Transmembrane proteins across cellular membranes: Emerging roles in non-cancerous diseases (Review)

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Abstract. Transmembrane proteins (TMEMs) are encoded by genes sharing the 'TMEM' root symbol, historically assigned to genes predicted to encode membrane-spanning proteins of unknown function. Although TMEMs have been studied extensively in cancer, their roles in non-cancerous diseases have received comparatively less attention. The present review summarizes the experimentally supported subcellular localizations of TMEMs and organizes their associations with non-cancerous diseases according to shared biological mechanisms, including ion channel and phospholipid scrambling activity, store-operated Ca^{2+} entry, lysosomal and autophagic function, mitochondrial homeostasis, endoplasmic reticulum function and membrane trafficking, immune sensing, mechanotransduction, cytoskeletal regulation and signal transduction. The type and strength of evidence supporting each association are indicated, distinguishing human causal variants from genetic susceptibility, experimental and expression data. This framework reveals that apparently unrelated diseases can arise from disruption of the same cellular process, that a single TMEM, such as TMEM16A, can act through different mechanisms in different tissues, and that homologous paralogs may diverge in function. Strong human causal evidence remains restricted to a few TMEMs, such as TMEM16F, ORAI1, TMEM240 and TMEM126B. Translational feasibility, current knowledge gaps and future directions for developing TMEMs as therapeutic targets and biomarkers are also discussed.

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Abbreviations: Akt, protein kinase B; ASD, autism spectrum disorder; ATF5, activating transcription factor 5; CaCCs, Ca^{2+}-activated Cl^- channels; ECM, extracellular matrix; EDMD2, Emery-Dreifuss muscular dystrophy type 2; ER, endoplasmic reticulum; FTLD, frontotemporal lobar degeneration; GWA, genome-wide association; IL-1β, interleukin-1β; MECP2, methyl-CpG-binding protein 2; Mrgpr, Mas-related G protein receptor; NCL, neuronal ceroid lipofuscinosis; PAR2, protease-activated receptor 2; PLSCR, Ca^{2+}-dependent phospholipid scramblase; ROS, reactive oxygen species; SCA21, spinocerebellar ataxia type 21; SDHA, succinate dehydrogenase flavoprotein subunit A; SOCE, store-operated Ca^{2+} entry; TDP, transactive response DNA-binding protein; TGF-β1, transforming growth factor-β1; TMEMs, transmembrane proteins; TRPA1, transient receptor potential ankyrin 1; VAMP3, vesicle-associated membrane protein 3

Key words: molecular mechanisms, non-cancerous diseases, subcellular localization, transmembrane proteins

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1. Introduction

Transmembrane proteins (TMEMs) are a group of genes that share the 'TMEM' root symbol, a nomenclature historically applied to genes, predicted on the basis of hydrophobicity and

topology analysis, to encode proteins that span the biological membranes of various cellular organelles, at a time when the specific function of each gene remained unestablished. Transmembrane molecules are also present in species other than humans, such as spiders and plants, indicating their evolutionary conservation and biological importance (1,2). The TMEM family mediates autophagy balance, apoptosis, inflammation, fibrosis and other physiological processes (3). Dysregulation of TMEMs has been demonstrated to be associated with various diseases, including cancer and non-cancerous diseases. Several articles have reviewed the association between TMEMs and cancer (4,5). The present review focuses on the roles of TMEMs in non-cancerous diseases, organized according to the cellular mechanisms through which TMEMs act. Several TMEMs are involved in multiple diseases, highlighting their biological and clinical importance. TMEMs regulate cellular functions through diverse molecular mechanisms and are distributed across various subcellular localizations. These topics are summarized and discussed in the present review.

2. Distribution of TMEMs

TMEMs are a protein family that traverse biological membranes. The distribution of TMEMs is diverse and reflects their function across various organelles, including the plasma membrane, endoplasmic reticulum (ER), Golgi apparatus, mitochondria, lysosomes and nuclear envelope, for regulating the transport of molecules and ions, as well as maintaining the structure and function of these organelles (6-8). Organelle localizations reported for each TMEM in the present review were curated from primary experimental studies rather than assigned computationally. For each protein, localization was accepted only when it was supported by direct experimental evidence in the cited source, including immunofluorescence co-staining with organelle-specific markers, subcellular fractionation followed by immunoblotting, live-cell imaging of epitope- or fluorescent-protein-tagged constructs or mass-spectrometry-based proteomic profiling of isolated organelle fractions. Where a TMEM was reported to localize to >1 compartment across independent studies, all reported localizations are listed under the corresponding organelle sections, with the supporting reference indicated in each case. The experimental methods underlying the localization assignments of representative TMEMs are summarized in Table SI.

The distribution of TMEMs includes the plasma membrane, which plays multiple roles for cells, such as protecting the cell from the extracellular environment, as a selective barrier, regulating cellular events and homeostasis. Defects in these mechanisms are related to several diseases (9). Several TMEMs are located in the plasma membrane, such as TMEM16F (10), TMEM16A (11), TMEM88 (12), TMEM116, TMEM30B, TMEM213, TMEM207, TMEM72, TMEM20 (13-15), TMEM92 (16), TMEM127 (17) and TMEM229A (18).

The ER regulates several cellular pathways, including protein synthesis, quality control, lipid synthesis and homeostasis. Dysregulation of ER functions induce ER stress and contribute to the development of diseases (19). The TMEMs located in the ER include TMEM63A (20), TMEM72 (15,21), TMEM39 (22), TMEM38, TMEM178, TMEM173, TMEM203, TMEM110, TMEM20, TMEM66 (14), TMEM116, TMEM30B, TMEM213, TMEM207 (21) and TMEM100 (23).

The Golgi apparatus is important in several cellular homeostatic functions, such as trafficking, sorting and modifications of proteins or lipids. Defects of Golgi apparatus induce mislocalization and accumulation of undegraded proteins resulting in the pathogenesis of certain diseases (24). TMEM45A, TMEM176A/B, TMEM59 and TMEM173 are associated with the Golgi apparatus (25-29).

Mitochondria are important organelles which generate ATP through oxidative phosphorylation to support energy for all biochemical reactions of the cell. Dysfunctional mitochondria result in several clinically and genetically heterogeneous disorders (30). Within mitochondrial membranes, TMEM135 (31), TMEM126B (32), TMEM70, TMEM242 (33), TMEM14A (34), TMEM65 (35,36), TMEM38, TMEM178, TMEM173, TMEM203, TMEM110, TMEM20 and TMEM66 (14) are observed.

Lysosomes break down cell components to serve as a waste-disposal system for cells. Lysosomal dysfunction is correlated with numerous diseases (37), with TMEM106B, TMEM63A and TMEM127 situated in lysosomes (17,20,38).

The obvious function of the nucleus is genome compartmentalization. The nuclear envelope is also involved in numerous cellular functions, such as signaling, transport, gene regulation, DNA repair and cell division (39). TMEM48 and TMEM201 (Samp1) are situated in the nuclear envelope (40,41).

A summary of TMEM localization in cells is provided in Fig. 1, showcasing the diverse biological functions across different cellular compartments.

3. TMEM-regulated non-cancerous diseases grouped by shared biological mechanisms

A total of >300 TMEMs have been identified to date (14). While some of these TMEMs are phylogenetically related, their structures and biological functions remain incompletely understood (8). These proteins exhibit diverse functions, including transport and channel activity. Store-operated Ca^{2+} entry (SOCE) is a major pathway for calcium signaling, with ORAI serving as one of the core mediators of the SOCE pathway. ORAI proteins are categorized as members of the TMEM family (14). More broadly, TMEMs participate in the regulation of Ca^{2+} (14), in cancer progression (6,8,42,43), the mediation of autoimmune diseases (44), the regulation of mitochondrial dynamics (31) and the activation of mast cells (45). Dysfunction in these processes contributes to disease pathogenesis. Their multifaceted functions highlight their importance in maintaining cellular homeostasis and proper organismal development for the maintenance of health.

To highlight the common biological principles that link TMEMs to disease, the non-cancerous diseases discussed in the present review are organized according to the cellular mechanism through which each TMEM is known or proposed to act, rather than by organ system (Table SII). In total, 11 mechanistic categories are considered: i) Ion channels, transporters and phospholipid scrambling; ii) calcium signaling through SOCE; iii) lysosomal biology and autophagy; iv) mitochondrial homeostasis; v) ER function and membrane

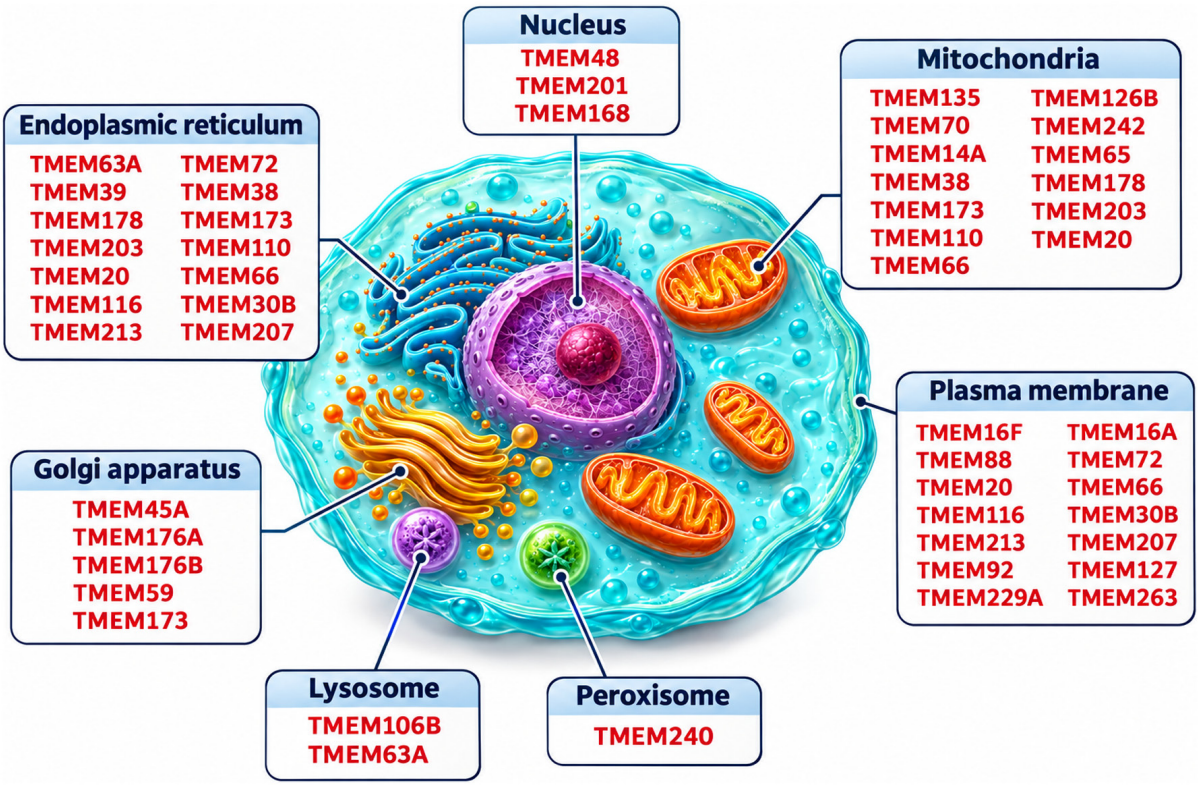


Figure 1. Subcellular distribution of TMEMs. TMEMs discussed in the present review are listed against the organelles for which they have been experimentally localized, including the plasma membrane, endoplasmic reticulum, Golgi apparatus, mitochondria, lysosomes, peroxisomes and nucleus. TMEMs reported in >1 compartment are listed under each corresponding organelle. TMEMs, transmembrane proteins.

trafficking; vi) immune sensing; vii) mechanotransduction and sensory transduction; viii) nuclear envelope organization; ix) cytoskeletal regulation and neuronal morphogenesis; x) signal transduction and RNA regulation; and xi) disease associations for which a mechanism has not yet been defined. Within each category, individual diseases are presented as examples of how disruption of a shared cellular process can give rise to distinct pathological phenotypes. TMEMs that participate in more than one process, most notably TMEM16A, are discussed in the context of each relevant mechanism, with cross-references between subsections. The strength of the evidence supporting each disease association is summarized in Table SII, together with the type of study from which each finding was derived [human genetic, cohort or population-based studies; single-patient case reports; studies of human tissue or patient-derived cells; *in vitro* experiments in cell lines or primary cells; animal models; invertebrate models (*C. elegans* or *Drosophila*); or review articles], and a disease-oriented overview of the same TMEMs is provided in Fig. 2 for readers seeking information on a specific condition. The type of study is also indicated for each finding described below, since results obtained in cell lines, animal models or invertebrates do not necessarily translate directly to human disease.

Ion channels, transporters and phospholipid scrambling. Several TMEMs form or regulate channels and transporters that move ions or lipids across membranes, and loss or dysregulation of these activities alters membrane lipid asymmetry (TMEM16F) (10,45), calcium-activated chloride conductance underlying smooth muscle contraction and epithelial secretion (TMEM16A) (11), putative mechanosensitive channel activity (TMEM120A) (46), lysosomal potassium and zinc homeostasis (TMEM175 and TMEM163), in which rare variants have been reported in patients with Parkinson's disease (47,48) or neuronal excitability (TMEM263 and TMEM16A) (11,49,50). The TMEM16 (anoctamin) family is the best-characterized example, comprising both Ca^{2+}-activated Cl^- channels (CaCCs), such as TMEM16A, and Ca^{2+}-dependent phospholipid scramblases (PLSCRs), such as TMEM16F (10,11).

Scott syndrome and bleeding disorders. TMEM16F is supported by strong human genetic and functional evidence as the causal gene for Scott syndrome, a rare bleeding disorder. Expression cloning in mouse lymphocyte cell lines identified TMEM16F as a Ca^{2+}-dependent phospholipid scramblase; TMEM16F directly mediated phosphatidylserine exposure in cells loaded with a Ca^{2+} ionophore, whereas TMEM16F-deficient cells failed to expose phosphatidylserine, and a TMEM16F mutation was identified in cells from a patient with Scott syndrome (51). Pathogenic TMEM16F variants identified in affected individuals are associated with defective Ca^{2+}-dependent phospholipid scrambling and impaired phosphatidylserine exposure in platelets. Platelets from patients with Scott syndrome fail to externalize aminophospholipids (phosphatidylserine and phosphatidylethanolamine) even after stimulation with thrombin and rotenone. This finding directly links TMEM16F deficiency to defective procoagulant membrane remodeling and highlights its potential relevance to the management of bleeding disorders and to transfusion therapy (45,52). TMEM16F-mediated phosphatidylserine

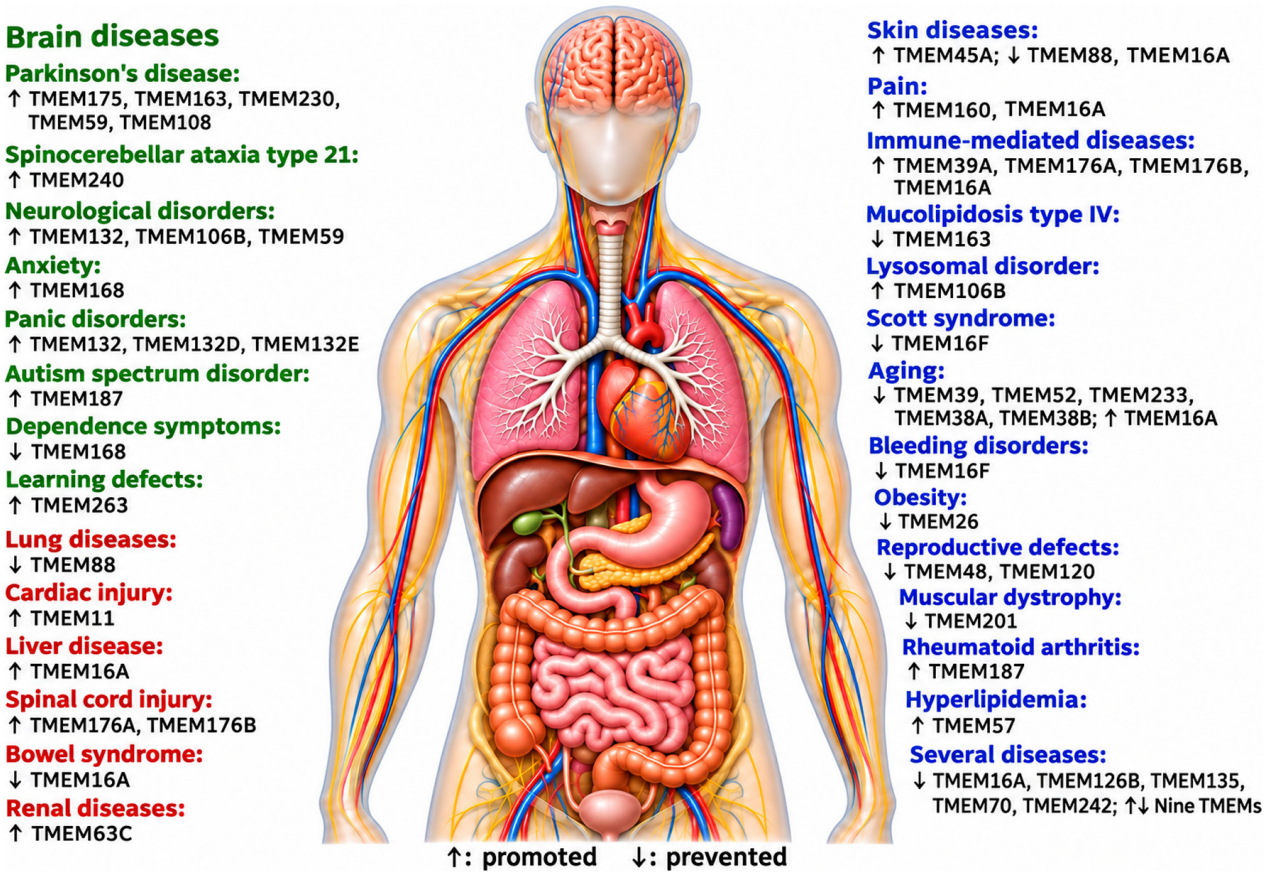


Figure 2. Overview of TMEMs and their associated non-cancerous diseases. The mechanistic categories through which these TMEMs act are summarized in Table SII and Fig. 3. Arrows indicate promoted (↑) or prevented (↓). TMEMs, transmembrane proteins.

exposure has also been described in activated mast cells (*in vitro* studies summarized in a previous review) (45). Mechanistically, TMEM16F acts as a PLSCR in the plasma membrane, and five acidic amino acids within TMEM16F are critical for Ca^{2+} binding and PLSCR activity, indicating that Ca^{2+} binds directly to TMEM16F to induce its activity (10).

Short bowel syndrome. In the gastrointestinal tract, TMEM16A functions as a CaCC in the interstitial cells of Cajal, where Cl^- efflux depolarizes these pacemaker cells to generate the slow waves that drive rhythmic smooth muscle contraction, and TMEM16A knockout mice show diminished rhythmic gastrointestinal contraction (53). Consistent with a role for this conductance in intestinal motility, TMEM16A has emerged as a potential regulator of intestinal motility in microarray screening. In rats, both the jejunum and ileum express TMEM16A mRNA and protein, and both levels are reduced in rats with short bowel syndrome showing dysmotility, including enlarged intestinal loops and delayed emptying (54). These findings suggest that reduced TMEM16A-mediated Cl^- conductance contributes to intestinal dysmotility after bowel resection, although the evidence is correlative and causality has not been established.

Sweat production. TMEM16A expression was detected in the skin and apical ectodermal ridge at embryonic day E10.5 in mice using whole-mount RNA *in situ* hybridization (55), in the human sweat gland cell line NCL-SG3 and in isolated human eccrine sweat gland biopsy samples (56). In human sweat gland cells, Ca^{2+} influx through SOCE is required to activate TMEM16A and trigger agonist-induced Cl^- secretion. Accordingly, patients with loss-of-function mutations in ORAI1 or stromal interaction molecule (STIM)1 (skin biopsies from three patients) (57) and mice with ectodermal tissue-specific deletion of Orai1 or Stim1/Stim2 fail to sweat despite normal sweat gland development (57). Notably, expression of TMEM16A and the water channel aquaporin 5 (AQP5) was preserved in the absence of SOCE, indicating that the impaired chloride secretion lies in TMEM16A activation rather than in TMEM16A expression. Thus, TMEM16A functions as the Cl^- channel downstream of SOCE in sweat production in humans and mice (57).

Smooth muscle contraction and other TMEM16A-related disorders. TMEM16A is present in numerous cell types and plays essential roles in smooth muscle contraction, sensory signal transduction and epithelial secretion (11,53,58). CaCCs regulate the excitability of several classes of sensory neuron, including olfactory sensory neurons, somatosensory neurons and photoreceptors (53). TMEM16A has been observed in airway smooth muscle cells, the smooth muscle of the reproductive tracts, including the oviduct and ductus epididymis, the gastrointestinal tract and the interstitial cells of Cajal (the pacemaker cells whose depolarization governs rhythmic smooth muscle contraction) rather than in gastrointestinal smooth muscle cells themselves (53). These observations underscore the physiological importance of TMEM16A as an essential component of CaCCs (11). TMEM16A is also present in smooth muscle myocytes of the carotid artery, thoracic aorta

and portal vein of mice, and TMEM16A-GFP transfected into 293 cells produces currents closely resembling native CaCCs, with steep outward rectification, slow kinetics and sensitivity to niflumic acid, supporting a role in murine vascular smooth muscle cells (58). Dysregulation of TMEM16A has been linked to nociception, hypertension and gastrointestinal dysfunction, as well as to several cancer types that are outside the scope of the present review, as summarized in a previous review article (59).

Mucolipidosis type IV. TMEM163 functions as a zinc transporter. Decreased levels of TMEM163 RNA and protein were observed in cultured fibroblasts from patients with mucolipidosis type IV, a condition associated with elevated tissue zinc levels, and knockdown of TMEM163 increased intracellular zinc levels in 293 cells. These findings indicate an important role of TMEM163 in regulating cellular zinc balance (60,61). TMEM163 variants have also been reported in Parkinson's disease (47).

Learning defects. Mass spectrometric analysis revealed that TMEM263 co-purifies with both anti-Slick and anti-Slack antibodies in the mouse brain. Slick and Slack are sodium-activated potassium channels found throughout the mammalian central nervous system that contribute to hyperpolarization, depolarization and stabilization of the resting potential, and human mutations in Slack are associated with learning and developmental defects (49). It was therefore proposed that TMEM263 directly partners with Slick and Slack in the mouse brain (50), although direct evidence linking TMEM263 to human learning disorders is lacking.

Aging-related skeletal muscle disorders. Analysis of The Genotype-Tissue Expression RNA-sequencing database (bioinformatics study) revealed that TMEM52, TMEM233, TMEM38A/TRIC-A and TMEM38B/TRIC-B are preferentially transcribed in skeletal muscle (62). Skeletal muscle loss is a critical contributor to aging and various diseases, including drug-induced myopathy, myotonia, cachexia, sarcopenia and muscular dystrophy. TMEM233 is preferentially expressed in skeletal muscle, myoblasts and myotubes, while the neighboring genes TMEM52 and CALML6 share a 6-kb skeletal-muscle super-enhancer that appears to upregulate TMEM52 preferentially, as reflected by their skeletal-muscle expression levels (82 vs. ~7 TPM) and by the strong promoter chromatin present at TMEM52 but not CALML6 (62). TMEM38A/TRIC-A and TMEM38B/TRIC-B encode trimeric intracellular cation channels of the sarcoplasmic and endoplasmic reticulum that conduct K^+ as counter-ions, supporting Ca^{2+} release through ryanodine and IP_3 receptors. TRIC-A is enriched in excitable tissues including skeletal and cardiac muscle, whereas loss-of-function mutations in TMEM38B cause autosomal recessive osteogenesis imperfecta type XIV through dysregulated endoplasmic reticulum Ca^{2+} handling in osteoblasts. Consistent with this, TMEM38A-null mice show a subtle skeletal-muscle phenotype, whereas TMEM38B-null mice die of respiratory failure (62). The preferential skeletal-muscle expression of these genes suggests roles in muscle differentiation and maintenance, with potential implications for exercise, aging and muscle-related disease, although the strength of the supporting evidence differs among them (62) (Table SII). TMEM38 proteins have also been implicated in the regulation of SOCE (14) (discussed below).

Calcium signaling through SOCE. SOCE is a major route of Ca^{2+} entry in non-excitable cells. Depletion of ER Ca^{2+} stores is sensed by STIM proteins, which then gate ORAI channels in the plasma membrane, and the resulting Ca^{2+} influx refills the ER and drives downstream processes, including gene expression, secretion and proliferation (14). ORAI1, ORAI2 and ORAI3 were originally designated TMEM142A, TMEM142B and TMEM142C, respectively, and additional TMEMs, including TMEM66/SARAF, TMEM38/TRIC, TMEM178, TMEM203, TMEM173/STING, TMEM110/STIMATE, TMEM97 and TMEM20/POST, modulate SOCE (14). Among these, ORAI1 and SARAF have the most direct evidence linking altered SOCE to non-cancerous disease in humans or animal models and are discussed below; the contributions of the remaining SOCE-related TMEMs to non-cancerous disease remain to be defined (14).

Immunodeficiency. ORAI1 (TMEM142A) forms the pore of the Ca^{2+} release-activated Ca^{2+} (CRAC) channel, which opens when STIM1 senses ER Ca^{2+} depletion. Patients with a hereditary form of severe combined immunodeficiency were homozygous for a single missense mutation in ORAI1 (R91W) (63), which abolished store-operated Ca^{2+} influx and CRAC currents in their T cells, and re-expression of wild-type ORAI1 in patient T cells restored these responses (63,64). Consistent with these findings, Orai1-deficient mice showed markedly reduced SOCE, CRAC currents and cytokine production in T cells, as well as impaired Ca^{2+} influx and proliferation of B cells (65), and mast cells derived from Orai1-deficient mice showed defective degranulation, leukotriene C4 release and TNF-α production (66). Loss of ORAI1-mediated SOCE also abolishes thermoregulatory sweating through failure to activate TMEM16A in sweat glands (57), illustrating how two TMEM-dependent mechanisms, Ca^{2+} entry and Ca^{2+}-activated Cl^- conductance, operate in series to support a single physiological function.

Acute pancreatitis. SARAF (TMEM66) is an ER membrane protein that associates with STIM1 to promote slow Ca^{2+}-dependent inactivation of SOCE, thereby limiting refilling of intracellular Ca^{2+} stores and protecting cells from Ca^{2+} overload, as demonstrated by overexpression, RNA interference-mediated knockdown and electrophysiological experiments in 293 and Jurkat T cells (67). Excessive Ca^{2+} influx into pancreatic acinar cells is a central event in acute pancreatitis. Saraf knockout mice developed more severe caerulein- or L-arginine-induced pancreatitis, with increased Ca^{2+} influx in acinar cells, whereas overexpression of SARAF in acinar cells reduced Ca^{2+} influx, inflammation and disease severity (68). In addition, SARAF mRNA levels were reduced in pancreatic tissues from patients with pancreatitis (68). These findings suggest that SARAF protects against pancreatitis by restraining SOCE, although human evidence is currently limited to expression data.

Lysosomal biology and autophagy. Lysosomes degrade cellular material delivered by endocytosis and autophagy, and lysosomal dysfunction is a common feature of neurodegenerative and lysosomal storage disorders. Several TMEMs localize to the endo-lysosomal compartment, where they regulate lysosomal function, positioning or ion homeostasis.

Lysosomal disorders. TMEM106B, a lysosomal protein, has been identified as a risk factor for frontotemporal lobar

degeneration (FTLD) characterized by transactive response DNA-binding protein 43 kDa (TDP-43) accumulation, and upregulation of TMEM106B leads to lysosomal dysfunction. Neuronal ceroid lipofuscinosis (NCL) is a lysosomal storage disorder to which progranulin (GRN) deficiency may contribute. Both GRN and TMEM106B exhibit elevated levels in mouse models of NCL, and increased levels of TMEM106B were observed in the brains of patients with FTLD-TDP/GRN. Consequently, TMEM106B was proposed as an important factor in FTLD-TDP/GRN and NCL (69).

Neurodegenerative disorders. Antibodies that recognize the C-terminal fragment of TMEM106B, termed TMEM106B C-terminal immunoreactive (TMEM-ir), can detect TMEM106B in human post-mortem brain tissue using immunohistochemistry. TMEM-ir accumulates in Alzheimer's disease, tauopathies, synucleinopathies, FTLD-TDP and aging brain tissue alike, and the presence of TMEM-ir aggregates appears to correlate with patient age in most cases. These results suggest that the accumulation of TMEM106B C-terminal fragments is an age-related phenomenon with potential utility as a biomarker for neurodegenerative diseases (38,70), although these data do not by themselves establish causality.

Spinocerebellar ataxia type 21 (SCA21). Missense and nonsense mutations in TMEM240 have been identified in patients with SCA21 (71,72). Models of the SCA21 mutants T80M and R116C have been established using HeLa cells, primary cultured cerebellar Purkinje cells and mice. Although the SCA21 mutants did not appear to disrupt clathrin-mediated endocytosis, they impaired the degradation of autophagic lysosomal proteins in HeLa cells. In cultured cerebellar Purkinje cells from rat embryos, the SCA21 mutants hindered dendritic development through lysosomal dysfunction. In addition, mice expressing SCA21 with mutant TMEM240 exhibited activated microglia and astrocytes and impaired motor coordination, and chaperone-mediated autophagy was compromised in their cerebella. These results suggest that mutant TMEM240 drives SCA21 pathogenesis through lysosomal dysfunction and early glial activation (73).

Lysosome positioning and autoimmune diseases. In *Caenorhabditis elegans*, mutations in the TMEM39A ortholog result in lysosome tubularization, reduced lysosome mobility and accumulation of the lysosome-associated membrane protein LMP-1. Similarly, knockout of TMEM39A in 293T cells results in the redistribution of lysosomes from the perinuclear region to the cell periphery. TMEM39A binds the dynein intermediate chain DYNC1I2 to regulate lysosome distribution through mTOR signaling. These findings suggest that TMEM39A maintains proper lysosome distribution, which may be relevant to the lysosomal abnormalities observed in human autoimmune diseases (74).

Parkinson's disease. Through whole-exome sequencing in a patient cohort study, a total of 45 rare variants spanning six TMEMs were identified among 743 patients with unrelated early-onset Parkinson's disease. Notably, variants affecting TMEM175 at position 176 (K>E) and TMEM163 at position 33 (P>R) were linked to Parkinson's disease at the allele level, and three missense variants of TMEM163 were observed exclusively in patients. Hence, these variants of TMEM175 and TMEM163 may serve as risk factors for Parkinson's disease (47). TMEM175 functions as a K^+ channel in endosomes and lysosomes and regulates lysosomal function (75), and TMEM163 regulates cellular zinc balance (60,61), suggesting that these variants may act through lysosomal and ion homeostasis; however, causality and disease mechanisms remain insufficiently established.

Mitochondrial homeostasis. Mitochondrial respiratory complexes, ATP synthase and the mitochondrial fission-fusion machinery determine cellular energy production, reactive oxygen species (ROS) generation and metabolic adaptation. Several TMEMs act as assembly factors or regulators of these processes, and their dysfunction contributes to metabolic and mitochondrial disorders.

Mitochondrial complex I deficiency and metabolic dysfunction. TMEM126B encodes a mitochondrial complex I assembly factor. Deficiencies in mitochondrial complex I result in a range of clinical manifestations, including respiratory chain defects, neuropathy, hypotonia, retinopathy, seizures, developmental delay, cardiomyopathy and optic atrophy (76). Targeted exome sequencing followed by whole-exome sequencing in three adults with complex I-deficient phenotypes implicated TMEM126B defects in mitochondrial complex I deficiency (a case series of affected patients) (76). Mitochondrial complex I is also an important source of ROS, which are required for inflammasome activation and cytokine production in physiological and pathological contexts. Knockdown of TMEM126B in human macrophage-like cells *in vitro* reduced mitochondrial ROS production and the oxidation of succinate dehydrogenase flavoprotein subunit A (SDHA); oxidized SDHA maintains interleukin-1β (IL-1β) expression and stabilizes hypoxia-inducible factor-1α, underscoring the role of TMEM126B in ROS generation (32).

TMEM135 acts as a regulator of mitochondrial dynamics and has been implicated in obesity and non-alcoholic fatty liver disease, as well as in breast cancer prognosis (31). Through its colocalization with the mitochondrial fission mediator dynamin-related protein 1, TMEM135 influences mitochondrial fission (31). Disruption of TMEM135 alters mitochondrial size and number, and its upregulation increases membrane potential and mitochondrial fragmentation. Conversely, loss of TMEM135 reduces oxygen consumption and mitochondrial membrane potential, suggesting its involvement in mitochondrial fusion/fission dynamics and related functions such as lipid metabolism and peroxisomal activity, as summarized in a review of cellular and animal studies (31). In mice, an N-ethyl-N-nitrosourea-induced *Tmem135* mutation caused enlarged mitochondria through an imbalance between mitochondrial fission and fusion, together with accelerated age-dependent retinal pathologies, including early photoreceptor loss and features resembling age-related macular degeneration, whereas *Tmem135* overexpression caused excessive mitochondrial fragmentation (77). Transgenic mice overexpressing *Tmem135* also showed fragmented mitochondria in the heart, accompanied by cardiac hypertrophy and fibrosis (78).

TMEM70 and TMEM242 interact with subunit c of ATP synthase and with assembly factors for mitochondrial complex I, and deletion of TMEM70 and TMEM242 in human cell lines impedes the assembly of ATP synthase and mitochondrial complex I. Specifically, the removal of TMEM242

decreases the incorporation of subunits ATP6, ATP8, j and k into ATP synthase, highlighting the role of TMEM70 and TMEM242 in the assembly of these complexes (33).

ER function and membrane trafficking. The ER and the secretory pathway fold, modify and deliver proteins and lipids to their destinations. TMEMs located in the ER, the Golgi apparatus and vesicular membranes regulate cargo export, ER homeostasis and the fusion of transport vesicles with their target membranes.

Aging and collagen secretion. TMEM39 localizes within the ER to regulate the production and trafficking of procollagen, the precursor of collagen. Dysregulation of collagen synthesis has been observed in aging and tissue fibrosis in different organs (22). Knockdown of TMEM39 via RNA interference in *C. elegans* and *Drosophila* leads to defects in collagen secretion and induces a high ER stress response (22). In human cells, TMEM39 modulates collagen secretion and vesicular trafficking by binding to the cytosolic domain of Sec23A, a coat protein complex II vesicle coat protein. These findings suggest that the functions of TMEM39 in collagen processing and ER homeostasis are evolutionarily conserved (22).

Epidermal keratinization. TMEM45A, also termed DERP7, DNAPTP4 or FLJ10134, is highly expressed in epidermal keratinocytes; its expression is increased in human primary cultured keratinocytes and within the granular layer of the epidermis of normal human abdominal skin (25). TMEM45A is primarily localized to the Golgi apparatus, particularly the trans-Golgi network, and accumulates in both native and reconstructed epidermis in association with the keratinocyte differentiation markers KRT10 and FLG. These findings suggest the involvement of TMEM45A in epidermal keratinization (25).

Non-alcoholic fatty liver disease. TMEM16A (also termed anoctamin 1) is activated in hepatocytes and increased in the liver tissues of mice and patients with non-alcoholic fatty liver disease. Hepatocyte-specific TMEM16A deletion protects mice against hepatic glucose metabolic disorder, whereas hepatocyte-specific TMEM16A transgenic mice show the opposite phenotype. By binding vesicle-associated membrane protein 3 (VAMP3), hepatocyte TMEM16A disrupts the formation of VAMP3/syntaxin 4 and VAMP3/synaptosome-associated protein 23 complexes, impairing glucose transporter 2 translocation to the plasma membrane and glucose uptake. Thus, TMEM16A regulates hepatic glucose metabolism through a vesicle-trafficking mechanism, and hepatic TMEM16A may represent a therapeutic target in non-alcoholic fatty liver disease (79).

Immune sensing. Immune cells detect pathogens, tissue damage and antigens through membrane-associated sensing and antigen-processing pathways. TMEMs expressed in dendritic cells, lymphocytes and sensory neurons influence antigen presentation, susceptibility to autoimmunity and neuroimmune signaling.

Immune-mediated diseases. TMEM176A and TMEM176B are cation channels that accumulate in post-Golgi vesicles associated with the late endo-lysosomal system. Experiments using knockout mice demonstrated that these channels are required in dendritic cells for antigen processing and presentation to $CD4^+$ T cells. TMEM176A/B therefore act in the major histocompatibility complex class II compartment of dendritic cells to regulate antigen presentation and the priming of naive $CD4^+$ T cells and may serve as targets for therapeutic interventions in immune-mediated diseases (26).

Spinal cord injury. Dendritic cells play important roles in promoting recovery and protective autoimmunity after central nervous system injury as well as in inducing neuroprotection and neurogenesis in patients with stroke (80). Microarray screening of peripheral blood mononuclear cells, including dendritic cells, monocytes and macrophages, from patients with chronic spinal cord injury revealed upregulation of TMEM176A and TMEM176B, and high expression of TMEM176A and TMEM176B hindered the maturation and activity of dendritic cells. These findings suggest that altered TMEM176A and TMEM176B expression impedes the maturation and function of protective dendritic cells after spinal cord injury (80), although causality remains unresolved.

Autoimmune diseases. TMEM39A was identified as a susceptibility locus for autoimmune diseases, such as multiple sclerosis and systemic lupus erythematosus, through genome-wide association (GWA) studies. A large-scale multiracial replication study of systemic lupus erythematosus identified TMEM39A, together with IRF8 and IKZF3-ZPBP2, as a susceptibility locus (81). TMEM39A interacts with seven immune-related molecules, including tumor necrosis factor ligand superfamily member 13B, butyrophilin-like protein 8, 5-hydroxytryptamine receptor 3C and the IL-9 receptor, suggesting its involvement in immune processes such as inflammation, dysregulated type 1 interferon responses and autoantibody production, as summarized in a review of human GWA and protein-interaction studies (44).

Neuropathic pain. Male mice lacking TMEM160 showed delayed establishment of tactile hypersensitivity and decreased pain-associated self-grooming behavior after nerve injury. In cultured dorsal root ganglia, male mice with global TMEM160 knockout showed reduced neuroimmune signaling and transient receptor potential ankyrin 1 (TRPA1)-mediated activity, whereas female mice did not exhibit these changes. These findings suggest that TMEM160 acts as a sexually dimorphic neuroimmune factor influencing specific pain behaviors induced by nerve injury in male mice (82).

Mechanotransduction and sensory transduction. Mechanotransduction converts physical forces into biochemical or electrical signals, and related transduction mechanisms allow sensory neurons to detect noxious heat and pruritic stimuli. TMEM120A (TACAN) has been proposed as a mechanically activated molecule, and TMEM16A contributes to the transduction of noxious heat, pain and itch signals in sensory neurons.

Reproductive system defects. TMEM120A (TACAN) is postulated to function as a mechanically activated molecule. TMEM-120, the sole *C. elegans* ortholog of TMEM120A/B, is expressed throughout development, with notable expression in the germline, embryos and spermatheca. Deletion of the full-length TMEM-120 gene (TMEM-120Δ) leads to abnormal germline development, maternal sterility, reduced brood size and impaired spermathecal contraction, indicating that TMEM120 regulates reproductive physiology in

C. elegans (46). The relevance of these findings to human reproductive disease remains to be established.

Pain. TMEM16A senses noxious heat and mediates both acute and chronic pain in somatosensory neurons, as summarized in a review of cellular and animal studies (83). Spared nerve injury activates TMEM16A, MEK/ERK and neurokinin-1 receptor (NK-1) in rat dorsal root ganglia, where TMEM16A colocalizes with phosphorylated ERK and NK-1. Additionally, an ERK inhibitor and a TMEM16A antagonist prevent spared nerve injury-induced allodynia, indicating that ERK and NK-1 act downstream of TMEM16A activation (84). The number of TMEM16A-positive neurons and the TMEM16A expression levels are increased in the L4-6 dorsal root ganglia of rats with chronic constriction injury-induced neuropathic pain, and these effects can be reversed by the TMEM16A antagonist T16Ainh-A01 (85). TMEM16A also physically interacts with transient receptor potential vanilloid 1 (TRPV1) in dorsal root ganglion neurons, where Ca^{2+} influx through TRPV1 activates TMEM16A and the resulting Cl^- efflux further depolarizes the neurons, thereby enhancing action potentials and capsaicin-evoked pain-related behaviors (86). 4-isopropylcyclohexanol relieves pain by inhibiting both TRPV1 and TMEM16A, suggesting its potential as an analgesic agent, as summarized in a review (87). In addition, TMEM16A and protease-activated receptor 2 (PAR2) are co-expressed in the dorsal root ganglion neurons of rats with chronic constriction injury and increased inositol 1,4,5-trisphosphate (IP3) levels, supporting a role for TMEM16A, PAR2 and IP3 in the development of neuropathic pain (88). Several molecules modulate TMEM16A activity, as shown in *in vitro* and animal studies, including liquiritigenin, phosphatidylinositol 4,5-bisphosphate, cholesterol regulators, Eact, N-aroylaminothiazole and capsaicin (89-92). Overall, TMEM16A is a potential therapeutic target for neuropathic pain, as proposed in previous reviews (93,94), although clinical validation is lacking.

Itch. TMEM16A also mediates itch signals of Mas-related G protein-coupled receptor (Mrgpr)-dependent pathways. Genetic deficiency of TMEM16A in mouse dorsal root ganglion neurons reduces scratching behaviors in response to dry skin-induced epidermal hyperplasia and in acute and chronic Mrgpr-dependent itch models, whereas TMEM16A overexpression alters itch responses in the dorsal root ganglion neurons of TMEM16A-deficient mice. Therefore, TMEM16A mediates Mrgpr-dependent itch signaling (95).

Nuclear envelope organization. The nuclear envelope controls nucleocytoplasmic transport through nuclear pore complexes and, in differentiated muscle cells, serves as a microtubule-organizing center. TMEMs within the nuclear envelope contribute to both functions.

Embryonic development defects. TMEM48, also termed NDC1, is situated within the nuclear pore wall. Knockdown of TMEM48 disrupts the assembly of nuclear pore complexes in human HeLa cells. In *C. elegans*, loss of TMEM48 function results in defective nuclear pore complex formation and elevated larval and embryonic mortality. These findings underscore the essential role of TMEM48 in nuclear pore complex assembly (40).

Emery-Dreifuss muscular dystrophy. TMEM201, also termed Samp1, localizes to the nuclear poles in normal human myoblasts and myotubes, where the nuclear envelope serves as a microtubule-organizing center. Farnesylated prelamin A is essential for muscle cell differentiation and regulates the localization of TMEM201 at the nuclear poles of myotubes (96). Emery-Dreifuss muscular dystrophy type 2 (EDMD2) is associated with mutations in the Lamin A gene, and in patients with EDMD2 and reduced levels of prelamin A in muscle cell nuclei, TMEM201 is absent from the nuclear poles of myotubes (*in vitro* studies of patient-derived muscle cells). Consequently, TMEM201 may regulate microtubule nucleation from the myotube nuclear envelope and may contribute to the pathogenesis of EDMD2 (96), possibly as a modifier rather than a primary causal factor.

Cytoskeletal regulation and neuronal morphogenesis. Neuronal morphogenesis depends on dynamic remodeling of the actin cytoskeleton, which is regulated in part by the WAVE regulatory complex. Members of the TMEM132 family are expressed throughout the developing nervous system and have been linked to this process.

Neurological disorders. Members of the TMEM132 family have been implicated in neurological and neuropsychiatric disorders, as discussed below. Through *in situ* hybridization, TMEM132 family RNAs were detected in whole-mount mouse embryos and tissue sections, with expression of different family members in both the central and peripheral nervous systems, including the early nervous system, trigeminal ganglia, caudal forebrain, cerebral cortex, hippocampus and cerebellar granule layer. These findings suggest that TMEM132 family members have overlapping functions during mouse nervous system development (97).

Panic disorders. TMEM132 in *C. elegans*, the ortholog of human TMEM132D, has been implicated in panic disorder, anxiety and major depressive disorder. Loss-of-function mutations in TMEM132 result in abnormal morphology of dopaminergic posterior deirid neurons in *C. elegans*. NAP1, a component of the WAVE regulatory complex that regulates F-actin dynamics, directly interacts with TMEM132D, and overexpression of TMEM132D in mammalian cells reduces components of the WAVE regulatory complex and weakens actin nucleation and cell motility. These findings suggest that TMEM132 family proteins play evolutionarily conserved roles in regulating neuronal morphogenesis through the WAVE regulatory complex (98). In addition, three single-nucleotide polymorphisms in TMEM132E (rs887231, rs887230 and rs4795942) were shown to be associated with panic disorder in a case-control association study, primarily in a Danish cohort (among cohorts from the Faroe Islands, Denmark and Germany), suggesting that TMEM132E may contribute to panic disorder risk (99). This association is based on limited genetic evidence, and a TMEM132E-specific mechanism has not been established.

Signal transduction and RNA regulation. Several TMEMs modulate intracellular signaling pathways, including transforming growth factor-β (TGF-β)/Smad, β-catenin, protein kinase B (Akt), AMP-activated protein kinase (AMPK)/mTOR complex 1 (mTORC1) and inflammatory kinase cascades, or regulate gene expression at the RNA level. Through these

pathways, TMEMs influence cell proliferation, fibrosis, survival, senescence and behavior.

Cardiac injury. TMEM11 overexpression impairs neonatal cardiomyocyte proliferation and regeneration in mice. TMEM11 directly interacts with the methyltransferase METTL1, increasing the N7-methylguanosine methylation of activating transcription factor 5 (ATF5) mRNA. The resulting increase in ATF5 expression upregulates the cyclin-dependent kinase inhibitor INCA1, ultimately inhibiting cardiomyocyte proliferation. Thus, targeting the TMEM11/METTL1/ATF5 axis may enhance heart regeneration after cardiac injury (100).

Pleural fibrosis. TMEM88 regulates fibrogenesis in pleural fibrosis, a condition associated with various lung diseases. TMEM88 expression is decreased in tissues affected by pleural fibrosis, and overexpression of TMEM88 inhibits the TGF-β1-induced proliferation of human pleural mesothelial Met-5A cells. TMEM88 overexpression also prevents TGF-β1-induced accumulation of extracellular matrix (ECM) molecules, such as collagen I and fibronectin, reverses changes in the epithelial-mesenchymal transition marker E-cadherin, reduces the fibrosis markers vimentin and α-smooth muscle actin, and downregulates TGF-β receptors I/II and phosphorylated Smad2 and Smad3. Thus, TMEM88 inhibits pleural fibrosis by suppressing TGF-β1/Smad signaling *in vitro* (101).

Keloids. TMEM88 expression is low in human keloid tissues and in keloid-derived fibroblasts stimulated by TGF-β1. Increased TMEM88 suppresses cyclin D1, c-Myc and β-catenin protein levels, as well as the migration, proliferation and ECM expression of these fibroblasts, suggesting that TMEM88 acts as an inhibitor of TGF-β1-stimulated fibroblast activation and represents a potential therapeutic target for keloids (102).

Renal diseases. Angiotensin II stimulation upregulates TMEM63C expression in cultured human podocytes, which are pivotal in the development of renal diseases. Knockdown of TMEM63C reduces cell viability and Akt signaling and enhances apoptosis in angiotensin II-activated human podocytes, suggesting that TMEM63C serves as a pro-survival factor in human podocytes (103).

Kidney injury in aging. TMEM16A Cl^- channel activity is augmented by chloride channel accessory 1 (CLCA1), a protein increased in the kidneys of aged mice. Overexpression of human CLCA1 in kidney cells *in vitro* induces the senescence-associated secretory phenotype by inhibiting AMPK and stimulating mTORC1 signaling. Inhibition of TMEM16A reverses these signaling changes and prevents senescence-associated secretory phenotype alterations. Therefore, TMEM16A contributes to age-related kidney injury through AMPK/mTORC1 signaling (104).

Inflammation. TMEM16A expression and activity are promoted under inflammatory conditions, such as bacterial and viral infections, and inflammatory mediators, including cytokines, bradykinin, histamine and ATP/UTP, affect TMEM16A expression and/or activity. In turn, TMEM16A activates inflammatory signaling pathways, including ERK signaling, NF-κB signaling and IP3 receptor-mediated Ca^{2+} signaling, thereby contributing to the pathogenesis of several inflammatory diseases, as summarized in a review of cellular and animal studies (105).

Anxiety. Adeno-associated virus-mediated TMEM168 overexpression in the mouse nucleus accumbens (NAc) was shown to raise accumbal TMEM168 mRNA approximately seven-fold and induce anxiety-like behavior, reducing open-arm entries and time in the elevated plus-maze and time in the light compartment of the light/dark box, without affecting locomotion, cognition, social interaction or depression-like behavior; the anxiety was reversed by diazepam. TMEM168 overexpression also lowered basal extracellular GABA and blunted the high-K^+-evoked GABA increase in the NAc, while total NAc GABA content was unchanged (106).

Dependence symptoms. Upon repeated methamphetamine administration, TMEM168 is upregulated in the nucleus accumbens of mice, triggering adaptive changes associated with dependence. Mice with adeno-associated virus-mediated overexpression of TMEM168 in the nucleus accumbens show attenuated methamphetamine-induced hyperlocomotion, conditioned place preference and dopamine elevation, suggesting that TMEM168 inhibits methamphetamine-induced behavioral changes by regulating dopaminergic function in the nucleus accumbens and may be a therapeutic target for methamphetamine dependence (106,107).

Neural development. TMEM59, also termed DCF1, regulates neural stem cell differentiation. Overexpression of TMEM59 maintains neural stem cells in an undifferentiated state in the C17.2 mouse neural stem cell line (108), whereas knockdown of TMEM59 induces the differentiation of neural stem cells into neurons and astrocytes. Furthermore, miR-351 targets TMEM59 in both C17.2 cells and primary neural stem cells to regulate neural stem cell differentiation *in vitro*. These findings underscore the importance of TMEM59 in neural differentiation and migration during development and in related diseases (109).

Disease associations without a defined mechanism. For several TMEMs, disease associations are currently based on genetic association, candidate-variant or expression data, and a mechanism linking the protein to pathology has not been established. These associations are grouped separately to distinguish them from the aforementioned mechanism-supported relationships and should be regarded as hypotheses requiring replication and functional validation (Table SII).

Parkinson's disease. Whole-exome and whole-genome sequencing cohort analyses have identified variants in TMEM230, TMEM59 and TMEM108 in patients with Parkinson's disease. In total, three rare damaging missense variants of TMEM230 (S174F, Y165C and V9L) were found in four patients with sporadic Parkinson's disease but not in controls. Additionally, TMEM59 harbored 11 rare damaging missense variants in sporadic early-onset or familial cases, and TMEM108 harbored 24 rare missense variants in sporadic late-onset cases. These findings suggest genetic associations of these three TMEMs with various forms of Parkinson's disease (48), which require independent replication and functional validation.

Autism spectrum disorder (ASD). A mutation in TMEM187, located in Xq28 (c.708G>T; p.Gln236His), was detected by whole-exome sequencing in a patient diagnosed with high-functioning ASD (a single-patient case report). *In silico* STRING protein-protein interaction analysis indicated that TMEM187, which is expressed in the brain, interacts with four established ASD-related genes: i) Host cell factor 1;

ii) trimethyl lysine dioxygenase; iii) methyl-CpG-binding protein 2 (MECP2); and iv) gephyrin. Among these, MECP2 is notable for its role in determining brain structure and its association with autism. Consequently, TMEM187 has emerged as a potential candidate gene for ASD (110). However, this evidence remains preliminary, as it is based primarily on a single candidate variant and predicted protein interactions, and does not establish TMEM187 as a causal autism gene. TMEM187 is therefore described here as a possible susceptibility candidate requiring replication in larger cohorts and validation through targeted functional studies.

Rheumatoid arthritis. The Xq28 locus containing TMEM187 has been associated with polymorphisms linked to rheumatoid arthritis risk. In a study of 100 Egyptian patients and 100 age- and sex-matched healthy controls, TMEM187 (rs13397) polymorphisms were genotyped using quantitative PCR TaqMan allelic discrimination assays, and the major allele G of TMEM187 rs13397 was suggested to be a genetic risk factor for rheumatoid arthritis in this population (111).

Hyperlipidemia. An earlier GWA study identified an association between the TMEM57 locus and total cholesterol concentrations. Analysis of the rs873308 SNP near TMEM57 in a population-based association study revealed that T-allele carriers in the Han Chinese population had lower levels of serum total cholesterol, apolipoprotein B and high-density lipoprotein cholesterol, as well as lower levels of triacylglycerol, low-density lipoprotein cholesterol and apolipoprotein A1 and a lower apolipoprotein A1/apolipoprotein B ratio, whereas higher high-density lipoprotein cholesterol levels were recorded in T-allele carriers of the Mulao ethnic group. These findings suggest that the TMEM57 rs873308 SNP may influence serum lipid levels (112), although the causal gene and mechanism at this locus remain unresolved.

Obesity. TMEM26 is a marker of the browning of white adipose tissue. Brown adipose tissue counteracts obesity, and activating brown fat and browning white adipocytes are emerging strategies against obesity and its complications. Treatment with flavan-3-ols induces adipose tissue browning and increases TMEM26 expression in the brown adipose tissue of mice (113). Whether TMEM26 contributes causally to browning or serves only as a marker remains unresolved.

In summary, TMEMs contribute to non-cancerous diseases through a limited number of shared cellular mechanisms, and apparently unrelated conditions can reflect disruption of the same process; for example, immunodeficiency and anhidrosis both result from loss of ORAI1-mediated SOCE, whereas SCA21 and FTLD-TDP both involve TMEM-dependent lysosomal dysfunction. A disease-oriented overview of these TMEMs is shown in Fig. 2, and the mechanistic grouping and evidence strength for each association are summarized in Table SII.

4. Cross-mechanism convergence of TMEM function

The previous section grouped TMEM-associated non-cancerous diseases according to the cellular mechanisms through which the corresponding TMEMs act. The present section considers how these mechanisms intersect. In total, four recurring themes emerge: i) Ca^{2+} signaling as a common thread linking several mechanistic categories; ii) an interconnected network of organelle homeostasis involving the lysosome, ER and mitochondria; iii) the capacity of a single TMEM to act through different mechanisms in different cellular contexts; and iv) the convergence of TMEM paralogs and interaction partners on shared protein complexes and pathways. The mechanistic categories and representative TMEMs are summarized in Table I, and the molecules regulated by TMEMs in each category are illustrated in Fig. 3.

Ca^{2+} signaling as a common thread. Several TMEM-associated diseases that appear unrelated at the clinical level reflect defects at different steps of the same Ca^{2+} signaling sequence. At the step of Ca^{2+} entry, loss of ORAI1 (TMEM142A)-mediated SOCE causes immunodeficiency (64-66), and the same defect abolishes sweating since SOCE is required to activate the Ca^{2+}-activated Cl^- channel TMEM16A in sweat glands (57). At the step of termination, SARAF (TMEM66) limits SOCE, and its loss leads to Ca^{2+} overload in pancreatic acinar cells and more severe pancreatitis (67,68); TMEM38/TRIC proteins additionally support intracellular Ca^{2+} store function (14,62). Downstream of the Ca^{2+} signal, Ca^{2+}-dependent effectors translate elevated cytosolic Ca^{2+} into disease-relevant outputs: Ca^{2+} binding activates TMEM16F-mediated phospholipid scrambling, which is defective in Scott syndrome (10,45,52), TMEM16A-mediated Cl^- currents drive smooth muscle rhythmicity in the interstitial cells of Cajal (53,54) and TMEM16A modulates nociceptor excitability (83-85,87,88). In sensory neurons and inflammatory settings, TMEM16A is itself coupled to receptor-driven Ca^{2+} release through PAR2 and IP3 (88) and to IP3 receptor-mediated Ca^{2+} signaling (105). Thus, whether a defect in Ca^{2+} handling manifests as immunodeficiency, anhidrosis, pancreatitis, bleeding, dysmotility or pain depends largely on which step of the sequence is affected and in which cell type.

An interconnected network of organelle homeostasis. A second group of TMEMs maintains the function of the lysosome, ER and mitochondria. At the lysosome, TMEM106B (38,70), TMEM240 (71-73) and TMEM39A (74) regulate lysosomal function, autophagic degradation and lysosome positioning, and the Parkinson's disease-associated TMEM175 and TMEM163 variants (47) affect proteins involved in lysosomal K^+ conductance (75) and zinc homeostasis (60,61). In the ER, TMEM39 controls procollagen export and ER stress (22), and in mitochondria, TMEM126B, TMEM135, TMEM70 and TMEM242 regulate complex I and ATP synthase assembly, ROS generation and mitochondrial dynamics (31-33,76). Disorders arising from these TMEMs, including SCA21, FTLD-TDP, NCL, Parkinson's disease and mitochondrial complex I deficiency, frequently involve the nervous system, consistent with the high dependence of neurons on efficient organelle quality control. These compartments are also linked by shared signaling hubs; for example, mTOR signaling participates both in TMEM39A-dependent lysosome positioning (74) and in TMEM16A-associated renal senescence through AMPK/mTORC1 (104), suggesting that nutrient- and energy-sensing pathways may integrate TMEM-dependent organelle functions across tissues.

One TMEM, multiple mechanisms. The disease associations of individual TMEMs are not restricted to a single mechanism,

Table I. Different TMEMs share biological mechanisms.

Mechanism category	TMEMs	Representative function	(Refs.)
Ion channels and phospholipid scrambling	TMEM16A, TMEM16F, TMEM38A/B (TRIC-A/B) and TMEM163	Ca^{2+}-activated Cl^- conduction (16A); Ca^{2+}-dependent phospholipid scrambling (16F); sarcoplasmic reticulum ion channeling (38A/B); zinc transport (163).	(10,11,53, 58-62)
Lysosomal biology and autophagy	TMEM106B, TMEM63A, TMEM240 and TMEM39A	Lysosomal membrane protein/FTLD-TDP risk (106B); lysosomal localization (63A); autophagic-lysosomal protein degradation (240); lysosome positioning/mTOR signaling (39A).	(20,69, 73,74)
Mitochondrial homeostasis	TMEM126B, TMEM135, TMEM70, TMEM242 and TMEM65	Complex I assembly (126B); mitochondrial fission/DRP1 (135); ATP synthase/complex I rotor assembly (70,242); inner-membrane structural protein (65).	(31-33,35)
Membrane trafficking	TMEM39, TMEM45A, TMEM176A/B and TMEM39A	COPII-dependent procollagen secretion (39); Golgi/trans-Golgi trafficking (45A); post-Golgi vesicle cation channels (176A/B); lysosome trafficking via dynein (39A).	(22,25, 26,74)
ER function	TMEM39, TMEM63A and TMEM72	Procollagen/ER stress regulation (39); ER-to-lysosome trafficking axis (63A); ER export signal-mediated localization (72).	(13,20,22)
Immune sensing/antigen presentation	TMEM176A/B, TMEM39A and TMEM16A	MHC class II antigen presentation to $CD4^+$ T cells (176A/B); autoimmune-disease susceptibility locus (39A); inflammatory mediator-induced channel activity (16A).	(26,44, 80,105)
Mechanotransduction	TMEM120A (TACAN) and TMEM16A	Mechanically activated channel in germline/reproductive tissue (120A); mechanically/heat-activated nociceptive signaling (16A).	(46,84)
Calcium signaling (SOCE and related)	TMEM142/ORAI, TMEM66/SARAF, TMEM38/TRIC, TMEM178, TMEM203, TMEM173/ STING, TMEM110/STIMATE, TMEM97, TMEM20/POST, TMEM16A and TMEM16F	Core and accessory components of store-operated Ca^{2+} entry (142, 66 and others); Ca^{2+}-gated channel/scramblase activity downstream of SOCE (16A, 16F).	(10,11,14, 53,58,59, 63-68)
Nuclear envelope organization	TMEM48 (NDC1) and TMEM201 (Samp1)	Nuclear pore complex assembly (48); microtubule nucleation at the myotube nuclear envelope (201).	(40,96)
Cytoskeletal regulation/ neuronal morphogenesis	TMEM132, TMEM132D and TMEM132E	WAVE-regulatory-complex-dependent actin nucleation and neurite/process morphogenesis.	(98,99)
Signal transduction and gene/RNA regulation	TMEM11, TMEM88, TMEM63C and TMEM168	m^7G mRNA methylation via METTL1/ ATF5 (11); TGF-β1/Smad and Wnt/β-catenin signaling (88); Akt signaling (63C); osteopontin-dependent signaling (168).	(100-103, 106,107)
Disease associations without a defined mechanism	TMEM26, TMEM187, TMEM57, TMEM230, TMEM59 and TMEM108	Gene elevation (26), polymorphisms (187, 57), mutation (230, 59, 108) associated with various diseases.	(48,110-113)

TMEMs, transmembrane proteins; FTLD, frontotemporal lobar degeneration; TDP, transactive response DNA-binding protein; ER, endoplasmic reticulum; SOCE, store-operated Ca^{2+} entry.

and TMEM16A illustrates this most clearly. TMEM16A acts as a CaCC in interstitial cells of Cajal, vascular smooth muscle and sweat glands (53,54,57,58), as a regulator of vesicle trafficking through VAMP3 in hepatocytes, where it impairs glucose transporter 2 translocation in non-alcoholic fatty liver disease (79), as a transducer of noxious heat, pain and itch

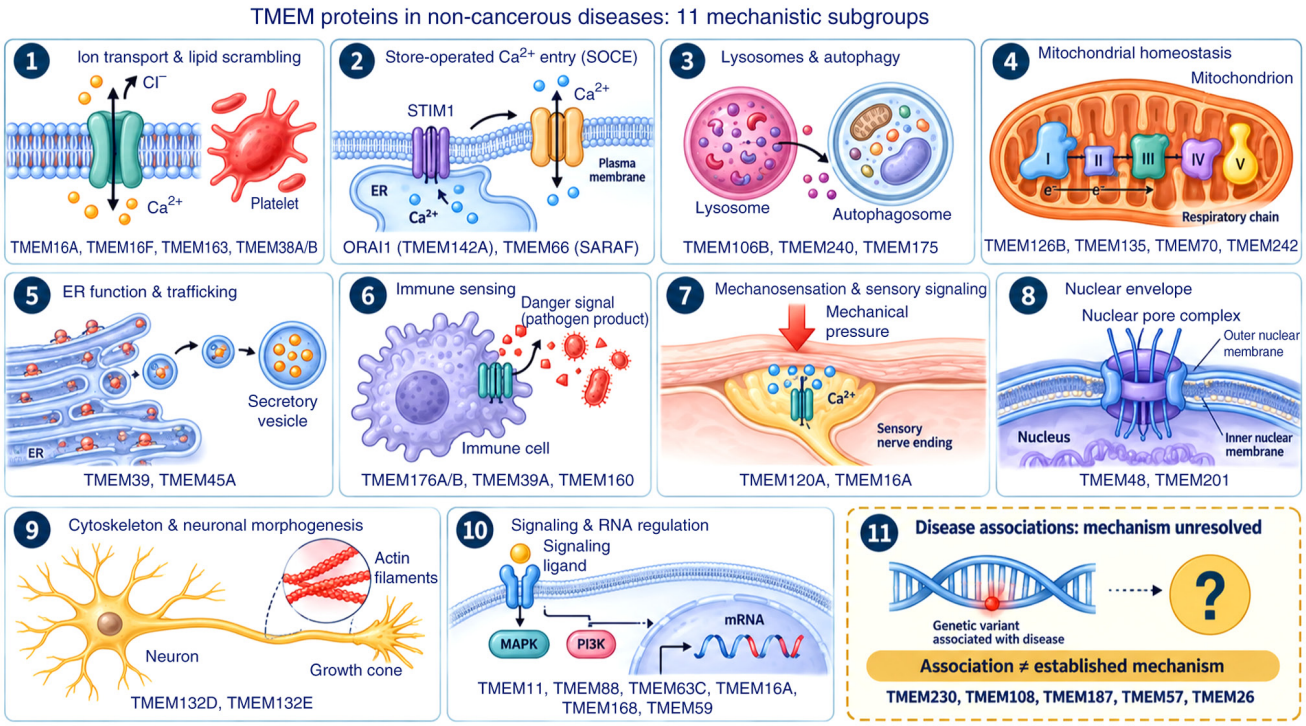


Figure 3. Molecules regulated by TMEMs in non-cancerous diseases, grouped by shared biological mechanism. The TMEMs are shown at their subcellular locations, together with the downstream molecules and signaling pathways they regulate, according to the mechanistic categories summarized in Table SII. Pointed arrows indicate activation or promotion, and blunt-ended lines indicate inhibition. TMEMs, transmembrane proteins.

in sensory neurons (59,83-85,87-95) and as an amplifier of inflammatory and senescence-associated signaling (104,105). Similarly, TMEM39A has been linked to autoimmune disease through genetic association (44) and to lysosome positioning through its interaction with DYNC1I2 (74). These examples indicate that the pathological consequences of TMEM dysfunction are determined by cell type, subcellular localization and interaction partners rather than by the protein alone. This context dependence has practical implications, as pharmacological modulation of a multifunctional TMEM, such as the use of TMEM16A inhibitors for neuropathic pain (85,87), may also affect its functions in other tissues, including smooth muscle contraction and epithelial secretion.

Convergence of TMEM paralogs and partners on shared complexes and pathways. Related TMEMs frequently act together on the same molecular machinery. TMEM70 and TMEM242 cooperate in the assembly of the ATP synthase rotor ring and interact with complex I assembly factors (33); TMEM176A and TMEM176B function together in dendritic-cell antigen processing (26); TMEM38A and TMEM38B encode sarcoplasmic reticulum ion channels in skeletal muscle (62); and members of the TMEM132 family, which are expressed throughout the developing nervous system (97), converge on the WAVE regulatory complex to control actin nucleation and neuronal morphogenesis (98). Convergence is also observed at the level of pathophysiological processes. For example, ECM accumulation is influenced both at the level of collagen export from the ER by TMEM39 (22) and at the level of TGF-β1/Smad and β-catenin signaling by TMEM88 in pleural fibrosis and keloids (101,102), indicating that fibrotic remodeling can be modulated by TMEMs acting in distinct mechanistic categories.

Evidence strength across mechanistic categories. The mechanism-based framework also reveals an uneven distribution of evidence. The strongest human causal evidence is concentrated in channel, transporter and organelle mechanisms, as exemplified by TMEM16F in Scott syndrome (45,52), ORAI1 in immunodeficiency (64), TMEM240 in SCA21 (71,72) and TMEM126B in complex I deficiency (76). By contrast, most associations in the signal transduction category are supported by cellular or animal studies (100-104,106), and those grouped in the final subsection rest on genetic association, candidate-variant or expression data without a defined mechanism (48,110-113). Testing whether these latter TMEMs converge on one of the aforementioned established mechanisms represents a rational strategy for their functional validation and is discussed further below.

5. Discussion

Subcellular localization of TMEMs shapes their functional roles in disease. TMEMs are distributed across several organelle membranes, including the ER, plasma membranes, mitochondria, lysosomes, Golgi apparatus and nuclear membranes. These organelles perform distinct cellular functions, underscoring the diverse roles of TMEMs within cells. For instance, the ER is involved in calcium storage, protein synthesis and lipid metabolism; its dysfunction, caused by ER stress, is implicated in diseases such as diabetes, neurodegeneration, cancer, cardiovascular disease and liver diseases (114-117). At least 10 TMEM members have been

identified in the membranes of the ER, highlighting their importance in maintaining ER homeostasis.

Plasma membranes are crucial for numerous cellular functions, including regulating cell death. Perturbations in cell death and survival signaling pathways influenced by the plasma membrane are associated with various diseases, such as autoimmune disorders, metabolic disorders, developmental disorders, neurodegenerative diseases, arteriosclerosis and acute and chronic organ damage (118-120). At least 12 TMEMs have been observed in plasma membranes, underscoring their crucial involvement in plasma membrane functions. Mitochondria serve as the primary sites for generating respiratory ATP, essential for eukaryotic life.

Dysregulation or defects in mitochondria are linked to various diseases, including aging, cancer, cardiomyopathy, neurodegenerative diseases and inflammatory conditions (121-123). At least 10 TMEM members within the mitochondria underscore their potential importance in diseases associated with mitochondrial dysfunction.

The Golgi apparatus plays a crucial role in maintaining cellular homeostasis functions through processes such as protein and lipid trafficking, sorting and modification. Dysregulation of these functions is associated with several diseases, including neurodegenerative diseases, cancer, infectious diseases and cardiovascular diseases (24). The presence of at least three TMEMs within the Golgi apparatus suggests their potential involvement in diseases associated with Golgi dysfunction.

Lysosomes serve as digestive organelles responsible for degradation, nutrient sensing and immunity. Lysosomal dysfunction contributes to atherosclerosis, neurodegeneration, autoimmune disease, pancreatitis, lysosomal storage disorders and cancer (124). TMEM106B and TMEM63A are important in lysosomal functions and are implicated in various diseases, underscoring the importance of TMEMs in preserving lysosomal functions (38,69).

The nucleus serves as the command center for genomic information within cells, playing critical roles in determining cellular fate and responding to diverse signals and stimuli. Aberrations in the nuclear envelope and chromatin organization are characteristics of several diseases, including heart disease, premature aging and cancer (125). Malfunctioning of nuclear pores leads to neurodegeneration (126). TMEM48 (a nuclear pore component) and TMEM201 (an inner nuclear membrane protein) contribute to cervical and lung cancer, as well as Emery-Dreifuss muscular dystrophy (96,127-129). However, there are currently no reports describing nuclear TMEMs related to neurodegeneration, but further investigations may lead to new discoveries in this area.

In summary, TMEMs are distributed across membranes of various organelles and are involved in diseases associated with the functions of these organelles. Although the membrane location of most TMEMs on organelles has not been extensively studied, ongoing research is expected to unveil more comprehensive insights into the mechanisms of TMEMs.

Functional divergence among homologous TMEM paralogs. Several aforementioned TMEMs belong to closely related paralog families, and comparing their mechanisms directly reveals that structural homology does not necessarily predict shared function or disease association. TMEM16A and TMEM16F share the anoctamin fold but diverge sharply, whereby TMEM16A acts as a CaCC mediating epithelial secretion, sensory transduction and smooth muscle excitability (11,53,57,58,83), whereas TMEM16F acts as a phospholipid scramblase, whose loss is related to the bleeding disorder Scott syndrome supported by strong human genetic and functional evidence (10,45,52). This illustrates divergent rather than redundant function despite close homology. The TMEM132 family instead shows unequal mechanistic characterization, whereby TMEM132D has been directly linked to cytoskeletal regulation and neuronal morphogenesis (98), while TMEM132E is associated with panic disorder only through genetic association without an established mechanism (99), despite both paralogs converging on overlapping neuropsychiatric phenotypes. TMEM176A and TMEM176B illustrate a third pattern, apparent but unresolved redundancy, having been studied mainly as a pair via double-knockout models in antigen presentation and dendritic cell maturation (26,80), without isolating individual contributions of each paralog. Similarly, TMEM38A and TMEM38B share channel architecture and skeletal muscle expression, yet only TMEM38B mutations have been linked to disease (62). Together, these four comparisons show that TMEM paralogs can diverge in at least three ways, including true functional divergence, unequal mechanistic depth and unresolved redundancy, and it is recommended that future studies use single-gene loss-of-function comparisons within the same cellular system to distinguish between these possibilities, as pairwise or family-level studies alone cannot.

Multidisease associations of TMEMs highlight their broad biological and pathological roles. Numerous TMEMs are implicated in >1 disease. For instance, TMEM16A functions as a subunit of CaCCs. Given the involvement of CaCCs in various diseases, TMEM16A presents therapeutic opportunities for conditions such as hypertension, stroke and cystic fibrosis (130). Additionally, TMEM16A is associated with head and neck squamous cell carcinoma, short bowel syndrome and several other diseases (11,53,54,58,59,131). TMEM168 is linked to human glioblastoma multiforme as well as anxiety and dependence symptoms (107,132). TMEM48 is involved in non-small cell lung carcinoma, cervical cancer and embryonic development (40,127,129). TMEM59 is implicated in Parkinson's disease and neural disorders (48,108,109). TMEM132 family members are associated with neurological and panic disorders (97-99). TMEM88 is associated with lung cancer, lung diseases and skin disorders (12,101,102), and TMEM176A and TMEM176B are linked to various tumors, spinal cord injuries and immune-mediated diseases (26,80,133). TMEM163 is implicated in Parkinson's disease and mucolipidosis type IV (47,60), while TMEM106B is associated with neurodegenerative diseases and lysosomal disorders (38,69). TMEM16F is involved in Scott syndrome, an inherited bleeding disorder (45,52), and TMEM45A is related to breast and liver cancer, as well as skin diseases (25,134). TMEM201 is linked to liver cancer and muscle diseases (96,135), while TMEM187 is associated with ASD and rheumatoid arthritis (110,111). These findings suggest that TMEMs are involved in diverse biological functions and

Table II. Associations of individual TMEMs with >1 disease.

TMEMs	Diseases
TMEM16A	Hypertension, stroke, cystic fibrosis and short bowel syndrome
TMEM168	Anxiety and dependence symptoms
TMEM48	Cancers and embryonic development
TMEM59	Parkinson's disease and neural disorders
TMEM132	Neurological and panic disorders
TMEM88	Lung diseases and skin disorders
TMEM176A and TMEM176B	Spinal cord injuries and immune-mediated diseases
TMEM163	Parkinson's disease and mucolipidosis type IV
TMEM106B	Neurodegenerative diseases and lysosomal disorders
TMEM16F	Scott syndrome and bleeding disorders
TMEM45A	Cancers and skin diseases
TMEM201	Cancers and muscle diseases
TMEM187	ASD and rheumatoid arthritis

TMEMs, transmembrane proteins; ASD, autism spectrum disorder.

are crucial for organismal health. TMEMs implicated in multiple diseases warrant particular attention. The association of a single TMEM with >1 disease is summarized in Table II. In summary, TMEMs are located in different cellular contexts and some are associated with multiple diseases. They participate in disease pathology through distinct mechanisms, thus underscoring their importance in pathological processes and mechanisms of action.

Several TMEMs act as protective factors in one context but as pathogenic drivers in another, rather than following a uniform 'loss is harmful' or 'gain is harmful' rule. For example, TMEM16A is essential for gastrointestinal motility and sweat gland secretion under normal conditions (53,54,57,58), but its upregulation drives metabolic dysfunction in hepatocytes (79) and its overactivation promotes pain, inflammation and kidney injury elsewhere (59,83-85,87-95,104,105). TMEM126B sustains complex I-derived mitochondrial ROS that drive SDHA oxidation and IL-1β expression in activated macrophages (32), whereas its loss causes isolated complex I deficiency with muscle weakness (76). TMEM168 promotes anxiety-like behavior at baseline (106), but protects against methamphetamine-induced addiction behaviors when upregulated (107). TMEM106B fragment accumulation is linked to neurodegeneration (38,69), yet also occurs in normal-aged brains, suggesting it may become pathogenic only above a certain threshold or with additional insults such as GRN deficiency (38,70). Finally, TMEM88 is anti-fibrotic in non-cancerous diseases (101,102), but promotes invasion in lung cancer (12), showing that disease context itself, not just cell type, determines its effect. Together, these examples show that the pathological importance of TMEMs depends on tissue, physiological state and disease context rather than protein identity alone, and it is recommended that future studies test both loss- and gain-of-function within the same cellular context, using this framework of context-dependent duality to guide the evaluation of TMEMs as therapeutic targets.

Toward a conceptual synthesis of TMEM biology in disease. The multi-disease associations of TMEMs reflect two patterns, including tissue-distribution pleiotropy, whereby a single function produces distinct disease phenotypes across tissues, such as TMEM16A Cl^- channel activity underlies anhidrosis, gut dysmotility and neuropathic pain (11,53,57,83), and pathway-hub pleiotropy, whereby the role of a TMEM in a core cellular process yields divergent downstream disease labels, such as TMEM106B in neurodegeneration and lysosomal storage disorders (38,69). TMEM48 is observed to play a role in cancer and developmental defects (40,127-129). Organelle specialization more reliably predicts mechanistic convergence than function, whereby ER TMEMs converge on Ca^{2+} homeostasis via store-operated Ca^{2+} entry (including TMEM38, TMEM178, TMEM173, TMEM203, TMEM110, TMEM20, TMEM66 and TMEM97) (14) and mitochondrial TMEMs on respiratory chain/ATP synthase assembly (including TMEM126B, TMEM70 and TMEM242) and fission/fusion (including TMEM135) (31-33). However, plasma membrane and Golgi TMEMs remain mechanistically heterogeneous. Invertebrate-validated TMEMs, such as TMEM48/NDC1 (40), TMEM39/TMEM39A (22,74), TMEM132D (98) and TMEM120A/TACAN (46), retain conserved housekeeping functions rather than disease-specific roles, indicating that disease associations arise from tissue-specific consequences of disrupting an ancestral function, with unstudied TMEMs constituting an evidence gap rather than evidence against conservation. Among candidate therapeutic targets, TMEM16A is the most advanced, with strong supporting evidence, multiple small-molecule modulators (including liquiritigenin, Eact, T16Ainh-A01 and capsaicin analogs) (89-94) and preclinical efficacy in pain and non-alcoholic fatty liver disease models (79,85). TMEM16F has comparably strong evidence in Scott syndrome (45,52) but, as a loss-of-function target, is more suited to protein/gene replacement. TMEM106B shows promise as a diagnostic biomarker across FTLD-TDP, tauopathies and NCL (38,69,70) despite limited pharmacological development. Finally, peptide/protein strategies, including the TMEM39AS41 peptide and recombinant TMEM219 protein (136,137), remain at an earlier stage. Therefore, TMEM16A represents the leading near-term therapeutic candidate, with TMEM106B and TMEM16F offering complementary biomarker and rare-disease replacement strategies.

Translational challenges and target feasibility of TMEMs. Although disease association nominates several TMEMs as candidate therapeutic targets, feasibility for drug development depends on additional factors, such as tissue specificity, physiological redundancy, potential toxicity, druggability, availability of pharmacological tools and current translational stage, which merit critical consideration alongside genetic and mechanistic evidence (Table SII). TMEM16A illustrates this tension most clearly, whereby it is the most pharmacologically advanced target discussed in the present review, with several small molecule modulators

available (89-94). However, the anhidrosis and heat intolerance that result when its SOCE-dependent activation is lost in ORAI1/STIM1-deficient patients and mice (57), together with broad essential expression across sweat glands, gut, smooth muscle, the liver and sensory neurons (11,53,54,57,58,79,83), indicate that systemic inhibition (the strategy proposed for its pain and inflammatory indications) carries a predictable thermoregulatory toxicity risk. Tissue-restricted or biased delivery would therefore likely be required, and no candidate modulator has yet advanced beyond the preclinical tool-compound stage. TMEM16F is equally well-supported genetically, with loss-of-function variants causing Scott syndrome (45,52), but this loss-of-function relationship favors replacement over inhibitory strategies, and its broad hematopoietic expression (10,45) raises bleeding-risk toxicity concerns for any activator. TMEM106B lacks a druggable catalytic or channel function, as its pathology arises from fragment accumulation rather than aberrant enzymatic activity (38,69,70). It is therefore currently more supported as a diagnostic biomarker than as a direct drug target. TMEM176A/B present an unresolved redundancy problem, having been functionally characterized only as a double knockout (26), leaving the contribution of each paralog, and thus the target validity of either alone, undetermined. Peptide- and protein-based modalities such as the TMEM39AS41 peptide and recombinant TMEM219 (136,137) remain early-stage, with no development reported beyond animal models. Taken together, these considerations suggest that TMEM16A remains the leading near-term candidate but likely requires tissue-restricted or biased delivery rather than systemic inhibition. TMEM16F and TMEM106B are more suited to replacement- and biomarker-oriented strategies, respectively, and paralog redundancy together with the general scarcity of chemical starting points for most other TMEMs indicate that the field remains at an earlier stage than the 'potential therapeutic target' language may suggest.

6. Perspectives

TMEMs are found in the membranes of several organelles within the cell, highlighting the diverse roles of these proteins. They are involved in a multitude of cellular functions, underscoring their importance. It is hypothesized that numerous additional TMEMs remain to be discovered. While several TMEMs have yet to be identified and further notions of established TMEMs have to be elucidated, their importance is becoming increasingly apparent. Studying TMEMs within the organelles where they reside can elucidate the mechanisms underlying organelle function, as well as the roles of TMEMs themselves. For instance, membranes serve as the boundaries of cells and organelles, and the transport and reaction mechanisms of biological membranes are still not fully understood. It is reasonable to assume that they regulate multiple activities of biological membranes. Therefore, gaining an improved understanding of TMEMs could aid in unraveling the mysteries of biological membranes and deepening the present understanding of organismal physiology. Furthermore, TMEMs hold therapeutic potential for diseases. For example, TMEM39AS41, a synthetic peptide derived from the human TMEM39A protein, induces cell death by inhibiting autophagy/inflammation pathways both *in vitro* and *in vivo* in models of human non-small cell lung cancer with KRAS mutations (136). Furthermore, TMEM219, also termed insulin-like growth factor-binding protein 3 receptor, acts as a death receptor and activator of autophagy. Recombinant TMEM219 constructs, such as h6-TMEM219, have been expressed and purified, and these purified forms may serve as diagnostic and therapeutic agents against the IGFBP-3/TMEM219 signaling pathway in diseases such as diabetes and Alzheimer's disease (137). Therefore, the prospects of understanding TMEMs holds value for both fundamental cellular research and biomedical/clinical applications.

In addition, the scope of the present review is defined by the 'TMEM' gene nomenclature established by the HUGO Gene Nomenclature Committee, and it therefore does not encompass the numerous other biologically important TMEMs that carry different official gene symbols but nonetheless illustrate similar principles of multifunctionality across enzymatic, trafficking and signaling domains. A representative example is prostate-specific membrane antigen (PSMA), which is encoded by FOLH1 (also termed glutamate carboxypeptidase II/NAALADase), a type II transmembrane glycoprotein that hydrolyzes N-acetylaspartylglutamate to regulate glutamate neurotransmission in the central nervous system, hydrolyzes dietary polyglutamated folates to support intestinal folate absorption, undergoes clathrin-dependent endocytosis and additionally functions as a membrane-associated signaling scaffold independent of its enzymatic activity. These properties parallel several of the shared mechanisms discussed for TMEM-designated proteins in the present review (Table I), including enzymatic activity, membrane trafficking and signal transduction, despite PSMA bearing no relationship to the TMEM nomenclature. Individuals interested in the physiological and pathological functions of PSMA are directed to a recent comprehensive review of its molecular biology (138). More broadly, it is anticipated that a systematic, mechanism-based comparison spanning TMEM-designated and non-TMEM-designated multifunctional TMEMs alike, beyond the nomenclature-defined scope adopted in the present review, represents a valuable direction for future review efforts.

7. Conclusions

TMEMs represent a versatile family traversing biological membranes and are distributed across various cellular compartments, including plasma membranes, nuclear membranes, ER, Golgi apparatus, mitochondria and lysosomes. These proteins serve diverse functions, including roles in calcium regulation, autoimmune diseases and mitochondrial dynamics. The activities of TMEMs are closely associated with various disease processes. TMEMs play important roles in several diseases such as Parkinson's disease, SCA21, neurological disorders, anxiety, panic disorders, ASD, dependence symptoms, learning defects, lung diseases, cardiac injury, short bowel syndrome, renal diseases, spinal cord injury, skin diseases, pain, autoimmune diseases, immune-mediated diseases, mucolipidosis type IV, lysosomal disorders, Scott syndrome, obesity, embryonic development defects, muscular dystrophy, rheumatoid

arthritis and hyperlipidemia. Moreover, the relationships between TMEMs and disease summarized in the present review are supported by heterogeneous types of evidence and should not be interpreted as equivalent. Human pathogenic variants causing a reproducible Mendelian phenotype provide the strongest evidence for a causal gene-disease relationship, particularly when supported by functional validation and an established disease mechanism. Genetic susceptibility loci, GWA study associations and candidate variants indicate possible risk modification but do not necessarily demonstrate causality. Patient-tissue expression or protein-accumulation studies may identify disease-associated biomarkers or pathological correlates, although altered expression can represent a consequence rather than a cause of disease. Mouse models and cellular gain- or loss-of-function experiments provide valuable mechanistic support, but their relevance to human disease depends on model validity, experimental design and reproducibility. Protein-interaction and localization studies are useful for generating mechanistic hypotheses but are insufficient alone to establish disease causation.

The diverse locations of TMEMs are closely linked to their involvement in different diseases, and they participate in disease processes through various mechanisms, including modulation of dopamine, Slick and Slack, TGF-β1/Smad, ATF5, INCA1, VAMP3/syntaxin, Akt, KRT10, FLG, b-catenin, cyclin D1, c-Myc, AQP5, TRPA1, phospho-ERK/NK-1, AMPK signaling, CaCCs, ATP synthase and mitochondrial complex I. Several TMEMs are implicated in multiple diseases, underscoring the importance of further investigation of these proteins, such as TMEM16A, TMEM168, TMEM48, TMEM59, TMEM132, TMEM176A, TMEM176B, TMEM163, TMEM16F, TMEM45A, TMEM201 and TMEM187.

In summary, TMEMs play crucial roles in cellular function, health and disease, and further studies promise deeper insight into membrane biology and physiology. Several gray areas remain: Most TMEMs have been characterized only in cell line or animal models, with limited human clinical evidence; structural information is incomplete for most TMEMs; overlapping function among subfamily members (such as TMEM16) complicates attributing phenotypes to individual genes; and validated pharmacological tools remain scarce, limiting both mechanistic and therapeutic progress. Addressing these gaps will require cryo-EM and artificial intelligence-based structural prediction, CRISPR-based and single-cell multi-omics approaches to resolve member-specific effects, development of selective modulators (as shown for TMEM39AS41 and h6-TMEM219) and larger human cohort studies to validate preclinical findings. Future work should prioritize structural/functional annotation of understudied TMEMs, development of selective modulators for non-cancerous disease applications, validation of TMEMs as clinical biomarkers [for example, TMEM211, whose high expression is associated with metastasis and poor survival in colon cancer (139)] and integrative studies linking TMEMs localization to organelle-specific disease mechanisms. Despite the current limited knowledge of TMEMs, their emerging importance suggests that several more discoveries are to be expected. Therefore, continued exploration of TMEMs is likely to yield valuable insights into disease mechanisms, their diagnosis and therapeutic potentials.

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PFL, YFC and CWS contributed to conceptualization, writing, reviewing and editing the manuscript and funding acquisition. CHC and HHW contributed to writing and editing the manuscript. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

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Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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