high-molecular-weight HA (HMW-HA) in multiple tissues, to an extent far exceeding the phenotypes observed upon HYAL1 and HYAL2 deficiency ^[20,21], suggesting that TMEM2 plays an important role in systemic HA catabolism and turnover *in vivo*.

However, evidence questioning the direct enzymatic activity of human TMEM2 also deserves attention. A study published by Sato et al. ^[16] in 2023 found that human TMEM2 lacks the key catalytic residues of classical hyaluronidases, and no significant HA-degrading activity of recombinant human TMEM2 protein was detected in *in vitro* systems; the team subsequently reported that naked mole-rat TMEM2 (nmrTMEM2) likewise lacks physiological hyaluronidase activity ^[18]. Accordingly, Sato et al. proposed that TMEM2 may not be an enzyme that directly catalyzes HA degradation, but rather acts as a regulatory factor of HYBID (KIAA1199/CEMIP) and HAS2 expression, indirectly influencing HA metabolism ^[16].

Taken together, a more reasonable understanding at present is that the evidence for the HA-degrading function of TMEM2 is relatively robust in mouse models and *in vivo* studies ^[8,19], whereas whether human TMEM2 possesses stable and reproducible intrinsic catalytic activity still requires confirmation by more direct structural biology and biochemistry evidence ^[9,10]. TMEM2 may participate in HA metabolism through both direct enzymatic activity and indirect regulation (such as the regulation of HYBID/HAS2 expression), and these two pathways are not mutually exclusive; their relative contributions may differ across cellular contexts and experimental systems ^[9,16,17]. In summary, the current consensus is that TMEM2 plays an important role in HA metabolism *in vivo*; the divergence lies in the manner in which human TMEM2 functions: direct catalysis versus indirect regulation. This divergence is critical: if human TMEM2 mainly serves as a regulatory factor rather than a catalytic enzyme, drug design strategies targeting its enzymatic activity need to be re-evaluated, and the interpretation of its tumor-promoting mechanisms should incorporate the contribution of cooperating molecules such as HYBID. Clarifying this controversy will help accurately interpret the role of TMEM2 in tumor ECM remodeling and guide the selection of appropriate experimental systems for subsequent research.

2.3. Roles in cellular stress responses and development

In addition to its HA-degrading function, TMEM2 is also involved in endoplasmic reticulum (ER) stress responses and the regulation of cellular homeostasis. In 2019, Schinzel et al. ^[22] discovered that TMEM2 is a novel ER stress regulator that promotes the maintenance of ER homeostasis through the CD44-MAPK signaling pathway, and this function is independent of the classical unfolded protein response (UPR); in *Caenorhabditis elegans*, loss of the TMEM2 homolog shortened lifespan, whereas its overexpression extended lifespan, suggesting an evolutionarily conserved cytoprotective function ^[22].

In 2024, Zhang et al. ^[23] further revealed that HA degradation products generated by TMEM2 can act as signaling molecules to regulate the dynamic balance of mitochondrial fission and fusion; upon TMEM2 loss, the accumulation of high-molecular-weight HA led to aggravated mitochondrial fragmentation and oxidative

phosphorylation dysfunction, thereby triggering cellular senescence. These findings directly link ECM remodeling to the regulation of cellular metabolism and provide a theoretical basis for understanding the role of HA in tumor metabolic reprogramming^[22,23].

In terms of developmental biology, Inubushi et al.^[35] found that TMEM2 deficiency caused severe developmental defects in mouse neural crest-derived tissues and led to embryonic lethality, suggesting that TMEM2 can clear a path for migrating cells through local HA degradation and is an indispensable molecule for embryonic development^[35].

3. TMEM2-mediated extracellular matrix remodeling

3.1. Cell-surface HA degradation and focal adhesion dynamics

Local degradation of cell-surface HA is essential for cell migration. In 2021, Irie et al.^[24] found that TMEM2 localizes to focal adhesions (FAs) and directly binds integrins $\alpha 5 \beta 1$ and $\alpha L \beta 2$ through its ectodomain, precisely targeting HA-degrading activity to the cell-matrix adhesion interface and promoting the dynamic reorganization of adhesion structures; loss of TMEM2 led to abnormal focal adhesion turnover and a significant decline in cell migration capacity. This finding refines the function of TMEM2 from generalized HA degradation to spatiotemporally specific ECM remodeling^[24].

It is worth noting that the pericellular matrix (PCM) formed by HA on the cell surface can reach a thickness several times the cell diameter, constituting a physical barrier to cell migration^[25]. Degradation of HA by TMEM2 at focal adhesions can disrupt the integrity of the PCM, creating space for the extension of cellular protrusions (such as lamellipodia and filopodia); when its activity is lost, excessive PCM accumulation hinders cell morphological changes and migration^[24,25], providing a cell-level explanation for the role of TMEM2 in tumor invasion and metastasis.

3.2. ECM mechanical properties and tumor invasion

The ECM is not a passive cellular scaffold but an active microenvironment with dynamic mechanical properties. HA accumulation can increase ECM hydration and elevate interstitial fluid pressure (IFP), forming a dense matrix barrier that limits drug penetration and immune cell infiltration^[5,6,31]. In pancreatic ductal adenocarcinoma (PDAC), massive HA deposition is an important contributor to tumor stromal fibrosis and vascular compression; studies by Provenzano et al.^[5,6] demonstrated that degrading tumor stromal HA with the hyaluronidase PEGPH20 reduced IFP, improved vascular function and chemotherapeutic drug delivery, enhanced the efficacy of gemcitabine, and prompted several clinical trials of combination chemotherapy^[2].

As an endogenous cell-surface hyaluronidase, TMEM2 plays a more refined role in the mechanical remodeling of the ECM. Unlike traditional secreted hyaluronidases (such as the systemic degradation strategy of PEGPH20), the local degrading activity of TMEM2 at the cell-matrix interface enables precise regulation of HA distribution in the microenvironment rather than global depletion of HA^[24]. Such precise regulation may be of great significance for maintaining the functional architecture of the ECM microenvironment. A 2025 study by Yao et al.^[26] showed that restoring TMEM2 expression in PDAC can rearrange collagen fibers by degrading stromal HA, thereby reducing tumor stromal density, improving drug permeability, and ultimately sensitizing chemotherapy. This finding reveals the potential application of TMEM2 in ECM

normalization strategies, that is, improving the tumor microenvironment and promoting therapeutic efficacy through fine-tuned regulation rather than complete eradication of the ECM ^[26].

In addition, the HA degradation products mediated by TMEM2, namely low-molecular-weight HA (LMW-HA) fragments, are themselves biologically active. Contrary to the anti-inflammatory and anti-angiogenic effects of high-molecular-weight HA, LMW-HA can activate Toll-like receptors (TLR2/TLR4) and the CD44 receptor, promoting inflammation, angiogenesis, and tumor progression ^[4,29]. Therefore, the ECM-remodeling activity of TMEM2 has dual effects: it can provide spatial conditions for tumor invasion by degrading HA, but may also exacerbate the malignant transformation of the microenvironment by generating tumor-promoting LMW-HA fragments; its net effect depends on the tumor type, the spatiotemporal distribution of HA molecular-weight spectra, and the integration of receptor signaling ^[4,29].

4. Mechanisms of TMEM2 in tumor development and progression

4.1. Tumor cell proliferation and survival

Available evidence suggests that TMEM2 may promote tumor cell proliferation and survival through multiple pathways. First, LMW-HA fragments generated by HA degradation can serve as ligands for CD44, activating downstream PI3K/AKT and MAPK/ERK signaling pathways and promoting cell cycle progression and the expression of anti-apoptotic genes ^[29]. Second, TMEM2 participates in the formation and maturation of focal adhesions through direct interaction with integrin $\alpha 5 \beta 1$, which may contribute to integrin-mediated cell adhesion and survival signaling ^[24]. In breast cancer cells, SOX4-dependent transcriptional activation of TMEM2 significantly promotes anchorage-independent growth of tumor cells by enhancing the activity of the above signaling pathways ^[11].

The protective effect of TMEM2 on cell survival is also reflected in the regulation of ER stress ^[22]: factors such as hypoxia, nutrient deprivation, and oxidative stress in the tumor microenvironment continuously trigger ER stress, and TMEM2 enhances ER folding capacity and maintains calcium homeostasis through the CD44-MAPK pathway, which may confer a survival advantage to tumor cells under stress conditions ^[22]; its mediation of mitochondrial homeostasis regulation may also support tumor cell proliferation under high metabolic demand ^[23].

4.2. Epithelial-mesenchymal transition

EMT is a key process by which epithelial-derived tumors acquire invasive and metastatic capabilities. During this process, epithelial cells lose apical-basal polarity and intercellular junctions and acquire the spindle-shaped morphology and migratory capacity of mesenchymal cells ^[27]. Multiple research teams have suggested that TMEM2 promotes EMT in various tumor types. Using chromatin immunoprecipitation sequencing (ChIP-seq) and luciferase reporter assays in prostate and breast cancer cells, Lee et al. ^[11] demonstrated that the transcription factor SOX4 directly binds to the promoter region of the TMEM2 gene to activate its transcription; TMEM2 in turn alters cell-matrix adhesion properties through HA degradation, inducing the upregulation of mesenchymal marker genes (such as Vimentin and N-cadherin) and the downregulation of the epithelial marker gene E-cadherin.

In GBM, Gao et al. ^[13] found that high TMEM2 expression was significantly associated with the mesenchymal subtype, which is the most invasive molecular subtype of GBM with the worst prognosis. Mechanistic studies showed that TMEM2 activates core EMT transcription factors such as Snail and ZEB1

through downstream effects of the CD44-HA signaling axis, driving the EMT-like mesenchymal program and invasive migration of GBM cells ^[13]. Given that GBM is not a typical epithelial-derived tumor, all references to EMT in GBM in this review refer to EMT-like mesenchymal transition. In addition, Gan et al. ^[14] suggested that, in triple-negative breast cancer (TNBC), miR-518a-3p suppresses TMEM2 expression by targeting the 3'-UTR of TMEM2 mRNA, thereby reversing the EMT process and weakening tumor cell migration and invasion. This study not only revealed the post-transcriptional regulatory mechanism of TMEM2 but also provided a potential therapeutic strategy of restoring miRNA expression to inhibit the TMEM2-EMT axis ^[14].

4.3. Tumor drug resistance

Tumor drug resistance is the main cause of treatment failure and disease progression. The physical barrier effect of the ECM is one of the important mechanisms underlying insufficient chemotherapeutic drug penetration and resistance. As mentioned above, HA accumulation leads to tumor stromal densification and elevated IFP, severely hindering the entry of macromolecular and small-molecule drugs from blood vessels into the tumor parenchyma ^[5,6,31]. By degrading HA to reduce IFP and improve vascular perfusion, TMEM2 may overcome this type of chemoresistance based on the ECM physical barrier ^[26]. The study by Yao et al. ^[26] directly supports this hypothesis: in a PDAC mouse model, restoration of TMEM2 expression combined with gemcitabine treatment significantly reduced tumor volume, accompanied by a marked increase in drug concentration in tumor tissue.

In addition, TMEM2 can mediate intrinsic drug resistance of tumors through EMT and signaling pathway regulation. In GBM research, Gao et al. ^[13] found that high TMEM2 expression conferred significant resistance to temozolomide (TMZ) in GBM cells. At the mechanistic level, TMEM2 enhanced the expression of O6-methylguanine-DNA methyltransferase (MGMT), the main determinant of TMZ resistance, through HA-CD44 signaling, while simultaneously activating the PI3K/AKT pathway to promote cell survival signals, weakening the cytotoxicity of TMZ on both fronts ^[13]. After TMEM2 knockdown, the sensitivity of GBM cells to TMZ was significantly restored, indicating that targeting TMEM2 may be a feasible strategy to overcome TMZ resistance in GBM ^[13].

4.4. Comprehensive regulation of the tumor microenvironment by ECM remodeling

The impact of TMEM2-mediated ECM remodeling on the TME goes far beyond the elimination of physical barriers. Research evidence indicates that TMEM2 activity regulates the cellular composition and functional states of the TME in multiple dimensions. First, LMW-HA fragments produced by TMEM2-mediated HA degradation can recruit and activate tumor-associated macrophages (TAMs) and cancer-associated fibroblasts (CAFs), promoting the formation of an immunosuppressive TME ^[4,29]. Second, the mechanical relaxation of the ECM caused by HA degradation can release various growth factors locked in the matrix, such as vascular endothelial growth factor (VEGF), transforming growth factor- β (TGF- β), and basic fibroblast growth factor (bFGF), further promoting angiogenesis and fibrosis ^[29,31].

Through bioinformatics analysis and functional experiments, Srivastava et al. ^[30] identified TMEM2 as one of the CAF markers in PDAC, suggesting that TMEM2 may exert bidirectional regulatory functions in tumor-stroma communication. Tumor cell-derived TMEM2 degrades HA to generate signaling molecules, which act on CAFs and thereby remodel the stromal environment, forming a positive feedback loop that

exacerbates tumor progression ^[30]. The study by Yao et al. ^[26] more directly demonstrated the importance of the TMEM2/HA axis in TME remodeling: restoring TMEM2 expression led to the reprogramming of CAFs in PDAC tumor tissue, shifting them from a tumor-promoting phenotype (such as myofibroblasts with high α -smooth muscle actin (α -SMA) expression) toward a relatively quiescent phenotype, while increasing the infiltration and activity of CD8+ T cells. This suggests that the ECM state regulated by TMEM2 may be a key factor determining the immune landscape of the TME ^[26].

Taken together, TMEM2 appears to exert important regulatory effects in the TME through a multi-level cascade of mechanisms involving HA degradation, ECM mechanical remodeling, signaling molecule release, and immune microenvironment remodeling ^[28]. Understanding the complexity of this regulatory network is crucial for designing precise therapeutic strategies targeting TMEM2. Simply inhibiting TMEM2 may lead to HA accumulation and further stromal densification, which is detrimental to drug delivery; whereas excessive activation of TMEM2 may generate large amounts of tumor-promoting LMW-HA fragments and aggravate invasion and metastasis. Therefore, precisely modulating TMEM2 activity or intervening in its downstream effector pathways in a spatiotemporally specific manner may be the direction of future therapeutic development ^[9,10].

5. Research progress of TMEM2 in various tumors

The main research evidence for TMEM2 in various tumors is summarized in **Table 1**.

Table 1. Summary of research evidence for TMEM2 in different tumors

Tumor type	Expression and prognostic association	Main mechanisms	Evidence type	References
Breast cancer	High expression associated with shortened overall survival and distant metastasis-free survival	SOX4 transcriptional activation; miR-518a-3p targeting; EMT	Clinical samples + cell-based experiments + public database analysis	[11,14]
Pancreatic ductal adenocarcinoma	High expression associated with lymph node metastasis, higher TNM stage, and shortened overall survival; concurrent high expression with KIAA1199 indicates worse prognosis	ECM normalization sensitizing chemotherapy; CAF phenotype regulation	Clinical samples + animal models + cell-based experiments	[12,26,30,32]
Glioblastoma	High expression associated with shortened overall survival; combination with IDH/1p19q improves molecular subtyping	EMT-like mesenchymal transition; TMZ resistance (MGMT upregulation, PI3K/AKT activation)	Public database analysis + cell-based experiments	[13,33]
Laryngeal cancer	High expression associated with increased postoperative recurrence risk (included in a 9-gene recurrence prediction model)	Recurrence prediction model construction	Public database analysis	[34]

5.1. Breast cancer

Breast cancer is one of the tumor types in which TMEM2 was first studied in depth. In a landmark study published in *Cancer Research* in 2016, Lee et al. ^[11] used the Cancer Genome Atlas (TCGA) database and paired clinical sample analysis to show that TMEM2 is significantly overexpressed in breast cancer tissue and positively correlated with SOX4; ChIP-seq confirmed that the transcription factor SOX4 can directly bind the TMEM2 promoter and activate its transcription, and SOX4-dependent overexpression of TMEM2 enhanced the migration, invasion, and experimental lung metastasis of breast cancer cells ^[11]. Clinically,

patients with high TMEM2 expression had significantly shorter overall survival and distant metastasis-free survival. This study established a signaling axis linking SOX4, TMEM2, HA degradation, and cell migration/invasion ^[11].

In TNBC, Gan et al. ^[14] further enriched the understanding of TMEM2 at the post-transcriptional regulatory level. Through bioinformatics prediction combined with luciferase reporter assays, the study suggested that miR-518a-3p can directly target the 3'-UTR region of TMEM2 mRNA and inhibit its translation. In TNBC tissues, miR-518a-3p expression was downregulated and negatively correlated with TMEM2 protein levels. Restoring miR-518a-3p expression effectively suppressed TMEM2 protein levels, reversed the expression of EMT markers, and reduced the number of lung metastatic nodules in in vivo models ^[14]. This finding provides a potential therapeutic approach for restoring the negative regulatory network of TMEM2 using miRNA mimics or small-molecule compounds, and also suggests that TMEM2 expression is precisely controlled by multi-level regulatory networks ^[14]. The above evidence mainly derives from bioinformatics analyses and in vitro cell-based experiments, and validation in in vivo studies and preclinical models remains limited.

5.2. Pancreatic cancer

Pancreatic cancer (especially PDAC), owing to its dense fibrotic stroma and extremely poor prognosis, is a key tumor type for research on HA metabolism and ECM remodeling. In 2020, Kudo et al. ^[12] first systematically evaluated the expression and prognostic value of TMEM2 in PDAC. Immunohistochemical analysis of 110 surgically resected PDAC specimens showed that TMEM2 protein was highly expressed in approximately 70% of PDAC tissues, and that high expression was independently associated with lymph node metastasis, higher TNM stage, and significantly shortened overall survival. Multivariate Cox regression analysis indicated that TMEM2 is an independent prognostic factor for PDAC ^[12]. Unexpectedly, the study also found that small interfering RNA (siRNA) knockdown of TMEM2 in human PDAC cell lines did not inhibit cell migration as expected, but instead led to a compensatory enhancement of migration capacity, accompanied by upregulation of HYBID (KIAA1199/CEMIP) mRNA levels. This finding suggests that a functional compensation mechanism between TMEM2 and HYBID may exist in PDAC ^[12].

In a 2022 follow-up study, Kudo et al. ^[32] further examined the combined prognostic value of TMEM2 and KIAA1199 in PDAC. Dual immunohistochemical analysis of 167 resected PDAC specimens showed that the median overall survival of the group with concurrent high expression of TMEM2 and KIAA1199 was only 12.5 months, significantly lower than the 30.2 months of the group with concurrent low expression; after adjustment for age, tumor size, lymph node metastasis, and margin status, concurrent high expression remained an independent adverse prognostic factor (HR = 3.2) ^[32]. These results provide a new molecular indicator for prognostic stratification of PDAC and highlight the synergistic pathogenic role of the two HA-degrading enzymes in PDAC.

A study published by Yao et al. ^[26] in *Cancer Letters* in 2025 provided important insights into the function of TMEM2 in PDAC from a therapeutic perspective. The study suggested that CEMIP2 (TMEM2) normalizes the ECM by degrading HA in the tumor stroma, a process that involves not only the removal of physical barriers but also the rearrangement of collagen fibers and the phenotypic remodeling of CAFs. PDAC mice with restored CEMIP2 expression showed a tumor volume reduction of more than 70% compared with the control group after receiving gemcitabine combined with nab-paclitaxel, accompanied

by a significant increase in CD8⁺ T cell infiltration and a decrease in regulatory T (Treg) cells. This study provides evidence in animal models for the potential of ECM normalization strategies in sensitizing PDAC treatment, and offers an experimental basis for exploring the conversion of TMEM2 from a tumor-promoting molecule into a therapeutic target ^[26].

In 2024, Srivastava et al. ^[30] reported NSC777201, a small-molecule candidate compound targeting TMEM2. Molecular docking simulations showed that NSC777201 can stably bind to TMEM2; in PDAC cell models, NSC777201 treatment reduced TMEM2 expression, inhibited the activity of cancer-associated fibroblasts (CAFs) and induced their senescence, and rescue experiments supported that its effect depends on TMEM2; in mouse models, NSC777201 inhibited tumor growth and improved the tumor microenvironment ^[30]. Although the selectivity and in vivo efficacy of NSC777201 remain to be systematically evaluated, this study provides preliminary proof of concept for the development of TMEM2-targeted drugs ^[30]. The studies by Kudo et al. provided clinical relevance evidence based on clinical sample analyses, while Yao et al. further provided in vivo functional evidence through animal models and single-cell sequencing.

5.3. Glioblastoma

GBM is the most common primary malignant brain tumor in adults, notorious for its high invasiveness and therapeutic resistance. In 2023, through analyses of the TCGA and Chinese Glioma Genome Atlas (CGGA) databases, Gao et al. ^[13] found that TMEM2 mRNA levels in GBM tissue were significantly higher than those in lower-grade glioma and normal brain tissue, and that high expression was associated with shorter overall survival and progression-free survival; gene set enrichment analysis (GSEA) showed significant enrichment of EMT pathways and HA metabolism pathways in the high-expression group ^[13]. Functional experiments suggested that overexpression of TMEM2 induced typical EMT-like morphological changes in GBM cells, including a transition toward a spindle-shaped mesenchymal morphology, accompanied by downregulation of E-cadherin, upregulation of N-cadherin and Vimentin, and enhanced cell invasion. Conversely, short hairpin RNA (shRNA) knockdown of TMEM2 reversed the above phenotypes ^[13].

More importantly, this study revealed the important role of TMEM2 in TMZ resistance in GBM. TMEM2 overexpression increased the half-maximal inhibitory concentration (IC₅₀) of TMZ in GBM cells by approximately 3-fold, accompanied by a significant rise in MGMT protein levels. Use of the MGMT inhibitor O6-benzylguanine (O6-BG) partially restored the cytotoxicity of TMZ, indicating that TMEM2-mediated TMZ resistance depends at least in part on MGMT upregulation. In addition, TMEM2 enhanced pro-survival signals by activating the PI3K/AKT pathway, providing another layer of protection for drug resistance in GBM cells ^[13]. This study suggests that TMEM2 may be one of the important molecules linking HA metabolism, EMT-like mesenchymal transition, and chemoresistance in GBM, providing a theoretical basis for developing TMEM2-targeted strategies against GBM ^[13].

Regarding the molecular classification of GBM, in 2021 Jiang et al. ^[33] found through integrated analysis of the TCGA and CGGA datasets that TMEM2 expression levels, combined with isocitrate dehydrogenase (IDH) mutation status and 1p19q co-deletion status, can be used to construct a more refined molecular subtyping system for glioma: among IDH-wildtype gliomas, the TMEM2 high-expression subgroup had significantly worse prognosis than the low-expression subgroup, and the inclusion of TMEM2 markedly improved the accuracy of the model in predicting 3-year and 5-year overall survival ^[33]. The infiltration proportion of immunosuppressive cells (such as M2 macrophages) was also increased in TMEM2 high-

expression tumors^[33]. The above studies are mainly based on public database analyses and in vitro cell-based experiments, and in vivo validation and prospective clinical studies still need to be strengthened.

5.4. Other tumors

In addition to the intensively studied tumor types described above, multiple studies suggest that TMEM2 may exert important functions in a broader spectrum of tumors.

In laryngeal cancer, Xiang et al.^[34] constructed a recurrence prediction model using combined mRNA-lncRNA expression profiles, in which TMEM2 was identified as one of the important genes, and its high expression was significantly associated with an increased risk of postoperative recurrence of laryngeal cancer. The area under the receiver operating characteristic curve (AUC) of this model exceeded 0.8 in both the training and validation sets, demonstrating good predictive performance^[34]. The widespread abnormal expression of TMEM2 across different tumor types suggests that it may be a pan-cancer tumor-promoting factor, but its expression regulation mechanisms, downstream effector pathways, and functional dependencies may differ depending on tissue origin and genetic background. Future pan-cancer multi-omics integrated analyses will help systematically map the functional and dependency landscapes of TMEM2 across different tumor types.

6. Prospects and challenges of TMEM2 as a therapeutic target

The tumor-promoting effects of TMEM2 in various tumors and its association with poor prognosis make it an attractive potential therapeutic target. However, translating TMEM2 from basic research into a clinical therapeutic target still requires overcoming multiple challenges.

6.1. Current status of small-molecule targeted drug development

In terms of drug development, NSC777201, reported by Srivastava et al.^[30], is currently the first small-molecule candidate compound targeting TMEM2, providing preliminary clues for drug research and development in this field. However, its inhibitory potency, selectivity, and pharmacokinetic characteristics against TMEM2 have not been systematically evaluated, and it remains far from clinical translation. In the future, lead compounds need to be optimized through structure-based drug design (SBDD) and high-throughput screening of compound libraries to obtain more potent and highly selective TMEM2 inhibitors. Meanwhile, given the differences in the catalytic activity of TMEM2 between humans and mice^[16,17,18], drug development must fully consider the impact of species differences on efficacy evaluation and select appropriate humanized models for preclinical validation.

6.2. Complexity of targeting strategies and combination therapy

In terms of therapeutic strategies, TMEM2 targeting faces complex decision-making challenges arising from its dual effects: inhibiting TMEM2 may lead to HA accumulation in tumor tissue and aggravate ECM densification, thereby impairing drug delivery^[5,6]; activating TMEM2 can improve drug penetration through ECM normalization^[26], but may generate tumor-promoting LMW-HA fragments and accelerate the EMT process^[4,29]. Neither simple inhibition nor activation is an ideal strategy. More refined approaches may include:

(1) spatiotemporally controlled modulation of TMEM2 activity (such as transient activation before

- chemotherapy to promote drug penetration);
- (2) combined targeting of its downstream effector pathways (such as CD44 antagonists or PI3K/AKT inhibitors);
- (3) combination with immune checkpoint inhibitors. The efficacy and safety of the above strategies still need to be systematically evaluated in preclinical models ^[9,10].

The functional relationship between TMEM2 and HYBID (KIAA1199/CEMIP) also provides important implications for the design of therapeutic strategies. The findings of Kudo et al. ^[12] indicate that inhibiting TMEM2 alone may achieve little due to compensatory upregulation of HYBID. Therefore, strategies that target TMEM2 and HYBID simultaneously, or broad-spectrum inhibitors that block both HA-degrading enzymes, may be more effective therapeutic directions. The finding of Kudo et al. ^[32] that the median survival of PDAC patients with concurrent high expression of both hyaluronidases was only 12.5 months provides strong clinical demand support for this combination strategy. However, the potential systemic side effects of comprehensively inhibiting the HA-degrading enzyme system, such as HA accumulation in normal tissues including joints, skin, and kidneys, must be fully considered in the evaluation of the therapeutic window ^[19,21].

Notably, the study by Yao et al. ^[26] provides a new idea for TMEM2-targeted therapy: rather than inhibiting TMEM2, its ECM normalization function can be exploited to improve the efficacy of existing treatments. This approach of using ECM remodeling to improve the efficacy of existing therapies has precedents in the field of oncology: in pancreatic cancer, clinical trials of enhancing chemotherapy by degrading HA with PEGPH20 have achieved preliminary results ^[2,5]. However, unlike the systemic HA degradation of PEGPH20, restoration of endogenous TMEM2 expression may achieve more physiological and spatiotemporally precise ECM remodeling, thereby reducing side effects such as the musculoskeletal toxicity observed in PEGPH20 treatment ^[2]. If gene therapy or mRNA delivery technologies can achieve tumor-specific transient expression regulation of TMEM2, this strategy may have significant advantages in terms of safety.

6.3. Translational application as a prognostic biomarker

Biomarker development is another key link in the translational application of TMEM2-targeted therapy. At present, TMEM2 as a prognostic biomarker has been validated in multiple retrospective studies ^[12,32,33], but prospective evidence is still lacking for its use as a predictive biomarker to screen patient populations who may benefit from TMEM2-targeted therapy. Future clinical translational research needs to:

- (1) establish standardized detection methods for TMEM2 protein/activity to ensure the comparability of data across studies;
- (2) conduct prospective cohort studies to validate the prognostic and predictive value of TMEM2 in larger independent cohorts;
- (3) explore the interaction between TMEM2 and the efficacy of approved targeted drugs, for example, whether PDAC patients with high TMEM2 expression respond differently to anti-fibrotic drugs or immunotherapy ^[26,32];
- (4) develop non-invasive TMEM2 detection methods (such as liquid biopsy) to achieve dynamic monitoring during treatment.

6.4. Limitations of current research

Although the value of TMEM2 in tumor research is increasingly prominent, several limitations remain:

- (1) direct tumor research on TMEM2 is still concentrated in a few tumor types (breast cancer, pancreatic cancer, and glioblastoma); direct experimental evidence in other tumor types is insufficient, and most correlational conclusions derive from database analyses rather than functional experimental validation;
- (2) whether human TMEM2 possesses stable intrinsic hyaluronidase catalytic activity remains controversial, affecting the definitive interpretation of its participation in tumor mechanisms as an HA-degrading enzyme;
- (3) the functional compensation and synergistic relationship between TMEM2 and HYBID increase the complexity of single-target intervention;
- (4) existing studies are dominated by retrospective clinical sample analyses and in vitro cell-based experiments, lacking prospective clinical studies and rigorously controlled animal models;
- (5) the small-molecule compound NSC777201 targeting TMEM2 is still in the preclinical research stage, and its safety, selectivity, and pharmacokinetic characteristics remain to be systematically evaluated.

These limitations suggest that research on TMEM2 tumor biology is still in an early stage of development, and more direct functional validation in additional tumor types and preclinical model studies are needed in the future.

7. Conclusions and future perspectives

Since Yamamoto et al. ^[8] first identified TMEM2 as a cell-surface hyaluronidase in 2017, research on this molecule has made remarkable progress. Existing studies suggest that TMEM2 plays an important role in HA metabolism in vivo and, through its unique cell-surface localization and local degrading activity, exerts key biological functions at multiple levels, including ECM remodeling, cell migration, EMT, ER stress tolerance, and mitochondrial homeostasis ^[9,10,15]. In the field of oncology, existing studies suggest that TMEM2 is highly expressed in various solid tumors, including breast cancer ^[11,14], pancreatic cancer ^[12,26,32], and GBM ^[13,33], and is associated with poor patient prognosis; it may participate in tumor invasion, metastasis, and drug resistance through both HA degradation-dependent and -independent mechanisms.

However, as described in Section 6.4, TMEM2 tumor research still faces multiple challenges in terms of catalytic activity confirmation, functional context analysis, and clinical translation.

Looking ahead, TMEM2 research can be advanced in the following directions:

- (1) at the functional mechanism level: using single-cell sequencing, spatial transcriptomics, and other technologies to reveal the differential functions of TMEM2 in different cell populations of the TME;
- (2) at the structural pharmacology level: developing highly selective inhibitors or activity modulators through artificial intelligence-assisted drug design based on the high-resolution structure of its ectodomain ^[36];
- (3) at the clinical translation level: conducting prospective biomarker studies to validate its value in diagnosis, prognostic assessment, and efficacy monitoring;
- (4) at the interdisciplinary integration level: integrating the multiple functions of TMEM2 in ECM mechanics ^[6,24], mitochondrial metabolism ^[23], and immune regulation ^[26] into a unified network model of HA metabolism and TME interactions.

In summary, TMEM2, as a late-discovered but significant molecule in the field of HA metabolism, is gradually deepening our understanding of tumor ECM remodeling and TME regulation. Although the path to translating it into clinical benefit is full of challenges, based on the research evidence accumulated so far, TMEM2 has preliminarily demonstrated its potential value as an intersection of basic tumor research and clinical translation. Future systematic research across multiple disciplines is expected to fully reveal the biological complexity of TMEM2 and provide a new research foundation and translational direction for improving the prognosis of tumor patients.

Disclosure statement

The authors declare no conflict of interest.

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