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Review Article

Roles, molecular mechanisms, and signaling pathways of TMEMs in neurological diseases

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Abstract: Transmembrane protein family members (TMEMs) span the entire lipid bilayer and act as channels that allow the transport of specific substances through biofilms. The functions of most TMEMs are unexplored. Numerous studies have shown that TMEMs are involved in the pathophysiological processes of various nervous system diseases, but the specific mechanisms of TMEMs in the pathogenesis of diseases remain unclear. In this review, we discuss the expression, physiological functions, and molecular mechanisms of TMEMs in brain tumors, psychiatric disorders, abnormal motor activity, cobblestone lissencephaly, neuropathic pain, traumatic brain injury, and other disorders of the nervous system. Additionally, we propose that TMEMs may be used as prognostic markers and potential therapeutic targets in patients with various neurological diseases.

Keywords: TMEMs, tumor, psychiatric disorder, abnormal action, nervous system

Introduction

Transmembrane protein family members (TMEMs), which belong to a class of proteins that cross biofilms, are usually located in the lipid bilayer of the plasma membrane. Some of the TMEMs may also be located in the membranes of organelles such as the mitochondria, endoplasmic reticulum, lysosomes, and Golgi bodies. Currently, TMEMs are classified into α-helical proteins and β-barrel proteins according to their basic or topological structure, which is based on the location of their N-terminal and C-terminal domains [1, 2]. TMEMs exist in many types of cells and participate in important physiological processes, playing multiple roles in regulation of ion channel transport, signal transduction, cellular chemotaxis, adhesion, apoptosis, and autophagy [3].

Differences in TMEM expression have been observed in many neurological diseases such as glioma (TMEM16A, TMEM45A, TMEM97, TMEM140), glioblastoma (TMEM168, TMEM176A) (**Figure 1**), anxiety (TMEM16B, TMEM168), phobias (TMEM132D, TMEM132E), depressive disorders (TMEM176A), autism (TMEM187), motor learning disorders (TMEM16B), aggressive behavior (TMEM16B), hyperlocomotion (TMEM168), cobblestone lissencephaly (TMEM5), NSC differentiation (TMEM59), traumatic brain injury (TMEM97), neuropathic pain (TMEM97), frontotemporal degeneration (TMEM106B) and spinocerebellar ataxia type 21 (TMEM240) (**Figure 2**).

An increasing number of studies have examined the effects of TMEMs. However, due to the complex nature of neurological diseases, a systematic understanding of TMEM-mediated mechanisms in these disorders is still lacking. In this review, we summarized the currently known functions and molecular mechanisms of TMEMs in neurological diseases. We aimed to enhance the understanding of how TMEMs function in the nervous system so as to provide possible targets for therapeutic intervention for patients with neurological disorders.

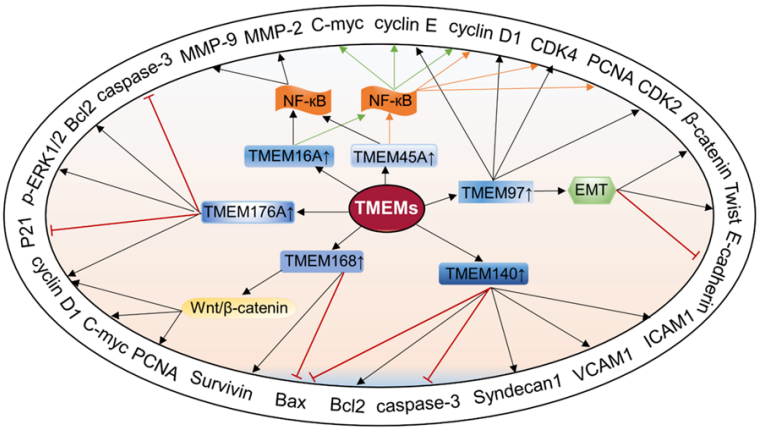

Figure 1. TMEM-mediated molecular mechanisms in neurotumors. TMEM expression is increased in glioma. In glioma, TMEM16A and TMEM45A promote tumor-cell migration and proliferation by regulating the expression of MMP2/9 and cell-cycle-associated proteins via NF-κB activity. Upregulated expression of TMEM97 in glioma also promotes tumor-cell metastasis by regulating the expression of cyclins and EMT-related proteins. TMEM140 upregulates the expression of cell adhesion proteins, increases tumor-cell adhesion, inhibits the expression of apoptotic proteins, upregulates the expression of anti-apoptotic proteins, and promotes tumor-cell survival. TMEM168 shortens the cell cycle, reduces apoptosis, and promotes tumor-cell proliferation via the Wnt/β-catenin pathway. TMEM176A regulates the growth cycle of GBM cells, inhibits apoptosis, and accelerates tumor progression.

TMEMs in neuro-oncology

TMEMs in glioma

Glioma is the most common tumor of the central nervous system (CNS) and one of the most intractable primary cancers [4]. Glioma spreads by invading the surrounding brain parenchyma, is difficult to remove surgically, and is one of the leading causes of cancer-related mortality [5]. The 5-year survival rate for patients with glioma is the lowest among all cancer patients. Glioblastoma multiforme (GBM) is considered the most aggressive and fatal malignant form of glioma [6]. The average survival rate for patients with GBM is only 14 months, and only 2.2% of GBM patients survive for more than 3 years [7]. New prognostic indicators and effective therapeutic targets need to be identified for the treatment of patients with gliomas. Presently, several studies have suggested that some members of the TMEM family are involved in the development of glioma and GBM.

TMEM16A in glioma: TMEM16A is located on chromosome 11q13 and is frequently amplified in many malignancies [8]. Knockout of TMEM16A expression can inhibit cellular proliferation, migration, and invasion, suggesting that TMEM16A expression can promote the invasiveness of glioma cells [9]. Nuclear factor κB (NF-κB) is a key regulator in tumorigenesis and is involved in the survival of cancer cells, metastasis, and angiogenesis [10]. The proto-oncogene c-myc plays an important role in controlling cell growth and viability [11]. C-myc and cyclin are important signaling molecules in cell-cycle progression. Overexpression of TMEM16A can activate NF-κB signaling, promote upregulation of cyclin D1, cyclin E, and c-myc expression, shorten cell-growth time, reduce the cellular reproductive cycle, and promote the proliferation of tumor cells [12, 13]. The genes encoding matrix metalloproteinases (MMPs), which are targets of NF-κB, are involved in tumor-progression processes, such as cell migration and invasion [14, 15]. MMP-2 and MMP-9 are closely associated with tumor progression and have been shown to modulate cell migration and glioma invasiveness. TMEM16A can modulate MMP-2 and MMP-9 expression via the activity of the NF-κB pathway, thereby promoting glioma metastasis and invasion [16].

Glioma metastasis is also closely related to ion transport. GBM participates in abnormal Ca^{2+} and Cl^- activity, regulates cell-volume signaling, causes cell-volume alterations, and enhances the proliferation, migration, and invasion of tumor cells [9]. TMEM16A regulates the activation of Ca^{2+} channels by activating EGFR signaling, allowing Ca^{2+} to enter cells [17]. TMEM16A activity is Ca^{2+}- and voltage-dependent. In the nervous system, increases in intracellular Ca^{2+} levels enable TMEM16A to more dynamically regulate the sensory pathways of neurons connected to downstream signaling and rapidly regulate cellular excitability by changing the time and duration of increases in action potential [18, 19]. Upregulated Ca^{2+} channel activity can activate the activity of ion Cl^- channels. The outflow of ions and water leads to contraction

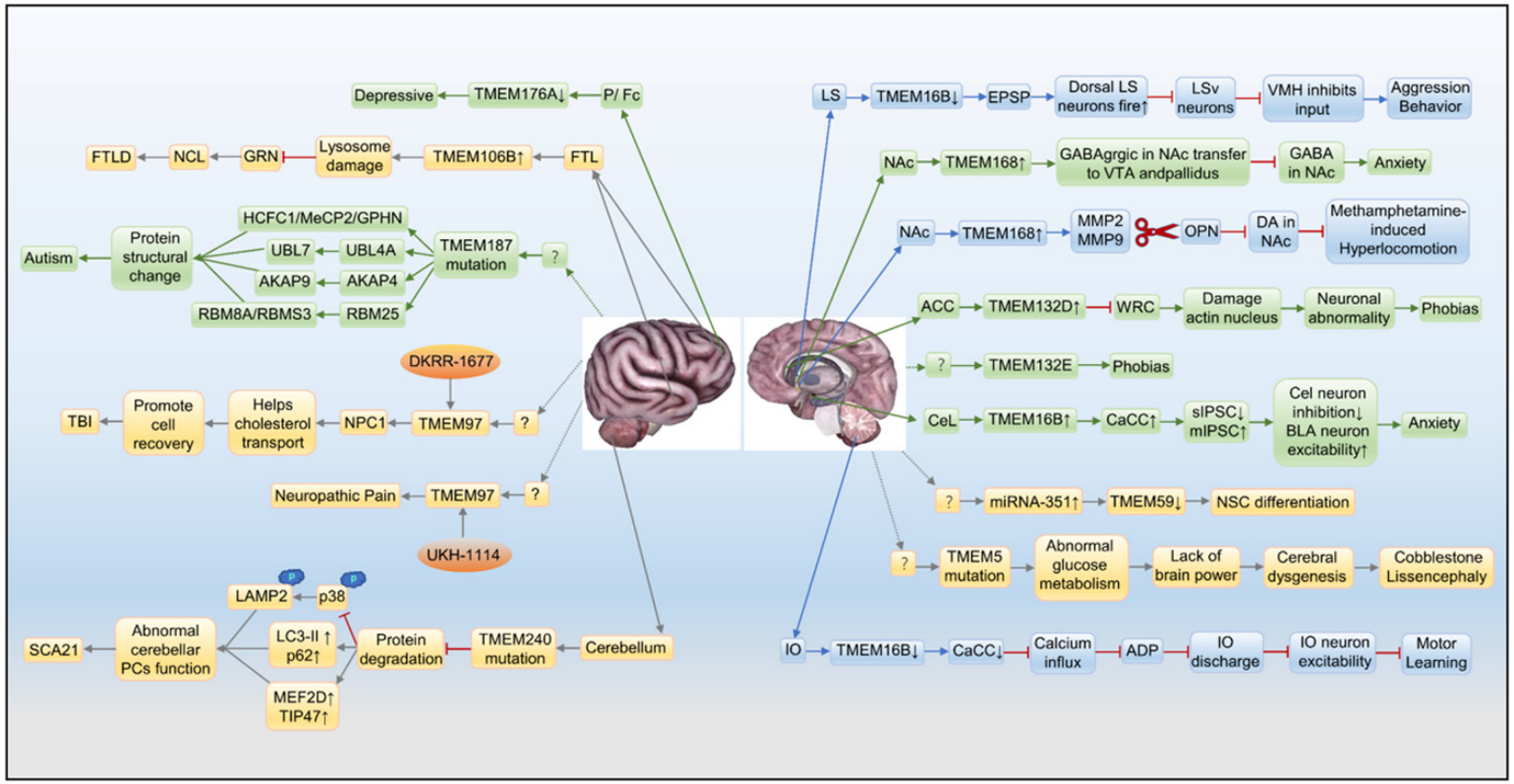

Figure 2. TMEM-mediated molecular mechanisms in neurological diseases not involving tumors. Psychiatric Disorders; Abnormal Action; Other NS Diseases; Agonist; Phosphorylation.

of glioma cells, and glioma cells with decreased volume are more likely to metastasize [20, 21]. Meanwhile, high expression of epidermal growth factor receptor variant III (EGFRvIII) is a common feature of malignant GBM [22]. EGFRvIII is resistant to chemotherapy and radio therapy and promotes tumorigenesis and development of GBM cells [23]. Therefore, EGFRvIII is a specific marker of glioblastoma stem cells. TMEM16A plays a crucial role in the maintenance of stemness and invasiveness in glioblastoma stem cells by regulating the expression of EGFRvIII and related signaling molecules. These findings indicate that TMEM16A is a promising therapeutic target in the treatment of patients with GBM [17].

TMEM45A in glioma: TMEM45A contains 275 amino acids and is a multi-channel membrane protein [24]. TMEM45A expression is significantly increased in glioma tissues compared with that of non-tumor brain tissue. Levels of TMEM45A mRNA are positively correlated with glioma histological grade [25]. As a membrane channel protein, TMEM45A plays a key role in the proliferation and metastasis of glioma cells. TMEM45A siRNA downregulates the expression of cell-cycle- and invasion-related genes in glioma cells. Treatment using TMEM45A siRNA significantly downregulates the expression of cyclin D1, cyclin-dependent kinase 4 (CDK4), and proliferating cell nuclear antigen (PCNA), promotes cell-cycle transformation, and inhibits the cellular growth cycle and tumor-cell proliferation [26, 27]. Knockout of TMEM45A expression can also downregulate the expression of cell-invasion promoting proteins MMP-2 and MMP-9 and inhibit the invasion and metastasis of tumor cells. This is one of the mechanisms involved in TMEM45A-mediated promotion of glioma invasion and metastasis [25].

A study conducted to examine the effects of TMEM45A on the survival of glioma patients showed that TMEM45A is highly expressed in these patients and cell lines A172 and U251 [28]. TMEM45A expression is positively correlated with that of NF-κB in glioma cells, and TMEM45A promotes increased expression of NF-κB. Knockout of TMEM45A expression can reduce NF-κB levels and inhibit the proliferation of glioma cells, suggesting that TMEM45A may play a role in regulating NF-κB signaling. These data suggest that the TMEM45A/NF-κB signaling pathway may be a potential target for the diagnosis and treatment of gliomas [28].

TMEM97 in glioma: TMEM97 has been identified as a sigma-2 receptor and is expressed in human glioma cell lines. The sigma-2 receptor ligand is a biomarker of cancer and target for potential anticancer drugs [29, 30]. As a sigma-2 receptor, TMEM97 is closely related to brain tumors. An in vitro study showed that inhibition of TMEM97 expression inhibits the proliferation, migration, and invasion of human glioma cell lines U87 and U373 [31]. TMEM97 is also known as meningioma-associated protein [32]. Overexpression of TMEM97 in glioma tissues is closely related to tumor histological grade and overall survival time of the patients. mRNA and protein levels of cyclin D1, cyclin E, CDK2, and CDK4 are decreased after the silencing of TMEM97 expression in vitro [33]. Cyclin D1-CDK4 and E-CDK2 complexes are key factors in G1/S transition, further confirming that TMEM97 participates in the G1/S transition of glioma cells [34]. Activation of epithelial-mesenchymal transition (EMT)-related genes is also observed in glioma cells after TMEM97 knockout. EMT is a key process in the invasiveness of tumor cells [35]. Knockout of TMEM97 significantly downregulates the expression of β-catenin and Twist and upregulates that of E-cadherin [36, 37]. These data suggest that inhibition of TMEM97 expression inhibits the invasiveness of glioma cells via regulation of EMT [34, 38].

TMEM140 in glioma: Alterations in chromosome 7 are closely related to the development of glioma, breast and prostate cancer, and other cancers [39, 40]. The TMEM140 gene is located on chromosome 7q33, which may be involved in glioma development. Studies have shown that expression of TMEM140 in glioma tissues is significantly higher than that in normal brain tissues and that TMEM140 expression is closely related to tumor size and histological grade and to the survival rate of patients [41]. Li et al. showed that TEME140 expression affects glioma cells by regulating the expression of adhesion factors and apoptosis. Cell adhesion, migration, and invasiveness are key steps in tumor progression [42, 43]. Knockout of TMEM140 expression significantly downregulates the expression of cell adhesion mole-

cules ICAM1, VCAM1, and syndecan1 compared with that in control cells [41]. Therefore, inhibition of TMEM140 expression can reduce the adhesion, migration, and invasiveness of glioma cells. TMEM140 is also involved in regulating apoptosis and cell survival in glioma cells. TMEM140 knockout can upregulate the expression of pro-apoptotic proteins, such as caspase-3 and Bax, and downregulate that of anti-apoptotic proteins such as Bcl2. Treatment with TMEM140 siRNA induces apoptosis in glioma cells at a rate that is approximately 12 times higher than that in control cells, thus accelerating the apoptosis of tumor cells [41]. In conclusion, knockout of TMEM140 expression can inhibit adhesion and metastasis and accelerate apoptosis in glioma cells, thereby inhibiting the development of tumors. These findings suggest that TMEM140 may be a therapeutic target for the treatment of patients with glioma [44].

TMEM168 in glioblastoma: TMEM168 is located in the cell membrane and consists of 697 amino acid residues [45]. At present, the details of TMEM168-mediated mechanisms in human GBM remain unclear. The levels of TMEM168 mRNA in the brain tissues of 85 GBM patients and 10 corresponding healthy individuals were evaluated using RT-PCR in a study conducted at the Huzhou Central Hospital [7]. The results of that study showed that TMEM168 expression was increased in the brain tissues of GBM patients and that the survival time of patients with low GBM expression was significantly longer than that of GBM patients with high GBM expression. These findings suggest that TMEM168 expression may be a prognostic factor in human GBM. That study also showed that siTMEM168 can downregulate the expression of c-myc and cyclin D1; c-myc and cyclin D1 are positive regulators of G1/GS progression [46]. Downregulation of c-myc and cyclin D1 expression can induce glioma cell-cycle arrest in the G0/G1 phase and inhibit the growth rate of tumor cells [47, 48]. siTMEM168 also decreases the expression of PCNA and survivin (which is an anti-apoptotic factor) and increases that of Bax, which promotes cellular apoptosis. Apoptosis is 3 and 5 times higher in U87 and U373 cells treated with siTMEM168 than that in control cells, respectively [7]. C-myc, cyclin D1, and survivin signal downstream of the Wnt/β-catenin signaling pathway [49, 50]. Knockout of TMEM168 expression significantly reduces the expression of the Wnt/β-catenin signaling pathway and its downstream signaling molecules (C-myc, cyclin D1, and survivin), suggesting that siTMEM168 affects glioblastoma proliferation by regulating the Wnt/β-catenin signaling pathway to inhibit glioma cell growth and promote tumor-cell apoptosis [7]. In conclusion, TMEM168 knockout can inhibit tumor proliferation and metastasis in human GBM cells; this inhibition is achieved by blocking the Wnt/β-catenin signaling pathway.

TMEM176A in glioblastoma: TMEM176A is located on human chromosome 7q36.1 [51]. Numerous studies have shown that TMEM176A may be potentially valuable in the treatment of certain cancers [52]. One study showed that TMEM176A mRNA and protein levels are increased in the brain tissues of GBM patients. The survival time of GBM patients is also negatively correlated with the expression level of TMEM176A, indicating that TMEM176A expression level may be one of the factors affecting the prognosis of patients with GBM [53]. TMEM176A affects glioma cells by regulating cell-cycle-related factors. The cyclin D1/P21 signaling pathway plays a crucial role in tumor growth and invasion [54, 55]. As an important positive regulator of the cell cycle, cyclin D1 is dependent on the activation of the ERK pathway, and cyclin D1 upregulated expression can promote the proliferation of tumor cells [56]. P21, a generic inhibitor of cyclin-dependent kinases (CDKs), can negatively regulate the cell cycle [57]. Inhibition of TMEM176A expression inhibits that of cyclin D1 and upregulates that of P21, thereby inhibiting the growth cycle of GBM cells [58, 59]. ERK1/2, P38, JNK1/2, AKT, STAT3, and mTOR are also involved in cell-signal transduction [60]. Silencing the expression of TMEM176A decreases the phosphorylation level of these proteins. In GBM cells, knockout of TMEM176A strongly inhibits the expression of p-ERK1/2 [53], suggesting that inhibition of TMEM176A expression can inhibit GBM cell signal transduction and that this inhibition occurs via ERK1/2 signaling [61, 62].

Knockout of TMEM176A expression downregulates that of p-ERK1/2 and Bcl2, upregulates that of caspase-3, decreases that of anti-apoptotic proteins, and increases that of pro-apoptotic proteins [53]. This indicates that TMEM176A siRNA can accelerate tumor-cell

apoptosis [52, 63]. Overexpression of TMEM-176A significantly increases the level of p-ERK1/2 and inhibits the apoptosis of tumor cells. Treatment with specific ERK1/2 inhibitors decreases p-ERK1/2 expression and proliferation ability of tumor cells and increases tumor cell apoptosis [64, 65]. These results indicate that ERK1/2 phosphorylation is an essential part of TMEM176A-mediated promotion of GBM cell proliferation. Additionally, ERK1/2 may be a direct target of TMEM176A in GBM cells [53].

TMEMs in psychiatric disorders

TMEMs in anxiety and phobias

Anxiety is defined as an anticipation of future threats. Anxiety is characterized by disruptive feelings of uncertainty, dread, and fearfulness and can lead to behavioral disorders that can significantly impact people's daily lives [66]. Before the 20th century, anxiety was considered a normal human emotion [67]. Excessive anxiety, or that exceeding human psychological adaptation to anxiety, can be mentally debilitating [68]. At present, the incidence of anxiety is increasing. The age range for the onset of anxiety has also been gradually increasing. Indeed, anxiety has become a common disorder that can negatively impact people's lives [69]. The causes of anxiety and fear are complex. At present, studies have shown that certain neural circuits and signaling molecules in the brain are involved in regulating anxiety and fear.

TMEM 16B in anxiety: Anxiety disorders are characterized by excessive fear [70]. In rodent models, the amygdala, hippocampus, nucleus accumbens, periaqueductal gray matter, and prefrontal cortex have been identified as key brain regions containing neural circuits associated with fear responses [71-73]. Among these, the amygdala plays a central role in the expression and elimination of fear responses [74]. As a transmembrane protein with multiple physiologic functions, TMEM16B is highly expressed in brain regions such as amygdala, lateral septum, and the hippocampus [75]. TMEM16B is mainly expressed in the central lateral amygdala (CeL), which is composed of several GABAergic inhibitory neurons. Notably, abnormal GABAergic neurotransmission is related to anxiety [76]. TMEM16B-mediated regulation of Ca^{2+} levels may also be involved in anxiety-related behavior and fear memory [77]. TMEM16B encodes an evolutionarily conserved Ca^{2+}-activated Cl^- channel (CaCC) [78]. TMEM16B-CaCC mainly exists in somatostatin-positive (SOM+) GABAergic inhibitory neurons in the CeL. In order to verify whether TMEM16B-CaCC affects GABAergic neurotransmission in the CeL, Li et al. measured spontaneous inhibitory postsynaptic current (sIPSC) and action potential-independent miniature IPSC (mIPSC) in the lateral central amygdala of TMEM16B KO mice and control mice. Their results showed that knockout of TMEM16B expression increased the amplitude and frequency of GABAergic sIPSC and reduced the frequency of the activity of mIPSC-dependent presynaptic voltage-gated Ca^{2+} channel [79]. This provides further evidence for the functional significance of TMEM16B in the activity of presynaptic nerve endings. Elimination of TMEM16B-CaCC expression results in prolonged action potential and increased sIPSC in CeL SOM+ neurons, which is similar to the effect of diazepam on SOM+ neurons [80]. This neuronal signaling alludes to the inhibitory activity of the central nucleus in the amygdala. For example, increased synaptic inhibition in SOM+ CeL neurons can inhibit the excitatory input from basal lateral amygdala (BLA) to SOM+ neurons, which drives the expression of fear [81, 82]. Inhibition of SOM+ CeL neurons in TMEM16B KO mice reduces the excitability of neurons in the BLA, thereby reducing fear- and anxiety-related behaviors [79, 83]. These results indicate that TMEM16B plays key roles in regulating the signaling of SOM+ GABAergic neurons in the medial lateral amygdala. Improved understanding of the regulation of neuronal signaling by TMEM16B-CaCC will aid in the development of strategies for the treatment of anxiety-related disorders.

TMEM 168 in anxiety: The occurrence of anxiety involves numerous neural circuits and complex signaling processes [84]. Nucleus accumbens (NAc) is a central relay structure between the amygdala, basal ganglia, ventral tegmental area (VTA), and the prefrontal cortex. As such, NAc plays an important role in anxiety-related signal transduction [85, 86]. GABA is a major inhibitory neurotransmitter, and decreases in GABA concentration are related to abnormal regulation of emotion, which may lead to increased anxiety [87, 88]. Antianxiety drugs, such as diazepam, are known to promote the

transmission of GABAergic signaling by binding to GABA receptors [89]. Studies have shown that overexpression of TMEM168 weakens GABA neurotransmission in NAc and induces anxiety-related behaviors, while diazepam can reverse anxiety induced by overexpression of TMEM168 [90, 91]. Transfection of local NAc neurons with TMEM168 inhibits the release of GABA, and most of the GABAergic signaling is then projected to other brain regions. Among these regions, VTA and pallidus act as direct targets, which affect GABA energy transfer and cause anxiety-related behaviors [90]. These results suggest that overexpression of TMEM168 in the NAc neurons leads to interruption in the GABAergic projection of NAc, which, in turn, leads to decreased extracellular GABA levels in NAc, affecting the level of anxiety.

TMEM132 in phobias: TMEM132 is located on chromosome 17q11.2-q12, a candidate region for the location of the gene implicated in panic disorders. Microsatellite markers associated with panic attacks have been found on TMEM132E [92]. In order to analyze single nucleotide polymorphisms (SNPs) of TMEM-132E, Gregersen examined the TMEM132E-containing region of chromosome 17q11.2-q12 in people with panic disorders and found that TMEM132E was indeed associated with panic disorders in these individuals [93]. However, the function of TMEM132E in phobias is currently unknown. An SNP located 38 kb downstream of TMEM132E is associated with bipolar disorder. TMEM13E belongs to the TMEM132 family, which contains a total of five members [94]. Among these members, the TMEM132D gene may be associated with the panic syndrome [95, 96]. Activation of the cingulate cortex modulates amygdala-mediated responses to fear stimuli, thereby modulating fear expression in humans [97]. High-anxiety-related behaviors in mice are positively correlated with the expression of TMEM132D mRNA in the anterior cingulate cortex (ACC) [98, 99]. TMEM132D is a single transmembrane protein that is highly expressed in the cerebral cortex of humans and mice [96]. The expression of TMEM132D in animals is consistent with that in the frontal cortex of human brain tissue after death in phobias [98, 99]. High expression of TMEM132D is associated with increased anxiety levels [100]. Independent SNPs of this gene are also associated with panic disorders and can influence the severity of anxiety-related symptoms [101, 102]. TMEM132D is also highly expressed in neurons and functions in cell adhesion, connecting extracellular mediators with intracellular actin cytoskeleton, and participating in the transduction of neuronal signals related to panic-related behaviors [103]. TMEM132D can inhibit the influence of WRC on the actin cytoskeleton, damaging the actin nucleus and inhibiting cell motility; this can alter the morphology of neurons, thereby affecting the transmission of neuronal signals related to panic-related behaviors [104]. These findings indicate that TMEM132D and TMEM132E may influence the development of panic disorders, but this notion requires further study.

TMEM176A in depressive

Depression, one of the most common mental disorders affecting more than 350 million people worldwide, shows a lifetime prevalence of up to 20% [105]. The etiology of depression is complex, and genetic factors play an important role in the etiology of major depression [106]. Depression can cause emotional disorders such as sadness, emptiness, and irritability, as well as physical disorders and cognitive changes [107]. When depression lasts for a long time or worsens, life-threatening behaviors, such as suicide, may occur [108]. The Flinders Depression Sensitive (FSL) rats exhibit many of the key behavioral characteristics observed in human depression, including reduced appetite and activity and sleep disturbances [109, 110]. Genome-wide expression profiles of the hippocampus (HIP) and prefrontal/frontal cortex (P/FC) in Flinders models are used to explore the molecular signaling associated with depression-like disease. The results obtained in these studies indicate that TMEM176A expression in FSL rats differs greatly from that in Flinders Depression Resistant (FRL) rats [111]. HIP and P/FC are the major brain regions associated with depression [112]. The expression of the TMEM176A gene, which is nearly undetectable in FSL rats, shows high levels in both the cortex and hippocampus of FRL rats. The expression of TMEM176A is 35 times higher in P/Fc than in FSL and is increased 29 times in the HIP [111]. Thus far, these are some of the greatest differences in gene expression shown in a rodent model of depression. These findings suggest that TMEM176A may be a therapeutic target in the treatment of patients with depression.

TMEM187 in autism

TMEM187, located on the long arm of the X chromosome, consists of two exons [113]. TMEM187 is widely expressed in multiple organs of various systems throughout the body and interacts with four known autism-related genes [HCFC1, TMLHE, Methyl-CpG binding protein 2 (MeCP2), and GPHN] [114, 115]. HCFC1 causes mutations in the Xq28 gene, which is implicated in autism [116]. The distance between TMEM187 and HCCFC1 is only 2 kb, which makes these genes functionally similar [117]. Amino-acid variants of the MeCP2 protein have been implicated in brain morphology and several neurodevelopmental disorders including autism [118, 119]. GPHN encodes a protein involved in neuron assembly; mutations in this gene affect neural signaling, leading to autism [115]. TMEM187 is linked with the HCFC1, MeCP2, and GPHN genes and shows certain commonality in influencing the mechanisms of autism. TMEM187 also interacts directly with UBL4A, RBM25, and AKAP4 [120]. Transcriptional members of these genes (UBL7, RBM27, RBM8A, RBMS3, and AKAP9) are strongly associated with autism [121, 122]. I Changes in protein structure are also common in patients with autism. A mutation in TMEM187 is found among X-linked genes in a patient with autism, as shown by genetic testing and full exome sequencing. TMEM187 mRNAs, which are present in the extracellular vesicles of the nervous system, can stimulate target cells to convert inactive proteins into active forms, leading to structural changes in those proteins; this may be one of the mechanisms affecting autism [120].

TMEM in abnormal action

TMEM 16B in motor learning

The cerebellum integrates nerve impulses related to motor learning and regulates and corrects various movements through efferent fibers to maintain coordination [123-125]. The inferior olivary (IO) is a collection of brainstem nuclei near the boundary between the medulla oblongata and the pons. IO serves as a transit point between the spinal cord and the cerebellum [126]. TMEM16B participates in the olivecerebellar system of the mouse brain [76]. In IO neurons, TMEM16B increases excitability by promoting the production of high threshold calcium peaks [127]. TMEM16B-CaCC, a newly discovered calcium-sensitive conductor in IO neurons, plays an important role in controlling the firing of IO neurons and in cerebellar motor learning [128]. IO neurons rapidly generate somatic Na+ spikes via current injection, followed by post-depolarization (ADP) mediated by dendritic high-threshold voltage-gated Ca^{2+} (CaV) channels that modulate the firing of IO neurons [129, 130]. TMEM16B transcripts are highly expressed in IO; Ca^{2+}-activated Cl^- channels (CaCC) in TMEM16B can promote IO discharge and affect motor learning ability in mice [128]. Classical blink experiments have shown that inhibition of TMEM16B expression significantly reduces motor learning ability in mice. TMEM16B-CaCC can limit the range of Ca^{2+} influx and can maintain the morphology and duration of ADP, which is necessary for the normal firing pattern of neurons [131, 132]. Dendritic high-threshold CaV channels promote Ca^{2+} inflow to activate TMEM16B-CaCC expression. Inhibition of CaV channel activity terminates the major repolarization current of ADP [128, 133], leading to delayed ADP response and after-hyperpolarization. This cascade prolongs the preparation time and slows the recovery of the next action potential, triggered to varying degrees by electric excitation of the membrane, eventually reducing or halting the firing of IO neurons. These results suggest that TMEM16B-CaCC can shorten the duration of action potential, improve the threshold of synaptic potential generation, and dynamically regulate neuron signaling that is important in learning and memory [134]. Compared with wild-type IO neurons, the IO neurons of TMEM16B-deficient mice show a significantly reduced discharge, suggesting that TMEM16B knockout impairs the excitability and inhibits the discharge of IO neurons [128]. In IO neurons, TMEM16B-CaCC plays a key role in controlling cerebellar motor learning. The discovery of TMEM16B-CaCC in IO neurons and its ability to regulate the discharge of ADP and IO neurons mediated by dendritic CaV channels will help us understand the role and molecular mechanism of the olive-cerebellar system in motor learning.

TMEM 16B in aggression behavior

The lateral septum (LS) is a brain region that is highly associated with aggression and plays an

important role in aggressive behavior [135]. LS injury leads to an increase in mammalian biting, aggression, and defensive behavior [136]. Improved understanding of LS-mediated mechanisms of neural conduction is important in the regulation of aggression. LS is mainly composed of the caudal LS (LSc), rostral LS (LSr), and ventral LS (LSv) [137]. LS neurons can collate the glutamate synaptic input from the hippocampus, sending inhibitory projections to brain regions involved in emotional and motor behavior [138]. TMEM16B is expressed in excitatory glutamate receptors in the hippocampus and affects neurotransmitter release from hippocampal-LS synapses in LS neuronal subpopulations by regulating excitatory postsynaptic potential (EPSP) amplitude, peak duration, and/or peak frequency [75, 138]. The hippocampus, composed of GABAergic projection neurons, is the main input source of LS. TMEM16B is a type of CaCC, while the innervation of neurons and free calcium leads to LSv inhibition and ventromedial hypothalamus (VMH) deinhibition [139, 140]. The input received by VMH comes mainly from the LSv [141]. In TMEM16B KO mice, the release of neurotransmitters in the hippocampal-LS synapse is altered, and the peak discharge of dorsal LS neurons is increased [75]. The activation of dorsal LS suppresses the activity of downstream LSv neurons, thereby inhibiting their inhibitory input to VMH and triggering aggressive behavior [142, 143]. These findings indicate that TMEM16B is involved in the regulation of neuronal excitability and aggressive behavior in mice.

TMEM 168 in methamphetamine-induced hyperlocomotion

NAc is a key region of the reward system that is highly sensitive to changes in external stimuli [144]. NAc is connected mainly to the limbic system, and extracellular dopamine (DA) in NAc is derived from the NAc dopaminergic synaptic terminal [145]. Dopamine is a major neurotransmitter in NAc [146]. Dopamine transmits signals in the midbrain limbic nerve to regulate return-related behavioral responses [147]. DA neurons play an important role in motivation and reward processing. Abnormal rewards, such as stimulants and other drugs, can lead to changes in the synapses of the midbrain limbic DA system [148]. Methamphetamine causes addiction and nerve excitation, leading to behavioral changes in animals [149]. After repeated methamphetamine administration, TMEM168 and osteopontin (OPN) expression is increased in NAc mice [150]. OPN belongs to the extracellular matrix (ECM) family, while ECM is an important regulator of psychostimulant-induced changes observed in addiction; OPN participates in the reward system by controlling dopaminergic mesolimbic pathways [151]. TMEM168 may affect dopaminergic activity via OPN, which is related to methamphetamine-induced behavioral changes [150]. MMP-2 and MMP-9 are OPN-dependent molecules. In mice used to model methamphetamine-induced addiction, OPN is cleaved by MMP-2 and MMP-9, and enhancement of dopaminergic function in NAc leads to induced behavioral changes [150, 152, 153]. TMEM168 modulates OPN via DA-mediated functioning of NAc neurons, which is a pathway involved in the inhibition of methamphetamine-induced behavioral changes. Overexpression of TMEM168 directly affects the function of local neurons and inhibits the release-response of DA to activate the NAc neurons, which weakens the pharmacological effects of methamphetamine [150]. When TMEM168 is overexpressed in the mouse NAc, the levels of OPN protein are increased, which effectively reduces methamphetamine-induced hyperactivity, conditions position preference, and reduces DA expression in NAc, thereby inhibiting methamphetamine-induced addictive behavior [150]. TMEM168-regulated OPN is one of the most effective mechanisms for inhibition of the pharmacological effects of methamphetamine.

TMEM5 in cobblestone lissencephaly

The brain accounts for only 2% of the body weight but consumes approximately 20% of the body's energy. The brain's energy consumption increases during different mental activities [154]. Glucose is the main source of energy for the brain, supporting various types of brain activity, while glycogen consumption reduces brain activity [155]. Abnormal glucose use and brain energy operation can affect higher cognitive functions, leading to cognitive dysfunction and neurodegenerative changes such as pebble brain and Alzheimer's disease [156, 157]. Cobblestone lissencephaly, an autosomal recessive genetic disorder closely associ-

ated with abnormal glucose metabolism, is characterized by defects in the brain, eyes, and muscles [158]. Imaging manifestations observed in cobblestone brain include cortex malformations, myelin sheath abnormalities, brain stem dysplasia, and cerebellar cysts [159]. One study found TMEM5 mutations in 40 families with cobblestone lissencephaly. Mutations in TMEM5 accounted for 10% of the mutated genes involved, which was three times the involvement of the LARGE pebble brain gene [160]. TMEM5 encodes a transmembrane protein with a glycosyltransferase domain, which is involved in the glycosylation of antiglycoscan. Mutations in TMEM5 can lead to severe glucose-metabolism abnormalities [161]. Normal glucose metabolism in the brain promotes the growth and development of brain tissues, provides necessary energy for excitatory and inhibitory neurotransmission, maintains normal free metabolism level, improves cognitive function, promotes cell survival and angiogenesis, and plays a neuroprotective role [162]. Infants with TMEM5 mutations show severe brain abnormalities. These abnormalities may be caused by TMEM5 mutations affecting glucose metabolism, causing a lack of energy needed for nerve-cell development and resulting in abnormal brain development [160]. These findings indicate that TMEM5 is important in cobblestone lissencephaly.

TMEM59 in NSC

NSC can differentiate into neurons, astrocytes and oligodendrocytes, which are self-renewing and pluripotent cells [163]. By participating in activation or inhibition of different molecular procedures, stem cell transplantation may produce different therapeutic effects [164]. MicroRNAs (miRNA) are a class of small noncoding RNAs containing about 22 bp, which play a strong induction role in neural differentiation of embryonic stem cells. More and more evidence supported the involvement of miRNA in neurological diseases [165]. Among them, miRNA-351 can induce synaptic growth and formation of nerve cells, and this effect may be related to TMEM59. TMEM59 is a widely expressed transmembrane protein that regulates NSC differentiation, cell apoptosis and autophagy, and is closely related to neural development and neurological diseases [166, 167]. In both types of NSCs, overexpression of miRNA-351 decreased the expression of TMEM59 and induced morphological changes, suggesting that miRNA-351/TMEM5 is involved in NSC differentiation [168]. TMEM59 mRNA was reduced to 70% after overexpression of miRNA-351 in C17.2 NSCs cells. These results suggested that miRNA-351 may regulate the differentiation of NSC by inhibiting TMEM59 expression [168, 169]. When TMEM59 expression is inhibited, NSC differentiates into neurons and glial cells. In order to determine whether miRNA-351 directly targets regulation of TMEM59, Li et al. used HEK293T cells with low expression of TMEM59 to co-transfect miRNA-351 and TMEM59, and confirmed their targeting specificity. miRNA-351, as an endogenous regulator, can reduce TMEM59 expression at mRNA and protein levels. Increased miRNA-351 strongly inhibits TMEM59 expression, which may further lead to rapid differentiation of NSC into neurons and glial cells during critical periods of nervous system development [168, 170]. Although miRNA-351 can reduce TMEM59 expression in a variety of cells, the silencing efficiency varies among cell lines. miRNA-351 induced a stronger reduction of TMEM59 mRNA in primary NSC than in C17.2 and HEK293T cells, suggesting the existence of other inhibitory pathways in NSC [168]. In conclusion, TMEM5 is regulated by miRNA-351 and participates in the differentiation of NSC, which may become one of the therapeutic targets for NSC.

TMEM97 in TBI

Traumatic brain injury (TBI) refers to brain injury caused by blunt, penetrating, or acceleration/deceleration forces. TBI is manifested by loss of consciousness or decreased level of consciousness, memory loss or forgetfulness, other neurological or neuropsychological abnormalities, and even death [171]. The annual global incidence of TBI is more than 294 per 100,000 people [172]. After severe brain injury, changes in the intracellular environment cause cell necrosis and apoptosis [173]. During the first week after TBI, a large number of neurons and oligodendrocytes undergo apoptosis [174, 175]. One study showed that daily treatment with DKR-1677 during this period of time significantly reduces the apoptosis of neurons and oligodendrocytes, which may be mediated by the effect of DKR-1677 on TMEM97 expression

[176]. TMEM97 is widely distributed in the CNS and peripheral tissues. The affinity of DKR-1677 for TMEM97 is much higher than that for other targets in the CNS. DKRR-1677 can promote TMEM97 expression to maintain the stability of lysosomes, mitochondria, and other cellular structures, thereby protecting the survival of nerve cells [176]. TMEM97 expression can promote cholesterol transport and metabolism, which may underlie its promotion of cell recovery after TBI [177, 178]. Cholesterol, the most abundant sterol in the CNS, can regulate membrane fluidity and permeability and is crucial to cell survival and function [179]. TMEM97 is involved in the functional regulation of cholesterol homeostasis [180]. TMEM97 binds to cholesterol transporter-regulating protein Niemann-Pick1 (NPC1), promotes the availability of intracellular NPC1, alters intracellular cholesterol transport and storage, maintains cellular homeostasis, restores cellular function, and promotes cell survival [181]. These findings indicate that TMEM97 is involved in the regulation of TBI-related pathological processes and may be a new therapeutic target in the treatment of patients with TBI.

TMEM97 in neuropathic pain

Neuropathic pain, a common medical problem, is a subjective sensory symptom caused by a lesion or dysfunction of the peripheral or central somatosensory nervous system [182]. Neuropathic pain is characterized by spontaneous, continuous, or intermittent pain and can be of various types, including cold pain, stabbing pain, burning pain, or touching pain [183]. Neuropathic pain can also include neurodegenerative pain, such as postherpetic or trigeminal neuralgia, and post-stroke pain that involves physical, psychological, and emotional factors [184]. TMEM97, also known as the sigma 2 receptor (σ2R), is widely expressed throughout the body and is involved in intracellular ion regulation and neuronal survival [185]. σR consists of two members, σ1R and σ2R (TMEM97) [186]. σ1R is a pain signal, and numerous compounds that bind to σ1R exert antinociceptive effects [187]. However, few studies have examined the use of TMEM97 as a target in neuropathic pain. TMEM97 is expressed in various nerve cells, including glial and immune cells, which play important roles in the pathogenesis of neuropathic pain [188, 189]. Thus, TMEM97 is a promising target for the treatment of patients with neuropathic pain. As an agonist of TMEM97, UKH-1114 possesses high selectivity and affinity for TMEM97. UHK-1114 combined with TMEM97 produces an effect similar to that of gabapentin, a drug used widely in the treatment of neuropathic pain; however, at its peak, UKH-1114 is 10 times more potent than gabapentin, and the effects of UKH-1114 persist for longer durations than those of gabapentin. These findings strongly suggest that TMEM97 may be a promising pharmacological target for the treatment of patients with neuropathic pain [190].

TMEM106B in frontotemporal lobar degeneration

Frontotemporal lobar degeneration (FTLD) is the second most common form of dementia. Approximately one third of patients with FTLD have a family history of this condition [191]. The main pathological feature of FTLD variation, also named FTLD-TDP, is the presence of intracellular ubiquitin and TAR DNA-binding protein (TDP)-43-positive inclusion bodies [192]. FTLD-TDP is mainly caused by heterozygous loss-of-function mutations in the progranulin (GRN) gene. Complete deletion of GRN leads to neuronal ceroid lipofuscinosis (NCL), which is a neuronal lysosomal storage disease (LSD) [193, 194]. Lysosomal dysfunction is one of the main causes of neurodegeneration. Numerous studies have shown that neurodegenerative diseases, such as Alzheimer's and Parkinson's, are closely related to lysosomal dysfunction [195, 196]. Importantly, the brain tissue of patients with a GRN deficiency shows elevated levels of lysosomal proteins [197]. TMEM106B is a lysosomal protein, and TMEM106B mRNA and protein levels are elevated in patients with GRN mutations. Overexpression of TMEM106B can lead to lysosomal damage and affect the expression of GRN, thus leading to FTLD-TDP [197]. Lysosomal protein levels are increased not only in microglia but also in neurons, in which TMEM106B is widely expressed [198, 199]. GRN mutant mice also show elevated TMEM106B levels, increased expression of lysosomal hydrolase, impaired lysosomal stability, leakage of lysosomal contents into the cytoplasm, and widespread nerve-cell apoptosis, resulting in FTLD-TDP [197]. These findings indicate that TMEM106B is a risk factor for the development of FTLD-TDP.

TMEM240 in spinocerebellar ataxia type 21

Spinocerebellar ataxia type 21 (SCA21) is an autosomal dominant cerebellar syndrome, mainly characterized by mental retardation, ataxia, cognitive impairment, behavioral abnormalities, and significant reduction in the numbers of cerebellar Purkinje cells (PCs) [200]. PCs, which are the only output neurons in the cerebellar cortex, play core roles in motor learning [201]. TMEM240 contains 172 amino acids and is widely expressed in brain tissues, especially in the cerebellum, which is essential for the function and survival of cerebellar Purkinje cells [200]. In the cerebellum of SCA21 mice, TMEM240 mutation induces lysosomal damage, leading to morphological changes in PCs and inducing SCA21 [202, 203]. TMEM240 also affects the degradation of autophagosomal proteins, which are associated with membrane transport. According to different substrate transport routes, autophagic lysosomal degradation is divided into macroautophagy (MA), microautophagy (mA), and chaperone-mediated autophagy (CMA) [204]. Lysosomal-associated membrane protein 2A (LAMP2A), which shows pathogenic activity, is the receptor substrate in the lysosomal membrane of CMA. The distribution and binding of LAMP2A on lysosomal cell membrane directly affect CMA activity [205]. Mutations in TMEM240 significantly increase the activity of LAMP2A and inhibit p38 phosphorylation in the cerebellum of SCA21 mice [202]. p-p38 participates in CMA activation via LAMP2A [206]. Mutations in TMEM240 impair this process, resulting in the dysfunction of autophagosomal protein degradation. MA-mediated protein degradation is also significantly impaired by the expression of TMEM240 in SCA21 smutant mice. LC3-II and P62 are involved in the recognition and transfer of MA substrates to autophagosomes and are also degraded into MA substrates [207]. LC3-II and p62 expression is increased after the occurrence of TMEM240 mutation, which reduces MA-mediated protein degradation. In addition, SCA21 mutant TMEM240 significantly increases the levels of myocyte enhancer factor 2D (MEF2D) and TIP47, which are degradation substrates of mA [202]. These findings suggest that SCA21 mutant TMEM240 impairs MA, mA, and CMA, increases the accumulation of substrate proteins, disrupts the activity of autophagosomal protein degradation system, and affects cerebellar PC output and normal function, which may be one of the common mechanisms driving SCA pathogenesis.

Conclusion

TMEMs are distributed in almost every organ of the body, but its expression is particularly pronounced in the brain. The TMEM distribution pattern suggests that TMEMs play important roles in brain diseases. In this review, we summarized the roles and mechanisms of TMEMs in nervous system diseases and described how the TMEM family is involved in the regulation of various neurological diseases via multiple signaling pathways (**Table 1**). In brain tumors, TMEMs accelerate tumor invasion by decreasing the growth cycle and promoting the metastatic ability of tumor cells, thereby influencing patient survival and prognosis. In mental disorders, TMEMs affect neuronal signal transduction and alter neuronal morphology by regulating signal molecules in emotion-related brain regions. Abnormal movements are closely related to dysfunction in the cerebellum, nucleus accumbens, and lateral septum. Altered expression of TMEMs in these brain tissues leads to dysfunctional electrical activity in nerve cells, which triggers abnormal movement. The mechanisms of TMEM-mediated regulation of brain pathologies are highly complex, and the roles of TMEMS in neurological diseases remain unclear. TMEMs play different roles in the pathological processes of nervous system diseases by regulating a variety of different signaling pathways. For example, TMEM97 is involved in the maintenance of intracellular homeostasis via regulation of cholesterol levels, restoration of cellular function, and promotion of nerve-cell recovery after TBI. TMEMs are also involved in glucose metabolism and lysosomal autophagy. Abnormal glucose metabolism and lysosomal dysfunction are among the main causes of neurodegenerative changes. In addition, studies have shown that TMEM176A is associated with schizophrenia [208], while TMEM132D is associated with major depressive disorder [97] and FTD [209].

At present, the underlying mechanism of neuropathy-induced activation of TMEMs remains unclear. In this review, we discussed the potentials of TMEMs as novel therapeutic targets in the treatment of brain diseases. Several studies targeting TMEMs have shown promising results in cell and animal models, indicating that TMEMs may be used in novel therapeutic

Table 1. Published studies on the expression patterns and effects of TMEMs signaling in brain diseases

Disease	TMEMs	Study Models	Objects	Molecules	Conclusions	Re
GBM	TMEM16A	In vitro	GSCs (X08/0315)	TMEM16A-EGFRvIII	TMEM16A regulates the invasion of GBM stem cells by stabilizing EGFRvIII expression.	[17]
Glioma	TMEM16A	In vitro	U87MG	TMEM16A-NF-κB	Knockout of TMEM16A expression can inhibit the growth cycle and migration of glioma cells via inhibition of NF-κB signaling.	[16]
	TMEM45A	In vitro	U251/U373	TMEM45A-cyclin/ MMP-2/9	TMEM45A regulates cyclin expression, accelerates tumor-cell growth, and promotes tumor-cell migration, thereby affecting glioma.	[25]
	TMEM45A	In vitro	A172/U251	TMEM45A-NF-κB	Knockout of TMEM45A expression can inhibit the growth cycle and migration of glioma cells via inhibition of NF-κB signaling.	[28]
	TMEM97	In vitro	U373/U87	TMEM97-Cyclin/EMC	Knockout of TMEM97 expression can inhibit the growth cycle and migration of tumor cells, thereby inhibiting glioma-related processes.	[34]
	TMEM97	In vitro	U373/U87	sigma-2/TMEM97	Inhibition of TMEM97 expression can inhibit the proliferation, migration, and invasion of U87 and U373 human glioma cells.	[31]
	TMEM140	In vitro	U87/U373	TMEM140-adhesion molecules/apoptin	Knockout of TMEM140 expression can downregulate the expression of cell adhesion molecules (ICAM1, VCAM1, and syndecan1), promote apoptosis, and inhibit the migration and development of tumor cells.	[44]
	TMEM168	In vitro	U87/U373	TMEM168-Wnt/β-catenin	TMEM168 expression promotes cellular growth, inhibits apoptosis, and accelerates glioma progression by regulating the Wnt/β-catenin pathway.	[7]
	TMEM176A	In vitro	T98G/U87 A172	TMEM176A-ERK1/2	ERK1/2 phosphorylation is an essential part of TMEM176A-mediated promotion of GBM cell proliferation.	[53]
	TMEM 16A/45A 97A/140A 168/176A	Clinical	Human glioma tissue	TMEMs↑	The expression of TMEMs is significantly higher in glioma tissues than in normal tissues; high expression of TMEMs reduces the survival rate of glioma patients.	[7, 16, 25, 28, 34, 44, 53]
Anxiety	TMEM16B	In vivo	Mice	TMEM16B-CaCC	TMEM16B-CaCC can promote anxiety-like behavior by regulating the action potential of GABAergic neurons.	[79]
	TMEM168	In vivo	Mice	TMEM168-GABA	Overexpression of TMEM168 in NAc neurons leads to interruption of GABAergic projection and decreased GABA levels in NAc, leading to the development of anxiety.	[90]
Phobias	TMEM132E	Clinical	Human	TMEM132E-SNP	TMEM132E expression may influence the development of panic disorder.	[93, 95-97]
	TMEM132D	In vivo	Mice	TMEM132D↑	TMEM132D is highly expressed in neurons and participates in neuronal signal transduction involved in panic-related behaviors.	[98, 99, 101]
Depressive	TMEM176A	In vivo	Rats	TMEM176A↓	The expression of TMEM176A in P/Fc of FSL rats is significantly lower than that in the P/Fc of FRL rats.	[111]
Autism	TMEM187	Clinical	Human	TMEM187 mutation	TMEM187 mRNAs can stimulate target cells to convert inactive proteins into active proteins, leading to structural changes in those proteins; this may be one of the mechanisms affecting autism.	[120]
Motor Learning	TMEM16B	In vivo	Mice	TMEM16B-CaCC	TMEM16B-CaCC can regulate the firing of ADP and IO neurons via the dendritic CaV channel, which can improve motor learning behavior of the cerebellum.	[128]
Aggression Behavior	TMEM16B	In vivo	Mice	TMEM16B-CaCC	TMEM16B regulates excitability in LS neuronal subsets and mediates aggressive behavior in mice.	[75]
Hyp	TMEM168	In vivo In vitro	Mice COS-7	TMEM168-OPN	TMEM168 regulates OPN and inhibits DA expression in NAc, thereby inhibiting methamphetamine-induced addictive behavior.	[150]

CL	TMEM5	Clinical	Human	TMEM5-glucose metabolism	TMEM5 mutations affect glucose metabolism, resulting in shortage of energy required for nerve-cell development; this leads to abnormal brain development and results in cobblestone lissencephaly.	[160]
NSC	TMEM59	In vitro	NSC HEK293T	miRNA-351-TMEM59	Increased miRNA-351 inhibits the expression of TMEM59, leading to differentiation of NSC into neurons and glial cells.	[168]
TBI	TMEM97	In vivo	Mice	TMEM97-NPC1	TMEM97 expression, combined with that of NPC1, assists in cholesterol transport and storage, maintains cellular homeostasis, and promotes cell survival after TBI.	[176].
NP	TMEM97	In vivo	Mice	UKH-1114-TMEM97	UKH-1114 can stimulate the expression of TMEM97 to reduce neuropathic pain.	[190]
FTLD-TDP	TMEM106B	Clinical	Human brain tissue	TMEM106B↑	FTLD-TDP is associated with high expression of TMEM106B in the brain tissue of FTLD-TDP patients.	[197]
	TMEM106B	In vivo	Mice	TMEM106B-GRN	TMEM106B expression can cause lysosomal damage and affect the expression of GRN, resulting in FTLD-TDP.	[197]
SCA21	TMEM240	Clinical	Human	TMEM240 mutation	TMEM240 mutations are closely related to the development of SCA21.	[200, 210, 211]
	TMEM240	In vivo	Mice	TMEM240-lysosome	TMEM240 mutation induces lysosomal damage, resulting in morphological changes in PC that induce SCA21..	[202, 203]

strategies for the clinical treatment of neurological diseases in future.

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Disclosure of conflict of interest

None.

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