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Role of TRPM7 kinase in cancer

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ABSTRACT

Cancer is the second leading cause of death worldwide and accounted for an estimated 9.6 million deaths, or 1 in 6 deaths, in 2018. Despite recent advances in cancer prevention, diagnosis, and treatment strategies, the burden of this disease continues to grow with each year, with dire physical, emotional, and economic consequences for all levels of society. Classic characteristics of cancer include rapid, uncontrolled cell proliferation and spread of cancerous cells to other parts of the body, a process known as metastasis. Transient receptor potential melastatin 7 (TRPM7), a Ca^{2+}- and Mg^{2+}-permeable nonselective divalent cation channel defined by the atypical presence of an α-kinase within its C-terminal domain, has been implicated, due to its modulation of Ca^{2+} and Mg^{2+} influx, in a wide variety of physiological and pathological processes, including cancer. TRPM7 is overexpressed in several cancer types and has been shown to variably increase cellular proliferation, migration, and invasion of tumour cells. However, the relative contribution of TRPM7 kinase domain activity to cancer as opposed to ion flux through its channel pore remains an area of active discovery. In this review, we describe the specific role of the TRPM7 kinase domain in cancer processes as well as mechanisms of regulation and inhibition of the kinase domain.

1. Introduction

1.1. The TRP superfamily

Transient receptor potential (TRP) channels are a superfamily of ion channels first described in the fruit fly *Drosophila melanogaster,* wherein photoreceptors with *trp* gene mutations demonstrated a transient, rather than the typical sustained voltage response to prolonged stimulation with light in an electroretinogram [1]. The closest mammalian homologs of the *Drosophila* TRP channel are the TRPC channel subfamily members, the first of which to be cloned being TRPC1 [2]. TRP channels have since been found to be expressed in a multitude of multicellular organisms, including, but not limited to, humans, zebrafish, worms, and mice [2].

Unlike other ion channels, TRP channel subfamilies are defined by sequence homology and membrane topology instead of by ligand function or ion selectivity; channels within this superfamily are all characterized as having six transmembrane domains (S1-S6) believed to assemble into homo- or hetero- tetramers to form cation-selective channels and have a diverse variety of functions, some of which are still unknown [3–5]. In general, however, TRP channels are non-selective cation channels that mediate sensory transduction by acting as intrinsic sensors of the cellular environment and sensory receptors for external stimuli [3]. This sensory function includes involvement in the external sensory modalities of vision, touch, hearing, taste, olfaction, thermo- and osmo-sensation, as well as individual cellular sensation of changes in the local environment [2]. Additionally, TRP channels also play important roles in ion homeostasis, muscle contraction, vasomotor control, and bone remodeling [6]. TRP channels are differentially activated by a wide range of stimuli and have

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numerous binding partners, which are primarily involved in channel regulation and function [5]. When activated, TRP channels depolarize cells via the influx of monovalent or divalent cations; permeability for different cations varies between channels, resulting in differential cellular effects [5,7]. For instance, the influx of Ca^{2+} and Mg^{2+} ions across the cell membrane via a plethora of TRP channels play essential roles in a wide variety of physiological processes, including muscle contraction, neurotransmitter release, cell proliferation, gene transcription, and cell death [5,8]. Many TRP channels facilitate changes in $[Ca^{2+}]_i$ by acting as Ca^{2+}-permeable cation channels and thus participate in numerous physiological and pathological processes [5]. One of these pathological processes is the progression of cancer cells, as a growing body of evidence suggests that alterations in expression levels of TRP channels play a crucial role in cancer cell proliferation and migration [9–12]. The TRP channel superfamily is broadly divided into two groups based on transmembrane sequence identity, which are further divided into seven main subfamilies based on amino acid homologies for approximately 30 mammalian TRP channels [3,5]. Subfamilies differ substantially in their sequence homology and structure, thus leading to significant differences in physiological function.

1.2. The TRPM family

The TRPM ('Melastatin') subfamily is composed of eight homologs of its first identified member, melastatin-1 (now termed TRPM1), and can be further classified into 4 subgroups based on sequence homology: TPRM1/3, TRPM2/8, TRPM4/5, and TRPM6/7 [5,13]. Members of the TRPM subfamily share approximately 20 % of their amino acid sequence identity with TRPC channels, over a ~325 residue region that includes the C-terminal five transmembrane segments and the TRP domain [4]. To generalize, common characteristics of TRPM channels include the presence of six transmembrane domains and cytoplasmic C- and N-terminal domains [13] wherein the C-terminal domain contains a TRP motif and tetrameric coiled-coil domain, while the N-terminal domain has a unique TRPM homology region (MHR) with functions in channel assembly and trafficking [14].

The TRPM subfamily contains members of varying size, ion permeability, and channel function. Sequence lengths of TRPM channel family members (1000–2000 amino acids) vary mainly due to differences in a large region C-terminal to the transmembrane domains known as the TRP domain [4,14]. TRPM2, TRPM6, and TRPM7 are particularly distinct due to their highly uncommon C-terminal enzyme domains; TRPM6 and TRPM7 both have serine-threonine protein kinase domains (α-kinase domains) whereas TRPM2 has an ADP-ribose pyrophosphatase domain (NUDT9 homology domain) [4,14]. TRPM channels also vary in their permeability to Ca^{2+} and Mg^{2+}; TRPM6/7 are Ca^{2+}-permeable whereas TRPM4/5 are impermeable to Ca^{2+} [5,15,16]. The TRPM channels are summarized in Table 1. Although characterized by similarities in their domains, members of the TRPM subfamily differ greatly in ion permeability and function.

1.3. TRPM7

TRPM7, the seventh member of the TRPM subfamily, is a divalent cation channel characterized by its permeability to Ca^{2+}, Mg^{2+}, and trace metal ions and, notably, its kinase activity [17]. Termed a "chanzyme" (or channel-kinase) for this dual function, TRPM7 is an atypical ion channel due to the presence of a serine/threonine protein kinase within its C-terminal domain, a feature that is shared with TRPM6 [17–19]. Unlike TRPM6, however, TRPM7 is ubiquitously expressed, suggesting an essential role in cellular functioning [17]. TRPM7 plays an essential role in Mg^{2+} and Ca^{2+} homeostasis in a variety of cell types in both physiological and pathological situations [20,21]. Moreover, TRPM7 is centrally involved in the physiological processes of cell proliferation, viability, migration, adhesion, and apoptosis in response to certain intracellular triggers, necroptosis, exocytosis, organogenesis, and embryonic development [17,22–24]. Several experiments highlight the significant function of TRPM7 in cell proliferation, viability, and migration. DT-40 cells lacking TRPM7 lose their proliferation capabilities and die after several days in culture, a process that appears to involve depletion of intracellular Mg^{2+} levels, as supplementation of cultures with extracellular Mg^{2+} restores proliferation [19,21]. The role of TRPM7 in cell migration was first elucidated via experiments involving the colocalization of Ca^{2+}-dependent protease

Table 1
Summary of TRPM subfamily channels.

Channel	Group	Structural characteristics	Activation	Physiological Functions	Human tissue expression	References
TRPM1	1	TRPM1-S truncated N terminal, lacks six transmembrane domains	Pregnenolone sulfate, glutamate decrease	Tumour suppression in melanoma cells, bipolar cell depolarization	Retina ON bipolar cells, skin melanocytes	[13,14,115]
TRPM2	2	C-terminal ADP ribose-pyrophosphatase domain (NUDT9 domain)	ADP-ribose, reactive oxygen and nitrogen species (ROS/RNS), Ca^{2+}	Cellular reduction-oxidation sensation, core body temperature regulation, insulin secretion, immune response, apoptosis	Central nervous system, immune cells, pancreatic β cells, bone marrow	[13,14,116]
TRPM3	1	Longer N-terminal and C-terminal, two calmodulin binding sites	Heat, CIM0216, pregnenolone sulfate, nifedipine)	glucose homeostasis, heat sensation, inflammatory pain	Kidney, nociceptive neurons, CNS, testis, ovary pancreatic β cells	[14,117,118]
TRPM4	3	Serine 1044	Ca^{2+}, $PI(4,5)P_2$, PKC	Regulation of Ca^{2+} oscillations after T cell activation, regulation of cardiac conduction, regulation of smooth muscle contraction, taste sensation (sweet, umami, bitter)	Intestine, prostate, heart, liver	[13,14,119]
TRPM5	3	Serine 1044	Ca^{2+}, steviol glycosides, rutamarin	Taste sensation (sweet, umami, bitter), modulation of insulin secretion, post-ingestion chemosensation	Intestine, taste bud cells, Pancreatic β cells, solitary chemosensory cells	[13,119,120,121]
TRPM6	4	Serine-threonine protein kinase domain (α-kinase domain)	Mg^{2+}	Active Mg^{2+} reabsorption and homeostasis in kidney and intestine	Kidney, intestine	[13,14]
TRPM7	4	Serine-threonine protein kinase domain (α-kinase domain)	Mg ·ATP, breakdown of PIP2, increase in cAMP concentrations	Mg^{2+} and Ca^{2+} homeostasis, cell viability, cell adhesion, cell proliferation, cell migration, embryonic development	Ubiquitous	[2,6,14,17]
TRPM8	2		Cold temperatures (8−28 °C), cooling sensation compounds (e.g. menthol, eucalyptol, icilin)	Thermosensation, thermoregulation, pain sensation, bladder function, Ca^{2+} homeostasis, inflammation	Sensory neurons, prostate	[13,14,122,123,124]

m-calpain and TRPM7 to peripheral adhesion complexes [25]. Wound-healing assays showed that silencing TRPM7 via RNA interference significantly increased the motility of HEK-293 cells, suggesting that TRPM7 regulates cell adhesion and migration [25]. Furthermore, TRPM7 plays a role in Fas receptor-induced apoptosis, TNF-related apoptosis-inducing ligand (TRAIL)-induced apoptosis, and oxygen-glucose deprivation/reoxygenation (OGD/R)-induced neuronal apoptosis [26–28]. Several studies have shown that TRPM7 homozygous knock-out mice experience developmental arrest after embryonic day 7.5, demonstrating that the TRPM7 is essential for proper embryonic development [21,29,30]. Heterozygous knock-out mice for the kinase domain were viable but presented abnormalities in Mg^{2+} regulation, particularly intestinal Mg^{2+} absorption [21]. TRPM7 also has functions in neuronal cell death and regulation of both the cell cycle [31–33] and the immune response [34,35].

1.4. The TRPM7 kinase domain

The TRPM7 kinase domain very closely resembles members of the α-kinase family. Members of this family include the *Dictyostelium* myosin heavy chain (MHC) kinases A, B, and C, and elongation factor-2 kinase (eEF2k), which phosphorylate serine and threonine residues within α-helices rather than within irregular and flexible regions [19,36,37]. The TRPM7 kinase domain is a 95 kDa region located intracellularly at the C-terminus and exists in vivo as a 'dimer of dimers' [37–39]. The C-terminal lobe of the TRPM7 kinase domain contains a zinc finger homology domain, which is required to maintain kinase domain structural stability [39]. Functions of the TRPM7 α-kinase domain are not well-known; however, numerous potential substrates of the kinase have been identified, including histone H3 [38], annexin 1 (Ser5) [40,41], myosin IIA (Thr1800, Ser1803, Ser1808), IIB, and IIC [42,43], eEF2 (indirect) (Ser77 of eEF2k) [44], Smad2 (Ser465/467) [45], tropomodulin 1 [46], myelin basic protein [17], and phospholipase Cγ2 (PLCγ2) (Ser1164, Thr1045) [17,47]. Through the phosphorylation of cytoskeletal proteins, including myosin IIA heavy chain and tropomodulin 1, the TRPM7 kinase plays a role in cytoskeletal organization, cellular adhesion, and cell migration with specific involvement in Ca^{2+}-dependent actin and myosin (actomyosin) contractility and actomyosin remodeling [48,49]. Indeed, tropomodulin 1 controls actin filament dynamics by acting as a capping protein on both the pointed ends of filaments and free actin monomers [50]. Phosphorylation of tropomodulin 1 by TRPM7 impedes its actin capping ability and its affinity for actin [46]. Furthermore, the phosphorylation of myosin II heavy chain (MHC-II) by the TRPM7 kinase disrupts myosin II filament-forming ability and subcellular distribution in vitro, thereby altering filament stability and cell morphology [42,43,48]. TRPM7 channel-dependent Mg^{2+} influx has also been demonstrated to regulate myosin II activity in vivo [51]. As well, annexins such as the TRPM7 substrate annexin 1 interact with membrane phospholipids in the presence of Ca^{2+} to link Ca^{2+} signaling with actin dynamics and membrane function [52,53]. Phosphorylation of annexin 1 at Ser5 in the N-terminal α-helix is thought to interfere with its membrane interactions by preventing α-helical conformation and peptide-substrate binding [41]. However, the effects of annexin 1 phosphorylation on actin dynamics remain undefined and may contribute to the significant role of TRPM7 in cytoskeletal dynamics [49]. The activation of annexin 1 by TRPM7 has additionally been implicated in bradykinin-induced cell migration and invasion in human and murine vascular smooth muscle cells in conjunction with Mg^{2+} influx [54]. Distinct from any involvement in cytoskeletal dynamics, the TRPM7 kinase-mediated phosphorylation of PLCγ2 at Ser1164 in the C2 domain has been suggested to regulate the sensitivity of B cell receptor (BCR) signaling to Mg^{2+}. Deason-Towne et al. (2012) found that the PLCγ2 S1164A mutation in DT40 B cells produces reduced the B cell receptor (BCR)-mediated Ca^{2+} signal under low Mg^{2+} conditions compared to physiological Mg^{2+}-levels [47]. These results suggest the involvement of the TRPM7 kinase in the integration of environmental signals with the activation of the immune response [47]. Deason-Towne et al. (2012) also demonstrated that the TRPM7 kinase also phosphorylates PLCγ2 at Thr1045 in the linker region preceding the C2 domain [47]. Moreover, it was shown that proteolytic cleavage of the TRPM7 kinase domain enables the kinase to translocate to the nucleus and bind to components of chromatin remodeling complexes in a Zn^{2+}-dependent manner, resulting in phosphorylation of the Ser/Thr residues on histones [55]. These residues are involved in transcription regulation, DNA repair, mitotic chromatin condensation, and other cellular functions [55]; consequently, the TRPM7 kinase is involved in the regulation of gene expression [49]. Chromatin remodeling further implicates the TRPM7 kinase domain in the regulation of cell growth and proliferation in conjunction with indirect eEF2 phosphorylation [24]. The phosphorylation of eEF2 and PLCγ2 have been demonstrated to be regulated by external Mg^{2+} concentrations, suggesting that the kinase domain is dependent on external Mg^{2+} concentrations [44,47]. Under hypomagnesic conditions, TRPM7 phosphorylates eEF2k, which subsequently phosphorylates eEF2; thus, eEF2 is an indirect substrate of the TRPM7 kinase [37]. TRPM7 kinase inactivation has been found to lead to an Mg^{2+} deprivation resistance phenotype in mice; when fed Mg^{2+}-deficient diets, mice with inactive TRPM7 kinase domains survived three times longer than their wild-type counterparts, suggesting that the kinase domain is a sensor of Mg^{2+} status and coordinates cellular and systemic responses to Mg^{2+} deprivation [56]. In addition to its functions in regulating cytoskeletal dynamics, gene expression, and responses to decreases in Mg^{2+}, the TRPM7 kinase domain is known to modulate store-operated calcium entry (SOCE), which is essential for the maintenance of endoplasmic reticulum Ca^{2+} concentrations in resting cells, as well as the replenishment of intracellular Ca^{2+} stores after Ca^{2+} signalling events [57,58]. Hence, the TRPM7 kinase domain has a variety of substrates, leading to its involvement in cytoskeletal dynamics, SOCE, gene expression, cell growth and proliferation, and other functions (Fig. 1).

1.5. Interactions between the TRPM7 ion channel and kinase domain

Interactions between the ion channel and kinase domain are an ongoing area of investigation.

Studies have shown that the kinase activity of TRPM7 influences protein expression levels [25], the subcellular localization of the channel [59], and channel activity and sensitivity to Mg^{2+} and Mg·ATP inhibition [19]. Protein expression of TRPM7 has been found to be lower in cells expressing kinase-inactive mutants than wild type TRPM7 cells [25]. This suggests that kinase activity of TRPM7 may be crucial for channel expression.

TRPM7 kinase activity appears to be important for the biophysical properties of the channel. An initial report has suggested that the kinase domain is required for ion channel activity, as whole-cell current amplitudes of TRPM7 channels with mutant kinase domains were significantly decreased compared to wild-type TRPM7 in HEK-293 cells [60]. However, additional data show that while the kinase domain of TRPM7 may not be crucial for channel activation [61], evidence exists of functional coupling between kinase activity and Mg^{2+} and Mg·ATP sensitivity of TRPM7, where structural modifications to the kinase domain alter the sensitivity of the channel to suppression by intracellular Mg^{2+} and Mg·ATP [19]. Here, two separate single point mutations that left the kinase domain inactive enhanced heterologous TRPM7 currents and rendered them much less sensitive to Mg^{2+} and Mg·ATP suppression. At the same time, ablation of the kinase domain downstream of the protein's coiled-coil region had the opposite effect [19]. This suggested a role of TRPM7 in Mg^{2+} homeostasis that could be under regulatory influence through its kinase domain [19]. Indeed, subsequent in vivo work by two independent groups revealed that TRPM7 kinase inactivation in TRPM7 'kinase-dead' mutant mice does not significantly perturb native TRPM7 currents representing channel activity in peritoneal macrophages [56,61]: additionally, both studies showed that

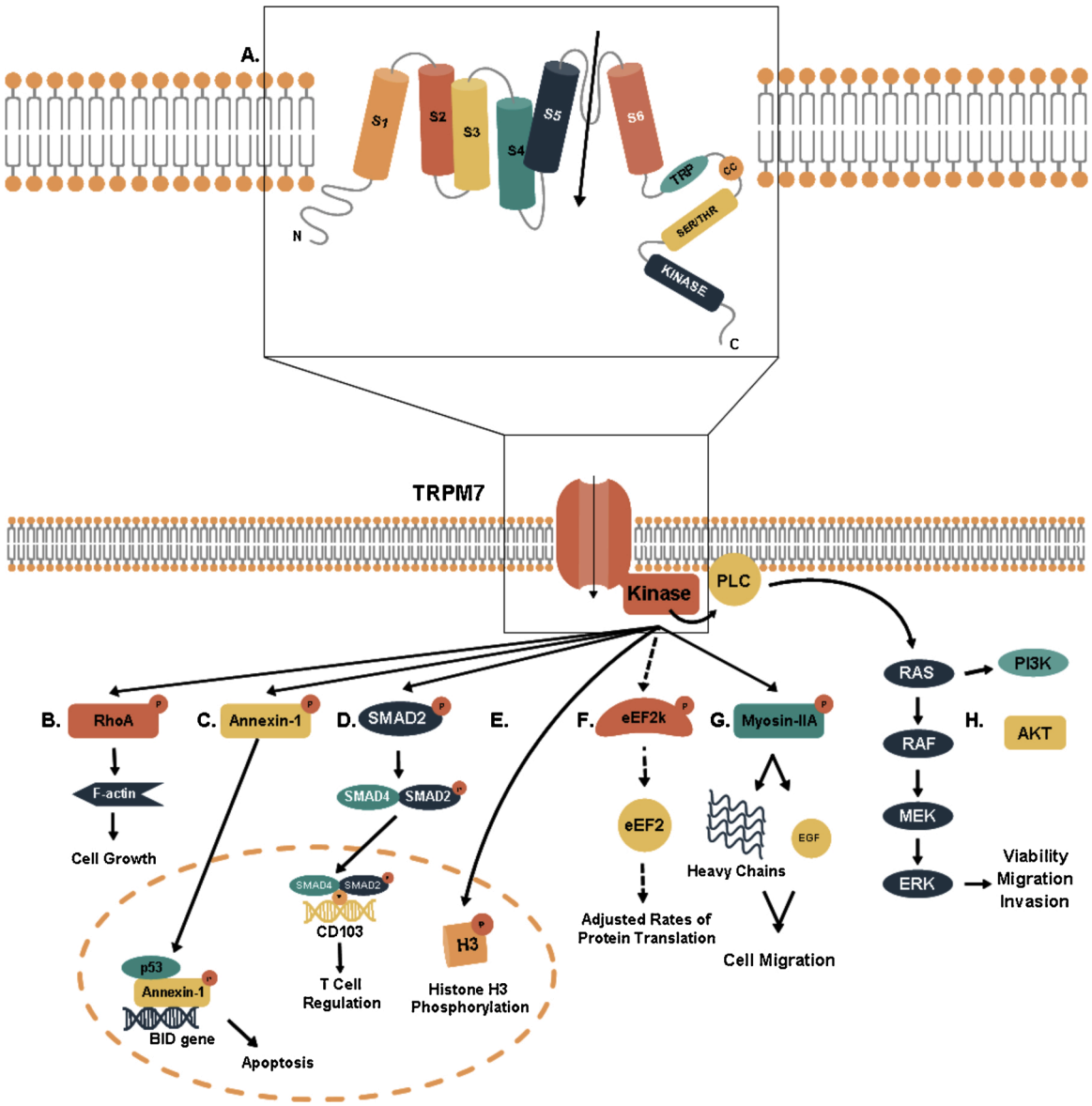

Fig. 1. Structure of the TRPM7, a nonselective cation channel, permeable to Ca^{2+}, Mg^{2+} and select divalent metal ions and schematic pathways of TRPM7 kinase function in the cell. A. Shown here to have 4 N-terminal MHR domains, six transmembrane segments, a 23-25 amino acid TRP domain, and a serine/threonine protein kinase on the C-terminal of the sixth transmembrane domain. TRPM7 plays an essential role in Ca^{2+} and Mg^{2+} homeostasis, influencing a variety of downstream effects. B. RhoA is phosphorylated to increase F-actin and form MRTF-A-Filamin A complex for cell growth [90]. C. Annexin-1 is a substrate of the TRPM7 kinase that is required to be phosphorylated for proper translocation into the nucleus, to then interact with the BID gene and p53 protein to induce apoptosis via the p53-BID-caspase-3 pathway [40,41,113]. D. SMAD2 can be phosphorylated and combined with SMAD4 to increase the transcription of CD103 to regulate T-cells [45]. E. Histone H3 can be phosphorylated by the TRPM7 kinase [38]. F. eEF2k can indirectly be phosphorylated by the TRPM7 kinase to increase eEF2 protein levels that may regulate the rates of protein translation in a cell [44]. G. Myosin IIA is another substrate of the TRPM7 kinase that can also assist Annexin-1 through the cytoplasm, but when phosphorylated can stabilize the Myosin II heavy chains and interacts with EGF, influencing a cell's ability to migrate [42,43]. H. TRPM7 kinase can also interact with phospholipase Cγ2 triggering the RAS and PI3K cascades to lead to increased cell viability, migration and invasion, making it a critical component to cancer cell investigation [47,114].

TRPM7 kinase-dead mutant mice had regular serum Mg^{2+} levels and exhibited normal development, indicating that kinase activity is not involved in channel function. Furthermore, neither macrophages [61] nor mouse embryonic fibroblasts [56] isolated from TRPM7 kinase-dead mice demonstrated any changes in maximum TRPM7 current activity compared to wild-type mice [56,61]. However, basal TRPM7 channel activity representing the channel-kinase's activity in an intact cell was, as predicted, significantly potentiated in kinase-dead mice [61] due to lower channel sensitivity to intracellular Mg^{2+} [19], further implicating the TRPM7 kinase domain in mediating channel sensitivity to Mg^{2+}. It is tempting to speculate that such enhanced basal TRPM7 channel activity might contribute to the relative resistance of kinase-dead mice to the side effects of hypomagnesemia, which include allergic reactions and increased mortality [56]. On the opposite spectrum, mice heterozygotic for a TRPM7 kinase deletion developed significant hypomagnesemia in vivo [21]. Aligned with this finding was the observation that native TRPM7 currents, assessed in mutant mast cells with TRPM7 kinase deletions, were strongly supressed compared to wild type [21].

Cai et al. (2018) described another relationship between the two in which kinase activity functionally regulates ion channel stability and subcellular localization [59]. It appears that kinase activity plays a critical role in regulating proteasome-mediated turnover of the channel. Measurement of TRPM7 protein levels after inhibition of protein synthesis in tetracycline-inducible HEK-293 cells expressing either

wild-type TRPM7 and kinase-inactive TRPM7 (TRPM7-K1646A) found that wild-type (WT) protein levels were significantly more resistant to protein synthesis inhibition than kinase-inactive protein levels [59]. Indeed, wild-type TRPM7 protein levels remained relatively stable over 24 h after inhibition of protein synthesis whereas kinase-inactive protein levels decreased rapidly with a half-life of 8.1 h [59]. As protein synthesis inhibition blocks an early step in the protein turnover cycle in order to observe effects on degradation, we can thus conclude that degradation is greater in TRPM7 kinase mutants compared to WT TRPM7 and thus, the TRPM7 kinase is involved in decreasing protein turnover. Coimmunoprecipitation of either WT or K1646A TRPM7 with FLAG-ubiquitin revealed that only the kinase-inactive mutant coimmunoprecipitated with ubiquitin, suggesting that kinase-inactivated TRPM7 may be targeted by ubiquitin for degradation via the ubiquitin-proteasome pathway [59], thus contributing to protein turnover. Analysis of subcellular localization showed that WT-TRPM7 channels heterologously expressed in opossum kidney (OK) cells normally localize to the basolateral membrane, whereas K1646A-TRPM7 was retained intracellularly and did not localize readily to the basolateral side of the cells [59]. Failure to localize in kinase-inactive TRPM7 OK cells is thought to occur due to the absence of TRPM7 autophosphorylation-dependent 14-3-3θ binding [59]. Therefore, autophosphorylation by the kinase domain may affect the cellular localization of the TRPM7 channel. Furthermore, proteasome inhibition assays confirmed that K1646A TRPM7 channels in OK cells are more disposed to proteasome-mediated degradation compared to WT [59]. In general, activity of the TRPM7 α-kinase domain appears to contribute to channel-kinase function in Ca^{2+} homeostasis and plays a role in Mg^{2+} homeostasis. Overall, further research seems justified to elucidate the relationship between the ion channel and kinase domain of TRPM7, including confirmation of the role of the kinase domain in channel function and Mg·ATP sensitivity.

1.6. TRPM channels in cancer

TRPM channels have been found to be involved in various types of cancer, including prostate cancer, pancreatic cancer, lung cancer, breast cancer, melanoma, and gastric cancer, among others [62]. TRP channels are associated with cancer progression due to their influence over Ca^{2+} and, in the case of TRPM7, Mg^{2+} cytosolic concentrations. High expression levels of these cation channels increase Ca^{2+} and Mg^{2+} influx, promoting ion-dependent proliferative pathways and resulting in the classic characteristics of cancer, including aberrant proliferation, differentiation, and apoptosis of cells [20,63,64]. The specific involvement of the eight TRPM channels varies depending on the cancer type. For example, TRPM1 is the main TRPM channel involved in melanoma, where decreased TRPM1 expression is associated with progression of primary cutaneous and vertical growth phase melanomas [62]. Indeed, TRPM1 mRNA is almost or entirely absent in most invasive primary melanomas, suggesting that the *Trpm1* gene is a tumour suppressor gene for melanoma [62]. Overexpression of TRPM2 promotes cancer cell proliferation and invasion and is associated with several forms of cancer, including breast, prostate, and pancreatic cancer, leukemia, and neuroblastoma [62]. TRPM2 is thought to protect genomic DNA in cancer cells by minimizing DNA damage, thereby enhancing tumor growth [65]. The role of TRPM4 in prostate cancer migration and invasion is well-documented [66] and the role of TRPM5 in lung metastasis has been reported [67]. Gene expression of TRPM4 is upregulated in prostate cancer; knockdown of the protein decreases migration but not proliferation of cancer cells via SOCE regulation [68]. TRPM5 is believed to be involved in lung cancer metastasis, as lung metastasis increases when TRPM5 expression is increased [62]. Moreover, TRPM5 activity increases acidic pH-induced matrix metalloproteinase-9 (MMP9) expression by activating nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) [62]. TRPM8 is abnormally overexpressed in a plethora of malignant solid tumours and correlates with tumour progression [69]. Emerging evidence has demonstrated that TRPM8 plays important roles in cancer cell proliferation, survival, and invasion of various cancers, including melanoma, osteosarcoma, breast cancer, prostate cancer, and bladder cancer [62,69]. In general, members of the TRPM subfamily have been extensively implicated in cancer progression and associated processes of a wide variety of cancer types.

1.7. TRPM7 in cancer

Due to its extensive involvement in Ca^{2+} and Mg^{2+} transmembrane transport, TRPM7 has been implicated in numerous physiological processes and pathologies, including cancer. TRPM7 is highly overexpressed in the cell lines and tissues of numerous cancers [70,71]. TRPM7 is the primary TRPM channel implicated in pancreatic cancer, where it is overexpressed 13-fold in cancerous tissues compared to healthy tissue and its expression is positively correlated with pancreatic ductal adenocarcinoma (PDAC) progression [62]. TRPM7 modulates migration of the human pancreatic cancer cell line BxPC-3 via an Mg^{2+}-dependent mechanism and increases PDAC cell invasion by regulating the proteolytic axis, Hsp90α/uPA/MMP-2 pathway [72,73]. This occurs when TRPM7 induces secretion of MMP-2 via the Hsp90α/uPA/MMP-2 axis, which then degrades the extracellular matrix (ECM) and enables invasion [72,73]. TRPM7 is also highly expressed in breast ductal adenocarcinoma (hBDA) along with TRPM8 and plays a role in proliferation, adhesion, and migration of breast cancer cells [62]. A study using a mouse xenograft model of human breast cancer showed that TRPM7 expression is required for tumour metastasis and is a predictor of poor clinical prognosis [74]. Mechanistically, TRPM7 regulates myosin II-based cell tension and the subsequent loss of cell matrix proteins, modulating cell-cell adhesion and polarized cell movement [74]. Knockdown of TRPM7 using shRNA in MDA-MB-435 and MDA-MB-231 triple-negative breast cancer cell lines increases cell contractility and the number of focal adhesions, which are strongly correlated with reductions in migration and invasion potential [74]. Mediation of the migration and invasion of the MDA-MB-435 cell line occurs via the mitogen-activated protein kinase (MAPK) signaling pathways, wherein TRPM7 expression is associated with increased Src and MAPK phosphorylation as well as enhanced migration and invasion potential [62]. TRPM7 overexpression is similarly related to a loss of cell adhesion by activating calpain II through channel-dependent activation of p38 MAPK and c-Jun N-terminal kinase (JNK) [25,75]. TRPM7 expression is also correlated with estrogen receptor (ER) presence: in ER-positive (ER+) hBDA, TRPM7 expression is higher in non-invasive cells whereas in ER-negative (ER-) hBDA, TRPM7 expression is higher in invasive cells [71,76]. Hence, TRPM7 is a reliable marker for breast cancer progression and metastasis. As well, TRPM7 is involved in the growth and survival of human gastric adenocarcinoma cells, the migration of lung cancer cells, and the migration and invasion of prostate cancer cells [62,77]. TRPM7 additionally plays a role in the cell proliferation of hypopharynx, thyroid, and retinoblastoma cancer cell lines in a Ca^{2+}-dependent manner, and in digestive system cancers via Mg^{2+} influx [71]. Interestingly, among the members of the TRPM subfamily, only TRPM7 is reported to be involved in nasopharyngeal carcinoma, wherein the channel-kinase promotes migration and metastasis via Ca^{2+} influx [62,78]. Similar to its effects on breast cancer cells, silencing TRPM7 via siRNA in nasopharyngeal cancer cells decreases cellular invasion and migration whereas overexpression of TRPM7 increases both processes [78]. In glioblastoma, inhibition of TRPM7 decreased viability, migration and invasion of U87 and U251 cells through regulation of MMP2 protein expression and phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) and mitogen-activated protein kinase kinase/extracellular signal-regulated kinase (MEK/ERK) signaling pathways [9,79]. Furthermore, prostaglandin E2 (PGE2) has been found to increase proliferation and migration of human glioblastoma cells through activation of TRPM7 via the prostaglandin EP_3

receptor/protein kinase A (EP3/PKA) signaling pathway [80]. These described studies characterize the known involvement of TRPM7 in the cellular proliferation, cell cycle progression, survival, invasion, and migration of multiple cancer cell lines [70]. However, the relative contribution of the α-kinase domain compared to the ion channel to these processes remains relatively undefined. Hence, the next section of this review will discuss ongoing research on the complex role of the TRPM7 α-kinase domain in human cancers before exploring methods of α-kinase regulation and potential kinase inhibitors that may enable further investigation of TRPM7 as a potential therapeutic target in cancer.

2. The role of the TRPM7 kinase in cancer

2.1. The TRPM7 kinase plays an essential role in the migration and invasion but not proliferation of certain cancers

Although the TRPM7 channel-kinase has been found to promote proliferation, migration, and invasion to various degrees in certain cancer cell types, studies have demonstrated that the α-kinase domain is specifically involved in cellular migration and invasion but not proliferation [71,74,76,81,82]. Initial investigation of TRPM7 knockdown using MTT and wound-healing assays in highly metastatic human ER- breast cancer cell lines MDA-MB-231 and MDA-MB-435S revealed no effect on cell proliferation but a significant reduction in migration compared to control [76]. As well, wound-healing assays demonstrated that migration of MDA-MB-231 cells was completely inhibited by silencing TRPM7 by siRNA (siTRPM7) [76]. Together, these findings implicate TRPM7 in breast cancer cell migration. Additional data showed that overexpression of zebrafish TRPM7 increased cellular migration in both weakly and highly metastatic breast cancer cell lines, an effect that was not mimicked by overexpression of the kinase domain truncated form of TRPM7 (**Δ**kinase-TRPM7) in highly metastatic cell lines [76]. Indeed, overexpression of **Δ**kinase-TRPM7 in highly metastatic breast cancer cell lines decreased cell migration compared to the wild-type channel, suggesting that the TRPM7 kinase domain is required for breast cancer cell migration [76]. Interestingly, overexpression of **Δ**kinase-TRPM7 in a weakly metastatic breast cancer cell line did not significantly affect cell migration [76]. In addition to demonstrating the effect of **Δ**kinase-TRPM7 on breast cancer cell migration, Guilbert et al. (2013) simultaneously reported that silencing TRPM7 via siRNA reduced migration in both low and high Ca^{2+} conditions [76]. As migration was reduced regardless of extracellular Ca^{2+} concentration, channel activity, specifically Ca^{2+} influx, is therefore not involved in cellular migration, further suggesting that TRPM7 may regulate the migration of breast cancer cells via its kinase domain [76]. However, as the experiment did not test the effect of external Mg^{2+} on cell migration, it is possible that the TRPM7 channel domain may be involved in cellular migration by mediating Mg^{2+} influx. Future experiments should investigate the role of TRPM7 channel activity in cell migration as represented by Mg^{2+} influx. Regarding the mechanism through which the kinase domain regulates breast cancer cell migration, Guilbert et al. (2013) also reported that western blotting revealed a TRPM7 knockdown-associated decrease in myosin IIA phosphorylation [76]. However, the experiment examined myosin IIA phosphorylation at Ser1943, which is phosphorylated by casein kinase 2 rather than TRPM7 [83]. In contrast, TRPM7 has been identified to phosphorylate the myosin IIA heavy chain at Ser1803, Ser1808, and Thr1800 [43]. Thus, it remains unclear whether the TRPM7 kinase domain regulates breast cancer cell migration by phosphorylating myosin IIA, although other evidence suggests this possibility. Middelbeek et al. (2012) have also demonstrated that TRPM7 contributes to breast cancer cell metastasis through the regulation of myosin II-based cellular tension, which influences the number of focal adhesions, cell-cell adhesion, and migration [74]. Myosin II is the primary motor protein controlling actomyosin contractility; these proteins form antiparallel dimers that interact with actin filaments to produce cellular tension [49]. Previous work has shown that the phosphorylation of the myosin IIA heavy chain enables TRPM7 to associate with the actomyosin cytoskeleton and regulate cell adhesion by preventing the self-assembly of myosin into bipolar filaments and decreasing cytoskeletal tension [42,43,48,49]. Furthermore, myosin IIA is involved in the epidermal growth factor (EGF) induced MDA-MB-231 migration, indicating the possible mechanistic involvement of EGF in TRPM7 kinase-mediated cellular migration [83]. The regulation of cell migration by TRPM7 is believed to involve cation conductance by the ion channel in addition to substrate phosphorylation by the kinase domain [49]. Indeed, Su et al. (2011) showed that overexpression of a kinase-inactive TRPM7 mutant was sufficient for rescue of the effects of TRPM7 knockdown on cell polarity, morphology, and migration, suggesting that channel activity is sufficient for this effect and thus that kinase activity is not required for TRPM7-dependent regulation of cell polarity [49,84]. Given that the TRPM7 kinase is dependent upon Mg^{2+} and Ca^{2+} for activity and substrate interaction, respectively, it is plausible that local cation fluxes through the ion channel regulate kinase function and downstream signaling [49]. However, conflicting evidence suggests a variable and indeterminate role of Ca^{2+} and Mg^{2+} in influencing cell adhesion dynamics and migration, either through Ca^{2+} 'sparks' at the leading lamella of fibroblasts, Ca^{2+} or Mg^{2+} influx regulating downstream targets, or another unelucidated mechanism that would therefore not require the TRPM7 kinase domain [49].

Recent studies similarly corroborate these findings on the selective involvement of the α-kinase domain in other cancer types. Transwell invasion assays and MTT assays from Wan et al. (2019) reported that A172 glioblastoma cells with α-kinase domain deletion (**Δ**kinase) or inactivation (M7-KR) experienced significant reductions in migration and invasion but not proliferation compared to cells transfected with wild-type TRPM7 [85]. Hence, the TRPM7 kinase domain appears to be required for migration in several cancer subtypes, including glioma. Future research may investigate the relationship between the kinase domain and cellular migration in other cancer variants to further characterize this association. Wan et al. (2019) further state that **Δ**kinase and M7-KR variants demonstrated the same significant time-dependent increase in A172 cell proliferation as wild-type TRPM7 [85]. Although TRPM7 mediates cellular proliferation, migration, and invasion, the kinase domain is only involved in the latter two processes whereas the ion channel portion appears to be required for cell growth. Indeed, new findings from Song et al. (2020) report that inhibition or suppression of the ion channel rather than the kinase domain of TRPM7 promote TRAIL-induced antiproliferative effects and apoptosis in triple-negative breast cancer (TNBC) cells [81]. Administration of the TRPM7 ion channel inhibitor NS8593 to TNBC cells facilitated TRAIL-induced anti-proliferative effects in a synergistic manner [81]. In contrast, cells treated with the TRPM7 kinase inhibitor TG100-115 did not produce any significant changes in proliferation in the presence of TRAIL [81]. This is consistent with Guilbert et al.'s (2013) earlier findings that TRPM7 α-kinase is not involved in the proliferation of breast cancer cells. Taken together, the observed results further indicate that the TRPM7-mediated increase in cell migration and invasion primarily occurs via the α-kinase domain whereas an increase in proliferation is the result of ion channel activity.

2.2. TRPM7 kinase and MRTF/SRF-dependent tumorigenic activity

A novel mechanism by which the TRPM7 α-kinase contributes to transcriptional and tumorigenic activity is through regulation of myocardin-related transcription factor (MRTF). MRTFs A and B are coactivators of Serum Response Factor (SRF), which mediates intermediate early gene expression for cellular proliferation, migration, and differentiation [86,87]. SRF transcriptional coactivation by MRTF-A is controlled by the dynamic equilibrium between assembly and disassembly of actin filaments, which exist in two forms: globular monomer

(G-actin) and polymerized filamentous structure (F-actin) [88,89]. G-actin associates with and restricts MRTF-A to the cytoplasm by reducing nuclear import and promoting nuclear export of MRTF-A [90]. RhoA activation induces actin polymerization, resulting in dissociation of the G-actin-MRTF-A complex and the translocation of MRTF-A to the nucleus [90]. Since MRTF-A nuclear localization is required for its transcriptional activity and oncogenic properties, redistribution to the cytoplasm may prevent the occurrence of tumorigenic activity [90]. The TRPM7 kinase has been found to phosphorylate and subsequently activate RhoA, leading to downstream effects and contribute to MRTF-A-dependent tumorigenic activity [90]. RhoA activation was prevented and interactions between RhoA and TRPM7 was inhibited in a kinase-dead human leukemia cell line (kinase-dead HAP1 cells), as assessed by immunoprecipitation and immunoblotting [90]. TRPM7 channel activity is required to increase Mg^{2+} concentration, which is essential for kinase activity to phosphorylate RhoA and facilitate its interaction with TRPM7. TRPM7 channel-mediated Mg^{2+} influx and phosphorylation of RhoA by TRPM7 kinase have been found to regulate RhoA activity, which subsequently regulates actin polymerization, MRTF-A-Filamin A complex formation and MRTF-A/SRF target gene expression [90]. Voringer et al. (2020) report that inhibiting TRPM7 using the channel inhibitor NS8593 blocks MRTF/SRF-dependent transcriptional and tumorigenic activity, resulting in growth arrest of hepatocellular carcinoma (HCC) cells and HCC xenografts due to oncogene-induced senescence (OIS) [90]. Similarly, inhibiting the TRPM7 kinase may prevent MRTF activity via the regulation of RhoA phosphorylation, thereby decreasing tumorigenesis.

2.3. TRPM7 kinase and actomyosin dynamics in cancer progression

Physical communication between a cell and the surrounding tissue is facilitated by cell adhesion sites and structures that monitor the cellular microenvironment for mechanical and chemical changes and accordingly induce adjustments in cytoskeleton dynamics and gene expression [91]. These adjustments maintain cellular inactivity in healthy cells; in malignant cells, disturbances to cellular adhesion and related signaling promote dedifferentiation, uncontrolled cell proliferation, tissue invasion, and pathogenesis [91]. Ion channels such as members of the TRP superfamily are often located at these cellular adhesion points, including focal adhesions and invadosomes, where changes to membrane stretch or cytoskeletal tension cause channel opening and subsequent cytoskeletal modifications and regulation of gene expression [91]. Indeed, more recent findings from Middelbeek et al. (2016) report that TRPM7 interacts with a large cytoskeletal protein complex mainly consisting of proteins involved in actomyosin dynamics and cell matrix interactions [91]. In particular, TRPM7 interacts with the cytoskeleton-regulating protein cofilin in the central nervous system (CNS), which is known to regulate neuronal spine density and morphology, synaptic plasticity, and memory [24,91,92]. Microarray-based gene expression analysis and a detailed literature study indicated that 55 % of these TRPM7 interactors are associated with cancer progression and metastasis formation [91]. Middelbeek et al. (2015) found that TRPM7 regulates cell mechanics and drives malignant activity in neuroblastoma by activating in vitro and in vivo development programs [93]. TRPM7 regulates cellular tension through Ca^{2+}- and kinase-dependent interactions with the actomyosin cytoskeleton [42,43,48]. In neuroblastoma cells, regulation of podosome formation follows a kinase-dependent mechanism [48]. Activation of TRPM7 results in kinase-dependent inhibition of myosin II function, potentially involving myosin IIA heavy chain phosphorylation [48]. This process results in the remodeling of the actomyosin cytoskeleton and the transformation of focal adhesions into podosomes [48]. TRPM7 kinase-dead mutant N1E-115 neuroblastoma cells promote cell adhesion and spreading but do not show any formation of podosomes, suggesting the important role of the kinase domain in the regulation of podosome formation. Based on the presence of TRPM7 in adhesion structures such as invadosomes, and because TRPM7 can be activated by mechanical stress, this cation channel may act to control cytoskeletal dynamics and downstream signaling pathways in response to mechanical cues to promote the progenitor-like features of neuroblastoma cells [42,43,48]. Since the myosin IIA heavy chain, a component of the actomyosin cytoskeleton, is a putative substrate of the TRPM7 kinase domain, it is plausible that TRPM7 kinase activity may regulate the function of the various cytoskeletal components within this protein complex [43]. Due to its involvement in actomyosin dynamics, the TRPM7 kinase therefore may be involved in the promotion of cancer progression and metastasis.

2.4. TRPM7 kinase and hypoxic tumour microenvironment-induced apoptosis

The TRPM7 kinase has been found to modulate oxygen-glucose deprivation/reoxygenation (OGD/R)-induced neuronal apoptosis, which has important implications for the tumor microenvironment (TME) [28,94]. Zhao et al. (2015) report that OGD/R, an in vitro model for ischemia-reperfusion injury, induces nuclear translocation of annexin 1 in primary cultured neurons, which is required for apoptosis [28]. Accordingly, the TRPM7 kinase-mediated phosphorylation of annexin 1 is required for its translocation into the nucleus [28,40]. Myosin IIA, another putative substrate of the TRPM7 kinase, is required for annexin 1 transport through the cytoplasm [28]. Western blotting and coimmunoprecipitation revealed that removal of the TRPM7 kinase or a point mutation in Ser5 of annexin 1 interferes with TRPM7 kinase-annexin 1 binding, decreasing annexin 1 nuclear translocation and thereby reducing neuronal apoptosis [28]. It is plausible that ablation of the TRPM7 kinase would also prevent the phosphorylation of myosin IIA, further hindering the translocation of annexin 1 into the nucleus. Indeed, Western blotting also demonstrated that inhibiting myosin IIA with the myosin IIA antagonist blebbistatin in primary neuron and HEK293 cells can also downregulate annexin 1 translocation [28]. The lessons from this OGD/R experiment can be applied to the TME, wherein rapid, uncontrolled proliferation of tumours causes them to quickly develop beyond sizes supported by the surrounding vasculature, thus limiting the amount of oxygen available for local cells [95]. Consequently, hypoxia, or an insufficient supply of oxygen due to reduced blood flow, is a common characteristic of the microenvironment of almost all solid tumours [95]. Although rapid tumour growth can stimulate abnormal disorganized *de novo* angiogenesis [95], disorganized vasculature reduces oxygen diffusion ability and allows hypoxic conditions to persist.

The TME promotes cancer progression by stimulating anti-apoptosis and proliferation in malignant cells [96,97]. Tumour cells adapt quickly to hypoxia whereas normal cells do not; tumour cells become more aggressive and develop therapeutically resistant phenotypes [95]. Hypoxia induces changes in gene expression and subsequent proteomic changes that have many significant effects on cellular and physiological functions, ultimately enabling tumour cell survival [95]. In hypoxia, expression of oxygen-regulated transcription factor hypoxia-inducible factor 1α (HIF-1α) is increased [95]. HIFs promote the adaptation and selection of both cancer and stromal cells to the surrounding hypoxic conditions, thus encouraging changes that favour cancer progression [98]. In cancer, the hypoxic TME causes the adaptation of tumour cells to become resistant to apoptosis whereas healthy cells are increasingly vulnerable to the effects of hypoxia-induced apoptosis. As TRPM7 is a modulator of annexin 1 in the initiation of neuronal apoptosis, inhibition of the kinase domain may prevent annexin 1-TRPM7 kinase binding and subsequent annexin 1 nuclear translocation, therefore decreasing hypoxia-induced apoptosis of normal neurons. However, it should be considered whether inhibition of the TRPM7 kinase may similarly have an anti-apoptotic effect on tumour cells or whether inhibition will alternatively suppress the HIF-1α/annexin signaling pathway, reducing the migration and invasion of cancer cells. Future studies should examine the effect of TRPM7 kinase inhibition on tumour cell and

normal cell apoptosis in hypoxic conditions.

In contrast to hypoxia-induced apoptosis, the role of TRPM7 in extrinsic Fas-induced apoptosis depends on TRPM7 ion channel function and not the kinase domain [26]. In response to Fas-signaling, TRPM7 undergoes residue-specific caspase 8-mediated cleavage to produce two distinct proteins, the TRPM7 channel and TRPM7 kinase [26]. The dissociated TRPM7 kinase domain retains phosphotransferase activity but does not modulate Fas-receptor signaling, whereas ion channel activity is greatly increased upon cleavage and enables Fas-induced apoptosis [26]. Hence, the TRPM7 kinase may be involved in the phosphorylation of annexin 1 during neuronal apoptosis in the TME but is not involved in Fas-induced apoptosis.

3. Regulation of the TRPM7 kinase domain

Given the role of TRPM7 in the tumorigenesis of various cancers and the specific contribution of the kinase domain to these processes, it is therefore critical to discuss regulation of the TRPM7 α-kinase domain and the role of the α-kinase in regulating protein function.

It is generally accepted that free intracellular Mg^{2+} inhibits the TRPM7 channel. Additional research has found that pyrimidine and purine magnesium nucleotides can also inhibit TRPM7 and actually enhance the inhibition efficacy of Mg^{2+} through a non-physical, cooperative interaction between the nucleotide binding site on the kinase domain and a Mg^{2+} binding site on the channel domain [99]. In this interaction, the combined effects of Mg^{2+} and Mg·nucleotides produce a mutually synergistic inhibition and shift the dose-response curves of both molecules [99]. Consequently, Mg^{2+}-mediated inhibition of TRPM7 is partially coordinated through the kinase domain.

Halides have also been found to regulate TRPM7 through the kinase domain [100]. TRPM7 has two known Mg^{2+} binding sites that differ in affinity, one of which is located on the protein's kinase domain and coincides with the Mg·nucleotide binding site [19,100]. This Mg^{2+} binding site mediates the sensitivity of TRPM7 to various Mg ·nucleotides [99]. The second Mg^{2+} binding side is found on the channel domain and has a strong affinity for Mg^{2+} [19]. The Mg ·ATP binding site of the α-kinase domain coordinates the inhibition of TRPM7 channel and kinase function by the halides chloride and bromide, wherein Mg^{2+} and nucleotides function as obligatory cofactors [100]. Increasing intracellular Mg^{2+} increases the level of inhibition by chloride and Mg^{2+}, which cannot be reversed in acidic or divalent ion-free conditions [100]. Thus, TRPM7 currents are only inhibited by increases in intracellular chloride in the presence of intracellular Mg^{2+} [100]. However, in the absence of the kinase domain, chloride inhibitory activity becomes independent of Mg^{2+}, suggesting that the chloride binding site is located on the channel domain and is modulated by the kinase domain [100]. Unlike chloride and bromide, iodide is capable of inhibiting TRPM7 channel activity independent of any cofactors by binding directly to the channel, albeit less potently [100]. Other ions also regulate the TRPM7 kinase domain; Mg^{2+} and Mn^{2+} stimulate kinase activity whereas Ca^{2+} has no effect and Zn^{2+} and Co^{2+} inhibit the kinase domain [38,101]. It is important to note that having no effect on kinase activity is not considered a form of regulation.

Considering the necessity of the α-kinase domain in inhibiting TRPM7 via halides and magnesium nucleotides, it is reasonable to expect that the kinase domain plays a significant role in modulating the ion channel. Indeed, TRPM7 activity is mediated by its kinase domain, which is reported to mechanistically respond to changes in intracellular levels of cyclic adenosine monophosphate (cAMP) caused by G-protein coupled receptors (GPCRs) [102]. Takezawa et al. (2004) describe a mechanism in which G_s- and G_i-coupled receptors raise and lower cAMP levels, respectively, leading to changes in protein kinase A (PKA) activity that are converted by the endogenous kinase domain into altered channel activity [102]. Conversely, stimulating cAMP levels with prostaglandin E1 (PGE1) has no effect on Ca^{2+} influx through bradykinin-activated TRPM7, demonstrating that cAMP is not involved in TRPM7-mediated Ca^{2+} influx in N1E-115 cells [103]. However, more recent data from 2019 has shown that cAMP actually blocks the influx of Ca^{2+} through TRPM7 in a PKA-dependent manner at Ser1269 in N1E-115 cells [104]. Due to these conflicting data, more research is required to elucidate the mechanism through which the kinase domain mediates TRPM7 channel activity. As well, it is uncertain whether this cAMP-dependent modulation of TRPM7 is a separate mechanism from the Mg·ATP-mediated regulation.

Aside from regulating TRPM7 channel function, the TRPM7 α-kinase itself is regulated via multiple mechanisms. In particular, specific dimer interactions regulate the activity of the kinase domain [105]. The TRPM7 α-kinase domain assembles into a homodimer by exchanging a 27-residue-long N-terminal sequence [39]. This sequence is split into an 'activation sequence' that is required for kinase activity but not dimer formation and a 'dimerization sequence' that is crucial for both functions [105]. Dimer interactions between the α-kinase domain of one subunit and the exchanged N-terminal segment of the other subunit are essential for kinase activity [105]. Site-identified mutagenesis identified Tyr1553 and Arg1558 within the activation sequence as crucial residues for kinase function; the residues help position a catalytic loop containing the invariant Asp1765 residue in the second subunit [105]. Hence, covalent modifications or binding interactions that alter the conformation of the N-terminal segment may potentially regulate kinase domain activity.

The TRPM7 kinase is also regulated via autophosphorylation of the Ser/Thr-rich domain, immediately N-terminal to the catalytic α-kinase domain [49]. Massive autophosphorylation at the C-terminus of TRPM7 may facilitate substrate recognition, leading to increased rates of substrate phosphorylation [106]. Two of the identified autophosphorylation sites (Ser1511 and Ser1567) do not seem to affect channel activity [101]. Given that autophosphorylation does not appear to be required for TRPM7's catalytic activity, it is suggested that massive autophosphorylation produces an electrostatic docking site enabling interactions with TRPM7 kinase substrates [49].

4. Inhibitors of the TRPM7 kinase domain

Although numerous inhibitors of TRPM7 have been identified, very few known kinase domain-specific inhibitors exist. In 2014, at the time of publication of a review on natural and synthetic modulators of the TRPM7 channel, no drugs were known to selectively act on the TRPM7 kinase [107]. There are some modulators, including FTY-720 and rottlerin, that have been proposed to inhibit TRPM7 kinase activity but also affect channel activity or other kinases. FTY-720, a synthetic homolog of sphingosine, was identified as a known inhibitor of both TRPM7 channel and kinase activity capable of inducing apoptosis in neuroblastoma cells [108]. FTY-720 treatment in neuroblastoma cells decreased the TRPM7 kinase-mediated phosphorylation of myosin IIA and histone H3 [108]. Current density, however, was also reduced with in FTY-720-treated neuroblastoma cells, suggesting that FTY-720 inhibits both the TRPM7 channel and kinase [108]. In addition, rottlerin was known to be a protein kinase inhibitor that inhibits the phosphorylation of myelin basic protein by TRPM7 with an IC_{50} of 35 μM [38]. However, rottlerin has long been known to also inhibit the α-kinase eEF-2 and protein kinase C (PKC), suggesting its function as a general α-kinase inhibitor rather than a specific TRPM7 kinase inhibitor [109]. Furthermore, the inhibition potency of rottlerin on the TRPM7 kinase is quite low compared to its effect on PKC [110]. NH125, another non-selective kinase inhibitor that has been reported to inhibit TRPM7 kinase activity in addition to eEF-2 kinase and ERK2 [111]. In 2017, however, Song et al. reported TG100-115, the first documented potent TRPM7 kinase inhibitor [82] which is also known as a selective PI3Kγ/PI3Kδ inhibitor [112]. TG100-115 was discovered by using the LANCE *Ultra* time-resolved fluorescence resonance energy transfer (TR-FRET) assay to screen a library of kinase inhibitors [82].

By using CREB peptide as an in vitro substrate of the TRPM7 kinase

domain, the study revealed that TG100-115 significantly inhibited the phosphorylation of CREB at Ser133 in a dose-dependent manner with an IC50 of 1.07 ± 0.14 μM [82]. Moreover, TG100-115 inhibited TRPM7 kinase-regulated phosphorylation of the metastasis markers myosin IIA heavy chain and focal adhesion kinase [82]. TG100-115 is therefore a far more potent inhibitor of TRPM7 compared to other known inhibitors, with an IC_{50} of 1.07 ± 0.14 μM [82]. In this regard, TG100-115 has been found to effectively suppress breast cancer invasion and migration but not proliferation [82]. However, TG-100-115 can still inhibit TRPM7 channel activity; TG100-115 has also been shown to reversibly suppress TRPM7 and TRPM7-like currents, albeit at much higher concentrations (i.e. 100 μM) [82]. Currently, TG100-115 remains the only known potent TRPM7 kinase domain inhibitor, which likely contributes to the gap in available knowledge on TRPM7 kinase-specific functions. The identification of other effective, specific TRPM7 kinase domain inhibitors may assist in expanding current knowledge on the unique and varied functions of the TRPM7 α-kinase domain.

5. Conclusion

The TRPM7 kinase domain is functionally distinct from the ion channel and the protein as a whole. In human cancer, the kinase domain of TRPM7 has been identified to play a unique role in numerous tumorigenic processes via the phosphorylation of TRPM7-specific substrates, thus providing a novel target for therapeutic treatments. Our understanding of the functions of the TRPM7 kinase is still developing and further research is required to fully elucidate the complex roles of this kinase domain in both physiology and pathology.

Declaration of Competing Interest

Authors declare no competing interests.

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