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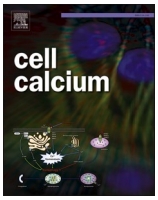

TRPM7 in neurodevelopment and therapeutic prospects for neurodegenerative disease

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ABSTRACT

Neurodevelopment, a complex and highly regulated process, plays a foundational role in shaping the structure and function of the nervous system. The transient receptor potential melastatin 7 (TRPM7), a divalent cation channel with an α-kinase domain, mediates a wide range of cellular functions, including proliferation, migration, cell adhesion, and survival, all of which are essential processes in neurodevelopment. The global knockout of either TRPM7 or TRPM7-kinase is embryonically lethal, highlighting the crucial role of TRPM7 in development *in vivo*. Subsequent research further revealed that TRPM7 is indeed involved in various key processes throughout neurodevelopment, from maintaining pluripotency during embryogenesis to regulating gastrulation, neural tube closure, axonal outgrowth, synaptic density, and learning and memory. Moreover, a discrepancy in TRPM7 expression and/or function has been associated with neuropathological conditions, including ischemic stroke, Alzheimer's disease, and Parkinson's disease. Understanding the mechanisms of proper neurodevelopment may provide us with the knowledge required to develop therapeutic interventions that can overcome the challenges of regeneration in CNS injuries and neurodegenerative diseases. Considering that ion channels are the third-largest class targeted for drug development, TRPM7's dual roles in development and degeneration emphasize its therapeutic potential. This review provides a comprehensive overview of the current literature on TRPM7 in various aspects of neurodevelopment. It also discusses the links between neurodevelopment and neurodegeneration, and highlights TRPM7 as a potential therapeutic target for neurodegenerative disorders, with a focus on repair and regeneration.

Abbreviations

TRP	transient receptor potential
TRPC	transient receptor potential canonical
TRPM	transient receptor potential melastatin
TRPML	transient receptor potential mucolipin
TRPA	transient receptor potential ankyrin
TRPV	transient receptor potential vanilloid
TRPP	transient receptor potential polycystin
MHR	melastatin homology regions
CNS	central nervous system
cryo-EM	cryo-electron microscopy
ATP	adenosine triphosphate
GTP	guanosine triphosphate
MCAO	middle cerebral artery occlusion
AD	Alzheimer's disease

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PD	Parkinson's disease
ALS	amyotrophic lateral sclerosis
2-APB	2-aminoethoxydiphenyl borate
ERK	extracellular signal-regulated kinases
JNK	c-Jun N-terminal kinases
iPSC	inducible pluripotent stem cell
NS	neural stem
NP	neural progenitor
OCT	octamer-binding protein
FGF	fibroblast growth factor
TS	trophectoderm stem
ESC	embryonic stem cell
ICM	inner cell mass
Dvl	Dishevelled
PSD-95	postsynaptic density protein-95
CA1	cornu ammonis1
LTP	long-term potentiation
NGF	nerve growth factor
MBP	myelin basic protein
GTPase	guanosine triphosphatase
TrkA	tropomyosin receptor kinase A
Aβ	amyloid-beta peptide
APP	amyloid precursor protein
PIP2	phosphatidylinositol 4,5-bisphosphate
shRNA	small hairpin RNA
LC3	microtubule-associated protein 1A/1B-light chain 3
DA	dopaminergic
SN	substantia nigra
MPTP	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MPP+	1-Methyl-4-phenylpyridinium
6-OHDA	6-hydroxydopamine
ROS	reactive oxygen species
PNS	peripheral nervous system

1. TRP superfamily

The transient receptor potential (TRP) channel superfamily, comprising cation channels with unique structures, has been a prominent area of research in physiology and pathophysiology. TRP channels are expressed in a diverse range of cell types and are predominantly localized within the plasma membrane [1,2]. Currently, 28 distinct mammalian TRP channels have been identified, which can be further grouped into six subfamilies based on amino acid sequence homology: TRPC (Canonical), TRPM (Melastatin), TRPML (Mucolipin), TRPA (Ankyrin), TRPV (Vanilloid), and TRPP (Polycystin) [1,2]. These channels exhibit permeability to cations, including calcium (Ca^{2+}), magnesium (Mg^{2+}), sodium (Na^{+}), potassium (K^{+}), and Zinc (Zn^{2+}) [1–3]. Various external and internal stimuli have been identified to activate these channels, thereby affecting a wide spectrum of physiological and pathological processes [1–3]. Functioning as cellular sensors, TRP channels modulate sensory responses such as temperature sensitivity, pain sensation, stress perception, vision, and taste [2,3].

2. TRPM subfamily

The mammalian TRPM subfamily consists of eight members (TRPM1 to TRPM8) and represents the largest members of the TRP superfamily [2]. All members of the TRPM subfamily possess conserved melastatin homology regions (MHR 1–4) in their amino (N-) terminal, spanning approximately 700 amino acids, and a variable carboxyl (C-) terminal domain, ranging from 732 to 1611 amino acids in length [4]. The overarching structure of TRPM channels comprises six transmembrane segments, with the ion channel pore situated between the fifth and sixth segments [4].

3. TRPM7

TRPM7 is a non-selective divalent cation channel permeable to Ca^{2+}, Mg^{2+}, Zn^{2+}, and trace metal ions. It is ubiquitously expressed across various cell types and tissues [5,6]. In the central nervous system (CNS), TRPM7 is expressed in neurons, astrocytes, microglia, oligodendrocytes, and vascular endothelial cells. The activity of TRPM7 can be modulated by an array of intracellular and extracellular factors, including Mg^{2+} and Mg^{2+}-complexed nucleotides [7,8], extracellular pH [9,10], and osmolarity [11]. TRPM7 constitutes a tetrameric channel, with each subunit featuring six transmembrane domains flanked by cytosolic N- and C-termini. What distinguishes TRPM7 is the presence of an atypical α-kinase domain in its C-terminal region, which confers kinase functionality to the channel, making it a bifunctional channel-kinase or chanzyme [6].

The closed state structures of the mouse TRPM7 channel domain have been elucidated at atomic resolutions of 3.3, 3.7, and 4.1 Å across different ionic environments by cryo-electron microscopy (cryo-EM) techniques [12]. These high-resolution structures highlight an ion binding site in the selectivity filter, occupied putatively by partially hydrated Mg^{2+} ions [12]. Recently, high-resolution cryo-EM achieved a 2.19 Å resolution of TRPM7 in its closed apo state, which illustrated crucial coordination across its domains for tetramerization [13]. The transmembrane domain, with its six helices and a pore loop, resembles those found in voltage-gated and TRP channels [13]. The first four helices form a voltage sensing-like domain, while the subsequent segments, including an amphiphilic TRP helix, underscore the characteristic features of TRPM7 within the TRP channel family. The C-terminal domain, with rib and pole helices, forms a coiled-coil crucial for tetramerization in mammalian TRPM7 [13,14] but not in zebrafish TRPM7 [15].

Targeted mutagenesis revealed that the side chains of N1097 in mouse TRPM7 establish a Mg^{2+} regulatory site at the lower gate of the channel, highlighting the structural foundations constituted by N1097 that is pivotal for the regulation of TRPM7 channel activity by cytosolic Mg^{2+} [16]. Subsequently, by combining cryo-EM, electrophysiology, and molecular dynamics results, the exploration of the activation mechanism of TRPM7 involving the N1098Q mutation highlights the importance of the Y1085 tyrosine and N1097/N1098 hydrogen bonds in maintaining structural integrity and constitutive activity of the channel [13]. Additionally, these studies documented the role of naltriben in inducing the open state and structural modifications of TRPM7, with activation binding sites confirmed by mutagenesis and functional assays at subunit interfaces [13]. To investigate the structural mechanisms of TRPM7 channel inhibition and pinpoint antagonist-binding locations, two inhibitors, VER155008 and NS8593, have been demonstrated to bind to vanilloid-like sites [13]. Mutations in these sites affect inhibition efficacy, indicating the antagonists stabilize the closed conformation of TRPM7 and substitute endogenous lipids at the binding pocket [13].

Research on the TRPM7 kinase domain reveals a configuration that combines elements of traditional protein kinases and ATP-grasp fold enzymes, which enhances understanding of the enzymatic structure and function of TRPM7 [17]. Key catalytic residues, aspartate and glutamine, are distinctively positioned on a β-strand, interacting with the α-phosphate group and the adenine ring of ATP [17]. TRPM7 α-kinase domain mediates pathophysiological processes through phosphorylation of specific substrates, positioning itself as an innovative therapeutic target. Possessing the capacity for autophosphorylation and phosphorylation of serine and threonine residues, it exhibits specificity for ATP and lacks the ability to utilize GTP as a substrate [17,18]. Currently, its identified substrates include itself (self-phosphorylation) [6], histone H3 [18], annexin 1 [19], myelin basic protein, myosin IIA, IIB, and IIC [20], eukaryotic translation elongation factor 2 [21], tropomodulin 1 [22], phospholipase c gamma 2 [23], and several T cell-related proteins [24].

Under physiological conditions, TRPM7 regulates Mg^{2+} and Ca^{2+} homeostasis as well as key cellular processes such as cell growth,

proliferation, adhesion, migration, and survival [5,21]. Notably, TRPM7's fundamental role in embryonic development and organogenesis has been highlighted by studies that demonstrate global TRPM7 gene deletion results in early embryonic lethality in murine models [25,26]. TRPM7 has also been implicated in cellular stress and various pathological conditions, including hypertension, cancer, cardiovascular diseases, and neurological disorders [27–31]. In the context of cerebral ischemia and/or hypoxia, studies from our group and others have consistently demonstrated that TRPM7 contributes to neuronal cell death, both *in vitro* and *in vivo* [32–34]. A pioneering *in vitro* investigation revealed the significant role that TRPM7 plays in anoxic-induced neuronal cell death [32]. Subsequently, several studies have reported elevated expression of TRPM7 mRNA and protein in focal cerebral ischemia via the middle cerebral artery occlusion (MCAO) model, indicating the involvement of TRPM7 in stroke pathology [35,36]. Our group conducted the first comprehensive *in vivo* study highlighting the role of TRPM7 in global cerebral ischemia by employing virally mediated gene silencing [33]. Through *in vivo* tests of multiple pharmacological inhibitors, we further confirmed the involvement of TRPM7 channel in neuronal death induced by ischemic-hypoxic brain injury [34,37,38]. Beyond the implication of its channel function, a point mutation in the TRPM7 kinase domain that abolishes the kinase activity, as illustrated by another group, resulted in compromised thrombus formation, reduced infarction volume, and improved neurological outcomes following transient MCAO in mice [39]. Additionally, the dual functionality of TRPM7 chanzyme is involved in the pathogenesis of neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) [40–43].

4. Importance of studying TRPM7 in neurodevelopment

Neurodevelopment is an intricate and highly regulated process that unfolds during early embryogenesis and extends postnatally. During early embryogenesis, gastrulation leads to the formation of three germ layers (ectoderm, mesoderm, and endoderm) and establishes the cranial/caudal axis [44]. The neuroectoderm, derived from the ectoderm, comprises neural progenitor cells with the potential to develop into various types of nerve cells [44]. A critical event in neurodevelopment is the formation and closure of the neural tube, with its cranial and caudal ends ultimately developing into the brain and the spinal cord [44]. Subsequent neurogenesis leads to the proliferation, migration, and differentiation of neurons and glia, with axon guidance and synaptogenesis facilitating the establishment of functional neural circuits. Meanwhile, synaptic regression and pruning, refine the neural connections while myelination enhances signal conduction and maintains axonal integrity [44]. Together, these processes orchestrate the formation and organization of a complex network of neurons and supporting glial cells that ultimately give rise to the mature nervous system [44].

Emerging studies have suggested that TRPM7 is a critical player throughout neurodevelopment, including maintaining pluripotency, regulating gastrulation, neural tube closure, axonal outgrowth and maturation, glial proliferation, migration, synaptic density, and learning and memory. Notably, processes often observed in neurodevelopment are typically altered in neurodegeneration, such as neural death, axonal retraction, synaptic loss, and demyelination. Restoring or promoting neuroregeneration under conditions of CNS injury and neurodegeneration, thus, represents a potential therapeutic strategy. Given TRPM7's involvement in both neurodevelopment and neurodegeneration, understanding the cellular and molecular mechanisms mediated by TRPM7 and its α-kinase domain holds promise for novel therapeutic interventions (Table 1). The present review aims to provide an overview of the proposed roles of TRPM7 in neurodevelopment as well as to highlight its therapeutic potential for ameliorating neurodegenerative conditions (Fig. 1).

5. TRPM7 in early embryogenesis

The pivotal role of TRPM7 in embryo development has been well-studied through genetic manipulations. In mouse embryos, TRPM7 expression significantly increased from embryonic day (E) 10.5, with widespread expression persisting until E14.5 [25]. Global deletion of TRPM7 (the entire channel) or deletion of TRPM7's kinase domain resulted in embryonic lethality [25,26]. While *Trpm7*$^{+/-}$ mice are viable at birth, they exhibit increased mortality, impaired Mg^{2+} homeostasis, and severe clasping during development [26]. Using tamoxifen-inducible disruption of TRPM7 and various Cre recombinase lines, Jin et al. demonstrated a temporal, tissue-specific requirement of TRPM7 during embryogenesis. Specifically, conditional knockout of TRPM7 at E7-E9, but not at E14.5, results in embryonic lethality accompanied by abnormal morphology and body pattering, suggesting that TRPM7 is most indispensable at the early stages of embryogenesis [45]. In terms of neurogenesis, early disruption of neural crest TRPM7 results in the loss of neural crest-derived dorsal root ganglion sensory neurons whereas late disruption of brain-specific TRPM7 after E10.5 does not alter normal brain development [45]. These results suggest that TRPM7 is required for neural progenitor cells but becomes dispensable once the progenitors are committed [45]. Consistently, TRPM7 disruption *in vitro* does not affect most terminally differentiated cells. In multipotent neural stem (NS/NP) cells, TRPM7 disruption does not affect self-renewal and *Trpm7*$^{-/-}$ NS/NP cells are capable of differentiating into neurons, astrocytes and oligodendrocytes [45]. In contrast, disruption of TRPM7 in iPSCs induces apoptosis while TRPM7 kinase-deficient embryonic stem cells exhibit arrested proliferation [26,45]. One potential explanation is that TRPM7 is required for the maintenance of pluripotent stem cells, and TRPM7 disruption is associated with reduced expression of OCT4, NANOG, and FGF13, FGF7 that are known to be critical for maintaining and regulating pluripotency and stem cell survival [25,45]. A recent study by Schütz et al. has shown that Trpm7$^{-/-}$ mouse embryos exhibit reduced cytoplasmic Ca^{2+} and Mg^{2+} as early as the two-cell stage (E1.5), yet without noticeable developmental defects in key stages of pre-implantation until E4.5. Impaired proliferation and adhesion of trophectoderm stem (TS) cells were reported from E4.5 onward, which may precede lethality in *Trpm7*$^{-/-}$ embryos at E6.5 [46]. This conclusion is primarily based on the inability to establish any *Trpm7*$^{-/-}$ TS cell culture from E3.5 *Trpm7*-deficient blastocysts derived from *Trpm7*$^{+/-}$ mice lacking exon 2. Even with extracellular Mg^{2+} (10 mM) supplementation, *Trpm7*$^{-/-}$ TS cells fail to grow out of the blastocyte, and no cell was obtained either with or without the zona pellucida, whereas embryonic stem cells (ESCs) from the inner cell mass (ICM) of *Trpm7*-deficient blastocysts can be established in culture and are capable of forming the embryo [46]. However, the study by Chubanov et al. led to the isolation of *Trpm7*-deficient TS cells from E3.5 blastocysts derived from *Trpm7*$^{\Delta 17/+}$ mice, yet these *Trpm7*$^{-/-}$ TS cells were not able to proliferate and completely lacked divalent cation currents [47]. Proliferation of TS cells can be rescued with additional Mg^{2+}, suggesting that Mg^{2+} influx via TRPM7 is essential [47]. The discrepancies in findings from these studies may be attributed to differences in genetic backgrounds between different TRPM7 mouse models, as well as to variations in isolation and culture methods. More recently, Gupta et al. further suggested that TRPM7 is required during the preimplantation stage, even before the blastocyst stage [48]. *Trpm7* KO zygotes, produced either after mating or by *in vitro* fertilization, exhibit a reduction in Mg^{2+}, impairment during cleavage stage, and failure to advance to the blastocyst stage [48]. RNA-seq analysis demonstrated the channel and kinase domains regulate Mg^{2+} homeostasis and cell division while preventing oxidative stress in embryos [48]. Moreover, early supplementation with Mg^{2+} at the 2-cell stage restores embryo development, while delayed Mg^{2+} supplementation at the 4-cell or 8-cell stage did not fully recover blastocyst cell number and/or rates, suggesting a time-dependent increase in the demand for Mg^{2+} during preimplantation [48]. These findings are in line

Table 1
Summary of signaling pathway of TRPM7 and its α-kinase domain in neurodevelopment and neurodegenerative diseases.

	Model studied	Regulation on TRPM7	Main Result	Signaling Pathway	References
Early Embryogenesis	Mouse, induced pluripotent stem cells	Global disruption of TRPM7	Early embryonic lethality Pluripotent stem cell death	TRPM7 disruption → reduced expression of OCT4, NANOG, STAT3 FGF13, FGF7, midkine	[25,45]
	Mouse, embryonic stem cells	Deletion of TRPM7 kinase domain	Early embryonic lethality Proliferation arrest	Mg^{2+} regulation	[26]
	Mouse, mouse embryonic stem cells	TRPM7 knockout and point mutations in TRPM7 kinase	Affecting cell differentiation and embryonic development by epigenetic chromatin covalent modification	TRPM7 kinase → binds transcription factors and subunits of chromatin remodeling complexes → phosphorylates histone H3 (Zn^{2+} dependent)	[54]
	Mouse, embryonic stem cells, trophoblast stem cells, peri-implantation embryo	TRPM7 knockout and pharmacological inhibition of TRMP7	Impaired peri-implantation in embryo and developmental arrest	TRPM7 knockout → reduced cytoplasmic Ca^{2+} and Mg^{2+}	[46,48,49]
Gastrulation and Neurulation	Xenopus embryos	Depletion of the endogenous TRPM7 protein	Severe developmental defects, characterized by shorter and curved anterior-posterior axis with an opened neural tube	TRPM7 channel, but not its kinase domain → regulates mediolateral intercalation via non-canonical Wnt signaling and modulation of Dvl, and GTPase Rac activity TRPM7 and TRPM6 can form heterooligomer and regulate neurulation	[55,56]
Neurogenesis	Embryonic mouse hippocampal neurons	Knockdown with target-specific shRNA and pharmacological inhibition of TRMP7 channel	Enhanced axonal outgrowth and maturation of hippocampal neurons	TRPM7 channel → Ca^{2+} influx → F-actin and α-actinin-1 protein complex TRPM7 channels function as a mechanosensitive regulator of neuronal cytoskeleton	[65,67]
	Embryonic mouse cortical astrocytes, HEK293 cells	siRNA-mediated knockdown and pharmacological inhibition of TRMP7 channel	Impairment in cortical astrocyte proliferation and migration	TRPM7 knockdown → decreased intracellular basal Mg^{2+} concentration → reduction in phosphorylation of ERK and JNK	[70]
Synaptic Regulation	Mouse, rat, hippocampal neurons	TRPM7 knockdown and knockout	Reduction in structural synapse density *in vitro,* learning and memory impairment and declined synapse density and synaptic plasticity *in vivo*	TRPM7 knockdown → lower levels of PSD-95, and synaptophysin TRPM7 α-kinase domain → inhibition of cofilin through phosphorylation	[73]
	HEK293T cells, rat SCG neurons	TRPM7 overexpression and knockdown	Regulation on EPSP amplitudes and kinetics, and acetylcholine release in sympathetic neurons	TRPM7 → forms a molecular complex with proteins of the vesicular fusion machinery (synapsin I synaptotagmin I, snapin) → facilitates cholinergic vesicle fusion	[74,75]
	Mouse, HEK 293 cells, neonatal chromaffin cells and cortical neurons	TRPM7 knockout	Impairments in synaptic vesicle endocytosis and short-term synaptic plasticity in both excitatory and inhibitory neurons	TRPM7 channel → presynaptic Ca^{2+} influx in endocytosis → PIP2 metabolism and synaptic vesicle recycling	[76]
	Zebrafish larvae, SH-SY5Y cells, cultured melanocytes, HEK-293 cells	TRPM7 mutation and forced expression of a channel-dead variant of TRPM7 TRPM7 knockdown	Impaired dopamine-dependent developmental transition in larvae Modulation in neurotransmitter release at central synapses during larvae development	TRPM7 mutation → elevated oxidative stress → dopaminergic signaling irregularities and neuron death	[77,78]
AD	Mouse embryonic fibroblasts, HEK293, Neuro2a, and CHO cells	TRMP7 channel inhibition	Contribution to AD pathogenesis	Familial Alzheimer's disease-associated presenilin mutation → imbalance in PIP2 metabolism → Aβ42 generation and TRMP7 channel inhibition	[80]
	SH-SY5Y cells, CHO cells, HEK293 cells	Pharmacological activation of TRMP7 channel	Prevention on AD-related Aβ neuropathology	TRPM7 channel activation → Ca^{2+} influx and activated autophagic signaling (AMPK-LC3-II) → co-localization of LC3 and APP → decreased Aβ42	[41,81]
	Hippocampal tissues from AD patients and mouse models, primary mouse hippocampal neuronal cultures	Overexpression of TRPM7 kinase domain	Prevented Aβ deposition, synaptic loss, and memory impairments	TRPM7 kinase domain → interacts with and activates MMP-14 → Aβ degradation	[43]
PD	Zebrafish larvae, SH-SY5Y cells, cultured melanocytes, HEK-293 cells	TRPM7 mutation and forced expression of a channel-dead variant of TRPM7	A hypomotile phenotype, increased sensitivity to MPP+, decreased expression of tyrosine hydroxylase, and dopaminergic cell death	TRPM7 mutation → elevated oxidative stress → dopaminergic signaling irregularities and neuron death	[77]
	SH-SY5Y cells, mouse and human substantia nigra samples	Overexpression of TRPM7	Protection against MPP^{+}-induced dopaminergic neuron death	TRPM7 overexpression → Mg^{2+} homeostasis → inhibition on pro-apoptotic signaling (caspase-3 and Bax)	[87]
	Mouse	Pharmacological inhibition of TRMP7 channel	Reduction in motor deficits and loss of tyrosine hydroxylase in	TRPM7 channel inhibition → decreased caspase-3 levels	[88]

(*continued on next page*)

Table 1 (*continued*)

	Model studied	Regulation on TRPM7	Main Result	Signaling Pathway	References
			substantia nigra and striatum induced by 6-OHDA		
	Rat	Pharmacological inhibition of TRMP7 channel	Amelioration in motor impairment and decreased tyrosine hydroxylase levels in dorsal striatum and substantia nigra induced by reserpine	Unknown	[89]
	PC12 Cells and SH-SY5Y Cells	Downregulation of TRPM7 expression	Cytoprotective effects against 6-OHDA-induced PC12 cell apoptosis	MicroRNA-22 overexpression → TRPM7 downregulation → reduction in ROS production and caspase-3 activity	[42]
ALS and Parkinsonism Dementia	Human brain samples, HEK-293 cells	A variant in TRPM7 allele	Pathogenesis of ALS and Parkinsonism Dementia	A variant in TRPM7 channel → increased sensitivity to inhibition by intracellular Mg^{2+}	[40]

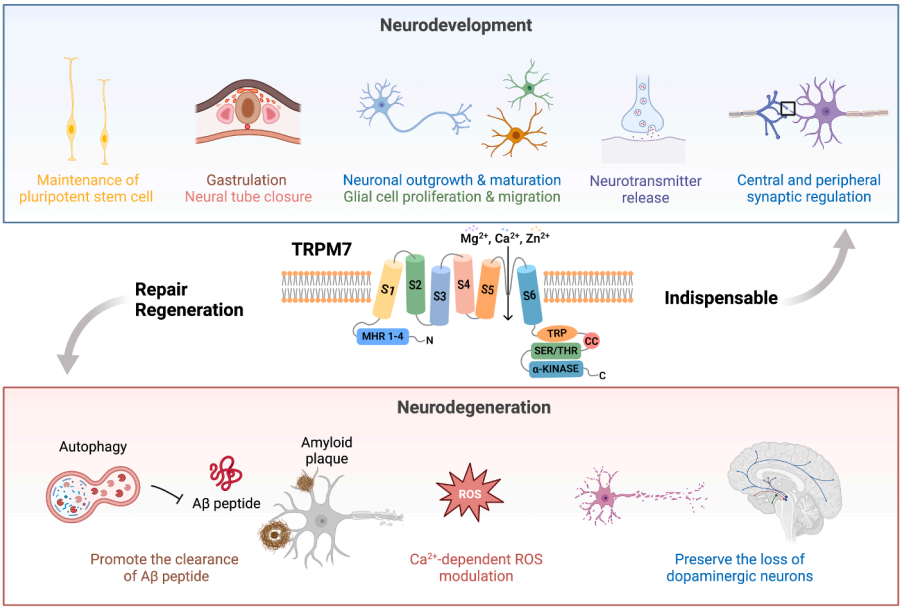

Fig. 1. Schematic representation of TRPM7 structure and proposed function of TRPM7 in neurodevelopment and neurodegenerative diseases. Created with BioRender.com.

with a previous pharmacological study showing that inhibition of TRPM7 by 10 μM NS8593 delays the pre-implantation development at the early cleavage stage [49].

Unlike TRPM7 global KO mice and TRPM7 kinase KO mice, which are embryonically lethal, mice expressing an inactive or 'kinase-dead' TRPM7 mutation are able to develop normally with respect to viability, body weight, and locomotor activity [50,51]. This 'kinase-dead' mutant possesses a K1646R point mutation at lysine 1646, which is essential for Mg^{2+}-ATP binding, rendering the catalytic activity of the kinase completely inactive [50,52]. The difference between mice with a kinase domain deletion and those with a 'kinase-dead' mutation can be attributed to the structural role of the TRPM7 kinase domain. The complete deletion of the full kinase domain leads to a significant alteration in the overall structure of the protein, resulting in channel inactivation. $TRPM7^{\Delta kinase/\Delta kinase}$ mice, therefore, may exhibit a phenotype that mirrors that of $TRPM7^{-/-}$ mice [51]. Furthermore, $TRPM7^{K1646R/K1646R}$ and $TRPM7^{K1646R/+}$ mice maintain normal levels of Mg^{2+} in serum and bone, comparable to their littermates under physiological conditions [50,53]. However, under stress conditions, specifically severe dietary Mg^{2+} deprivation, $TRPM7^{K1646R/K1646R}$ mice demonstrate resistance, indicating that TRPM7 kinase activity may be required in sensing and responding properly to changes in Mg^{2+}.

The function of the TRPM7 kinase activity has also been proposed *in vitro*. Krapivinsky et al. demonstrated that the kinase domain can undergo proteolytic cleavage, leading to distinct TRPM7 cleavage patterns in different cell types, including neural progenitor cells [54]. Subsequently, the kinase domain translocates to the nucleus, where it directly binds to transcription factors of the chromatin remodeling complexes and phosphorylates histone H3 in a Zn^{2+}-dependent manner [54]. These epigenetic modifications may underlie tissue-specific and time-dependent requirements of TRPM7 during early embryonic development.

TRPM7 has also been implicated in regulating gastrulation and neurulation. In Xenopus embryos, TRPM7 is highly expressed in dorsal mesoderm and ectoderm during gastrulation, and in the neural plate during neurulation [55]. Downregulation of TRPM7 by morpholino oligonucleotides induced severe developmental defects, characterized by a shorter and curved anterior-posterior axis with an opened neural tube [55]. Interestingly, these defects could be rescued by Mg^{2+} supplementation or co-injection of its close homolog TRPM6 RNA. This indicates that Mg^{2+} influx through TRPM channels is critical for gastrulation and neural tube closure, with TRPM6 potentially playing a complementary role to TRPM7 [55]. Later studies have further demonstrated that TRPM7 and TRPM6 can form heterooligomers, and both are required for proper closure of the neural tube [56,57]. TRPM7 regulates mediolateral intercalation (convergent extension movement), while TRPM6 regulates radial intercalation [56,57]. Failure to execute either of these two polarized cell movements can result in neural tube

defects. It has been suggested that TRPM7's channel domain, rather than its kinase domain, regulates the convergent extension movement, and this regulation is potentially mediated through non-canonical Wnt signaling and the modulation of Dishevelled (Dvl) and GTPase Rac activity [58].

Deletion studies have suggested that TRPM7 is involved in organogenesis. In mice, TRPM7 contributes to cardiogenesis at E9.5-E12.5, and nephrogenesis at E11.5-E18.5 [25,45,59]. Growth deficits have been reported in zebrafish with various TRPM7 mutations. Specifically, *trpm7 morpholino* mutants exhibit bradycardia [59]. *Trpm7^{j124e2} (nutria)* mutants, exhibit defective skeletogenesis characterized by altered sequence and timing of ossification, as well as nephrolithiasis [60,61]. Defects in pancreatic development have also been associated with zebrafish *sweetbread(swd), tct/trpm7^{j124e1}* and *tct/trpm7^{b508} mutations* [62]. In summary, TRPM7 plays an indispensable role in early embryogenesis, contributing to pluripotency maintenance, gastrulation, and neural tube closure, likely through Mg^{2+}-dependent pathways.

6. TRPM7 in neurogenesis

Although knocking out TRPM7 after E10.5 does not impact brain development, studies from others and our lab have suggested that TRPM7 continues to play a significant role in regulating subsequent stages of neurodevelopment. In the developing nervous system, each neuron extends an axon to reach its destination and ultimately establish interconnected neural networks [63]. Growth cones are dynamic structures located at the tips of the growing axons that facilitate axonal navigation by responding to different environmental cues [63]. Movements of the neuronal growth cone are highly regulated by intracellular Ca^{2+} [64]. We have previously shown that TRPM7 regulates axonal outgrowth and maturation in mouse primary hippocampal neurons. We found that TRPM7 channels are highly expressed in the peripheral domain, specifically the distal end of the growth cones, compared to the central domain [65]. Knockdown of TRPM7 with shRNA reduces TRPM7-mediated Ca^{2+} influx and significantly increases neurite length, indicating enhanced axonal outgrowth [65]. Waixenicin A, a natural product isolated from the soft coral *Sarcothelia edmondsoni*, has previously been shown to be a selective and potent inhibitor of TRPM7. Accordingly, selective inhibition of TRPM7 by waixenicin A at a concentration of 500 nM enhances neuronal polarization and accelerates the branching of axons and dendrites [65,66]. We further demonstrated that TRPM7 interacts with cytoskeletal component F-actin and the α-actinin-1 protein complex, thereby regulating neuronal growth in a Ca^{2+}-dependent manner. A previous study by Wei et al. using embryonic fibroblasts has indicated that TRPM7 possesses 'calcium flicker activity', promoting directional movements by transducing local mechanical stress into intracellular Ca^{2+} signals in migrating cells [67]. Our findings also suggest that TRPM7 may serve as a mechano-sensitive regulator of neuronal cytoskeleton, and negatively regulates axonal outgrowth and maturation. This potential regulatory role may help to prevent excessive growth, undesired connections, and premature axonal specification during neurodevelopment. Another study using isolated hippocampal CA1 neurons obtained from neonatal rats has indicated that the neurotropic factor NGF regulates TRPM7-like currents through TrkA, which may be involved in neurodevelopment [68]. Furthermore, neurite outgrowth mediated by TRPM7 is subject to hypoxic conditions. Short-term hypoxia reduces TRPM7 activity and enhances axonal outgrowth of hippocampal neurons, whereas chronic hypoxia potentiates TRPM7 activity and leads to progressive retraction of axons and dendrites [69].

Glial cells are recognized in modulating neurogenesis, and TRPM7 has been implicated in glial proliferation and migration. In contrast to our findings in neurons, both siRNA-mediated knockdown and non-selective inhibition of TRPM7 with 2-aminoethoxydiphenyl borate (2-APB) at a concentration of 100 μM significantly impair cortical astrocyte proliferation and migration, potentially by reducing the phosphorylation of extracellular signal-regulated kinases (ERK) and c-Jun N-terminal kinases (JNK) [70]. Similarly, TRPM7 has been proposed to enhance microglia migration [71]. A recent study has also indicated that pro-BDNF upregulates surface expression of TRPM7 and TRPM-mediated Ca^{2+} influx in microglia, although its specific contribution to neurodevelopment remains to be elucidated [72]. Overall, TRPM7 remains critical beyond early embryonic development by tightly regulating neuronal growth and maturation as well as glial cell proliferation and migration.

7. TRPM7 in synaptic regulation

Synapses are the functional connections between neurons and are fundamental for transmitting signals and forming neural circuits that underlie brain function. The establishment and refinement of synapses, in both developing and adult brains, facilitates learning, memory, and overall cognition. Studies have suggested that TRPM7 regulates synaptic density and synaptic transmission in both central and peripheral synapses. In neuronal cultures, shRNA-targeted TRPM7 knockdown reduces synaptic density, characterized by a decrease in the spine, PSD-95, and synaptophysin puncta [73]. Consistently, brain-specific deletion of TRPM7 at an early postnatal stage reduces CA1 synapse density, long-term potentiation (LTP), and leads to impairments in learning and memory in mice [73]. The reduction in synaptic density and plasticity can be significantly rescued by the restoration of α-kinase activity, but not by the ion channel domain or the extracellular presence of Mg^{2+} or Zn^{2+} [73]. This indicates that the regulation of synapses depends on the kinase domain rather than TRPM7-mediated divalent cation influx. The study further demonstrated that the α-kinase domain directly interacts with and inhibits cofilin through phosphorylation, while cofilin disinhibition leads to synaptic loss and cognitive dysfunction [73]. In sympathetic neurons, TRPM7 is expressed in the membrane of synaptic vesicles, where it can assemble with synaptic vesicle proteins synaptotagmin I, synapsin I, and snapin to regulate neurotransmitter release [74]. Alterations in presynaptic expression or activity of TRPM7 affects postsynaptic responses, including EPSP amplitudes and kinetics, and acetylcholine release [74]. A later study from the same group further suggested that the conductance of TRPM7 across the vesicle membrane is required for vesicle fusion with the plasma membrane [75]. Using cortical neurons obtained from conditional TRPM7 knockout pups, a recent study has suggested that TRPM7 may also contribute to synaptic vesicle endocytosis and short-term synaptic plasticity in both excitatory and inhibitory neurons [76]. Consistent with these findings, zebrafish TRPM7 has been shown to modulate neurotransmitter release at central synapses during larvae development. TRPM7 is required for the differentiation and function of sensory neurons and dopaminergic neurons, contributing to early touch-evoked escape responses and locomotor patterns [77,78].

While TRPM7′s direct role in myelination is not well-established during development, its kinase domain has been shown to phosphorylate myelin basic protein (MBP) at serine and threonine residues, a process critical for the formation and maintenance of myelin in the CNS [18]. Future studies are needed to fully understand TRPM7′s involvement in development processes, including myelination and synaptic pruning. Nevertheless, its role in synaptic density, synaptic transmission, and neurotransmitter release underscores its significance in neurodevelopment.

8. TRPM7 in neurodegeneration

It is noteworthy that TRPM7 not only plays a critical role in early embryonic development, neuronal outgrowth and maturation, proliferation and migration of neuroglial cells, and synaptic regulation **but also contributes** to a range of neurodegenerative pathologies through its aberrant expression and dysfunction.

9. Alzheimer's disease

AD represents the predominant form of neurodegenerative disease, leading to neuronal loss, cognitive deficits, memory decline, and behavioral dysfunction [79]. Central to the pathophysiological mechanisms underlying AD is the cerebral aggregation of amyloid-beta peptide (Aβ), which forms insoluble plaques in the brain tissues of Alzheimer's patients [79]. While Aβ40 is the primary cleavage product of the amyloid precursor protein (APP), Aβ42, a longer isoform, possesses greater amyloidogenic potential and is considered a more significant contributor to the etiology of AD [79]. Furthermore, Aβ42 has been increasingly associated with both the TRPM7 channel and its kinase function, highlighting the potential role of TRPM7 in AD pathogenesis [43,80].

In various cell types with AD-associated presenilin mutations, TRPM7 currents were found to be consistently suppressed and responsible for ion channel dysfunction [80]. Concurrently, this mutation leads to the disruption of phosphatidylinositol 4,5-bisphosphate (PIP2) metabolism, a key cellular effector associated with Aβ42 regulation [80]. Landman et al. demonstrated that impairments in TRPM7-mediated Ca^{2+} entry, observed in AD-associated mutant cells, can be rectified by PIP2 supplementation. These findings suggest that preserving TRPM7 channel function via PIP2-dependent mechanisms may help control Aβ production and mitigate AD progression [80]. Previous studies have revealed the co-localization of APP and Aβ within autophagosomes in both APP-overexpressing cells and mouse models of AD, suggesting autophagy in Aβ clearance [81]. Notably, Ca^{2+} entry via the TRPM7 channel modulates basal autophagy levels [81]. This was evidenced by a reduction in basal autophagy when TRPM7 was down-regulated in SH-SY5Y cells using shRNA, or upon administration of 5 μM waixenicin A. Oh et al. further suggested that the specific TRPM7 activator, naltriben at a concentration of 10 μM, triggers Ca^{2+} influx, initiates autophagic pathways, and facilitates LC3 and APP co-localization while diminishing Aβ42 content in SH-SY5Y cells [27]. More importantly, impaired basal autophagy was observed in AD-associated presenilin-1 ΔE9 mutant cells, whereas 10 μM naltriben restored autophagic activity and downregulated Aβ42 [41]. These results collectively suggest that TRPM7 channel activation could potentially mitigate AD-associated Aβ pathology through Ca^{2+}-dependent autophagic modulation [41].

Recent evidence also highlights TRPM7′s kinase activity in promoting the degradation of Aβ42. A significant reduction in TRPM7 expression was observed in hippocampal tissues derived from AD patients as well as from two murine AD models, indicating a correlation between the downregulation of TRPM7 expression and the onset of AD-like pathology [43]. In mouse hippocampal neuron cultures induced by exogenous Aβ, overexpression of either the full-length TRPM7 or its active kinase domain was effective in preventing synapse loss, while this protective effect was not observed upon overexpression of the ion channel domain alone or a kinase-deficient TRPM7 mutant [43]. Accordingly, overexpressing the kinase domain in the hippocampus of AD mice prevented Aβ deposition, synaptic loss, and memory impairments [43].

10. Parkinson's disease

PD is a neurodegenerative disorder characterized by the progressive loss of dopaminergic (DA) neurons in the substantia nigra (SN) pars compacta, leading to both motor and non-motor symptoms, including cognitive decline, autonomic dysfunction, mood and sleep irregularities, and gut disorder [82]. A common model of PD involves the administration of neurotoxin MPTP, which can be metabolized into the toxic cation MPP^+. MPP^+ subsequently induces neuronal death by disrupting mitochondrial function in DA neurons [82,83]. Studies have increasingly emphasized Mg^{2+} in neuroprotection against MPP^+-induced toxicity and PD pathology, with a specific focus on the involvement of TRPM7 in Mg^{2+} homeostasis and its therapeutic implications in PD [30,84,85].

TRPM7 channels are expressed in SN neurons and a marked decline in TRPM7 mRNA levels has been observed in the SN region of PD patients [86]. TRPM7 mutant zebrafish showed impairments in dopaminergic signaling, increased sensitivity to MPP^+, and a hypomotile phenotype [77]. Additionally, the forced expression of a non-functional TRPM7 variant induces cell mortality in differentiated SH-SY5Y cell lines that model characteristics of human DA neurons [77]. A recent study demonstrated that exposure to MPP^+ markedly reduced TRPM7 expression in both SH-SY5Y cells and the SN pars compacta of a mouse model, concomitant with a reduction in Mg^{2+} influx [87]. Overexpression of TRPM7, however, suppressed the expression and activation of pro-apoptotic proteins, thereby preventing neuronal loss *in vivo* [87]. Using the TRPM7 inhibitor carvacrol, Dati et al. demonstrated the involvement of TRPM7 in the pathogenesis of hemiparkinsonism induced by 6-hydroxydopamine (6-OHDA) *in vivo* [88]. At a concentration of 40 mg/kg, carvacrol reduces the loss of dopaminergic neurons while preserving tyrosine hydroxylase immunostaining, an indirect measure of dopamine concentrations, in mice [88]. In addition, carvacrol treatment (12.5 and 25 mg/kg) provides neuroprotection against reserpine-induced PD in rats by mitigating motor decline and preserving tyrosine hydroxylase immunostaining, specifically in the SN pars compacta and dorsal striatum [89]. In *in vitro* models of PD, microR-22 overexpression exerted cytoprotective effects against 6-OHDA-induced PC12 cell injury and reactive oxygen species (ROS) production by downregulating TRPM7 expression [42]. It has been reported that the excessive generation of ROS is a critical factor in neurodegenerative pathologies, including AD and PD [90–92]. Activation of TRPM7 channels by ROS leads to elevated intracellular Ca^{2+} levels, and this Ca^{2+} elevation, in turn, exacerbates oxidative stress, ultimately culminating in neuronal death [32,35,93,94]. Collectively, these findings underscore the neuroprotective role of TRPM7 in preserving dopaminergic neurons in PD.

11. Amyotrophic lateral sclerosis and parkinsonism dementia

ALS is a neurodegenerative disease marked by motor neuron degeneration in the CNS, leading to progressive muscle weakness and paralysis. Parkinsonism dementia, though distinct, shares clinical symptoms and underlying pathogenic mechanisms with ALS and often presents comorbidities [40]. Previous studies have identified a variant in TRPM7 allele within a subset of ALS and Parkinsonism dementia patients in Guam, Japan [40]. This variant results in a missense mutation of the TRPM7 channel and confers increased sensitivity of the channel to inhibition by intracellular Mg^{2+}, yet it leaves the TRPM7 kinase catalytic activity unaffected [40]. Given the primary role of TRPM7 in mediating Mg^{2+} and Ca^{2+} influx, this mutation conceivably disrupts Mg^{2+} and Ca^{2+} homeostasis, which may influence critical cellular signaling pathways, including those regulated by elevated oxidative stress and those triggering proinflammatory cascades [95]. These results, taken together, suggest that dysfunction in the TRPM7 channel may be implicated in the onset and progression of ALS and Parkinsonism dementia.

12. TRPM7: a potential therapeutic target for repair and neuroregeneration

Neurodegenerative manifestations predominantly occur later in life, whereas neurodevelopmental processes primarily occur during the early stages of life. While neurodevelopment and neurodegeneration differ mechanistically, there are overlaps in molecular and cellular pathways between them [96]. Understanding the mechanisms of proper neurodevelopment may provide us insights for developing novel therapeutic strategies aimed at promoting neuroregeneration. Unfortunately, the rate of regeneration within the nervous system lags considerably behind that of other bodily systems. This relative delay is partially ascribed to two factors: 1) the inadequate ability for cellular waste elimination,

compounded by 2) the restricted potency of neural cells to proliferate or self-renew [97,98].

Neurodegenerative disorders are characterized by the progressive accumulation of pathologically misfolded proteins within the brain. For instance, AD is marked by Aβ deposition, PD by α-synuclein, and ALS by ubiquitinated proteins [99]. Concurrently targeting the disaggregation and degradation of these pathogenic proteins may alleviate the neurotoxic effects, facilitating the restoration of physiologically functional proteins, and thereby promoting neuronal health and neuroregeneration [99]. Taking AD as a paradigmatic example, the Aβ protein directly hinders the proliferation and differentiation of neural progenitors, accelerates neuronal apoptosis, and exacerbates oxidative stress, which, in turn, further amplifies the production of Aβ [79]. This process accelerates and perpetuates the detrimental cycle underlying AD pathogenesis [79]. Recent studies have elucidated that activation of the TRPM7 channel can enhance the clearance of AD-associated Aβ via Ca^{2+}-dependent autophagic initiation [43]. Overexpression of the TRPM7 kinase domain in the hippocampus of AD mice has been observed to prevent Aβ deposition, while preserving synaptic loss and cognitive impairments [43]. These findings, together, suggest that restoration of TRPM7 function and/or expression may offer a more favorable environment for neuroregeneration and repair by facilitating the degradation of pathogenic proteins.

A notable distinction of the adult CNS, in contrast to the peripheral nervous system (PNS), is its limited regenerative capacities. For years, the prevailing belief was that neurons within the CNS were incapable of regeneration post-injury, and the brain's capability to produce new neurons was limited to a specific developmental phase [79,98]. Nevertheless, recent murine and human research has revealed the sustained nature of adult neurogenesis throughout an individual's lifespan. While the process tends to diminish with age, studies confirm the existence of newborn cells in the brains of centenarians and patients with AD [100]. Notably, postmortem studies have identified a marked elevation in neurogenesis-associated markers in AD patients compared to healthy age-matched controls, suggesting a potential compensatory response to neurodegeneration [101]. While various targets associated with neurogenesis and neuronal regeneration have been identified, suggesting significant potential for designing small molecules to promote repair and regeneration, only a limited number of therapeutic compounds have been shown to stimulate neuroregeneration *in vivo* [102]. Considering TRPM7′s proposed capabilities in regulating neuronal growth and maturation, facilitating glial cell proliferation and migration, as well as modulating synaptic plasticity and acetylcholine release, along with its regulatory effects in neurodegenerative diseases, targeting TRPM7 emerges as a promising therapeutic approach.

An increasing number of pharmacological inhibitors and activators targeting TRPM7 have been identified and subjected to experimental investigation within the fields of neurodegeneration, providing prospects for therapeutic intervention through the modulation of TRPM7. The natural products carvacrol and xyloketal B stand as examples of TRPM7 channel inhibitors that have been extensively investigated across various models, showing efficacy *in vivo*. Treatment with carvacrol has demonstrated neuroprotection in the PD rat model induced by reserpine, as well as in the hemiparkinsonism mouse model triggered by 6-OHDA [88,89]. Both carvacrol and xyloketal B have exhibited protective properties across several models for cerebral ischemia and hypoxia, suggesting their potential therapeutic utility in mitigating neurodegenerative and ischemic conditions [37,38,103,104]. Among natural inhibitors, the marine-sourced compound waixenicin A stands out with the highest *in vitro* potency, demonstrating an IC50 value as low as 16 nM [66], coupled with *in vivo* inhibition targeting TRPM7. Notably, it has been validated to offer protection against neonatal hypoxic-ischemic brain injury *in vivo* and to promote neurite outgrowth *in vitro* [34,65,69]. Other TRPM7 inhibitors with *in vitro* potency under 10 μM include FTY720, AA861, spermine, MK886, sphingosine, nordihydroguaiaretic acid, NS8593, and VER155008, though IC50 values were not determined for all [105,106]. FTY720, sphingosine, and VER155008 are notable, with low IC50 values of 0.7, 0.6, and 0.11 μM, respectively [105,106]. While several TRPM7 inhibitors have been identified, few are acting on the kinase domain. Song et al. reported TG100–115, the first documented potent TRPM7 kinase inhibitor, which is additionally recognized as a selective PI3Kγ/PI3Kδ inhibitor [107,108]. Currently, TG100–115 stands as the sole potent TRPM7 kinase domain inhibitor, underscoring the need for further exploration in this direction. Naltriben, a previously identified delta-opioid receptor antagonist, has been recognized as a selective agonist for TRPM7 channels. Activating TRPM7 channels without the prerequisite of intracellular Mg^{2+} depletion, its IC50 was determined to be approximately 20 μM [109]. Naltriben has been reported to induce Ca^{2+} influx, activating autophagic pathways, promoting the colocalization of LC3 and APP, and consequently reducing the levels of Aβ42 in SH-SY5Y cells [41]. Mibefradil has emerged as a new class of benzimidazole agonists for the TRPM7 channel, leading to an increase in TRPM7-mediated Ca^{2+} influx and the amplification of whole-cell currents [110]. Compared with naltriben, mibefradil effectively stimulates TRPM7 currents solely under physiological levels of intracellular magnesium, with its activation effect being negated in the presence of elevated internal Mg^{2+} concentrations [110].

Although the above pharmacological agents modulating TRPM7 have been identified, their study in neurodegeneration-related experiments has mainly been aimed at attenuating pathological damage. The current research evidence regarding TRPM7′s contribution to neurogenesis and regeneration in neurodegenerative conditions remains limited, representing a gap in our understanding and a potential avenue for future investigations.

CRediT authorship contribution statement

Zhengwei Luo: Writing – review & editing, Writing – original draft. **Xinyang Zhang:** Writing – review & editing, Writing – original draft. **Andrea Fleig:** Writing – review & editing, Supervision, Resources, Funding acquisition. **Daniel Romo:** Funding acquisition, Resources, Writing – review & editing. **Kenneth G. Hull:** Funding acquisition, Resources, Writing – review & editing. **F. David Horgen:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition. **Hong-Shuo Sun:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Zhong-Ping Feng:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare no conflict of interest.

Data availability

No data was used for the research described in the article.

Author contributions

All authors listed made direct and substantial contribution to this manuscript.

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