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REVIEWS

Mutation of TRPML1 Channel and Pathogenesis of Neurodegeneration in Haimeria

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Abstract

Neurodegenerative diseases, a group of debilitating disorders, have garnered increasing attention due to their escalating prevalence, particularly among aging populations. Alzheimer's disease (AD) reigns as a prominent exemplar within this category, distinguished by its relentless progression of cognitive impairment and the accumulation of aberrant protein aggregates within the intricate landscape of the brain. While the intricate pathogenesis of neurodegenerative diseases has been the subject of extensive investigation, recent scientific inquiry has unveiled a novel player in this complex scenario—transient receptor potential mucolipin 1 (TRPML1) channels. This comprehensive review embarks on an exploration of the intricate interplay between TRPML1 channels and neurodegenerative diseases, with an explicit spotlight on Alzheimer's disease. It immerses itself in the intricate molecular mechanisms governing TRPML1 channel functionality and elucidates their profound implications for the well-being of neurons. Furthermore, the review ventures into the realm of therapeutic potential, pondering the possibilities and challenges associated with targeting TRPML1 channels as a promising avenue for the amelioration of neurodegenerative disorders. As we traverse this multifaceted terrain of neurodegeneration and the enigmatic role of TRPML1 channels, we embark on a journey that not only broadens our understanding of the intricate machinery governing neuronal health but also holds promise for the development of innovative therapeutic interventions in the relentless battle against neurodegenerative diseases.

Keywords Neurodegeneration · TRPML1 channels · Alzheimer's disease · Therapeutic potential

Abbreviations

AD	Alzheimer's
TRPML1	Transient receptor potential mucolipin 1
TRP	Transient receptor potential
cryo-EM	Cryo-electron microscopy
PI(3,5)P2	Phosphatidylinositol 3,5-bisphosphate
PI(4,5)P2	Phosphatidylinositol 4,5-bisphosphate
VSD	Voltage sensing domain
PD	A pore domain
PMD	Pore mucolipin domain
ER	Endoplasmic reticulum
PSEN1	Presenilin 1
PSEN2	Presenilin 2
APOE	Apolipoprotein E
β-CTF	C-terminal fragments
APP	Amyloid precursor protein
HD	Huntington's disease
AJ	Ashkenazi Jewish
NJ	Non-Jewish
APP	Amyloid precursor protein

Introduction

Neurodegenerative diseases represent an increasingly pressing healthcare challenge, imposing a substantial burden on individuals and societies globally [1]. Among these insidious conditions, Alzheimer's disease (AD) reigns as a formidable adversary, marked by its relentless erosion of cognitive faculties and the insidious accumulation of pathological protein aggregates within the intricate architecture of the brain. As we confront the escalating impact of neurodegenerative diseases, emerging research has unveiled a captivating nexus between these disorders and a class of enigmatic

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molecular entities—transient receptor potential mucolipin 1 (TRPML1) channels [1].

In this comprehensive review, we embark on a journey through the labyrinthine landscape of neurodegenerative diseases, delving deep into the intricate mechanisms that govern their pathogenesis. Our primary focus is directed toward Alzheimer's disease, a pervasive and relentless neurodegenerative disorder that exacts a profound toll on both individuals and healthcare systems worldwide. At the heart of this exploration lies the captivating role of TRPML1 channels, a novel player in the intricate tapestry of neuronal degeneration.

Neurodegenerative diseases are a formidable adversary, collectively affecting millions of individuals across the globe. These conditions, characterized by the gradual decline of neurological function, have far-reaching implications for both patients and their caregivers [2]. Among the various neurodegenerative disorders, AD emerges as a particularly pervasive and challenging adversary. It stands as the most prevalent form of neurodegeneration, marked by the inexorable erosion of cognitive abilities and the insidious accumulation of pathological protein aggregates within the complex neural networks of the brain [3, 4].

The aim of this comprehensive review is to delve into the intricate web of neurodegenerative diseases, with a specific focus on the formidable specter of AD. While the pathogenesis of these disorders has been the subject of extensive investigation, recent scientific inquiries have cast a spotlight on a previously underappreciated player in the neurodegenerative drama—TRPML1 channels [1, 5].

Our journey into this realm of scientific inquiry takes us through the multifaceted landscape of neurodegenerative diseases, seeking to unravel their complex etiology and progression. Within this expansive field, AD looms large, demanding our keen attention. We delve into the heart of AD's pathogenesis, exploring the molecular intricacies that underlie its relentless assault on neuronal health [5].

At the heart of our exploration lies the enigmatic role of TRPML1 channels, a group of membrane proteins that have recently emerged as potential key players in the neurodegenerative cascade. We navigate through the molecular mechanisms that govern TRPML1 channel function, deciphering their profound impact on the delicate equilibrium of neuronal well-being [6].

Furthermore, this review extends its reach into the realm of therapeutic possibilities. We contemplate the tantalizing prospect of targeting TRPML1 channels as a novel avenue for mitigating the ravages of neurodegenerative disorders. As we traverse this intricate terrain, our goal is not only to deepen our comprehension of the complex machinery that orchestrates neuronal health but also to illuminate potential paths towards innovative therapeutic interventions in our ongoing battle against neurodegenerative diseases.

TRPML1 Channels: Structure and Function

TRPML1 channels are members of the transient receptor potential (TRP) channel superfamily and play a crucial role in maintaining cellular calcium homeostasis [7]. In this review, we will delve into the detailed examination of the structure and function of TRPML1 channels, shedding light on their significance in neuronal health.

Structural Features of TRPML1 Channels: TRPML channels share a common structural framework comprising six transmembrane helices (S1–S6), two-pore helices (PH1 and PH2), and an approximately 25 kD luminal domain (Fig. 1A). Notably, TRPML1's S2 extends beyond the membrane, distinguishing it from other channels in the superfamily. Furthermore, the N-terminal S1 features an extension (pre-S1) housing three small α-helices (α1–α3), a unique feature of TRPML channels [8].

Activation by Lipid Ligands: Recent cryo-electron microscopy (cryo-EM) structures and functional analyses have illuminated the activation mechanisms of TRPML1 channels [9, 10] and also, they have identified two lipid ligands, phosphatidylinositol 3,5-bisphosphate (PI (3,5) P2) as an agonist and phosphatidylinositol 4,5-bisphosphate (PI(4,5) P2) as an antagonist [10, 11]. Both lipids bind to the extended helices of S1-S3 of TRPML1 (Fig. 1B) [12]. Specifically, Y355 in the cytosolic interface of S3 forms a π-cation interaction with R403 at the C-terminus of S4 when bound to PI (3,5) P2, leading to allosteric activation [11, 13]. This activation involves the movement of the S4-S5 linker, influencing the channel pore opening.

Regulation by Subcellular Localization: TRPML1 channels are regulated by their subcellular localization. They are primarily found within the lysosomal compartment, where PI (3,5) P2 is enriched and PI (4,5)P2 is depleted. This localization enables the channel to remain active within the lysosome. During lysosomal exocytosis, when the lysosome fuses with the surface, exposure to surface PI(4,5)P2 inactivates TRPML1 channels, acting as an "off" switch [14–16].

Distinct Properties of TRPML3: TRPML1 shares similarities with TRPML2 but differs significantly from TRPML3. TRPML3 exhibits distinct properties, including strong inhibition by low pH and high sodium. This sensitivity to pH and sodium is vital for its role in the secretion of neutralized lysosomes and expulsion of bacterial pathogens from infected cells [17–19].

Ligand Binding Sites and Implications: TRPML channels share ligand-binding sites, such as PI(3,5)P2 and PI(4,5)P2. However, recent research suggests that additional natural ligands, such as rapamycin, may activate TRPML channels, opening new avenues for understanding the regulation of autophagy and lysosomal biogenesis [19, 20].

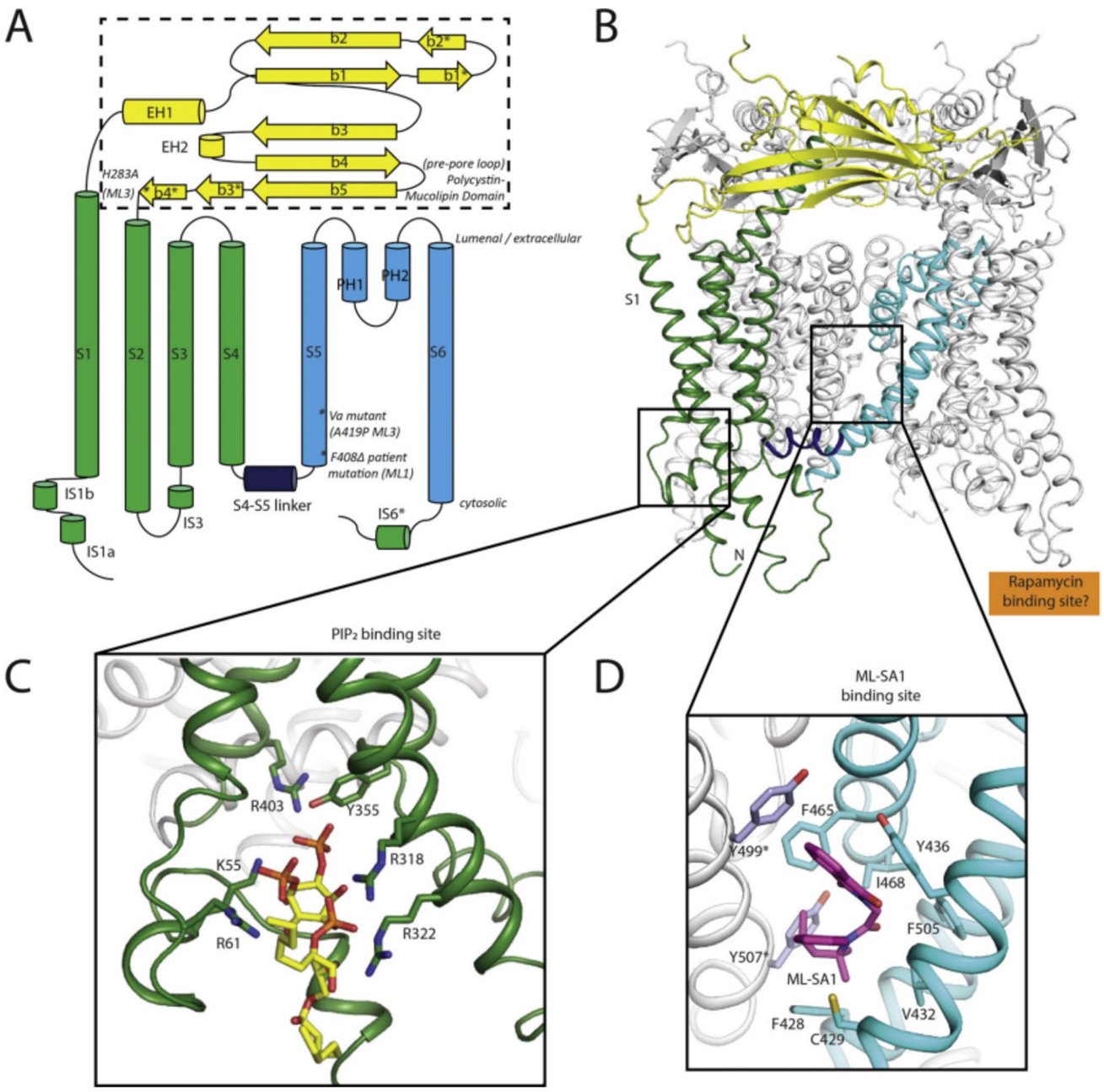

Fig.1 **A** Schematic representation of the secondary structure of TRPMLs. Approximate location of key residues H283A and varitint–waddler mutation for TRPML3, and the mucolipidosis type IV patient mutation F408Δ for transient receptor potential mucolipin 1 (TRPML1) resulting in partial channel function and mild phenotype. **B**, **C**, **D** The structure of TRPML1 with detailed inset indicating PI (3,5) P2 and PI (4,5) P2 binding site (PI (3,5)P2 shown) as well as the artificial agonist ML-SA1-binding site. (PDB code: 5WJ9 and 6E7Z). The binding site for rapamycin and sphingomyelin is currently unknown, permission from [23]

Structure of PKD Channels: In addition to TRPML channels, this review briefly discusses polycystin (PKD) channels. PKD2, a representative member, consists of a voltage sensing domain (VSD), a pore domain (PD) containing S5, S6, and pore helices (PH1 and PH2), and an extracellular pre-pore mucolipin domain (PMD). PKD2L1, a related channel, also shares structural homology but exhibits differences in ion selectivity [21, 22].

Ca2 + Dysregulation in Neurodegenerative Diseases

Calcium (Ca2 +) dysregulation is a prominent feature in the pathogenesis of AD, a progressive neurodegenerative disorder characterized by memory impairment and cognitive decline. This review explores the intricate relationship between Ca2 + dysregulation and synaptic defects in AD, shedding light on potential therapeutic targets to mitigate the devastating effects of this disease [24, 25].

Ca2 + Dysregulation Disrupts Synaptic Networks in AD

The synapse is a critical hub for neuronal communication, memory encoding, and learning, all of which are profoundly affected in AD. Emerging evidence suggests that AD is marked by "calciumopathy"—abnormal Ca2 + regulation—leading to "synaptopathy," synaptic dysfunction. Post-mortem brain tissue from AD patients exhibits reduced synaptic density, emphasizing the significance of synaptic alterations in AD [26]. Interestingly, synaptic deficits manifest even before the appearance of amyloid plaques, implicating Ca2 + dysregulation as a potential culprit [27].

Ca2 + dysregulation in AD is characterized by exaggerated Ca2 + responses to synaptic stimuli and disrupted Ca2 + homeostasis. These abnormalities result in elevated resting cytosolic Ca2 + levels, which have been observed in both AD patients and older non-AD rodent models [28].

Normal cognitive function relies on acetylcholine signaling, and α7 nicotinic acetylcholine receptors (α7nAChRs) are highly permeable to Ca2 + . Cholinergic neurons, which degenerate in AD, express α7nAChRs, indicating their significance in memory and cognition. Hippocampal α7nAChRs, present on mossy fiber terminals and CA1 interneurons, contribute to Ca2 + influx, modulating synaptic transmission and long-term potentiation (LTP) [6].

Aβ, a hallmark of AD, binds strongly to α7nAChRs, leading to noncompetitive inhibition of receptor function [29]. Reduced α7nAChR expression in AD patients and mice is associated with Aβ binding, which triggers Ca2 + influx [30, 31]. However, α7nAChR activation can rescue LTP deficits and cognitive impairments in AD models, suggesting a complex role for these receptors in AD pathophysiology.

Currently, only two classes of FDA-approved drugs, memantine and acetylcholinesterase inhibitors, are used to manage AD symptoms [32]. Both classes target synaptic sites of action, highlighting the importance of synaptic dysfunction in AD. However, there is a pressing need for disease-modifying treatments [33].

Numerous studies have identified potential therapeutic targets, including NMDA receptors, α7nAChRs, ryanodine receptors (RyRs), and sarco/endoplasmic reticulum Ca2 + -ATPase (SERCA) [34–36]. Despite promising preclinical results, few compounds have advanced to clinical trials. Some FDA-approved drugs, like varenicline and levetiracetam, have been repurposed for AD treatment, demonstrating the potential of using existing medications to bypass extensive drug development [37].

Maintaining low cytosolic Ca2 + levels is crucial for neuronal function, with the endoplasmic reticulum (ER) playing a pivotal role in this regulation. Dysregulation of ER Ca2 + channels, particularly ryanodine receptors (RyRs), is implicated in AD pathogenesis [38]. Mutations in presenilin 1 (PS1) gene, associated with familial AD, affect Ca2 + regulation and RyR function, contributing to Ca2 + dysregulation in AD [39].

RyR-mediated Ca2 + responses are increased in AD neurons, exacerbating synaptic dysfunction. Targeting RyRs with dantrolene, an FDA-approved medication, has shown promise in reversing synaptic and cognitive deficits in AD animal models. In addition to RyRs, IP3 receptors and SERCA pumps on the ER membrane contribute to Ca2 + regulation in synaptic compartments [40, 41].

TRPML1 Channels in Neuronal Function

TRPML1

Channels are a class of cation channels primarily localized to lysosomal membranes. While their essential role in cellular homeostasis has been established, recent research has shed light on their significance in neuronal function. This article delves into the multifaceted roles of TRPML1 channels in neurons, emphasizing their involvement in calcium signaling and lysosomal function, as well as highlighting the potential consequences of TRPML1 dysfunction in these cells.

(A) Role of TRPML1 Channels in Neuronal Function: Calcium Signaling

TRPML1 channels are integral components of intracellular calcium signaling in neurons. These channels facilitate the release of calcium ions from lysosomal stores into the cytoplasm in response to various cellular cues [42]. This phenomenon is essential for several neuronal processes:

I. Synaptic Transmission: TRPML1-mediated lysosomal calcium release contributes to presynaptic calcium signaling, impacting neurotransmitter release and synaptic plasticity. It modulates the probability of neurotransmitter release, thereby influencing synaptic strength and facilitating synaptic transmission.

II. Neuronal Excitability: Calcium ions released via TRPML1 channels participate in the regulation of membrane excitability. Elevated cytosolic calcium levels affect the activity of calcium-dependent ion channels, such as voltage-gated calcium channels and calcium-activated

potassium channels, thereby influencing neuronal firing patterns [43].

III. Neuronal Survival: Proper calcium signaling is crucial for neuronal survival. TRPML1 channels play a role in buffering excessive cytosolic calcium levels, preventing excitotoxicity and cell death in response to pathological stimuli [15, 44].

Lysosomal Function

TRPML1 channels are primarily located in lysosomal membranes, where they serve as key regulators of lysosomal physiology. Their contributions to neuronal lysosomal function include the following:

I. Lysosomal Trafficking: TRPML1 channels are involved in regulating the movement of lysosomes within neurons. Proper lysosomal trafficking is essential for maintaining neuronal health and preventing the accumulation of toxic cellular waste products [45, 46].

II. Autophagy and Degradation: TRPML1 channels participate in autophagy, a cellular process crucial for degrading damaged organelles and protein aggregates. Dysfunctional TRPML1 channels can disrupt autophagic processes, leading to the buildup of cellular debris and contributing to neurodegenerative diseases [47].

(B) Consequences of TRPML1 Dysfunction in Neurons: Dysregulation or dysfunction of TRPML1 channels in neurons can have profound consequences:

I. Neurodegeneration: Impaired lysosomal function due to TRPML1 dysfunction can lead to the accumulation of toxic materials within neurons. This accumulation is associated with neurodegenerative disorders such as lysosomal storage diseases and Parkinson's disease.

II. Synaptic Impairments: Altered calcium signaling mediated by TRPML1 channels can disrupt synaptic transmission, impair synaptic plasticity, and contribute to cognitive deficits observed in various neurological conditions.

III. Neuronal Hyperexcitability: Dysfunctional TRPML1 channels may result in abnormal calcium handling, leading to increased neuronal excitability and susceptibility to excitotoxicity, which is linked to neurodegeneration.

TRPML1 channels, initially recognized for their role in lysosomal function, have emerged as pivotal players in neuronal function. Their involvement in calcium signaling and lysosomal processes underscores their significance in maintaining neuronal health and function. Dysfunction of TRPML1 channels can have detrimental consequences, contributing to neurodegenerative diseases and synaptic impairments. Understanding the intricate roles of TRPML1 channels in neurons is crucial for developing potential therapeutic strategies aimed at preserving neuronal function and mitigating neurodegenerative conditions [48–50].

TRPML1 Channels in Alzheimer's Disease

AD is a complex neurodegenerative disorder characterized by progressive cognitive decline and the accumulation of amyloid-beta plaques and tau tangles in the brain [51]. The quest for a deeper understanding of the molecular mechanisms underlying AD pathogenesis has led to the investigation of various ion channels and transporters, including TRPML1 channels. This review explores the specific contributions of TRPML1 channels to AD pathogenesis and reviews the experimental data linking these channels to AD-related neuronal degeneration [52].

(A) Examination of the Specific Contributions of TRPML1 Channels to AD Pathogenesis.

Mounting evidence suggests that TRPML1 channels are intricately involved in AD pathogenesis. While the precise mechanisms remain under investigation, several key aspects underscore the importance of these channels in AD:

An estimated 55 million individuals worldwide suffer from dementia, and nearly 10 million new diagnoses are made annually [53]. AD, initially described by German physician Alois Alzheimer in 1906, constitutes the most prevalent form of dementia, accounting for 60–70% of all diagnosed cases [54]. AD is characterized by a range of debilitating signs and symptoms, including memory loss disrupting daily life, repetitive questioning, forgetfulness in recent conversations, frequent item misplacement, difficulty recalling names of familiar individuals, word-finding difficulties, alterations in basic daily activities, temporal or geographic disorientation, anxiety, depression, ilogical thinking, and personality and behavior changes [55, 56]. AD encompasses both early- and late-onset forms, with genetic defects associated with each. Early onset AD (5–10% of cases) is linked to mutations in APP (amyloid precursor protein), presenilin 1 (PSEN1), and presenilin 2 (PSEN2), while late-onset AD is most consistently associated with apolipoprotein E (APOE) genetic variations [57]. Hallmarks of AD include extracellular amyloid-beta plaques and intraneuronal hyperphosphorylated tau protein accumulation in neurofibrillary tangles [39].

Recent research has brought the role of endolysosomal dysfunction in AD to the forefront. Abnormalities in early endosomes, crucial for amyloid-beta production, have been observed in postmortem AD patient neurons [58]. Genetic modifiers of AD risk are linked to proteins involved in the endocytic pathway. Additionally, AD-associated early endosome enlargement is associated with an accumulation of amyloid-beta C-terminal fragments (β-CTF), emphasizing

the significance of endosomal defects in familial AD [59, 60]. Late-onset AD risk genes such as BIN1, CD2AP, PICALM, PLD3, SORL1, and TREM2 are associated with the endolysosomal–autophagy pathway, suggesting that targeting the endolysosomal system may modify AD pathology [46, 61]. Enhancing lysosomal function has shown promise in counteracting key AD hallmarks like tau accumulation. Furthermore, alterations in v-ATPase activity, lysosomal pH, and Ca2 + homeostasis have implications in adult-onset neurodegenerative diseases like Parkinson's disease (PD) and AD [62].

In summary, selective modulators of lysosomal function hold great promise for effective treatments of neurodegenerative diseases. Understanding the role of endolysosomal cation channels, such as TRPMLs and TPCs, in neurodegenerative pathways opens avenues for therapeutic interventions, potentially ameliorating aberrant endolysosomal disease processes.

I. Lysosomal Dysfunction: AD is associated with impaired lysosomal function, leading to the accumulation of autophagic vacuoles and dysfunctional lysosomes. TRPML1 channels are instrumental in maintaining lysosomal integrity and function. Dysregulated TRPML1 activity could contribute to the impaired lysosomal degradation observed in AD [63].

II. Amyloid Precursor Protein (APP) Processing: APP is cleaved to generate amyloid-beta (Aβ) peptides, a hallmark of AD pathology. Emerging data suggest that TRPML1 channels may influence APP processing. Dysfunctional TRPML1 channels could potentially alter the balance between Aβ production and clearance [64].

III. Calcium Dysregulation: Intracellular calcium dysregulation is a common feature of AD. TRPML1 channels, by modulating lysosomal calcium release, may indirectly influence cytosolic calcium levels and contribute to calcium homeostasis disruption observed in AD [65].

(B) Review of Experimental Data Linking TRPML1 Channels to AD-Related Neuronal Degeneration.

Several lines of experimental evidence support the association between TRPML1 channels and AD-related neuronal degeneration:

I. Altered Lysosomal Function: Studies in AD models have shown altered lysosomal morphology and impaired lysosomal degradation. Genetic or pharmacological manipulation of TRPML1 channels in these models has been demonstrated to impact lysosomal function, indicating a potential link between TRPML1 channels and AD-related neuronal degeneration [66].

II. Aβ Accumulation: Dysfunctional TRPML1 channels may affect the clearance of Aβ peptides from neurons. Experimental data have suggested that restoring TRPML1 activity can reduce Aβ accumulation in AD models, emphasizing the role of these channels in Aβ metabolism [67].

iii. Neuronal Survival: Neuronal degeneration is a hallmark of AD. Studies utilizing TRPML1-deficient neurons have shown increased susceptibility to oxidative stress and neurotoxic insults, suggesting that the absence or impairment of TRPML1 channels may contribute to neuronal vulnerability in AD [68].

The intricate involvement of TRPML1 channels in lysosomal function, APP processing, and calcium regulation underscores their potential significance in AD pathogenesis. Experimental data linking TRPML1 channels to altered lysosomal function, Aβ accumulation, and neuronal survival provide compelling evidence for their role in AD-related neuronal degeneration. Further research is warranted to elucidate the precise mechanisms by which TRPML1 channels contribute to AD and explore their therapeutic potential as a target for AD intervention. Understanding the intricate interplay between TRPML1 channels and AD pathology may provide valuable insights into the development of novel therapeutic strategies for this devastating neurodegenerative disease [69].

Therapeutic Potential of Targeting TRPML1 Channels

As a medical scholar with expertise in neurodegenerative diseases and ion channel pharmacology, I would like to discuss the promising therapeutic potential of targeting TRPML1 (transient receptor potential mucolipin 1) channels. TRPML1 channels are a member of the TRP superfamily, and they are predominantly localized to intracellular compartments, including late endosomes and lysosomes. TRPML1 channels play a crucial role in regulating ion homeostasis within these vesicles and are involved in various cellular processes, making them attractive targets for therapeutic interventions [70]. In this discussion, I will explore potential therapeutic strategies to modulate TRPML1 channel activity and their implications for the treatment of neurodegenerative diseases [70].

(A) Potential Therapeutic Interventions Modulating TRPML1 Channel Activity.

Pharmacological Modulators: Developing small molecule modulators that can activate or inhibit TRPML1 channels is a promising avenue. Activation of TRPML1 can enhance lysosomal function and promote the clearance of protein aggregates, which is relevant in neurodegenerative diseases characterized by protein accumulation, such as AD and PD. Conversely, inhibiting TRPML1 may be beneficial in conditions where excessive lysosomal calcium release contributes to cell death, such as in lysosomal storage disorders [16].

Gene Therapy: Gene therapy approaches that aim to upregulate or downregulate TRPML1 expression could be considered [71]. Overexpression of TRPML1 might promote lysosomal function and autophagy, potentially reducing the burden of abnormal protein aggregates in neurodegenerative diseases. Conversely, downregulating TRPML1 could be explored when excessive lysosomal calcium release is detrimental [72].

Targeted Nanoparticles: Utilizing nanoparticles designed to deliver specific modulators or genetic therapies to lysosomes could be a precise way to manipulate TRPML1 channels. These nanoparticles could be engineered to release their cargo in response to disease-specific cues, allowing for localized and controlled interventions.

Monoclonal Antibodies: Monoclonal antibodies targeting TRPML1 could be developed to selectively modulate channel activity. Antibodies might be designed to enhance or inhibit TRPML1 function, depending on the therapeutic goals [73].

(B) Implications for Neurodegenerative Disease Treatment.

Targeting TRPML1 channels holds significant implications for the treatment of neurodegenerative diseases, including AD, PD, Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) [74].

AD: AD is characterized by the accumulation of beta-amyloid plaques and tau tangles. Modulating TRPML1 activity to enhance lysosomal function and autophagy could promote the clearance of these abnormal protein aggregates. This approach may slow down disease progression and preserve cognitive function [75].

PD: PD involves the degeneration of dopaminergic neurons. Targeting TRPML1 channels may help alleviate lysosomal dysfunction and improve the clearance of damaged proteins and dysfunctional mitochondria, which are hallmarks of PD pathology [76].

Huntington's Disease (HD): In HD, the mutant huntingtin protein leads to neuronal damage. Modulating TRPML1 channels could facilitate the removal of mutant huntingtin protein aggregates, potentially delaying disease onset and progression.

Amyotrophic Lateral Sclerosis (ALS): ALS is characterized by motor neuron degeneration. Targeting TRPML1 channels may help maintain neuronal health by regulating lysosomal function and reducing the burden of protein aggregates, offering a potential therapeutic strategy for ALS patients [77].

The Human Gene Mutation Database (HGMD) Professional and ClinVar databases were screened for TRPML1 mutations (Fig. 2).

Each symbol represents an individual (described in the literature or listed in databases), matched to its location of origin on the map. Two identical shapes on each side of the symbols represent a homozygous patient, different shapes

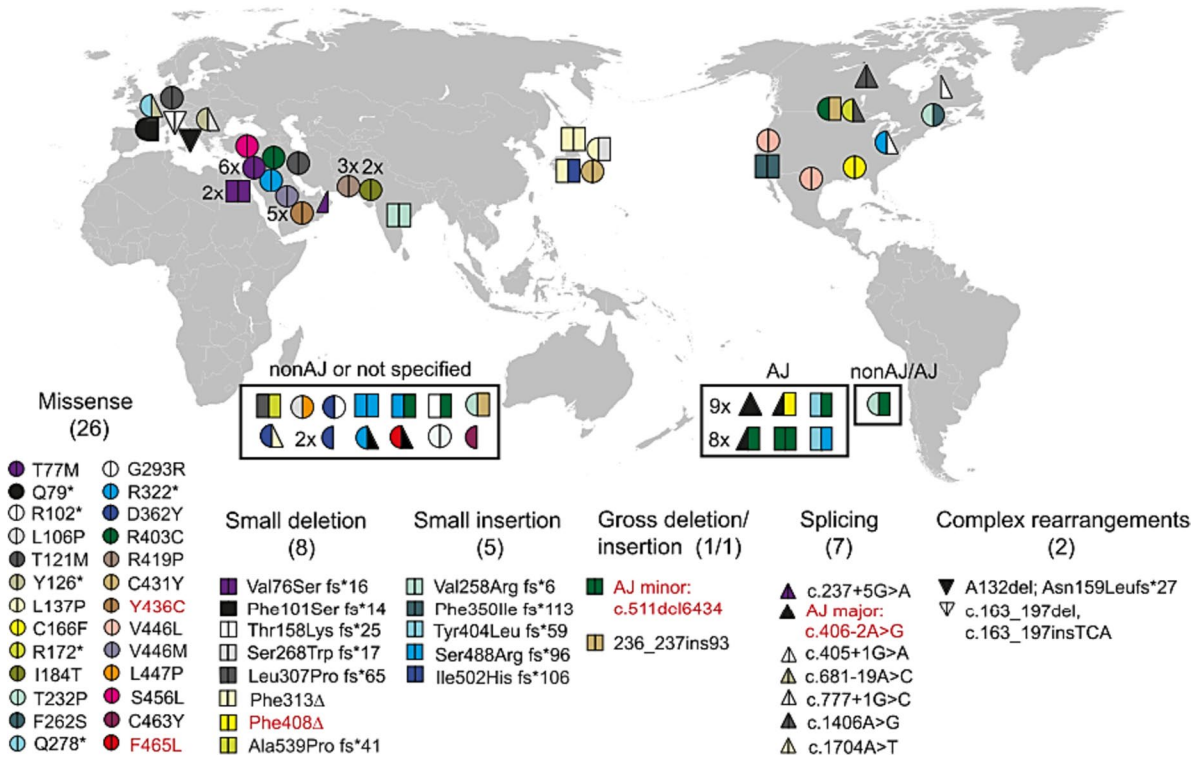

Fig. 2 Overview of the currently known mucolipidosis type IV (MLIV) causing TRPML1 (MCOLN1) mutations in humans

on each side represent heterozygous individuals. Symbols with a shape only on one side represent patients which were diagnosed with MLIV while no information about the other allele is available. Ashkenazi Jewish (AJ) cases were collected separately and individuals without information regarding origin were classified as Non-Jewish (NJ)/not specified. The two Ashkenazi founder mutations are labeled as AJ minor and AJ major in red. Point mutations confirmed not to be mislocalized (i.e., showing lysosomal localization) are likewise shown in red; fs, frame shift.

Conclusion

In summary, our comprehensive review has shed light on the pivotal role of TRPML1 channels in the context of neuronal degeneration, with a specific focus on their involvement in AD. This review has revealed several key findings and highlighted the critical significance of continued research in this field.

(a) Involvement of TRPML1 Channels in Neuronal Degeneration: Our analysis has elucidated the intricate connections between TRPML1 channels and AD-related neuronal degeneration. TRPML1 channels, primarily situated in intracellular compartments, play multifaceted roles encompassing signal transduction, membrane trafficking, and ion homeostasis, particularly within late endosomes and lysosomes. Disruptions in the function of TRPML1 channels have been linked to disturbances in calcium ion homeostasis, a hallmark feature of neurodegenerative diseases such as AD. Furthermore, these channels are instrumental in the trafficking of APP and the generation of amyloid-beta (Aβ) peptides, which are central players in the pathogenesis of AD. Their involvement in lysosomal function and autophagy further underscores their significance in maintaining neuronal health.

(b) Importance of Continued Research: It is imperative to underscore the vital importance of ongoing research endeavors aimed at exploring TRPML1 channels as potential therapeutic targets in neurodegenerative diseases, particularly AD. The intricate interplay between TRPML1 channels, lysosomal function, calcium homeostasis, and protein trafficking presents a promising avenue for the development of novel therapeutic interventions. Targeting TRPML1 channels holds the potential to modulate lysosomal function, enhance autophagy, and mitigate the accumulation of toxic protein aggregates, all of which are central pathological features of AD. Furthermore, considering the broader implications of TRPML1 channels in neuronal health and their potential involvement in other neurodegenerative diseases, further investigation is warranted.

In summary, the elucidation of the specific contributions of TRPML1 channels to neuronal degeneration, particularly in the context of AD, represents a crucial step in advancing our understanding of the mechanisms underlying neurodegenerative diseases. The journey toward innovative treatments for these devastating neurological conditions hinges upon continued and comprehensive research into the therapeutic potential of targeting TRPML1 channels. Such endeavors hold the promise of improving the quality of life for individuals affected by these formidable challenges.

Author Contribution JQG, XSC, HHL, and HL designed the search and wrote the manuscript, and assisted in the draft, collection of data, and revised the manuscript. All authors read and approved the final manuscript.

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Declarations

Ethics Approval and Consent to Participate Not applicable.

Consent for Publication Not applicable.

Competing Interests The authors declare no competing interests.

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