TRPM7

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Abstract

The channel kinases TRPM6 and TRPM7 are fusion proteins with an ion transport domain and an enzymatically active kinase domain. TRPM7 has been found in every mammalian tissue investigated to date. The two-in-one protein structure, the ubiquitous expression profile, and the protein's unique biophysical characteristics that enable divalent ion transport involve TRPM7 in a plethora of (patho)physiological processes. With its prominent role in cellular and systemic magnesium homeostasis, TRPM7 emerges as a key player in embryonic development, global ischemia, cardiovascular disease, and cancer.

Keywords

Magnesium • Calcium • Trace metals • Divalent cation • Transient Receptor Potential Channel • Adenosine triphosphate • Channel kinase • Magnesium homeostasis • Embryogenesis • Ischemia • Breast cancer

1 Gene

The official name of the TRPM7 gene is "transient receptor potential cation channel, subfamily M, member 7." In Homo sapiens, the TRPM7 gene is located on chromosome 15q21.2 (NCBI Gene ID 54822). Previous names for the gene include CHAK1, TRP-PLIK, and LTRPC7 (Ryazanov 2002; Runnels et al. 2001; Nadler et al. 2001). The human TRPM7 gene encodes an 1,865 amino acid protein (Schmitz et al. 2005). The molecule is unique in that it contains an ion transport domain (InterPro IPR005821) in its N-terminal section and an enzymatically active MHCK/EF2 kinase domain (InterPRo IPR004166) in the C-terminal section. Only two other mammalian genes (there are numerous channel enzymes in simple organisms) are known to code for ion channel and enzyme domain fusion proteins, namely, TRPM7's paralog genes TRPM6 and TRPM2 (Perraud et al. 2001; Schlingmann et al. 2002; Walder et al. 2002), described elsewhere in this book. TRPM7 gene orthologs with human amino acid sequence similarity of 94.3 % to 99.89 % have been identified in chimpanzee (*Pan troglodytes*), mouse (*Mus musculus*), rat (*Rattus norvegicus*), cow (*Bos taurus*), and dog (*Canis familiaris*; GeneCards). In zebrafish (*Danio rerio*), an important model organism in biology, TRPM7 is located on chromosome 18 and shares 75 % amino acid sequence identity with the human TRPM7 gene.

Virtually nothing is known about whether the kinase and channel encoding portions of the TRPM7 gene domains can be expressed independently from each other. A splice variant in rat lacking the channel domain has been reported (Runnels et al. 2001). Human *Trpm7* has 9 predicted splice variants (http://www.ensembl.org: ENST00000561267, TRPM7-001 through TRPM7-009); however, aside from the 1,865 amino acid encoding protein, the function of any of these variants remains unexplored. Finally, no genes coding for TRPM7 auxiliary subunits are known (Chubanov et al. 2004; Schmitz et al. 2005).

2 Expression

Early investigations of human tissue and cell lines by PCR with reverse transcription indicated a ubiquitous distribution pattern of TRPM7 transcripts (Nadler et al. 2001; Runnels et al. 2001). A comprehensive quantitative real-time reverse transcriptase polymerase chain reaction (qRT-PCR) analysis of human tissue showed that TRPM7 is widely distributed in the central nervous system as well as in the periphery, with highest expression levels in the heart, pituitary, bone, and adipose tissue (Fonfria et al. 2006).

TRPM7 is also ubiquitously expressed across mouse organs as investigated by qRT-PCR. These data show that, compared to other members of the TRP gene family, TRPM7 is the most abundantly expressed TRP channel in the majority of adult mouse organs investigated (Kunert-Keil et al. 2006). Particularly, mouse intestine, lung, kidney, and brain have strong TRPM7 expression (Kunert-Keil et al. 2006), as well as testis (Jang et al. 2012). While TRPM7 levels can vary significantly between mouse strains (Kunert-Keil et al. 2006), they seem quite constant within a particular type of strain (Vandewauw et al. 2013). Along with TRPM2, TRPM4, and TRPM8, mouse trigeminal ganglia show very high expression of TRPM7, and this gene product has a stronger representation in dorsal root ganglia along the vertebral column compared to other members of the TRPM family (Vandewauw et al. 2013). Gene expression patterns of TRPM7 during mouse development seem to occur in two waves, peaking at embryonic day 18 (E12), raising again after postnatal day 4, and maintaining stable levels into adulthood (Staaf et al. 2010). Additional studies have confirmed TRPM7 RNA expression in adult rat prostate tissue (Wang et al. 2007) and intralobar pulmonary arterial and aortic smooth muscle (Yang et al. 2006), as well as rumen epithelial cells isolated from sheep (Schweigel et al. 2008).

The assessment of TRPM7 at the protein level has been more challenging due to the paucity of highly specific antibodies. Fortunately, due to the electrogenic nature of TRPM7's ion channel function, biophysical techniques such as whole-cell patch-clamp technique and single-channel measurements allow an estimate of the number of proteins in the plasma membrane of single live cells (Hamill et al. 1981). Endogenous TRPM7-like currents were first reported in renal cells (human HEK293), mast cells (rat RBL-2H3), and T lymphocytes (human Jurkat T) (Nadler et al. 2001). Due to the inhibition of these currents by magnesium (Mg), Mg·ATP, as well as their ability to conduct metal ions, native TRPM7-like currents were coined *mag*nesium-*nu*cleotide-regulated *m*etal ion currents [MagNuM (Nadler et al. 2001; Hermosura et al. 2002)] and also *m*agnesium-*i*nhibited *c*ation current [MIC (Kozak et al. 2002b)]. Subsequent investigation reported native currents with biophysical characteristics ascribed to TRPM7 in a wide variety of cell types, including the heart (Gwanyanya et al. 2004), brain (Aarts et al. 2003), and intestine (Kim et al. 2009).

Of the three cell types in which MagNuM currents were originally described, Jurkat T cells had the highest current density under the experimental conditions used (Nadler et al. 2001). Taking into account a single-channel conductance of

40 pS (Nadler et al. 2001; Li et al. 2006), this still amounts to only an estimated 30 active channels in the plasma membrane per T cell and 40 channels per HEK293 or RBL-2H3 cell. Subcellular location of TRPM7 protein in heterologous overexpression systems is to be expected (Chubanov et al. 2007), and evidence exists of native functional subcellular location in synaptic vesicles of sympathetic rat neurons (Krapivinsky et al. 2006), in tubulovesicular structures (Oancea et al. 2006), and reticular formations of vascular smooth muscle cells (Yogi et al. 2009).

3 The Channel Protein Including Structural Aspects

In analogy to other members of the TRP channel family, TRPM7 monomers are thought to form tetrameric units, modeled after voltage-gated potassium (K) channels (Mederos y Schnitzler et al. 2008; Jiang et al. 2003; Chubanov et al. 2007). The 1,865 amino acids of a human TRPM7 subunit can be subdivided into distinct domains with variable homology to TRPM7 subunits identified in other species. Four unique melastatin amino-terminal regions are linked to the 6 putative transmembrane spanning helices (Nadler et al. 2001), with the putative pore region linking segments 5 and 6. The "TRP box," unique to all identified TRP ion channels, is a highly conserved and proline-rich 24 amino acid region C-terminal to the transmembrane domains (Venkatachalam and Montell 2007), followed by a cytoplasmic coiled-coil (CC) domain thought to underlie channel assembly and trafficking (Fujiwara and Minor 2008). The CC domain is predicted to have a four-stranded antiparallel arrangement which seems aligned with the dimer-forming atypical α-kinase domain architecture just C-terminal of the CC (Fujiwara and Minor 2008). The latter is indeed one of the unique features of TRPM7, which it shares with its paralog TRPM6: the fusion of an N-terminal functional ion channel and a C-terminally located and active serine/threonine protein kinase (Ryazanov 2002; Runnels et al. 2001; Nadler et al. 2001). Activation of caspase leads to separation of TRPM7's kinase domain from the channel without affecting the functionality of the kinase but enhancing ion channel activity (Desai et al. 2012).

Both the CC and α-kinase domain are currently the only two TRPM7 regions where X-ray crystallography has provided structural information (Yamaguchi et al. 2001; Fujiwara and Minor 2008). The kinase domain's 300 amino acid residues fold into a cleft-forming structure containing the active ATP-binding site. In addition, one zinc (Zn) and two Mg binding sites have been reported. Sequence analysis reveals little primary amino acid sequence similarity between catalytic domains of conventional protein kinases and TRPM7's atypical kinase despite an overall similarity in the folding structure (Drennan and Ryazanov 2004; Yamaguchi et al. 2001). Analysis of truncation mutants using mouse TRPM7 identified two important regions in the kinase domain: residues 1553 to 1562 are essential for kinase phosphorylation activity and residues 1563 to 1670 are needed for dimer assembly (Crawley and Cote 2009).

Mass spectrometric proteomic techniques have been used on mouse and human TRPM7 to identify key phosphorylation sites. This resulted in the confirmation as well as new identification of several phosphorylation sites that are all located on the cytoplasmic C-terminus (Kim et al. 2012; Madsen et al. 2012; Matsushita et al. 2005): 3 in the CC region, 7 in a serine-threonine-rich (Ser/Thr) domain (Matsushita et al. 2005), and two P-sites of unknown function distal to the kinase domain (Kim et al. 2012). Furthermore, phosphomapping by mass spectrometry identified 47 autophosphorylation sites on TRPM7, the majority of which are located in the Ser/Thr-rich domain N-terminal of the kinase region. This part of the TRPM7 region is thought to control kinase substrate binding (Clark et al. 2008c).

4 Interacting Proteins

Information on proteins interacting with TRPM7 remains scarce, even for the kinase domain. A yeast two-hybrid screen of a rat library identified phospholipase C (PLC) as interacting partner of the TRPM7 kinase (Runnels et al. 2001). Subsequent work showed that receptor-stimulated activation of PLC causes inhibition of TRPM7 channel activity through localized phosphatidylinositol 4,5-bisphosphate (PIP_2) hydrolysis (Runnels et al. 2002). Furthermore, hypomagnesemic conditions increase TRPM7-kinase-regulated Ser/Thr phosphorylation in the C2 domain of PLCγ2, leading to reduced Ca signaling (Deason-Towne et al. 2012).

Involvement of TRPM7 kinase in cell motility and adhesion has been linked to its ability to phosphorylate the assembly domains of non-muscle myosin IIA, IIB, and IIC and ATP-dependent motor proteins involved in actomyosin-based cell motility (Clark et al. 2006, 2008a, b). Annexin A1, a Ca-dependent membrane-binding protein with the ability to promote membrane fusion, is also phosphorylated by the TRPM7 kinase, providing a possible link to TRPM7's known involvement in cell growth and apoptosis (Dorovkov and Ryazanov 2004; Dorovkov et al. 2011). The TRPM7 kinase also mediates enhanced Thr phosphorylation at residue 56 of the eukaryotic elongation factor 2 (eEF2) through eEF2 kinase (Perraud et al. 2011). This specifically occurs under reduced dietary Mg and has been suggested to adjust protein translation rates to the availability of this important divalent ion.

To date, TRPM6 is possibly the best understood TRPM7-interacting protein as assessed in heterologous expression systems (Runnels 2011). Interestingly, recombinant and native TRPM6 seems to require TRPM7 for plasma membrane surface expression in mouse embryonic stem (ES), DT40, HEK293 cells, and *Xenopus* oocytes (Schmitz et al. 2005; Ryazanova et al. 2010; Chubanov et al. 2004, 2007), indicating that TRPM6 is inefficient in forming functional homomeric ion channels on its own. While this topic still remains somewhat controversial, supporting observations show that overexpression of TRPM6 cannot rescue cell growth arrest in chicken DT40 B cells lacking the TRPM7 protein (Schmitz et al. 2005) and, in

contrast to TRPM7, cannot alter motility and proliferation of HEK293 (Chubanov et al. 2004). Furthermore, a single-point mutation at amino acid residue S141 in TRPM6 disrupts heteromeric TRPM6/TRPM7 channel formation manifesting itself as hypomagnesemia with secondary hypocalcemia (Chubanov et al. 2004). Interestingly, when cloned into the pCINeo-IRES-GFP vector, TRPM6 can be overexpressed and forms functional homomeric channels in the plasma membrane (Voets et al. 2004; Li et al. 2006). While this seems to be the only vector able to do so for unknown reasons, it presents a valuable scientific tool to study the hypothetical behavior of TRPM6 if it were expressed natively. This may provide information as to why homomeric TRPM7 channels behave differently from the heterotetramer formed by TRPM6 and TRPM7 and as to what the underlying structural features might be. It would also be interesting to elucidate whether the noncoding sequence of the TRPM6-pCINeo-IRES-GFP expression construct can influence assembly and trafficking of TRPM6.

5 A Biophysical Description of the Channel Function, Permeation, and Gating

5.1 Channel Function

Aside from representing a fusion protein, TRPM7's most striking feature is its selectivity for divalent metal ions at hyperpolarized potentials (Monteilh-Zoller et al. 2003; Nadler et al. 2001). The strong outwardly rectifying current–voltage (I/V) signature of TRPM7 is due to voltage-dependent permeation block by extracellular divalent ions, mainly Ca and Mg (Kerschbaum et al. 2003; Nadler et al. 2001). Removal of divalent ions allows the assessment of TRPM7 single-channel characteristics at all physiological voltages, revealing a relatively large conductance of 40 pS and open times of several hundred milliseconds (Li et al. 2006). The channel itself shows no intrinsic voltage dependence, and the level of its constitutive activity is regulated by a surprising variety of intracellular and extracellular factors. Natively, most cells express only a few tens of TRPM7 proteins in the plasma membrane, and this can readily be assessed by the whole-cell patch-clamp method. However, the relative scarcity of endogenous TRPM7 in the cell's membrane hampers the use of other, less sensitive detection methods, such as immunofluorescence or biotinylation studies, or more global protein expression evaluations by Western blot.

5.2 Kinase Function

The identification of elongation factor-2 kinase revealed a new class of protein kinases with no sequence homology to conventional eukaryotic protein kinases in regard to their catalytic domains (Ryazanov et al. 1999). There are several members of this so-called atypical or α-kinase family in mammals, and two are fused to the

ion channels TRPM6 and TRPM7. The TRPM7 kinase specifically phosphorylates Ser and Thr residues in a Mg-dependent manner (Ryazanova et al. 2004). It autophosphorylates itself and phosphorylates myelin basic protein as well as histone H3. At least two of the identified autophosphorylation sites (S1511 and S1567) do not seem to influence channel behavior (Matsushita et al. 2005).

While manganese (Mn) can replace Mg to maintain kinase function, zinc (Zn) and cobalt (Co) inhibit kinase activity, while Ca plays no role (Matsushita et al. 2005; Ryazanova et al. 2004). Staurosporine, a common protein kinase inhibitor preventing ATP binding, does not interfere with TPRM7 kinase function, whereas rottlerin, a potent K^+ channel activator, suppresses kinase activity at high concentrations [$IC_{50} \sim 40$ μM (Ryazanova et al. 2004)].

5.3 Channel Permeation

The first indication that TRPM7 represents a bona fide divalent ion channel at negative voltages and allows monovalent ion flux only at depolarized voltages was published in one of the original reports on TRPM7 function (Nadler et al. 2001). Detailed studies followed confirming the channel's selectivity profile to be Zn = nickel (Ni) > barium (Ba) > Co > Mg > Mn > strontium (Sr) > cadmium (Cd) > Ca (Li et al. 2006; Monteilh-Zoller et al. 2003). Relatively large and complex structured polyamines can additionally act as permeant blockers of TRPM7 (Kerschbaum et al. 2003).

Several amino acid residues in the putative TRPM7 ion channel pore have been shown to control Ca and Mg permeability. Changing glutamic acid at residue 1047 or 1052 in the mouse channel into a neutral glutamine either strongly reduces (70 %) or even abolishes affinity to Ca or Mg, respectively (Li et al. 2007). On the other hand, changing residue E1047 into glutamine and Y1049 into proline results in linearized currents and loss of Ca permeation (Mederos y Schnitzler et al. 2008). Similar observations have been made for human TRPM7 (Numata and Okada 2008) with the corresponding key residues E1047 and E1052. In addition, aspartic acid at 1054 and 1059 also influences permeation block by divalent ions.

5.4 Channel Gating and Regulation

5.4.1 Magnesium

TRPM7 represents a constitutively active ion channel that is heavily regulated by a variety of physiological feedback mechanisms. One of the most important regulatory factors of channel activity is intracellular free Mg (Nadler et al. 2001), which can be mimicked by non-physiological Ba, Sr, Zn, and Mn (Kozak and Cahalan 2003). Detailed biophysical examination reveals that native TRPM7 in excised patches has two conductance states at 39 pS and 186 pS, with both reversibly inhibited by Mg (Chokshi et al. 2012c). The respective dose-response curves reveal

IC_{50} values of 25 μM and 91 μM. Mg seems to reduce the number of active channels rather than cause an overall reduction of single-channel conductance. Mg inhibition involves two separate binding sites on the protein (Chokshi et al. 2012b), one within the kinase domain and another on the channel proper (Schmitz et al. 2003). Mg inhibitory potency measured in excised patches is about 10- to 20-fold smaller than that seen in whole-cell patch-clamp experiments where 750 μM free Mg is needed to suppress channel activity by 50 %, both in overexpression and native cell systems (Nadler et al. 2001; Demeuse et al. 2006). This suggests that additional factors in the cellular environment of TRPM7 help regulate the channel's true physiological Mg sensitivity. Sites coordinating the Mg · ATP binding in the kinase domain are partially involved in regulating the overall affinity for Mg to the channel, since introduction of single-point mutations that abolish phosphotransferase activity (G1799D, K1648R) reduces TRPM7's sensitivity to intracellular Mg (Schmitz et al. 2003). In contrast, autophosphorylation does not seem to play a role here, since, at least for the single-point mutants investigated (S1511/S1567), no difference can be detected compared to the wild-type (wt) channel (Matsushita et al. 2005). Interestingly, intracellular Mg seems to synergize with a variety of factors regulating TRPM7 activity, including the highly specific TRPM7 inhibitor waixenicin A, intracellular chloride, and intracellular Mg·nucleotides (Zierler et al. 2011; Yu et al. 2013; Demeuse et al. 2006).

5.4.2 Mg·Nucleotides

There is general consensus that mammalian TRPM7 is regulated by free intracellular Mg (Penner and Fleig 2007). Evidence for intracellular adenosine triphosphate (ATP) as a feedback mechanism for TPRM7 was initially controversial. Runnels et al. reported facilitation of TPM7 activity by intracellular ATP (Runnels et al. 2001), whereas in a parallel study, Nadler et al. demonstrated an inhibitory effect of ATP in its physiologically relevant form bound to Mg (Mg·ATP) (Nadler et al. 2001). This issue has been resolved and the ATP-mediated activation of TRPM7 actually is due to a decrease in free Mg caused by supplemented Na·ATP. Subsequent analyses revealed that negative feedback inhibition by Mg·ATP requires an intact nucleotide-binding site of the kinase domain involving amino acid K1648 (Schmitz et al. 2003). The binding site also helps discriminate between Mg·nucleotide (Mg·NTP) species such as Mg·GTP or Mg·TTP, since point mutations of this residue or removal of the entire kinase domain renders the channel insensitive to intracellular nucleotide regulation (Demeuse et al. 2006). Mg·adenosine diphosphate (ADP), but not adenosine monophosphate (AMP), has similar inhibitory efficacy as Mg·ATP, indicating a protection against enhanced TRPM7 activation during variations of cell energy levels. Thus, Mg chelated to nucleotides seems key to interfere with TRPM7 gating. Furthermore, inhibition by Mg·nucleotides is synergistically enhanced by intracellular free Mg. In fact, nucleotides lose any efficacy below a minimal threshold of around 200 μM free Mg (Demeuse et al. 2006). The current model therefore postulates independent binding sites for Mg and Mg·ATP, synergistically regulating channel activity. Interestingly, kinase deletion at residue 1599 renders a nonfunctional channel

(Matsushita et al. 2005), while truncating the kinase domain at aa 1569 regains some channel function (Schmitz et al. 2003) and cutting the protein at residue 1510 fully recovers the ability to measure regular TRPM7 currents (Desai et al. 2012). Thus, it is tempting to speculate that the protein region between aa residues 1510 and 1599 is involved in coordinating the binding of Mg to the channel.

5.5 Receptor-Coupled TRPM7 Activity

Several studies have reported regulation of TRPM7 through PLC-dependent pathways. Co-overexpression of muscarinic receptor 1 and TRPM7 in HEK293 cells followed by charbacol stimulation leads to TRPM7 inactivation due to depletion of PIP_2 in the plasma membrane (Runnels et al. 2002). Endogenous TRPM7 in CA1 hippocampal neurons is sensitive to nerve growth factor via a PLC-dependent pathway (Tian et al. 2007), and in cardiac myocytes GTP analogues lead to TRPM7 inhibition through G-protein activity and PIP_2 metabolism (Macianskiene et al. 2008). In contrast, moderate overexpression of TRPM7 in neuroblastoma N1E-115 cells needs free intracellular Mg to fall below physiological levels for PLC-dependent inhibition to occur. Under normal Mg levels, TRPM7 currents are activated rather than inhibited following receptor stimulation through bradykinin, thrombin, or lysophosphatidic acid (Langeslag et al. 2007). Further evidence shows involvement of endogenous G_s/G_i-coupled receptors in TRPM7 regulation. Stimulation of acetylcholine receptors inhibits overexpressed TRPM7 currents in HEK293 cells. Isoproterenol stimulation of endogenous beta-adrenergic receptors, on the other hand, enhances TRPM7 activity and requires both a functional protein kinase A and an intact TRPM7 kinase domain (Takezawa et al. 2004).

5.6 Mechano-sensitivity and Volume

In vascular smooth muscle A7R5 cells overexpressing TRPM7, laminar flow-induced sheer stress causes channel translocation to the plasma membrane, implicating TPRM7 in cellular mechanotransduction of flow (Oancea et al. 2006). Endogenous TRPM7 in HeLa cells is directly activated by stretch or increased cell volume and does not involve exocytotic events for biomembrane incorporation (Numata et al. 2007). Exposing HEK293 cells expressing heterologous TPRM7 to varying osmotic gradients provides insight into the channel's osmo-sensitivity mediated by molecular crowding of solutes that affect channel activity without involvement of membrane stretch (Bessac and Fleig 2007). While results are currently controversial as to the exact mechanism, it seems safe to say that changes in cell volume will affect TRPM7 channel activity.

5.7 Acidity

Acidic extracellular conditions below pH 6 greatly potentiate TRPM7 currents at negative membrane potentials (Monteilh-Zoller et al. 2003). This is due to changes in selectivity of TRPM7 that enhance monovalent ion permeation caused by direct competition of protons with divalent ions for specific binding sites in the channel pore (Jiang et al. 2005). Specifically, mutating glutamic acid residues 1047 and 1052 into nonpolar glutamine in mouse TRPM7 decreases or abolishes not only divalent ion selectivity but also pH sensitivity (Li et al. 2007). In human TRPM7, overlapping glutamic acid or aspartic acid residues have been identified in the pore region with similar results [D1054, E1052, and D1059 (Numata and Okada 2008)]. The pH sensitivity of TRPM7's selectivity profile is an interesting biophysical feature that has to be taken into account under acidic pathological conditions.

5.8 TRPM7 Inhibitors

Several compounds have been reported to inhibit TRPM7, although most of them lack potency or specificity or both. Extracellular spermine blocks endogenous TRPM7-like currents in RBL-2H3 cells with an IC_{50} of 2.3 μM, whereas 20 μM of SKF-96365, a nonspecific TRP channel and voltage-gated Ca channel blocker (Singh et al. 2010), is needed for complete block (Kozak et al. 2002a). 2-Aminoethyl diphenylborinate (2-APB), a compound found to interfere with a variety of proteins involved in Ca signaling, inhibits overexpressed human TRPM7 currents with an IC_{50} of 174 μM (Li et al. 2006). Endogenous TRPM7-like currents can be reversibly inhibited at 50 μM 2-APB in Jurkat T lymphocytes (Prakriya and Lewis 2002). Interestingly, while 2-APB inhibits TRPM7, it activates its paralog TRPM6, making this compound a useful tool in discriminating between currents carried by these two proteins (Li et al. 2006). Furthermore, it is now known that 2-APB does not bind directly to TRPM7, but rather inhibits channel activity through an intracellular acidification mechanism (Chokshi et al. 2012a).

The first high-throughput drug-screening bioassay targeting TRPM7 was developed in 2010 using fluorescent-based Mn quench in HEK293 cells overexpressing human TRPM7 (Castillo et al. 2010). This led to the discovery of the first specific and highly potent TRPM7 inhibitor waixenicin A, a compound isolated from the soft coral *Sarcothelia edmondsoni* (Zierler et al. 2011). Waixenicin A blocks TRPM7 currents in a Mg-dependent manner with an IC_{50} of 16 nM, and TRPM7-dependent cell proliferation is inhibited with an IC_{50} of 3.2 μM in RBL-1 cells. Waixenicin A has no effects on other major pathways that regulate Ca influx such as TRPM2, TRPM4, and Ca release-activated Ca (CRAC) channels (Zierler et al. 2011), and the compound also does not inhibit TRPA1 at 10 μM concentrations (Zierler and Fleig unpublished data). Importantly, waixenicin A does not affect TRPM7's sister channel TRPM6, adding another pharmacological tool for differentiating between TRPM6 and TRPM7 (Zierler et al. 2011).

Using an aequorin bioluminescence-based assay, several small conductance Ca-activated K channel inhibitors were found to act on TRPM7 (Chubanov et al. 2012), including the antimalarial plant alkaloid quinine, CyPPA, dequalinium, NS8593, SKA31, and UCL1684. Of those, the most potent compound was NS8593 with an IC_{50} of 1.6 μM. NS8593 is thought to be a direct channel blocker and seems to interfere with the Mg-dependent regulation of TRPM7 while also inhibiting the mobility of HEK293 (Chubanov et al. 2012). The broad-spectrum serine protease inhibitor and anticoagulant nafamostat mesylate interfere with heterologous mammalian TRPM7 with an IC_{50} of 27 μM (Chen et al. 2010a), and several 5-lipoxygenase inhibitors (NDGA, AA861, and MK886) inhibit TRPM7 in the higher μM range (Chen et al. 2010a). Sphingosine, the primary component of sphingolipids in the plasma membrane, and fingolimod, a structural analogue of sphingosine and FDA-approved for treatment of multiple sclerosis, are inhibitors of TRPM7 with IC_{50}s of 600 nM and 720 nM, respectively (Qin et al. 2013). They act by reducing the open probability of the channel. Metabolites of sphingosine, such as sphingosine-1-phosphate or ceramides, have no effect. These properties are reminiscent of the sphingolipid effects reported for CRAC channels (Mathes et al. 1998). One known side effect of calcineurin inhibitors is hypomagnesemia. Cyclosporin A and FK506 (tacrolimus), important calcineurin inhibitors, affect Mg flux as assessed by MagFura measurements in the intestinal epithelial cell line CaCo (Gouadon et al. 2012). While cyclosporin A counteracts Mg accumulation, FK506 increases Mg influx without altering expression levels of TRPM6, TRPM7, or MagT1.

In conclusion, several compounds interfere with TRPM7 at various potencies or selectivity. Both 2-APB and waixenicin A could be useful tools to pharmacologically differentiate between TRPM6 and TRPM7.

6 Physiological Functions in Native Cells, Organs, and Organ systems

Early evidence pointed to TRPM7's possible involvement in cellular Ca and Mg homeostasis as well as cell viability and proliferation (Penner and Fleig 2007). Further studies identified central roles in cell migration, exocytosis, and development (Runnels 2011), and disruption of normal TRPM7 function has been associated with the progression of cancer, severity of brain ischemia, and cardiovascular disease.

6.1 Magnesium Homeostasis

The channel's involvement in cellular Mg homeostasis was shown through genetic knockout experiments in chicken B lymphocytes, leading to an arrest in cell proliferation and reduced intracellular Mg levels that could be rescued exclusively by high extracellular Mg supplementation (Schmitz et al. 2003). Interfering with

TRPM7 channel function by a genetic knockout of the kinase domain arrests mouse embryonic stem cell proliferation that again can be rescued by high external Mg (Ryazanova et al. 2010). Such rescue of TRPM7-deficient cells is now known to be mediated by endogenous expression of alternate Mg transporters such as SLC41A1 (Kolisek et al. 2008), SLC41A2 (Sahni et al. 2007), or MagT1 (Deason-Towne et al. 2011), depending on cell type.

TRPM7 is not only important for cellular Mg homeostasis but is also involved in maintaining systemic Mg levels (Ryazanova et al. 2010). Mice heterozygotic for a TRPM7 kinase domain deletion develop hypomagnesemia compared to control mice. This seems to be caused by a deficit in Mg absorption through the colon rather than reabsorption mechanisms through the kidney. On the other hand, tissue-specific deletion of TRPM7 in T lymphocytes of mice does not alter total Mg contents of these cells (Jin et al. 2008). This is not surprising, since selective tissue-specific deletion of TRPM7 is not expected to alter overall systemic Mg homeostasis, and T cells express compensating Mg transporters such as MagT1 (Li et al. 2011).

Amidst discussions of the importance of TRPM7 in cellular and systemic Mg homeostasis, it should be remembered that the channel represents a divalent ion influx mechanism for other divalent ion species, including Ca and trace metals (Monteilh-Zoller et al. 2003). Interestingly, TRPM7's ability to conduct Ca is currently linked to a disease-inducing role such as in neuronal ischemia or atrial fibrillation (Du et al. 2010; Aarts et al. 2003). The physiological role of Ca conductance by TRPM7 remains largely unexplored. Indeed, even TRPM7's role in cell migration seems to be linked to its ability to conduct Mg rather than Ca (Su et al. 2011), despite a close correlation between TRPM7 plasma membrane localization and cellular Ca hot spot microdomains thought to drive cell migration (Wei et al. 2009; Clark et al. 2006). Finally, recent work implicates TRPM7-mediated Cd uptake in osteoblast cytotoxicity (Martineau et al. 2010; Levesque et al. 2008), further emphasizing TRPM7's physiological role as a divalent ion channel mechanism.

6.2 Cell Proliferation, Cell Death, and Cell Differentiation

Genetic or pharmacological ablation of TRPM7 in proliferating tissue arrests cells at G0/G1 transition of the cell cycle (Zierler et al. 2011; Tani et al. 2007; Schmitz et al. 2003; Nadler et al. 2001; Abed and Moreau 2007; Sahni et al. 2010). When arresting RBL-2H3 cells at various stages of the cell cycle, endogenous TRPM7-like currents are significantly upregulated at the G0/G1 transition (Tani et al. 2007), further emphasizing the critical role of this channel at the transition stage from quiescence to proliferation. Differentiated mast cells, on the other hand, undergo apoptosis upon genetic suppression of TRPM7 (Ng et al. 2012), and similar observations are made in hepatic stellate cells, possibly involving the TNF-related apoptosis-inducing ligand (TRAIL) mechanism (Liu et al. 2012). Interestingly, proliferating rat embryonic hepatocytes and rat hepatoma show

higher TRPM7 expression levels than adult nondividing rat hepatocytes, indicating that downregulation of endogenous TRPM7 is linked to the differentiation process (Lam et al. 2012). Thus, it appears that TRPM7 is critical for the physiology of proliferating cells to maintain cell numbers, whereas differentiated cells reduce the expression of TRPM7 to levels that sustain supplementation of cells with Ca, Mg, and trace metals.

6.3 Migration

Early observations link TRPM7 activity to maintenance of cell structure, as TRPM7 overexpression in HEK293 cells leads to rounding and detachment of cells from the substrate, which requires functional m-calpain activity and depends on Ca influx through the TRPM7 channel domain (Nadler et al. 2001; Su et al. 2006). Activation of m-calpain by TRPM7 is thought to work through stress-dependent stimulation of p38 MAP kinase and JUN kinase, as inhibitors of these proteins inhibit the cell rounding and detachment caused by overexpressing TRPM7 (Su et al. 2010). TRPM7 seems to be partially responsible for supporting activated T cell migration as well as the velocity of migration (Kuras et al. 2012), and genetic suppression of TRPM7 in migrating WI-38 fibroblasts leads to a reduced number of Ca flickers accompanied by a disruption of normal cell migratory patterns (Wei et al. 2009). Interestingly, both intracellular Mg and Ca can influence m-calpain activity (Su et al. 2010), and indeed Rac- and Cdc42-dependent polarized cell movement of fibroblasts relies on the availability of intracellular Mg and not Ca (Su et al. 2011). Further studies identify TRPM7 as controlling actomyosin contractility and cell adhesion by increasing cellular Ca levels, and this involves a phosphorylation step utilizing the channel's kinase (Clark et al. 2006). Thus, it seems that divalent ion influx through TRPM7 is involved in cell adhesion and migration, whereas the protein's kinase domain supports actomyosin contractility.

7 Lessons from Knockouts

The role of TRPM7 in living organisms has been investigated in several genetically tractable animal models such as mouse (*M. musculus*), zebrafish (*D. rerio*), and frog (*Xenopus laevis*). The roles of TRPM7-related proteins have also been explored in invertebrate species such as fruit fly (*Drosophila melanogaster*) and roundworm (*Caenorhabditis elegans*).

7.1 Mouse *Trpm7*

Two *Trpm7* null mutant mice [$Trpm7^{\beta geo}$ and $Trpm7^{\Delta 17}$ (Table 1)] and mouse mutants lacking exons encoding the kinase domain [$Trpm7^{\Delta kinase/\Delta kinase}$ (Table 1)] die at embryonic day 6.5–7.5 (e6.5–e7.5) and e7.5, respectively (Ryazanova

Table 1 Mouse lines carrying mutant alleles in *Trpm7* gene

Allele	Targeting strategy	Functional outcome	References
$Trpm7^{\beta geo}$	Insertion of β-geo reporter sequence in the first intron of Trpm7	Constitutive loss of function and expression of β-galactosidase driven by Trpm7 promoter	Jin et al. (2008)
$Trpm7^{fl}$	LoxP sites flanking exon 17	Cre-mediated loss of function due to a frame shift	Jin et al. (2008, 2012)
$Trpm7^{\Delta 17}$	Deletion of exon 17 in $Trpm7^{fl}$	Constitutive loss-of-function due to a frame shift	Jin et al. (2008)
$Trpm7^{\Delta kinase}$	Deletion of exons 32–36	Constitutive deletion of the kinase domain	Ryazanova et al. (2010)

et al. 2010; Jin et al. 2008). The reasons for this remain unclear. As briefly discussed above, mice heterozygotic for the TRPM7 kinase ablation ($Trpm7^{\Delta kinase/+}$) have reduced Mg levels in the blood, bone, and urine (Ryazanova et al. 2010). In contrast to wild-type control mice, a substantial fraction of heterozygotic animals die shortly after placing them on a Mg-deficient diet. In addition, $Trpm7^{\Delta kinase/+}$ mice exhibit behavioral alterations indicative of Mg deficiency (clasping, tremors, and seizures). Embryonic stem (ES) cells isolated from these animals show reduced TRPM7 currents due to an increased sensitivity to intracellular Mg. Thus, experiments with $Trpm7^{\Delta kinase/+}$ mice indicate that a key aspect of TRPM7 function is a regulation of systemic Mg homeostasis.

Conditional mutagenesis of the *Trpm7fl* allele (Table 1) using Cre/loxP-recombination technologies has been employed to elucidate a spatiotemporal requirement for *Trpm7* during embryonic development. Here, an epiblast-restricted inactivation of *Trpm7* leads to lethality indicating that TRPM7 is required within the embryo proper (Jin et al. 2008). Furthermore, global disruption of *Trpm7* at different embryonic stages using a tamoxifen (TM)-inducible Cre-ER transgene uncovers embryonic lethality during e7–e9. In contrast, TM-induced mutagenesis of *Trpm7* at e14.5 is compatible with prenatal development since healthy *Trpm7* null pups are born with expected Mendelian inheritance. Surprisingly, the TM-induced inactivation of *Trpm7* in adults causes no obvious phenotype, suggesting that *Trpm7* is indispensable only before and during organogenesis (Jin et al. 2008). However, one caveat to keep in mind is the difficulty to accurately assess whether the incomplete deletion of *Trpm7* observed in the tissue of this mouse model is sufficient to induce a true *Trpm7* null phenotype.

Several Cre transgenic lines with tissue-specific recombination activity were used to elucidate the organ-restricted requirements of *Trpm7*. First, deletion of *Trpm7* in the T cell lineage disrupts thymopoiesis and leads to a developmental block of thymocytes and a progressive depletion of thymic medullary cells (Jin et al. 2008). Second, disruption of *Trpm7* in the embryonic ureteric bud causes ablation of the protein in collecting ducts of the postnatal kidney without obvious morphological alterations (Jin et al. 2012). In contrast, deletion of *Trpm7* in the embryonic metanephric mesenchyme leads to inactivation of the gene in renal

tubules of the kidney. The latter mutants show a reduction in glomeruli number, renal tubular dilation, and formation of cysts in the proximal tubules, indicating that *Trpm7* is essential for nephrogenesis. Third, disruption of *Trpm7* in neural crest (NC) cells at e10.5 results in loss of dorsal root ganglion sensory neurons and skin pigment cells (Jin et al. 2012). However, disruption of *Trpm7* in the embryonic neural stem (NS) cells at e10.5 does not influence normal brain development. Studies with NS cells in vitro reveal that *Trpm7* is not essential for their self-renewal and differentiation. In contrast, during in vitro differentiation of induced pluripotent stem cells to NS cells, *Trpm7* disruption prevents the formation of the NS cell monolayer. Thus, *Trpm7* seems essential for NC progenitors but dispensable once the progenitors are committed.

The role of *Trpm7* in cardiogenesis has been studied by heart-restricted mutagenesis of the conditional *Trpm7* allele (Sah et al. 2013). Cardiac deletion of *Trpm7* at e9.0 results in congestive heart failure and death. In contrast, inactivation of Trpm7 at e13.0 produces viable mice with normal ventricular function. Deletion of Trpm7 at an intermediate time point reduces viability of the mutants to 50 %. The surviving mutant mice develop cardiomyopathy associated with heart block, impaired repolarization, and ventricular arrhythmias.

7.2 Zebrafish and Frog

Several loss-of-function mutations in zebrafish *Trpm7* (*zTrpm7*) have been described. *zTrpm7*-deficient animals undergo normal early morphogenesis. However, mutant larvae exhibit multiple defects including loss of touch responsiveness, defective melanin synthesis and apoptotic death of melanophores, defective proliferation of epithelial cells in the exocrine pancreas, and lethality in late larval life (Yee et al. 2011; McNeill et al. 2007; Low et al. 2011; Elizondo et al. 2005, 2010). *zTrpm7* mutant larvae have reduced total levels of Mg and Ca, and addition of supplemental Mg, but not Ca, partially rescues melanophore survival and proliferation of cells in the exocrine pancreas (Yee et al. 2011; Elizondo et al. 2010). *zTrpm7* mutants develop kidney stones and express higher levels of stanniocalcin 1 (stc1) and anti-hyperphosphatemic factor, fibroblast growth factor 23 (fgf23) (Elizondo et al. 2010). Stc1 modulates total Mg and Ca levels both in mutant and wild-type larvae. The levels of Mg and Ca can be normalized in *zTrpm7* mutants by a block of stc1 activity, whereas the formation of kidney stones can be prevented by knockdown of fgf23.

A role of TRPM7 in early embryonic development has also been studied by genetic manipulation of *X. laevis* embryos. Knockdown of *Xenopus Trpm7* (*xTrpm7*) transcripts using morpholino oligonucleotides reveals that *xTrpm7* in conjunction with noncanonical Wnt signaling regulates cell polarity and migration during gastrulation (Liu et al. 2011). The gastrulation defect can be rescued by exogenous Mg and by overexpression of the Mg transporter SLC41A2 or a dominant negative form of Rac. This suggests that TRPM7-mediated entry of Mg plays an important role in vertebrate gastrulation.

7.3 Fruit Fly and Roundworm

D. melanogaster harbors a single *Trpm* gene (*dTrpm*) encoding a channel subunit that lacks a kinase domain. *dTrpm* is highly expressed in the Malpighian tubules (equivalent of mammalian kidneys). *dTrpm* null mutants develop slowly as larvae and arrest as prepupae with morphological defects in the Malpighian tubules (Hofmann et al. 2010). *dTrpm*-deficient larvae show increased Mg levels in the body when raised on Mg-enriched diets indicating that *dTrpm* regulates removal of Mg from the hemolymph by the Malpighian tubules. *dTrpm* may also regulate Zn homeostasis. It was reported that dTrpm-deficient larvae exhibit low Zn levels, and this phenotype can be rescued by Zn supplementation (Georgiev et al. 2010).

C. elegans has three TRPM channels genetically related to TRPM7: GON-2, GTL-1, and GTL-2. Like dTRPM, these channels do not contain enzyme domains. GON-2 and GTL-1 are expressed in the intestine and regulate Mg uptake, while GTL-2 controls Mg excretion by the excretory cells (Teramoto et al. 2005, 2010). Moreover, *gon-2/gtl-1* double mutants show reduced body Mg levels and a growth defect, which can be rescued by dietary Mg, but not Ca (Teramoto et al. 2010).

In summary, the experiments with genetically tractable animal models support the idea that TRPM7 and its genetic relatives are essential for early development, organogenesis, and regulation of Mg homeostasis.

8 Role in Hereditary and Acquired Diseases

TRPM7 is not the only ion channel whose activity is controlled by the availability of intracellular Mg · ATP. Early studies identified ATP-sensitive voltage-dependent chloride (Cl-) channels in the sarcoplasmic reticulum of rabbit skeletal muscle (Kourie 1997) and in the plasma membrane of various tissue, including mouse cortical collecting ducts (Meyer and Korbmacher 1996) and human T cells (Cahalan and Lewis 1988). CFTR ion channel gating is regulated by ATP binding and hydrolysis in synergy with intracellular Mg (Ikuma and Welsh 2000), and activity of the ATP-sensitive K^+ channels in pancreatic β-cells is determined by the intracellular concentration ratio of Mg · ATP over Mg · ADP (Tarasov et al. 2004). As such, these ion channels function as sensors of cell metabolism, and any changes in availability of either glucose or oxygen will affect their channel activity with varying impact on cell (patho)physiology. For TRPM7 this was most dramatically demonstrated in a mouse model of transient global ischemia, where small interfering RNA-induced suppression of TRPM7 in the right hippocampus protected neurons from undergoing cell death compared to control (Sun et al. 2009). Ample in vitro studies corroborate the involvement of TRPM7 in oxygen-glucose deprivation-induced neuronal cell death (Aarts et al. 2003; Zhang et al. 2011), either caused by activation of channels by reactive oxygen species (Aarts et al. 2003; Coombes et al. 2011), by changes in extracellular divalent ions (Wei et al. 2007), or by TRPM7-mediated Zn^{2+} accumulation (Inoue et al. 2010). Epidemiologic studies inspired by these findings have performed comparative gene

expression analyses in mice to link TRPM7 to brain-related diseases such as multiple sclerosis, Alzheimer's disease, and stroke and found TRPM7 to be one of 18 common genes to be regulated in these mouse disease models (Tseveleki et al. 2010). However, a prospective, nested case-control study did not find a connection between incident risk of ischemic stroke and variations in the TRPM7 gene (Romero et al. 2009).

The TPRM7 channel kinase seems to play a role in various cardiovascular diseases. Early reports located TRPM7-like currents in pig, rat, and guinea pig ventricular myocytes (Gwanyanya et al. 2004) and most recently in human atrial myocytes (Macianskiene et al. 2012; Zhang et al. 2012a), although the channel kinase's role in this tissue remains to be determined. More is known about TRPM7's function in human cardiofibroblasts, where increased TRPM7-mediated Ca influx has been linked to increased myofibroblast differentiation and fibrogenesis in patients prone to atrial fibrillation (Du et al. 2010).

TRPM7 is also linked to hypertension. Vascular smooth muscle cells (VSMC) from spontaneously hypertensive rats have lower TRPM7 mRNA levels and significantly reduced intracellular Mg levels compared to VSMC from Wistar control, and this is linked to angiotensin II stimulation (Touyz et al. 2006). Interestingly, chronic angiotensin II application increases intracellular Mg in a TRPM7-dependent way leading to enhanced DNA and protein production, indicating cell growth (He et al. 2005). VSMC isolated from the ascending aorta of mouse respond to angiotensin II stimulation by upregulating TRPM7 expression, which triggers a Ca-dependent switch from contractile cell characteristics to a phenotype supporting cell proliferation (Zhang et al. 2012b). In human aortic VSMC, vascular calcification can be prevented on the cellular level by exposing cells to increasing external Mg concentrations, and the use of pharmacological tools implicates TRPM7 to be involved in this process (Louvet et al. 2013). Renal TRPM7 (and TRPM6) is downregulated in a mouse model of hereditary hypomagnesemiar (Yogi et al. 2011), which is further exacerbated by aldosterone administration to induce hypertension (Sontia et al. 2008). Mg supplementation can alleviate the effects induced by aldosterone, including hypertension, inflammation, and fibrosis.

The central function of TRPM7 in processes driving cell growth, proliferation, differentiation, and migration identifies the protein as a possible target in cancer (Sahni et al. 2010). Indeed, reducing TRPM7 expression inhibits proliferation in human head and neck carcinoma (Jiang et al. 2007) and human gastric adenocarcinoma cells (Kim et al. 2008). In other cancer cell lines, this experimental manipulation affects cell migration and invasiveness, such as in A549 lung cancer (Gao et al. 2011), human nasopharyngeal carcinoma (Chen et al. 2010b), BXPC-3 human pancreas adenocarcinoma (Rybarczyk et al. 2012), or MDA-MB-435 breast cancer cells (Meng et al. 2013). When comparing tumor tissue with normal tissue, TRPM7 is generally upregulated as assessed in human pancreatic adenocarcinoma (Rybarczyk et al. 2012; Yee et al. 2011), human breast cancer (Middelbeek et al. 2012), and rat hepatoma (Lam et al. 2012). This has led to the identification of TRPM7 as an independent predictor of poor outcome in breast cancer patients due to increased metastasis formation (Meng et al. 2013; Middelbeek et al. 2012).

Patient survival is inversely related to TRPM7 expression levels in human pancreatic ductal adenocarcinoma, where TRPM7 levels increase at higher tumor staging (Rybarczyk et al. 2012).

Based on TRPM7's unique permeation profile for both Ca and Mg, epidemiologic studies have started to look at the ratio of Ca:Mg intake and cancer risk. The T1482I polymorphism in the TRPM7 gene, thought to contribute to familial amyotrophic lateral sclerosis and Parkinsonism dementia in Guam (Hermosura et al. 2005) but not in Kii, Japan (Hara et al. 2010), is associated with elevated risk of adenomatous and hyperplastic polyps, both risk indicators of colorectal adenoma. This association is particularly strong when the Ca:Mg intake ratio is high (Dai et al. 2007) and gave reason to initiate a randomized placebo-controlled intervention clinical trial investigating whether a reduction of dietary Ca:Mg ratio lowers the risk of adenoma and hyperplastic polyps in patients who do or do not carry the T1482I allele (clinicaltrials.gov: NCT01105169). A retrospective analysis in age-matched prostate cancer patients shows a parallel increase in the serum Ca:Mg ratio and TRPM7 expression levels (Sun et al. 2013). For postmenopausal breast cancer, the medical hypothesis was brought forth that a higher ratio of Ca:Mg serum levels might parallel increased risk (Sahmoun and Singh 2010). Thus, TRPM7 as a Ca- and Mg-conducting ion channel may represent a novel target to be considered in cancer prevention and control.

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