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Invited Mini Review

Emerging role of transient receptor potential (TRP) channels in cancer progression

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Transient receptor potential (TRP) channels comprise a diverse family of ion channels, the majority of which are calcium permeable and show sophisticated regulatory patterns in response to various environmental cues. Early studies led to the recognition of TRP channels as environmental and chemical sensors. Later studies revealed that TRP channels mediated the regulation of intracellular calcium. Mutations in *TRP* channel genes result in abnormal regulation of TRP channel function or expression, and interfere with normal spatial and temporal patterns of intracellular local Ca^{2+} distribution. The resulting dysregulation of multiple downstream effectors, depending on Ca^{2+} homeostasis, is associated with hallmarks of cancer pathophysiology, including enhanced proliferation, survival and invasion of cancer cells. These findings indicate that TRP channels affect multiple events that control cellular fate and play a key role in cancer progression. This review discusses the accumulating evidence supporting the role of TRP channels in tumorigenesis, with emphasis on prostate cancer. [BMB Reports 2020; 53(3): 125-132]

INTRODUCTION

The onset and progression of cancer is characterized by cell cycle dysregulation, leading to enhanced cell growth, concomitant with suppression of mechanisms responsible for cell death (1-4). Notably, dysregulated homeostasis of intracellular Ca^{2+} is involved in cancer. Altered Ca^{2+} signaling events induced by ion fluxes across various membrane channels and transporters mediate every step of cancer metastasis (5). Intracellular free calcium ions ($[Ca^{2+}]_i$) are the most abundant second messengers in human body playing a diverse role in cellular physiology, including cell motility, cell cycle control, gene expression, autophagy and apoptosis (6). Multiple mechanisms regulating cell growth or apoptosis are strongly dependent on $[Ca^{2+}]_i$ homeostasis, emphasizing the role of calcium-permeable ion channels. Excitable cells contain highly selective and voltage-sensitive Ca^{2+} channels, which induce sharp and sustained elevation in $[Ca^{2+}]_i$ required for exocytosis at nerve termini, and for rapid contraction of muscle fibers in heart and skeletal muscles. Non-excitable cells such as fibroblasts use a different mechanism. For example, ligand binding to several membrane receptors triggers a series of events, leading to the activation of phospholipase C (PLC) and synthesis of inositol-1,4,5-trisphosphate ($Ins(1,4,5)P_3$). $Ins(1,4,5)P_3$ opens the $Ins(1,4,5)P_3$ receptor (IP_3R), which is an intracellular ion channel and expressed mostly in the endoplasmic reticulum, resulting in the release of Ca^{2+} from the endoplasmic reticulum (7, 8). Ca^{2+} signals in the form of spikes, oscillations or waves are spatially and temporally tightly regulated (9) to avoid prolonged intracellular elevation of Ca^{2+} that is toxic and lethal for cells (10). The duration, frequency, and amplitude of $[Ca^{2+}]_i$ oscillatory signals determine the selective Ca^{2+}-specific activation of transcription factors for cellular proliferation and migration (11, 12). Downstream effectors, including nuclear factor-κB (NF-κB), nuclear factor of activated T-cells (NFAT), calmodulin (CaM), calmodulin-dependent protein kinase II (CaMKII) and calpain, decode the selective oscillatory $[Ca^{2+}]_i$ signals. Mechanistically, the differences in their on-/off-rates for Ca^{2+} enable subsequent activation of different cellular events (13-15). For example, calcineurin, a calcium-dependent serine-threonine phosphatase, and calpains, calcium-dependent cysteine proteases are crucial calcium-dependent factors that regulate the cell cycle. These findings emphasize the importance of subtle and local changes in $[Ca^{2+}]_i$ in the regulation of cell fate, prompting the investigation of alternate pathways regulating local delivery of Ca^{2+}.

Notably, a re-evaluation of accepted paradigms of intracellular regulation of Ca^{2+} appears to be imminent. Interestingly, many recent studies investigated new functions of specific members of the transient receptor potential (TRP) superfamily (16-18) that will be discussed with an emphasis on cancer biology. While the traditional role of TRP channels is confined to 'pain' perception via nociceptive neurons (19), drug discovery efforts targeting TRP channels have expanded into new disease areas such as chronic cough, asthma, chronic itch, obesity, overactive bladder, anxiety, stroke and cancer. In the

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last decade, the role of TRP channels in enhancing cellular proliferation, abnormal differentiation, and impaired death, resulting in uncontrolled expansion and invasion of cancer, has been increasingly reported (20-22). Metastasis, a major hallmark of cancer, is characterized by the spread and invasion of cancer cells from the primary location to distant organs (23, 24). When metastasis happens, cancer as a disease that can be potentially curable by surgical excision is converted into one that requires chemotherapy and may even become lethal. Studies investigating several cancer types have shown that tumor progression from early to late stages is often characterized by the altered expression of TRP channels. Indeed, TRPs have been implicated in cancers of prostate, breast, kidney, and bladder as well as in glioma and melanoma (20, 21). To date, TRP channels have been shown to play a role in various late stages of tumor progression rather than carcinogenesis.

TRP CHANNELS

The TRP superfamily is mostly conserved from nematodes to humans, and comprises a diverse group of polymodal ion channels. By altering membrane potential or $[Ca^{2+}]_i$ concentration, the TRP channels act as signal transducers. The era of TRP channels started in 1969 when blindness was classified as a phenotype even under constant bright light, based on a Drosophila study (25) and identification of the mutant *trp* gene revealed the first member of the TRP superfamily. The mammalian TRP channel superfamily is divided into six subfamilies: TRPC (Canonical), TRPML (Mucolipin), TRPM (Melastatin), TRPV (Vanilloid), TRPP (Polycystic), and TRPA (Ankyrin). As shown in Fig. 1, structural variance across the six subfamilies is compared. The first four subfamilies constitute group 1 and the last two represent group 2. Several TRP channels are known targets of S-nitrosylation, which has been shown to activate multiple TRP channels, indicating their role as nitric oxide (NO) sensors (26). Many oncoproteins undergo S-nitrosylation. Nevertheless, there is no direct evidence indicating that S-nitrosylation of TRP channels is directly involved in carcinogenesis (27). All TRPC members are characterized by an N-terminus ankyrin-like repeat domain (ARD), a TRP box after the sixth transmembrane segment, S6, and a Ca^{2+}-binding EF hand domain at the intracellular C terminus. Generally, the phospholipase C (PLC) signaling pathway activates all the TRPC channels. TRPC subunits assemble into homomeric channels, and many of the subunits also form heteromeric channels (28-31). TRPC1/TRPC5 (32), TRPC1/TRPC3 (33), TRPC1/TRPC4 (34), TRPC1/TRPC3/TRPC7 (35), TRPC3/TRPC4 (36), and TRPC4/TRPC5 (37, 38) are examples of heteromeric channels. Despite its function in other mammals, human TRPC2 is uniquely considered as a pseudogene.

TRPML1, 2, and 3 represent the TRPML subfamily, which primarily includes cytosolic proteins. Their subcellular localization appears to be determined by an ER retention-signaling domain in the intracellular C terminus. Co-assembly of TRPML subunits has also been reported (39, 40).

The mammalian TRPM subfamily includes TRPM1-8. TRPM channels are categorized into three subgroups: TRPM1/TRPM3, TRPM4/TRPM5 and TRPM6/TRPM7; TRPM2 and TRPM8 are separated from the rest of the subfamily. TRPM subunits contain a large TRPM homology region of around 700 amino acids in their very long N termini. Most TRPM subunits also contain a C-terminus TRP box and a coiled-coil domain (41). Among the TRP channels, TRPM4 and TRPM5 are unique in that they are monovalent cation-selective ion channels. Additionally, TRPM2, TRPM6, and TRPM7 contain a unique enzymatic domain in their C termini. TRPM6 and TRPM7 assemble to form heteromeric channels (42-45).

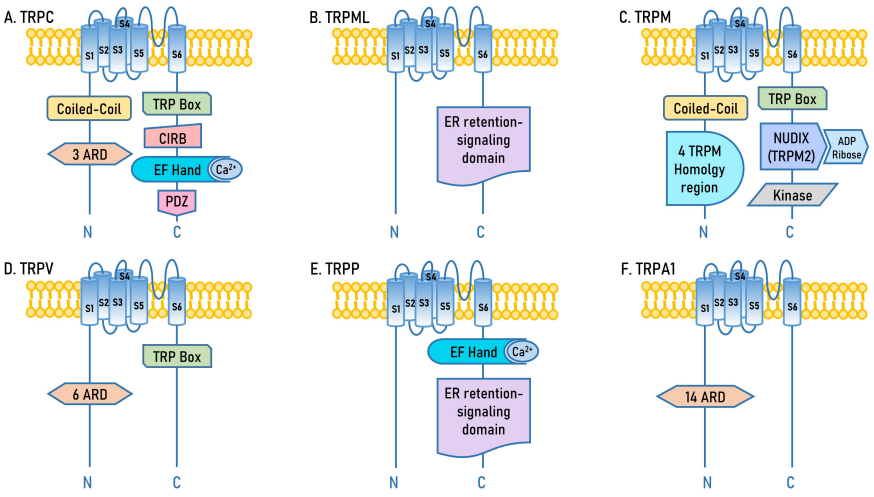

Fig. 1. A schematic diagram comparing the protein structures of TRP subfamilies. TRP proteins carry six transmembrane segments (S1 to S6). (A, E) TRPC and TRPP subfamilies contain EF hand domain that binds intracellular Ca^{2+}. (A) CIRB is a calmodulin/IP3R-binding domain. (B, E) TRPML and TRPP contain ER retention signlaling domain. (C) NUDIX, named after nucleoside diphosphate-linked moiety-X, is a homologous region in the phosphohydrolase family that binds to ADP ribose. The NUDIX represents a unique activation mechanism, gating by ADP ribose, on TRPM2. Other activators, such as cyclic ADPR and NAD+, as well as inhibitors also target the NUDIX. C-terminal serine/threonine kinase is similar in structure to protein kinase A. (D) TRPV contains ARD and TRP box, similar to TRPC. (F) TRPA1 contains more than 14 ARDs at its N-terminus.

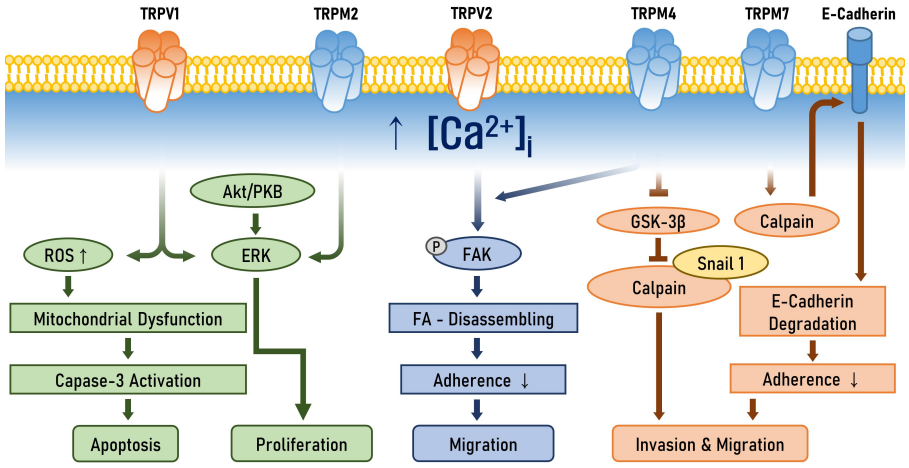

Fig. 2. A working model of the representative mechanisms of calcium signaling mediating the metastatic role of multiple TRP channels. FA: focal adhesion.

TRPV1-6 constitute the TRPV subfamily. TRPV channels are categorized into two groups: TRPV1-4 and TRPV5/TRPV6. The first group of TRPV1-4 form homomeric channels that are weakly Ca^{2+}-selective and activated by heat. Each subunit of the TRPV1-4 group can also co-assemble to form heteromeric channels (46-49). TRPV5 and TRPV6 form both heteromeric and homomeric channels and are highly Ca^{2+} selective but not heat activatable. Similar to TRPCs, subunits of this subfamily also contain an ARD and a TRP box domain. Subunit assembly is promoted by the specific interacting domains in the C terminus (50-52).

The TRPP subfamily comprises TRPP2 (also known as PKD2), TRPP3 (or PKD2L1), and TRPP5 (or PKD2L2). TRPP subunits also carry an ER retention-signaling domain in their C-termini. TRPA1 is the only member of the TRPA subfamily and is named after its ARD domain, carrying at least 14 large and unique repeats.

TRP CHANNELS IN CANCER METASTASIS

The mechanotransduction events during metastasis increasingly provide a new perspective for the understanding of mechanisms involved in cancer progression. The stiffness of tumor microenvironment in solid tumors enhances the activation of mechanotransduction signals in cancer cells to promote pro-metastatic architecture, including cancer cell invasion and metastasis, which are essential for the development of advanced disease (53-55).

Some members of the TRP channel superfamily are functionally related to cellular events and structures that are essential for mechanotransduction in cell migration, such as actin cytoskeleton and focal adhesions. Consequently, they are involved in mechanotransduction by significantly contributing to metastasis, presumably by strongly promoting cancer cell migration and invasion. In the context of metastasis, TRPM7, a Ca^{2+}-nonselective cation channel carrying α-kinase domain (56), appears to be the best studied TRP channel so far. TRPM7 regulates several events in cell motility such as polarization (57), adhesion (58, 59) and migration (60). We summarize the representative signaling mechanisms underlying the function of specific TRP channels, in Fig. 2.

A study with a mouse xenograft model of human breast cancer also showed that TRPM7 is necessary for tumor metastasis and that high mRNA expression of TRPM7 is correlated with reduced metastasis-free and recurrence-free survival in patients with primary breast cancer (61). Myosin-II-based cell tensions and loss of cell matrix proteins regulating cell-cell adhesion, and polarized cell movement occurred via TRPM7-dependent mechanisms (61). TRPM7 is activated by tension at the leading edge of migrating human embryonic lung fibroblasts, promoting Ca^{2+} entry to activate the IP3R2, resulting in local Ca^{2+} fluctuations necessary for cell migration (62). Overexpression of TRPM7 has also been linked to loss of cell adhesion via activation of calpain II (63). Accordingly, TRPM7 silencing via knockdown of MDA-MB-231 or MDA-MB-435 breast cancer cells increases contractility and the number of focal adhesions, which is strongly correlated with reduced migratory and invasive potencies (61). Notably, it has been suggested that the role of TRPM7 in calcium-independent regulation of migration is at least partly mediated via α-kinase domain, during the phosphorylation of myosin-IIA heavy chain (64-66).

In nasopharyngeal cancer, the increased expression of TRPM7 is associated with poor prognosis and metastasis (67). Similar to breast cancer cells, silencing of TRPM7 decreases the migration and invasion of metastatic cancer cells, and also the overexpression of TRPM7 increases both phenomena in nonmetastatic cancer cells (67). The contribution of TRPM7 to migration of human nasopharyngeal cancer cells is attributed to ryanodine receptor (RyR) activation, which consequently increases

$[Ca^{2+}]_i$ levels and cellular migration (68). Thus, TRPM7 directly affects the migration of diverse cancer cell types via mechanotransduction mediated by $[Ca^{2+}]_i$.

TRPM7 is also essential for progression and invasion of pancreatic ductal adenocarcinoma (PDAC) (69, 70). Increased expression of TRPM7 is correlated with poor patient prognosis (69, 71) and silencing of TRPM7 in PDAC cells reduces cancer cell invasion (70). Activation of TRPM7 induces secretion of MMP-2 from the Hsp90a/uPA/MMP-2 proteolytic axis, which degrades extracellular matrix (ECM) and facilitates cancer cell invasion (70).

In ovarian cancer (72) and bladder cancer, TRPM7 regulates cancer cell migration (60). TRPM7 also regulates proliferation of cancer cells (73-75), although silencing of TRPM7 does not affect the viability of breast cancer cells (61).

TRPM4 also regulates mechanotransduction in cell migration via promotion of focal adhesion disassembly, activation of FAK activation and Rac1, and actin cytoskeleton reorganization (76). Recently, it has been shown that TRPM2 regulates migration and invasion of gastric cancer cells in vitro, and also tumorigenesis and expression of N-cadherin, snail, slug, integrins, and MMPs that are representative epithelial-mesenchymal transition (EMT) markers in vivo (77).

Several members of TRPV subfamily that are known to regulate mechanostransduction and migration have also been associated with metastasis. Recent studies highlighted a novel role of TRPV4 in breast cancer metastasis (78). Studies based on phosphoproteomics revealed a significant upregulation of TRPV4 in breast cancer metastasis in model cell lines, via extravasation. TRPV4 expression in human clinical samples using public databases revealed an increase in TRPV4 expression in basal subtype of breast cancer and was associated with a more aggressive phenotype and poor survival. Both silencing of TRPV4 and pharmacological inhibition of TRPV4 lead to suppression of migration and invasion of the TRPV4-expressing 4T07 breast cancer cell line, further confirming the role of TRPV4 in metastasis (78). Further functional studies revealed the role of TRPV4 in regulating cancer cell stiffness and cell cortex dynamics during cancer cell metastasis (78). Subsequent studies by the same research group attempted to establish the precise mechanism underlying the pro-migratory and pro-metastatic effects of TRPV4 in breast cancer (79). The findings suggested that TRPV4 mediates breast cancer metastasis by regulating the softness of cancer cells via Ca^{2+}-dependent AKT/E-cadherin signaling as well as the expression of extracellular proteins involved in cytoskeleton and ECM remodeling (79). In addition to reports indicating TRPV4 function in breast cancer metastasis (78, 79), TRPV4 expression has been recently shown in gastric cancer metastasis (80). Activation of calcium-sensing receptor (CaSR), a Class C G-protein coupled receptor, induces growth and metastasis of human gastric cancer, mediated via TRPV4-evoked increases in Ca^{2+} influx, which in turn, activates AKT/β-catenin signaling pathway (80). The mechanosensitive ion channel TRPV4 has also been implicated in the migration of human hepatoblastoma HepG2 cells (81), which is one of the multiple steps involved in cancer metastasis (82). Application of a TRPV4 agonist, 4α-PDD resulted in an increase in lamellipodial dynamics of HepG2 cells pre-treated with hepatocyte growth factor, indicating that functionally expressed TRPV4 channel mediates Ca^{2+} influx required for the migration of HepG2 cells (81). Although studies investigating the potential role of TRPV4 in cancer metastasis are still in their infancy, current findings should prompt further research into the likelihood of TRPV4 as a drug candidate in cancer therapy, especially in the case of metastatic cancers.

In conclusion, several TRP channels participate in mechanotransduction during cell migration, and also play a role in the metastasis of multiple cancer types.

TRP CHANNELS IN PROSTATE CANCER

Prostate cancer (PCa) is the second most common cause of cancer deaths among males in industrialized Western countries. With increased access to reliable biomarker detection, effective treatments for advanced PCa are still limited. Indeed, no effective treatments are available for PCa, once it progresses to metastatic castration-resistant prostate cancer (mCRPC), which is refractory to current androgen deprivation therapy (ADT), and accounts for more than 250,000 cancer deaths worldwide, annually (83, 84). Several studies provide evidence supporting the role of TRP channels in PCa (85-87), especially, the members belonging to TRPV and TRPM subfamilies. TRP channels may be very promising players, because their expression and activity appear to regulate the progression of PCa (21, 88-91).

Silencing of TRPM4 reduces cell migration, but does not affect the growth of PC3 and DU145 cells, which are androgen-nonresponsive prostate cancer cell lines (92). miR-150 directly targets the *TRPM4* gene and suppresses TRPM4 expression in PCa tissues (93). Upregulation of miR-150 or silencing of TRPM4 suppresses EMT phenotypes, migration and invasion, leading to inhibition of metastasis (93). In an independent study with PC3 cells, silencing of TRPM4 decreased the expression of Snail1, an EMT transcription factor, and also multiple representative EMT markers, thus inhibiting cell migration and invasion and validating the TRPM4-mediated regulation of migration and invasion (94). The TRPM2 channel has been shown to regulate the proliferation of PCa cell. Increased expression of TRPM2 is observed in 75% of PCa cells compared with matched benign cells (16, 95) and silencing of TRPM2 inhibited cancer cell growth (16, 87). TRPM4 is another TRPM channel identified as a player in PCa progression. TRPM4 was suggested as a cancer driver gene in CRPC (96). TRPM4 downregulates store-operated Ca^{2+} entry (SOCE) in normal, human prostate epithelial cells and DU145 cells, decreasing the driving force for Ca^{2+} (92). Silencing of TRPM4 reduces the migration, without affecting the proliferation, of

PCa cells. TRPM7 also regulates the migration and invasion of PCa cells (97). TRPM7 is upregulated in PCa cells compared with prostate hyperplasia cells, and increases cancer cell migration. Silencing of TRPM7 in PCa cells reduced both migration and invasion of PCa cells from reversing their EMT status, downregulating MMPs and upregulating E-cadherin (97). Expression of TRPV1 is upregulated in high-grade PCa, when compared with tissues from healthy donors (98). Capsaicin, a TRPV1 agonist, inhibits proliferation of PC3 cells in a TRPV1-independent manner (99), via inhibition of coenzyme Q activity. Therefore, ROS generation is increased, and mitochondrial membrane potential is dissipated and caspase-3 is activated. By contrast, capsaicin was also found to stimulate TRPV1-dependent cell proliferation in androgen-responsive LNCaP cells, by decreasing ceramide levels and activating Akt and ERK pathways (100). The expression of TRPV2 in PCa was reported to be 12-fold higher in metastatic PCa than in non-metastatic PCa patients. TRPV2 overexpression in androgen-responsive LNCaP cells increases cell migration, while down-regulation of TRPV2 reduces both growth and invasiveness of xenograft tumors with PC3 cells. Constitutive activation of TRPV2 and increased level of $[Ca^{2+}]_i$, have been associated with TRPV2 function during the progression of androgen3-responsive PCa to aggressive CRPC (101). In addition to their known regulation of migration, invasion and growth in PCa cells, it is still unknown whether any of TRP channels are involved in castration resistance, associated with aberrant activation of androgen signaling and resulting non-responsiveness to ADT.

DISCUSSION

The emergence of TRP channels as novel regulators in cancer growth and progression is specifically associated with their role in mechanotransduction and migration of cancer cells. However, the functional role of TRP channels appears to be unclear, suggesting the need for comprehensive studies. The involvement of TRP channels in mechanotransduction raises a few outstanding questions suggesting that TRP channels may regulate specific mechanosensitive processes and structures other than focal adhesions and actin dynamics during migration, and that YAP/TAZ signaling, a representative regulator of mechanosensitive transcriptional programs, may be linked to TRP signaling events.

Further elucidation of the role of TRP channels and changes in TRP channel expression in cancer progression are required for delineation of novel targets for new therapeutic alternatives in the 'war on cancer'.

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CONFLICTS OF INTEREST

The authors have no conflicting interests.

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