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Review Article

Role of TRP channels in carcinogenesis and metastasis: Pathophysiology and regulation by non-coding RNAs

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A B S T R A C T

In 2021, David Julius and Ardem Patapoutian received Nobel Prize in Physiology or Medicine for their ground-breaking discoveries in the functional characterization of receptors for temperature and touch. Transient receptor potential (TRP) channels have captivated tremendous appreciation as promising drug targets over the past few years because of central involvement in different cancers. Based on the insights gleaned from decades of high-quality research, basic and clinical scientists have unveiled how Transient receptor potential channels regulated cancer onset and progression. Pioneering studies have sparked renewed interest and researchers have started to scratch the surface of mechanistic role of these channels in wide variety of cancers. In this review we have attempted to provide a summary of most recent updates and advancements made in the biology of these channels in context of cancers. We have partitioned this review into different subsections on the basis of emerging evidence about characteristically distinct role of TRPV (TRPV1, TRPV5), TRPM (TRPM3, TRPM7) and TRPC in cancers. Regulation of TRP channels by non-coding RNAs is also a very exciting area of research which will be helpful in developing a sharper understanding of the multi-step aspects of cancers.

1. Introduction

Cancer is a therapeutically challenging disease and modern high-throughput sequencing analyses have unprecedentedly identified wide ranging genes which play key role in cancer development and progression [1–3]. Increasingly it is being realized that deregulated signal transduction cascades, genetic/epigenetic changes and loss of apoptosis centrally steer the multi-step and multi-stage carcinogenesis and metastatic dissemination [4,5].

Over the past three decades, genetic, genomic and proteomic landscape of different cancers has broadened considerably. There has been an exponential increase in the number of tumor suppressors and oncogenes which play instrumental role in onset and progression of cancer.

TRP channels showcase a rich and relatively untapped vein of future therapeutic targets, but realization of their potential appears to be very challenging than previously surmised [6–9]. Transient receptor potential (TRP) channels serve as integrators of myriad of well-described signaling cascades, including those that are mediated by cell surface receptors (particularly, growth factor receptors and G protein-coupled receptors). TRP family is composed of 28 members categorically characterized into 6 sub-families: TRPA (TRPA1), TRPC (TRPC1–TRPC7), TRPM (TRPM1–TRPM8), TRPML (TRPML1–TRPML3), TRPP (TRPP1– TRPP3) and TRPV (TRPV1–TRPV6). These proteins form ion channels whose molecular structures have been uncovered to a greater extent. We have partitioned this review into different sections. Firstly, we have discussed about pivotal role of TRP channels in carcinogenesis and metastasis. Later, we have provided mechanistic analysis of the link between TRP channels and non-coding RNAs that stemmed from groundbreaking studies. Interplay between TRP channels and non-coding RNAs has been viewed as an exceedingly complex landscape superseded by convoluted paradigms not yet fully comprehended.

2. Role of TRPCs in carcinogenesis

Researchers are focusing on developing a better understanding of TRPC channels in health and disease. TRPC channels have diametrically opposed roles in different cancers. Available scientific evidence underlines both darker and brighter sides of TRPC channels in different cancers.

TRPC1 has been shown to promote thyroid cancer. Sphingosine-1-

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phosphate (S1P) has an important role in inflammation, vascular permeability and angiogenesis. S1P binds to S1P receptors and activates downstream signaling. VEGFR2 forms a signaling complex with S1P receptors and potentiates the migration of cancer cells. Re-expression of TRPC1 in the TRPC1-knockdown cells induced an increase in expression levels of S1P3 and VEGFR2. Knockdown of TRPC1 attenuated the expression of MMP2, MMP9 and HIF-1α in thyroid cancer cells [10].

TRPC1/3/6 have been shown to play contributory role in TGF-β1 induced epithelial-to-mesenchymal transition (EMT) in gastric cancer cells [11]. Levels of TRPC1/3/6 mRNAs and proteins were found to be considerably enhanced in TGF-β1-treated cancer cells. Pharmacological inhibition of TRPC1/3/6 severely impaired TGF-β1-induced EMT [11].

TRPC1 expression was noted to be upregulated during hypoxia in breast cancer cells. SNAIL, an important transcriptional factor associated with EMT was significantly downregulated in TRPC1-silenced breast cancer cells [12]. Phosphorylation of EGFR and STAT3 was evident in TRPC1 expressing breast cancer cells [12]. Overall, these findings clearly suggested that TRPC1 activated survival pathways and promoted EMT in breast cancer cells.

Activation of STIM1 (Stromal interaction molecule-1) induced recruitment of an Orai1/TRPC1 complex into lipid rafts containing SK3 channels in colorectal cancer cells [13]. Anchoring of Orai1/TRPC1 complex potentiated migratory capacity of colorectal cancer cells [13].

However, brighter side of TRPC channels cannot be overlooked. MTI-101, a first-in-class peptidomimetic effectively induced apoptosis in multiple myeloma cells [14]. However, MTI-101-mediated apoptosis was drastically abrogated in TRPC1-silenced multiple myeloma cells [14].

In line with this approach, different molecules have been identified which can activate TRPC channels. In this section we will summarize existing high-quality scientific evidence related to role of TRPC channels in RCC and how different molecules are currently being tested to modulate the activity of these channels.

Englerin A (EA) is a strong activator of TRPC4 and TRPC5. It has been shown that Englerin A induced an influx of calcium and depolarization of membrane in cells expressing higher levels of TRPC4 or TRPC5 [15]. Interestingly, englerin A induced current and englerin A mediated inhibitory effects on tumor growth were abrogated by ML204 (TRPC4/C5 inhibitor) [15]. However, off-target effects associated with Englerin A posed major stumbling blocks in utilizing its potential in the treatment of RCC.

Injection of Englerin A (EA) adversely affected mice for about an hour [16]. Mice had markedly reduced locomotor activity, after which they recovered fully. Another important finding of the study revealed that intravenous injection of EA did not induce adverse effects in TRPC4/TRPC5 double knockout mice. Pico 145, a selective and efficient inhibitor of TRPC4/TRPC5 did not cause adverse reactions and protected from EA-induced adverse conditions [16]. Contemporary studies also demonstrated various other molecules having notable capacity to modulate TRPC channels.

Keeping in view the adverse effects of Englerin A, a recently designed analogue of Englerin A acted as a competitive antagonist. EA evoked Ca^{2+} response in the TRPC5-expressing cells was abolished by A54. A54 inhibited EA-triggered activation of TRPC5 and TRPC4/TRPC1 [17].

Tonantzitlolone, a diterpene ester is a natural product and effectively activates TRPC1/4/5 channels [18]. Tonantzitlolone activated homomerically assembled TRPC4 and TRPC5 channels. Moreover, Tonantzitlolone also efficiently induced activation of heteromeric channels involving TRPC1. Intracellular Ca^{2+} levels were found to be considerably enhanced in A498 cells treated with Tonantzitlolone [18].

In A498 cells (renal cancer cells), TRPC4 channel activity was blocked by knockdown of PLCδ1 and almost completely eliminated by a PLCδ1 mutant (dominant-negative) and constitutively active RhoA mutants [19]. RhoA is a negative modulator of PLCδ1. Overall, the findings suggested that PLCδ1 and Gi/o played contributory role in TRPC4 activation. Functional role of TRPC4 needs to be critically investigated in RCC cells.

Englerin A and Tonantzitlolone have significant potential to induce apoptosis in cancer cells mainly through activation of TRPC1/4/5 channels. These chemicals need detailed research in animal models studies.

In the next section we will give a snapshot of (a) linchpin role of TRP channels in cancer and how TRP channels modulate downstream signaling in cancers. (b) Interplay of TRP channels and non-coding RNAs has also been brought from shadow to the limelight and we are expecting bigger strides towards demystifying the puzzling features of previously unprecedented intricacy of non-coding RNAs and TRP channels mediated downstream signaling.

3. Role of TRPMs in carcinogenesis

Activation of TRPM2, TRPM4 and TRPM5 is dependent on intracellular Ca^{2+}. TRPM6 and TRPM7 are channel kinases and have a critical role in homeostasis of Mg^{2+}.

Transient receptor potential (TRP) channels have captivated tremendous appreciation as promising drug targets over the past few years. D-3263, a TRPM8 agonist made its entry into Phase 1 (NCT00839631) for evaluation of its efficacy against TRM8-expressing cancer cells in metastatic prostatic cancer patients.

D-3263, a TRPM8 agonist worked effectively with enzalutamide or docetaxel and induced apoptotic death in prostate cancer cells [20]. Future studies should be focused on the validation of metastasis inhibitory role of D-3263 in experimental metastasis models and orthotopically transplanted tumor xenografts.

AMTB, a specific TRPM8 antagonist worked efficiently with low-dose cisplatin and inhibited tumor growth in mice subcutaneously injected with U2OS cells [21]. Likewise, AMTB worked combinatorially with γ-irradiation and inhibited melanoma progression in C57BL/6 mice transplanted with B16 melanoma cells [22].

MiR-204 is transcribed from intron 6 of the gene encoding TRPM3, which conducts Ca^{2+} and Zn^{2+} ions. However, excitingly, miR-204 directly targeted TRPM3 [23]. Stable knockdown of TRPM3 interfered with the tumor forming abilities of these cells in orthotopically xenografted mice. RCC cell lines with inactive VHL (A498, 786-O) had higher expression of TRPM3 [23]. Reconstitution of VHL in A498 and 786-O cells exerted repressive effects on the expression of TRPM3. Introduction of miR-204 reduced protein levels of TRPM3 in VHL^- RCC cell lines. Knockdown of Caveolin-1 (CAV1) resulted in the reduction in the expression levels of TRPM3. CAV1 knockdown also inhibited formation of the tumors by RCC VHL^- cells, but overexpression of Caveolin-1 in VHL^+ cells enhanced the tumor forming capacities of these cells [23]. Findings clearly demonstrated colocalization of TRPM3 and CAV1 in the plasma membrane and intracellularly, which indicated that Caveolin-1 played a role in regulation of shuttling or mobilization of TRPM3 to the membrane. TRPM3 was found to be essential for activation of cancer promoting autophagic response under starved condition in VHL^- RCC cells [23].

Central role of TRPM3 in Ca2+ influx regulation has been extensively studied and various lines of evidence highlight correlation between channel activity and calmodulin-regulated signaling pathways [23]. [Ca2+]i regulated autophagic pathway through calmodulin-dependent activation of CAMKK2 (Calcium/calmodulin-dependent protein kinase kinase-2) and AMPK phosphorylation, which, consequently phosphorylated ULKs. TRPM3KD-induced reduction in [Ca2+]i inhibited CAMKK2 and AMPK activities and resultantly, decreased ULK1 phosphorylation and autophagic activities (Fig. 1) [23]. CAMKK2 knockdown exerted inhibitory effects on autophagy and phosphorylation of AMPK and ULK1 in VHL^- cells which confirmed that autophagic flux required robust CAMKK2-driven activity. Same effects were achieved when VHL^- cells were treated with the CAMKK2 inhibitors [23]. It is relevant to mention that AMPK plays an instrumental role in activation of autophagic response. Autophagic loss and reduced

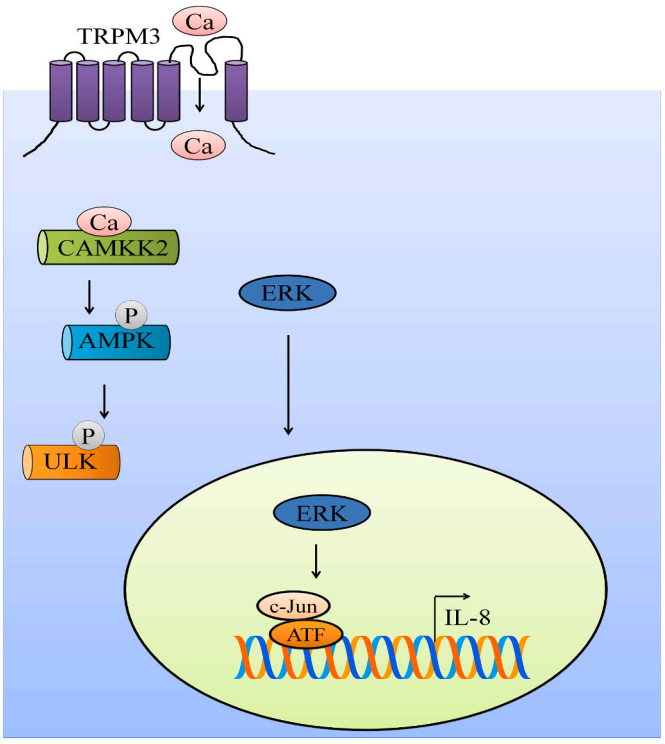

Fig. 1. Shows activation of Kinome in TRPM-activated cells. CAMMK2 is "switched on" in TRPM activated cells. CAMKK2 activated its downstream effector kinase AMPK. AMPK consequently phosphorylated ULK to induce autophagic response. ERK shuttles into the nucleus to promote ATF/c-Jun mediated activation of IL-8.

phosphorylated levels of AMPK and ULK1 in TRPM3-knockdown cells were rescued when constitutively active AMPK was re-expressed [23]. AMPKα1/AMPKα2 knockdown resulted in inhibition of autophagic pathway and ULK phosphorylation in VHL^{-} cells [23]. Therefore, these findings revealed that higher expression of TRPM3 in VHL^{-} cells activated cancer promoting autophagic pathway via CAMKK2-AMPK-ULK1 signaling cascade. TRPM3 levels were reduced in cells reconstituted with VHL. Moreover, miR-214 was upregulated in cells reconstituted with VHL. miR-214 was higher in wild-type VHL-expressing Caki-1 cells [23]. Enforced expression of TRPM3 in 786-O VHL^{+} induced a 2-fold downregulation of miR-214. MiR-214 was significantly inhibited by constitutively active AMPKα2 or CAMKK2 in TRPM3KD cells, however expression of miR-214 was induced in AMPKα1/AMPKα2 knockdown or CAMKK2 knockdown VHL^{-} cells. STO-609 (CAMKK2 inhibitor) also stimulated miR-214 expression (23).

Excitingly, there is a fascinating study which shows that TRPM7 can be cleaved by caspase-8 [24]. It has been reported that caspase-8 mediated processing of TRPM7 resulted in dissociation of kinase domain from the ion-conducting pore. Cleaved channel exhibited considerably higher activity and potentiated Fas receptor-induced downstream signaling to induce apoptotic cell death [24]. These findings are very crucial and it will be worthwhile to test if TRPM7 kinase domain is also cleaved in RCC [24]. Furthermore, in addition to Fas/FasL-mediated apoptosis, TRAIL/TRAIL-receptor signaling needs to be tested in TRPM-expressing RCC. If caspase-induced cleavage of TRPM7 is evident in RCC, it will be effective in context of targeting of RCC through TRAIL-based therapeutics.

Different molecules have been shown to effectively inhibit kinase activity of TRPM7 [25]. TG100-115 inhibited TRPM7 kinase regulated phosphorylation of myosin IIA heavy chain and FAK (focal adhesion kinase) [25].

4. Role of TRPVs in carcinogenesis

Capsaicin, a naturally occurring and biologically potent ingredient of green and red peppers and a ligand of TRPV1 has been demonstrated to suppress tumorigenesis in several cancers [26]. Capsaicin induced apoptosis in RCC cells partially through activation of TRPV1 [26]. Capsaicin-mediated activation of TRPV1 markedly inhibited metastasizing potential of thyroid cancer cells. Tumor weight and volume were also drastically reduced in capsaicin-treated xenografted mice [27].

Transient receptor potential vanilloid subfamily-5 (TRPV5) is a calcium channel mainly found in the kidney and plays essential role in maintenance of homeostasis of the intracellular calcium concentrations [28]. Studies revealed that Vitamin-D receptor (VDR) transcriptionally controlled TRPV5. Moreover, it had previously been reported that TRPV5 promoter contained multiple consensus Vitamin D-response elements. VDR overexpression considerably reduced the proliferation of 786-O and caki-1 cells [28]. Furthermore, expectedly, knockdown of VDR potentiated proliferation capacity of caki-1 and 786-O cells. TRPV5 expression was found to be significantly higher in VDR-silenced caki-1 cells [28]. Future studies must converge on comprehensive analysis of tumor forming abilities of TRPV5-overexpressing and TRPV5-silenced RCC cells in xenografted mice.

TRPV1-expressing cancers may be effectively targeted by either stimulating the release of endovanilloid or TRPV1 agonist therapy [29]. Neural precursor cells (NPCs) efficiently migrate to HGAs (high-grade astrocytoma) and induce shrinkage of glioma and prolong survival time. NPCs have been shown to release endovanilloids that activate TRPV1 on HGA cells and induce apoptotic cell death. Arvanil, a synthetic, blood-brain-barrier permeable vanilloid significantly improved survival of SCID mice orthotopically implanted with glioblastoma cells [29]. These findings are encouraging and it will be interesting to analyze further updates on therapeutic advancements related to TRPV1 agonists against TRPV1-expressing cancers in xenografted mice.

5. Regulation of TRP channels by non-coding RNAs in different cancers

Most recently, miRNAs have emerged as possible regulators. In fact, the discovery of non-coding RNAs has revolutionized the field of molecular cancer and we have witnessed ground-breaking achievements in our understanding related to post-transcriptional regulation of oncogenic and tumor suppressor genes [30–32]. MicroRNAs (miRNAs) [33–35], long non-coding RNAs (lncRNAs) [36–39] and circular RNAs (circRNAs) [40–42] have central role in the progression of cancer.

Excitingly, TRP channel biology will be incomplete without proper investigation of regulatory mechanisms of TRP channels by non-coding RNAs. It is worth mentioning that molecular biologists have started to focus on modulation of TRP channels by non-coding RNAs but available evidence is still limited and needs extensive research. In this section, we will discuss how different miRNAs, lncRNAs and circRNAs regulate TRP channels during cancer progression.

6. Regulation of TRPCs by miRNAs

There is a gradual increase in the number of scientific reports related to lncRNA-mediated control of TRPCs in different cancers. In this section, we have focused on different oncogenic lncRNAs reported to increase the expression of TRPCs during carcinogenesis (Fig. 2).

SNHG5 (small nucleolar RNA host gene 5), an oncogenic lncRNA sequestered miR-26a-5p away and stimulated TRPC3 expression in melanoma cells. SNHG5 inhibition significantly reduced proliferation and enhanced apoptotic rate in melanoma cells [43].

MiR-26a mediated targeting of TRPC3 can be blocked by DLX6-AS1 in laryngeal cancer cells [44]. TRPC3 expression was found to be considerably reduced in DLX6-AS1-silenced HEp-2 and Tu-177 cells. Furthermore, knockdown of TRPC3 suppressed the proliferation

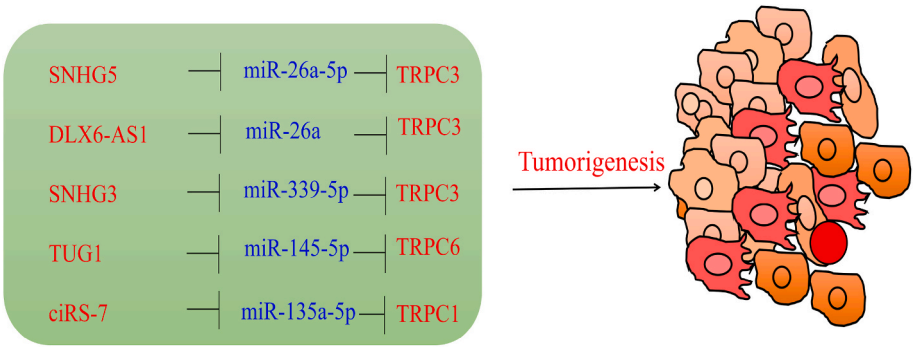

Fig. 2. Oncogenic lncRNAs and circRNAs promote the expression of TRPCs.

capacity of laryngeal cancer cells. Tumor growth was significantly reduced in mice xenografted with DLX6-AS1-silenced HEp-2 and Tu-177 cells [44].

SNHG3 interfered with miR-339-5p-mediated targeting of TRPC3 and potentiated tumorigenic properties of ovarian cancer cells. Tumor growth and average tumor weights were found to be decreased significantly in mice inoculated with SNHG3-knockdown HeyA8 cells [45].

Taurine upregulated gene 1 (TUG1), a lncRNA promoted carcinogenesis by interfering with miR-145-5p-mediated inhibition of TRPC6. TUG1 silencing led to inhibition of the growth of tumor xenografts in mice injected with TUG1-depleted-HCT116 cells [46].

OIP5-AS1 interacts with p53 and transcriptionally upregulates POX expression. TRPC6 causes disassembly of OIP5-AS1 and p53 and represses the expression of POX. TRPC6 promotes the progression of glioma principally through the blockade of OIP5-AS1/p53 mediated activation of POX [47].

TRPC1 acted as a pro-metastatic factor in gastric cancer cells [48]. MiR-135a-5p directly targeted TRPC1 in gastric cancer cells. CiRS-7, an oncogenic circular RNA interfered with miR-135a-5p-mediated targeting of TRPC1 and potentiated its expression [48].

Overall, these findings indicate that oncogenic lncRNAs are sophisticated regulators of TRPCs with a multifaceted involvement in the progression of cancer.

7. Regulation of TRPMs by miRNAs

7.1. TRPM1

TRPM1 has been shown to suppress melanoma metastasis [49]. TRPM1 encodes a channel protein and also transcribes miRNA-211 present in its sixth intron. KCNMA1 was directly targeted by miR-211 and protein levels of KCNMA1 were found to be significantly reduced in miR-211 expressing melanoma cells [49]. Findings suggested that use of miR-211 mimics can be helpful in suppressing cancer progression.

However, surprisingly, it had also been reported that miR-211 played dualistic role in melanoma. BRAF inhibitors (dabrafenib, vemurafenib) are used to treat patients with metastatic melanomas harboring $BRAF^{V600}$ mutations. MITF (Microphthalmia-associated Transcription factor) has been shown to transcriptionally upregulate TRPM1 [50]. Resultantly, miR-211–5p present within host TRPM1 gene is also transcribed. Vemurafenib sensitivity was reduced in miR-211-transfected melanoma cells. While miR-211–5p inhibition in a vemurafenib resistant cell line inhibited the proliferation [50]. Data clearly suggested that miR-211 behaved dualistically in melanoma. However, these findings need additional validation in different cancers.

In renal cell carcinoma, miR-211 acts as a tumor suppressor. Some of the studies demonstrated that miR-211–5p reduced tumor metastasis, particularly in the lung, liver and spleen. Metastatic foci were also found to be significantly reduced in mice treated with miR-211–5p [51]. Upregulation of miR-211–5p induced apoptosis in 786O and ACHN cells [52]. There is strong evidence of role of miR-211 in RCC as a metastasis inhibitor. Broader analysis of the regulatory pathways of miR-211 in RCC will be helpful in detailed evaluation of use of miRNA mimics for significant clinical outcome.

TRPM2: TRPM2-AS is a long non-coding RNA transcribed from TRPM2. Inhibition of TRPM2-AS induced apoptosis in breast cancer cells [53]. ELK1 transcriptionally upregulated TRPM2-AS in gastric cancer cells [54]. TRPM2-AS inhibition markedly reduced proliferation, migration and invasive potential of gastric cancer cells. TRPM2-AS blocked miR-195-mediated targeting of HMGA1 (high-mobility group AT-hook 1) [54].

TRPM2-AS promoted cancer by interfering with miR-612 and stimulating the expression of IGF2BP1 and FOXM1 [55]. IGF2BP1 and FOXM1 centrally drive metastasis. Lung metastatic burden was reported to be reduced in mice inoculated with TRPM2-AS-silenced gastric cancer cells [55].

TRPM2-AS has also recently been shown to stimulate the expression of SOX4 in laryngeal squamous cell carcinoma cells [56]. MiR-138 directly inhibited SOX4 and markedly suppressed epithelial to mesenchymal transition. However, TRPM2-AS interfered with miR-138-mediated targeting of SOX4 and promoted EMT [56].

TRPM3: miR-204 has been shown to directly target TRPM3 in RCC cells [23]. Stable knockdown of the TRPM3 interfered with the tumor forming abilities of these cells in orthotopically xenografted mice [23].

MiR-204 is situated inside the intronic sequence of TRPM3. There are some exciting pieces of evidence which provide clues about transcriptional repression of miR-204 also in gynecological cancers. Phosphorylated-STAT3 binds directly to STAT3-binding sites near TRPM3 promoter region upstream of miR-204–5p thus causing its transcriptional repression. Additionally, miR-204–5p induced tumor regression in xenografted mice [57]. Interleukin-6 promoted tumor formation and increased tumor nodules in mice. Interleukin-6 induces cisplatin resistance in epithelial ovarian cancer cells. Transcriptional repression of miR-204 has also been shown to potentiate resistance against cisplatin. Intraperitoneal administration of cisplatin caused tumor inhibition in mice inoculated with miR-204-transfected SKOV3 cells [58]. These findings suggest that miR-204 is essential for tumor inhibition and drug sensitivity. Moreover, JAK/STAT3 signaling transcriptionally represses miR-204. Use of STAT3 inhibitors and miR-204 mimics will be advantageous in the regression of the xenografted tumors.

CircPRRC2A, an oncogenic circular RNA promoted the expression of TRPM3 and EMT-associated markers in RCC cells [59]. There was a marked increase in the levels of *E*-cadherin and significant reduction in the levels of TRPM3 and *N*-cadherin in circPRRC2A-silenced ACHN cells. CircPRRC2A interfered with miR-514a-5p and miR-6776-5p-mediated targeting of TRPM3 (Fig. 3). There was a noteworthy reduction in metastatic nodules in the liver and lungs of the mice injected with circPRRC2A-silenced RCC cells [59].

CircATG9A significantly promotes the migratory and invasive

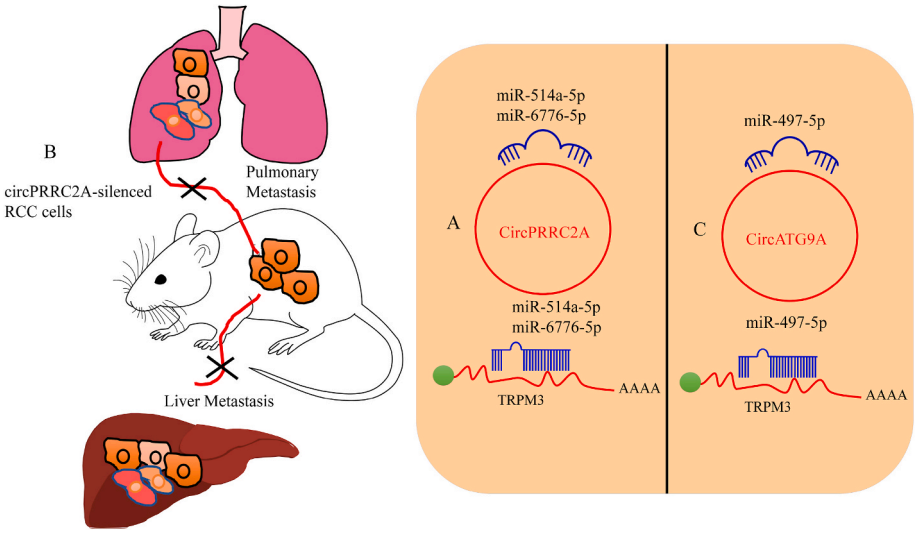

Fig. 3. CircRNAs stimulate the expression of TRPM3 mainly through inhibition of miRNA-mediated targeting of TRPM3. (A–B) CircPRRC2A interfered with miR-514a-5p and miR-6776-5p-mediated targeting of TRPM3. Pulmonary and liver metastasis is impaired upon the inhibition of circPRRC2A. (C) CircATG9A inhibits miR-497-5p-mediated targeting of TRPM3. CircATG9A promotes tumorigenesis.

properties of RCC cells. CircATG9A potentiates the expression of TRPM3 mainly through blockade of miR-497-5p-mediated targeting of TRPM3 (Fig. 3). Importantly, TRPM3 promotes carcinogenesis through activation of Wnt/β-catenin pathway. Overall, CircATG9A and TRPM3 play central role in carcinogenesis and metastasis. Levels of *E*-cadherin were found to be enhanced in CircATG9A and TRPM3 silenced cancer cells. Importantly, tumor volume and weights were noted to be reduced in mice inoculated with circATG9A-silenced cancer cells [60].

TRPM4: It has recently been convincingly revealed that miR-150 directly targeted TRPM4 in prostate cancer cells. More importantly, tumor growth was drastically reduced in mice xenografted with miR-150-overexpressing prostate cancer cells [61].

TRPM7: TRPM7 was directly inhibited by miR-543 in cervical cancer cells. TRPM7 activated oncogenic P13 K/AKT and p38-MAPK pathways in cervical cancer cells. Expectedly, miR-543 mimics considerably reduced tumor growth in mice inoculated with cervical cancer cells [62].

TRPM7 has been shown to fuel cancer progression [63]. There was a marked decrease in the migratory and invasive potential of TRPM7-silenced RCC cells. Phosphorylated levels of Src and AKT were drastically reduced in TRPM7-silenced RCC cells [63]. Detailed mechanistic insights further revealed that TRPM7 induced activation of AKT resulted in inhibition of nuclear accumulation of FOXO1 proteins [63]. Mechanistically it was shown that AKT phosphorylated FOXO1 and interfered with transportation into the nucleus and transcriptional regulation of target genes. MiR-129–3p mimics directly targeted TRPM7, whereas miR-129–3p inhibitors increased protein levels of TRPM7 [64]. Tumor growth was remarkably reduced in mice injected subcutaneously with TRPM7-silenced OSRC-2- cells into the dorsal flank. Overall, these results clearly demonstrated that TRPM7 played contributory role in RCC [64].

TRPM7 overexpression correlated significantly with glioma progression. TRPM7 positively regulates HOTAIR. Essentially, HOTAIR knockdown inhibited proliferative and invasive potential of glioma cells. TRPM7 mediated Ca^{2+} influx triggered activation of NFκB which transcriptionally activated HOTAIR. Furthermore, miR-301a-3p was upregulated significantly in TRPM7-knockdown glioma cells. HOTAIR interfered with miR-301a-3p-mediated targeting of FOSLI and promoted tumorigenesis [65].

Expression of non-coding RNAs is regulated by TRPM7 in cancer cells. Overexpression of miR-28–5p suppressed invasion of glioma cells. MiR-28–5p levels are low in TRPM7-expressing cancer cells. MiR-28–5p directly targeted Rap1b and inhibited invasive potential of glioma cells [66].

Hsa_circ_0023,305 potently enhanced the expression of TRPM7 in laryngeal squamous cell carcinoma. MiR-218–5p is a tumor suppressor having notable ability to target TRPM7. Hsa_circ_0023,305 acted as a sponge and blocked miR-218-5p-mediated inhibition of TRPM7 (Fig. 4). Hsa_circ_0023,305 silencing led to marked reduction in pulmonary metastatic dissemination in mice intravenously injected with hsa_circ_0023,305-depleted-AMC–HN–8 cells into tails [67].

METTL3 is a catalytically active subunit and transfers a methyl group to RNA. IGF2BPs are m6A readers [68–71]. IGF2BPs efficiently bind to the mRNA transcripts and promote the stability and storage of their target mRNAs. There was an increase in mRNA stability of TRPM7 in DGUOK-AS1 and IGF2BP2 overexpressing cancer cells. Furthermore, interaction between TRPM7 and IGF2BP2 was suppressed after knockdown of DGUOK-AS1 or METTL3. TRPM7 m6A levels were found to be reduced in METTL3 knockdown cancer cells. Likewise, there was an evident decline in the levels of TRPM7 upon the knockdown of METTL3, while TRPM7 expression was reported to be increased upon overexpression of IGF2BP2. Findings indicated that METTL3/IGF2BP2 axis promoted stabilization of TRPM7 mRNA by m6A-modifications in NSCLC cells (Fig. 4). Mechanistically, role of DGUOK-AS1 was evaluated in the pulmonary metastatic models established by tail vein injections of SK-MES-1 cells. Therefore, number of pulmonary metastatic tumor foci were detected to be reduced effectively after DGUOK-AS1 knockdown [72] (Fig. 4). These findings provide compelling evidence that oncogenic lncRNAs promote METTL3-mediated m6A modifications and stability of TRPM7.

8. Regulation of TRPVs by miRNAs

MYC and MAX are involved in transcriptional upregulation of LINC00958. Essentially, LINC00958 worked with transcriptional factors in LINC00958-bound regions and regulated the expression of TRPV3. Tumors derived from LINC00958-silenced-A549 cancer cells were smaller in size [73]. Collectively, these findings indicated that LINC00958 stimulated different oncogenes and promoted lung adenocarcinoma.

9. Concluding remarks

Pharmacological targeting of cancers is becoming increasingly

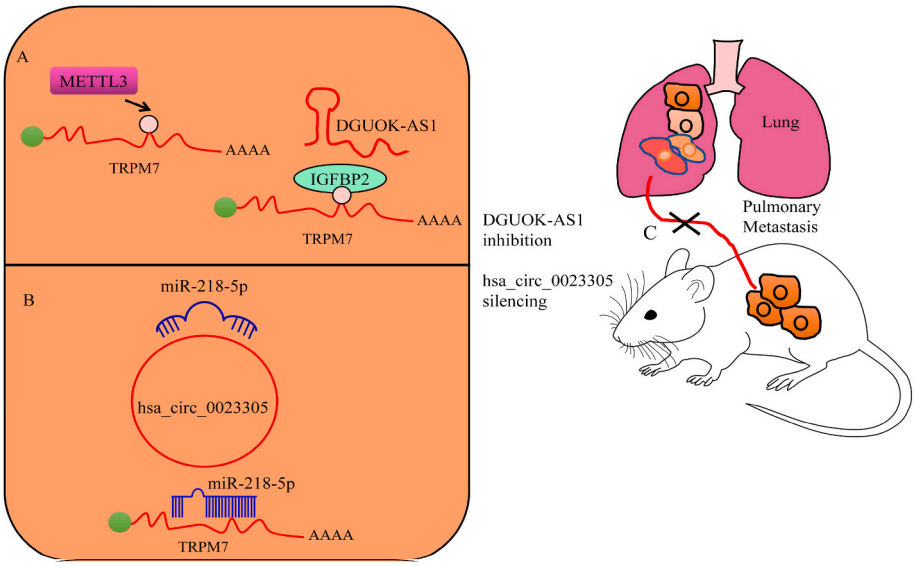

Fig. 4. (A) DGUOK-AS1 induced m6A modification of TRPM7 mainly through METTL3. IGFBP2 recognized m6A modification of TRPM7. DGUOK-AS1 inhibition led to reduction in the metastatic spread of cancer cells to the lungs. (B) Hsa_circ_0023,305 promotes metastasis mainly through inhibition of miR-218-5p-mediated targeting of TRPM7. Metastatic spread of cancer cells to the lungs was impaired because of the inhibition of hsa_circ_0023,305.

challenging because of intra and inter-tumor heterogeneity and development of resistance against various therapeutics. Furthermore, TRP channels have also emerged as central regulators of drug resistance and metastatic dissemination of cancer cells. In this review, we have attempted to summarize state-of-the-art advancements in exciting and sequentially evolving features of TRP channels and highlight recent breakthroughs and identify the knowledge-gaps associated with central role of TRP channels in different cancers.

Accumulating evidence has started to shed light on the diversity in the expression, functionalities and structural framework of TRP channels and provides the opportunities to generate novel, selective chemical entities which can be tested in various clinical settings. Molecules that target TRPV3 have made their entry into Phase I of clinical trials, and blockers of TRPA1, TRPM8 and TRPV4 have demonstrated efficacy in various preclinical disease models and did not show unexpected off-target or acute adverse effects which could limit their further evaluation. However, these molecules have to be tested in xenografted mice to see if growth of the tumor can be inhibited or not.

It seems surprising to note that there is a substantial broadening in the field of TRP channels and these aspects are being uncovered in different cancers. We have to learn some very important lessons from existing scientific evidence about role of TRP channels because translatability of these findings to clinical trials is necessary. There are some exciting clues which suggest that different miRNAs and lncRNAs are transcribed from host genes of TRP channels. Multiple miRNAs have also been reported to negatively regulate TRP channels in different cancers. Different TRP channels regulate the expression of lncRNAs (HOTAIR). Moreover, various lncRNAs stabilize TRP channels mainly through METTL3-mediated m6A modifications. Role of circular RNAs in carcinogenesis is intriguing and emerging evidence illuminates critical functions of circRNA sponges in miRNA-mediated gene regulation [74]. Non-coding RNA-mediated control of TRP channels needs to be tested more comprehensively in metastasis. Moreover, pharmacological targeting of different lncRNAs and miRNAs transcribed from TRP genes will be exciting in tumor-bearing mice. Collectively, these findings suggest that sophisticated ncRNA-based regulatory systems unravel an intricate interplay with TRP channels. Based on clues from known examples, molecular and cellular biologists have started to reveal the true complexity of what lies under the surface.

Conflict of interest

The Authors declare that they do not have any conflict of interest.

CRediT authorship contribution statement

Assiya Turgambayeva: Writing – original draft, Formal analysis, Data curation. **Samal Duisekova:** Writing – original draft, Formal analysis, Data curation. **Gulnara Tashenova:** Writing – original draft, Formal analysis, Data curation, Conceptualization. **Aigul Tulebayeva:** Writing – original draft, Formal analysis, Data curation, Conceptualization. **Gulnara Kapanova:** Writing – original draft, Supervision, Formal analysis. **Aida Akhenbekova:** Writing – original draft, Formal analysis, Data curation, Conceptualization. **Ammad Ahmad Farooqi:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

References

[1] S. Valastyan, R.A. Weinberg, Tumor metastasis: molecular insights and evolving paradigms, Cell 147 (2) (2011 Oct 14) 275–292, https://doi.org/10.1016/j.cell.2011.09.024.
[2] A. Puisieux, T. Brabletz, J. Caramel, Oncogenic roles of EMT-inducing transcription factors, Nat. Cell Biol. 16 (6) (2014 Jun) 488–494, https://doi.org/10.1038/ncb2976.
[3] A. Dongre, R.A. Weinberg, New insights into the mechanisms of epithelial-mesenchymal transition and implications for cancer, Nat. Rev. Mol. Cell Biol. 20 (2) (2019 Feb) 69–84, https://doi.org/10.1038/s41580-018-0080-4.
[4] L. Bejarano, M.J.C. Jordão, J.A. Joyce, Therapeutic targeting of the tumor microenvironment, Cancer Discov. 11 (4) (2021 Apr) 933–959, https://doi.org/10.1158/2159-8290.CD-20-1808.
[5] C. Eifert, R.S. Powers, From cancer genomes to oncogenic drivers, tumour dependencies and therapeutic targets, Nat. Rev. Cancer 12 (8) (2012 Aug) 572–578, https://doi.org/10.1038/nrc3299.
[6] M.M. Moran, M.A. McAlexander, T. Bíró, A. Szallasi, Transient receptor potential channels as therapeutic targets, Nat. Rev. Drug Discov. 10 (8) (2011 Aug 1) 601–620, https://doi.org/10.1038/nrd3456.
[7] X. Zhang, M. Hu, Y. Yang, H. Xu, Organellar TRP channels, Nat. Struct. Mol. Biol. 25 (11) (2018 Nov) 1009–1018, https://doi.org/10.1038/s41594-018-0148-z.
[8] T. Hof, S. Chaigne, A. Récalde, L. Sallé, F. Brette, R. Guinamard, Transient receptor potential channels in cardiac health and disease, Nat. Rev. Cardiol. (2019 Jan 21), https://doi.org/10.1038/s41569-018-0145-2.
[9] T.E. Woudenberg-Vrenken, R.J. Bindels, J.G. Hoenderop, The role of transient receptor potential channels in kidney disease, Nat. Rev. Nephrol. 5 (8) (2009 Aug) 441–449, https://doi.org/10.1038/nrneph.2009.100. Epub 2009 Jun 23.
[10] M.Y. Asghar, M. Magnusson, K. Kemppainen, P. Sukumaran, C. Löf, I. Pulli, V. Kalhori, K. Törnquist, Transient receptor potential canonical 1 (TRPC1) channels as regulators of sphingolipid and vegf receptor expression: implications

for thyroid cancer cell migration and proliferation, J. Biol. Chem. 290 (26) (2015 Jun 26) 16116–16131, https://doi.org/10.1074/jbc.M115.643668.
[11] P. Ge, L. Wei, M. Zhang, B. Hu, K. Wang, Y. Li, S. Liu, J. Wang, Y. Li, TRPC1/3/6 inhibition attenuates the TGF-β1-induced epithelial-mesenchymal transition in gastric cancer via the Ras/Raf 1/ERK signaling pathway, Cell Biol. Int. 42 (8) (2018 Aug) 975–984, https://doi.org/10.1002/cbin.10963.
[12] I. Azimi, M.J.G. Milevskiy, E. Kaemmerer, D. Turner, K.T.D.S. Yapa, M.A. Brown, E. W. Thompson, S.J. Roberts-Thomson, G.R. Monteith, TRPC1 is a differential regulator of hypoxia-mediated events and Akt signalling in PTEN-deficient breast cancer cells, J. Cell Sci. 130 (14) (2017 Jul 15) 2292–2305, https://doi.org/10.1242/jcs.196659.
[13] M. Guéguinou, T. Harnois, D. Crottes, A. Uguen, N. Deliot, A. Gambade, A. Chantôme, J.P. Haelters, P.A. Jaffrès, M.L. Jourdan, G. Weber, O. Soriani, P. Bougnoux, O. Mignen, N. Bourmeyster, B. Constantin, T. Lecomte, C. Vandier, M. Potier-Cartereau, SK3/TRPC1/Orai1 complex regulates SOCE-dependent colon cancer cell migration: a novel opportunity to modulate anti-EGFR mAb action by the alkyl-lipid Ohmline, Oncotarget 7 (24) (2016 Jun 14) 36168–36184, https://doi.org/10.18632/oncotarget.8786.
[14] M.F. Emmons, N. Anreddy, J. Cuevas, K. Steinberger, S. Yang, M. McLaughlin, A. Silva, L.A. Hazlehurst, MTI-101 treatment inducing activation of Stim1 and TRPC1 expression is a determinant of response in multiple myeloma, Sci. Rep. 7 (1) (2017 Jun 2) 2685, https://doi.org/10.1038/s41598-017-02713-0.
[15] C. Carson, P. Raman, J. Tullai, L. Xu, M. Henault, E. Thomas, S. Yeola, J. Lao, M. McPate, J.M. Verkuyl, G. Marsh, J. Sarber, A. Amaral, S. Bailey, D. Lubicka, H. Pham, N. Miranda, J. Ding, H.M. Tang, H. Ju, P. Tranter, N. Ji, P. Krastel, R. K. Jain, A.M. Schumacher, J.J. Loureiro, E. George, G. Berellini, N.T. Ross, S. M. Bushell, G. Erdemli, J.M. Solomon, Englerin A agonizes the TRPC4/C5 cation channels to inhibit tumor cell line proliferation, PLoS One 10 (6) (2015 Jun 22) e0127498, https://doi.org/10.1371/journal.pone.0127498 eCollection 2015.
[16] S.Y. Cheung, M. Henrot, M. Al-Saad, M. Baumann, H. Muller, A. Unger, H. N. Rubaiy, I. Mathar, K. Dinkel, P. Nussbaumer, B. Klebl, M. Freichel, B. Rode, S. Trainor, S.J. Clapcote, M. Christmann, H. Waldmann, S.K. Abbas, D.J. Beech, N. S. Vasudev, TRPC4/TRPC5 channels mediate adverse reaction to the cancer cell cytotoxic agent (-)-Englerin A, Oncotarget 9 (51) (2018 Jul 3) 29634–29643, https://doi.org/10.18632/oncotarget.25659.
[17] H.N. Rubaiy, T. Seitz, S. Hahn, A. Choidas, P. Habenberger, B. Klebl, K. Dinkel, P. Nussbaumer, H. Waldmann, M. Christmann, D.J. Beech, Identification of an (-)-englerin A analogue, which antagonizes (-)-englerin 'A at TRPC1/4/5 channels, Br. J. Pharmacol. 175 (5) (2018 Mar) 830–839, https://doi.org/10.1111/bph.14128.
[18] H.N. Rubaiy, M.J. Ludlow, K. Siems, K. Norman, R. Foster, D. Wolf, J.A. Beutler, D. J. Beech, Tonantzitlolone is a nanomolar potency activator of transient receptor potential canonical 1/4/5 channels, Br. J. Pharmacol. 175 (16) (2018 Aug) 3361–3368, https://doi.org/10.1111/bph.14379.
[19] D.P. Thakur, J.B. Tian, J. Jeon, J. Xiong, Y. Huang, V. Flockerzi, M.X. Zhu, Critical roles of Gi/o proteins and phospholipase C-δ1 in the activation of receptor-operated TRPC4 channels, Proc. Natl. Acad. Sci. U. S. A. 113 (4) (2016 Jan 26) 1092–1097, https://doi.org/10.1073/pnas.1522294113.
[20] S. Genovesi, R. Moro, B. Vignoli, D. De Felice, M. Canossa, R. Montironi, F. G. Carbone, M. Barbareschi, A. Lunardi, A. Alaimo, Trpm8 expression in human and mouse castration resistant prostate adenocarcinoma paves the way for the preclinical development of TRPM8-based targeted therapies, Biomolecules 12 (2) (2022 Jan 23) 193, https://doi.org/10.3390/biom12020193.
[21] Y. Liu, A. Leng, L. Li, B. Yang, S. Shen, H. Chen, E. Zhu, Q. Xu, X. Ma, P. Shi, Y. Liu, T. Liu, L. Li, K. Li, D. Zhang, J. Xiao, AMTB, a TRPM8 antagonist, suppresses growth and metastasis of osteosarcoma through repressing the TGFβ signaling pathway, Cell Death Dis. 13 (3) (2022 Mar 31) 288, https://doi.org/10.1038/s41419-022-04744-6.
[22] D. Nomura, R. Abe, M. Tsukimoto, Involvement of TRPM8 channel in radiation-induced DNA damage repair mechanism contributing to radioresistance of B16 melanoma, Biol. Pharm. Bull. 44 (5) (2021 May 1) 642–652, https://doi.org/10.1248/bpb.b20-00934.
[23] D.P. Hall, N.G. Cost, S. Hegde, E. Kellner, O. Mikhaylova, Y. Stratton, B. Ehmer, W. A. Abplanalp, R. Pandey, J. Biesiada, C. Harteneck, D.R. Plas, J. Meller, M. F. Czyzyk-Krzeska, TRPM3 and miR-204 establish a regulatory circuit that controls oncogenic autophagy in clear cell renal cell carcinoma, Cancer Cell 26 (5) (2014 Nov 10) 738–753, https://doi.org/10.1016/j.ccell.2014.09.015.
[24] B.N. Desai, G. Krapivinsky, B. Navarro, L. Krapivinsky, B.C. Carter, S. Febvay, M. Delling, A. Penumaka, I.S. Ramsey, Y. Manasian, D.E. Clapham, Cleavage of TRPM7 releases the kinase domain from the ion channel and regulates its participation in Fas-induced apoptosis, Dev. Cell 22 (6) (2012 Jun 12) 1149–1162, https://doi.org/10.1016/j.devcel.2012.04.006.
[25] C. Song, Y. Bae, J. Jun, H. Lee, N.D. Kim, K.B. Lee, W. Hur, J.Y. Park, T. Sim, Identification of TG100-115 as a new and potent TRPM7 kinase inhibitor, which suppresses breast cancer cell migration and invasion, Biochim. Biophys. Acta Gen. Subj. 1861 (4) (2017 Apr) 947–957, https://doi.org/10.1016/j.bbagen.2017.01.034.
[26] T. Liu, G. Wang, H. Tao, Z. Yang, Y. Wang, Z. Meng, R. Cao, Y. Xiao, X. Wang, J. Zhou, Capsaicin mediates caspases activation and induces apoptosis through P38 and JNK MAPK pathways in human renal carcinoma, BMC Cancer 16 (1) (2016 Oct 12) 790.
[27] S. Xu, L. Zhang, X. Cheng, H. Yu, J. Bao, R. Lu, Capsaicin inhibits the metastasis of human papillary thyroid carcinoma BCPAP cells through the modulation of the TRPV1 channel, Food Funct. 9 (1) (2018 Jan 24) 344–354, https://doi.org/10.1039/c7fo01295k.
[28] Y. Chen, X. Liu, F. Zhang, S. Liao, X. He, D. Zhuo, H. Huang, Y. Wu, Vitamin D receptor suppresses proliferation and metastasis in renal cell carcinoma cell lines via regulating the expression of the epithelial Ca2+ channel TRPV5, PLoS One 13 (4) (2018 Apr 16) e0195844.
[29] K. Stock, J. Kumar, M. Synowitz, S. Petrosino, R. Imperatore, E.S. Smith, P. Wend, B. Purfürst, U.A. Nuber, U. Gurok, V. Matyash, J.H. Wälzlein, S.R. Chirasani, G. Dittmar, B.F. Cravatt, S. Momma, G.R. Lewin, A. Ligresti, L. De Petrocellis, L. Cristino, V. Di Marzo, H. Kettenmann, R. Glass, Neural precursor cells induce cell death of high-grade astrocytomas through stimulation of TRPV1, Nat. Med. 18 (8) (2012 Aug) 1232–1238, https://doi.org/10.1038/nm.2827.
[30] A. Ahmad, Non-coding RNAs: a tale of junk turning into treasure, Noncoding RNA Res 1 (1) (2017 Jan 5) 1–2, https://doi.org/10.1016/j.ncrna.2016.12.001.
[31] I. Gareev, Y. Gileva, A. Dzidzaria, O. Beylerli, V. Pavlov, M. Agaverdiev, B. Mazorov, I. Biganyakov, A. Vardikyan, M. Jin, A. Ahmad, Long non-coding RNAs in oncourology, Noncoding RNA Res 6 (3) (2021 Aug 26) 139–145, https://doi.org/10.1016/j.ncrna.2021.08.001.
[32] J. He, W. Wu, Comprehensive landscape and future perspectives of long noncoding RNAs (lncRNAs) in colorectal cancer (CRC): based on a bibliometric analysis, Noncoding RNA Res 8 (1) (2022 Oct 11) 33–52, https://doi.org/10.1016/j.ncrna.2022.10.001.
[33] S. Volinia, G.A. Calin, C.G. Liu, S. Ambs, A. Cimmino, F. Petrocca, R. Visone, M. Iorio, C. Roldo, M. Ferracin, R.L. Prueitt, N. Yanaihara, G. Lanza, A. Scarpa, A. Vecchione, M. Negrini, C.C. Harris, C.M. Croce, A microRNA expression signature of human solid tumors defines cancer gene targets, Proc. Natl. Acad. Sci. U. S. A. 103 (7) (2006 Feb 14) 2257–2261.
[34] J.R. Lytle, T.A. Yario, J.A. Steitz, Target mRNAs are repressed as efficiently by microRNA-binding sites in the 5' UTR as in the 3' UTR, Proc. Natl. Acad. Sci. U. S. A. 104 (23) (2007 Jun 5) 9667–9672.
[35] B. Khraiwesh, M.A. Arif, G.I. Seumel, S. Ossowski, D. Weigel, R. Reski, W. Frank, Transcriptional control of gene expression by microRNAs, Cell 140 (1) (2010 Jan 8) 111–122.
[36] M.N. Cabili, M.C. Dunagin, P.D. McClanahan, A. Biaesch, O. Padovan-Merhar, A. Regev, J.L. Rinn, A. Raj, Localization and abundance analysis of human lncRNAs at single-cell and single-molecule resolution, Genome Biol. 16 (1) (2015 Jan 29) 20, https://doi.org/10.1186/s13059-015-0586-4.
[37] M.K. Iyer, Y.S. Niknafs, R. Malik, U. Singhal, A. Sahu, Y. Hosono, T.R. Barrette, J. R. Prensner, J.R. Evans, S. Zhao, A. Poliakov, X. Cao, S.M. Dhanasekaran, Y.M. Wu, D.R. Robinson, D.G. Beer, F.Y. Feng, H.K. Iyer, A.M. Chinnaiyan, The landscape of long noncoding RNAs in the human transcriptome, Nat. Genet. 47 (3) (2015) 199–208.
[38] M. Guttman, I. Amit, M. Garber, C. French, M.F. Lin, D. Feldser, M. Huarte, O. Zuk, B.W. Carey, J.P. Cassady, M.N. Cabili, R. Jaenisch, T.S. Mikkelsen, T. Jacks, N. Hacohen, B.E. Bernstein, M. Kellis, A. Regev, J.L. Rinn, E.S. Lander, Chromatin signature reveals over a thousand highly conserved large non-coding RNAs in mammals, Nature 458 (7235) (2009) 223–227.
[39] H.S. Chiu, S. Somvanshi, E. Patel, T.W. Chen, V.P. Singh, B. Zorman, S.L. Patil, Y. Pan, S.S. Chatterjee, A.K. Sood, P.H. Gunaratne, P. Sumazin, Pan-cancer analysis of lncRNA regulation supports their targeting of cancer genes in each tumor context, Cell Rep. 23 (1) (2018 Apr 3) 297–312.e12.
[40] S. Memczak, M. Jens, A. Elefsinioti, F. Torti, J. Krueger, A. Rybak, L. Maier, S. D. Mackowiak, L.H. Gregersen, M. Munschauer, A. Loewer, U. Ziebold, M. Landthaler, C. Kocks, F. le Noble, N. Rajewsky, Circular RNAs are a large class of animal RNAs with regulatory potency, Nature 495 (7441) (2013 Mar 21) 333–338, https://doi.org/10.1038/nature11928.
[41] T.B. Hansen, T.I. Jensen, B.H. Clausen, J.B. Bramsen, B. Finsen, C.K. Damgaard, J. Kjems, Natural RNA circles function as efficient microRNA sponges, Nature 495 (7441) (2013 Mar 21) 384–388, https://doi.org/10.1038/nature11993.
[42] C. Zhang, Y. Kang, F. Kong, Q. Yang, D. Chang, Hotspots and development frontiers of circRNA based on bibliometric analysis, Noncoding RNA Res 7 (2) (2022 Mar 21) 77–88, https://doi.org/10.1016/j.ncrna.2022.03.001.
[43] J. Gao, K. Zeng, Y. Liu, L. Gao, L. Liu, LncRNA SNHG5 promotes growth and invasion in melanoma by regulating the miR-26a-5p/TRPC3 pathway, OncoTargets Ther. 12 (2018 Dec 24) 169–179.
[44] Y. Liu, X. Liu, X. Zhang, J. Deng, J. Zhang, H. Xing, lncRNA DLX6-AS1 promotes proliferation of laryngeal cancer cells by targeting the miR-26a/TRPC3 pathway, Cancer Manag. Res. 12 (2020 Apr 21) 2685–2695.
[45] E.L. Liu, Y.X. Zhou, J. Li, D.H. Zhang, F. Liang, Long-chain non-coding RNA SNHG3 promotes the growth of ovarian cancer cells by targeting miR-339-5p/TRPC3 Axis, OncoTargets Ther. 13 (2020 Oct 28) 10959–10971, https://doi.org/10.2147/OTT.S249873.
[46] X. Wang, X. Bai, Z. Yan, X. Guo, Y. Zhang, The lncRNA TUG1 promotes cell growth and migration in colorectal cancer via the TUG1-miR-145-5p-TRPC6 pathway, Biochem. Cell. Biol. 99 (2) (2021 Apr) 249–260, https://doi.org/10.1139/bcb-2020-0017.
[47] W. Shao, Z.Y. Hao, Y.F. Chen, J. Du, Q. He, L.L. Ren, Y. Gao, N. Song, Y. Song, H. He, Y.Z. Wang, OIP5-AS1 specifies p53-driven POX transcription regulated by TRPC6 in glioma, J. Mol. Cell Biol. 13 (6) (2021 Sep 11) 409–421, https://doi.org/10.1093/jmcb/mjab001.
[48] Z. Zhang, L. Ren, Q. Zhao, G. Lu, M. Ren, X. Lu, Y. Yin, S. He, C. Zhu, TRPC1 exacerbate metastasis in gastric cancer via ciRS-7/miR-135a-5p/TRPC1 axis, Biochem. Biophys. Res. Commun. 529 (1) (2020 13) 85–90.
[49] J. Mazar, K. DeYoung, D. Khaitan, E. Meister, A. Almodovar, J. Goydos, A. Ray, R. J. Perera, The regulation of miRNA-211 expression and its role in melanoma cell invasiveness, PLoS One 5 (11) (2010 Nov 1) e13779, https://doi.org/10.1371/journal.pone.0013779.

[50] T.R. Lunavat, L. Cheng, B.O. Einarsdottir, R. Olofsson Bagge, S. Veppil Muralidharan, R.A. Sharples, C. Lässer, Y.S. Gho, A.F. Hill, J.A. Nilsson, J. Lötvall, BRAFV600 inhibition alters the microRNA cargo in the vesicular secretome of malignant melanoma cells, Proc. Natl. Acad. Sci. U. S. A. 114 (29) (2017 Jul 18) E5930–E5939, https://doi.org/10.1073/pnas.1705206114.

[51] K. Wang, W. Jin, P. Jin, X. Fei, X. Wang, X. Chen, miR-211-5p suppresses metastatic behavior by targeting SNAI1 in renal cancer, Mol. Cancer Res. 15 (4) (2017 Apr) 448–456, https://doi.org/10.1158/1541-7786.MCR-16-0288.

[52] J. Quan, X. Pan, T. He, C. Lin, Y. Lai, P. Chen, Z. Zhang, S. Yang, T. Wang, Y. Lai, Tumor suppressor miR-211-5p is associated with cellular migration, proliferation and apoptosis in renal cell carcinoma, Exp. Ther. Med. 15 (4) (2018 Apr) 4019–4028, https://doi.org/10.3892/etm.2018.5908.

[53] T. Sun, Y. Song, H. Yu, X. Luo, Identification of lncRNA TRPM2-AS/miR-140-3p/PYCR1 axis's proliferates and anti-apoptotic effect on breast cancer using co-expression network analysis, Cancer Biol. Ther. 20 (6) (2019) 760–773, https://doi.org/10.1080/15384047.2018.1564563.

[54] B. Huang, C. Chang, B.L. Wang, H. Li, ELK1-induced upregulation of lncRNA TRPM2-AS promotes tumor progression in gastric cancer by regulating miR-195/HMGA1 axis, J. Cell. Biochem. 120 (10) (2019) 16921–16933.

[55] J. Xiao, L. Lin, D. Luo, L. Shi, W. Chen, H. Fan, Z. Li, X. Ma, P. Ni, L. Yang, Z. Xu, Long noncoding RNA TRPM2-AS acts as a microRNA sponge of miR-612 to promote gastric cancer progression and radioresistance, Oncogenesis 9 (3) (2020) 29.

[56] N. Wang, L. Wang, X. Pan, Long non-coding RNA TRPM2-AS promotes cell migration and invasion by serving as a ceRNA of miR-138 and inducing SOX4-mediated EMT in laryngeal squamous cell carcinoma, Cancer Manag. Res. 12 (2020) 7805–7812.

[57] W. Bao, H.H. Wang, F.J. Tian, X.Y. He, M.T. Qiu, J.Y. Wang, H.J. Zhang, L. H. Wang, X.P. Wan, A TrkB-STAT3-miR-204-5p regulatory circuitry controls proliferation and invasion of endometrial carcinoma cells, Mol. Cancer 12 (2013 Dec 9) 155, https://doi.org/10.1186/1476-4598-12-155.

[58] X. Zhu, H. Shen, X. Yin, L. Long, X. Chen, F. Feng, Y. Liu, P. Zhao, Y. Xu, M. Li, W. Xu, Y. Li, IL-6R/STAT3/miR-204 feedback loop contributes to cisplatin resistance of epithelial ovarian cancer cells, Oncotarget 8 (24) (2017 Jun 13) 39154–39166, https://doi.org/10.18632/oncotarget.16610.

[59] W. Li, F.Q. Yang, C.M. Sun, J.H. Huang, H.M. Zhang, X. Li, G.C. Wang, N. Zhang, J. P. Che, W.T. Zhang, Y. Yan, X.D. Yao, B. Peng, J.H. Zheng, M. Liu, circPRRC2A promotes angiogenesis and metastasis through epithelial-mesenchymal transition and upregulates TRPM3 in renal cell carcinoma, Theranostics 10 (10) (2020 Mar 15) 4395–4409.

[60] Y. Shen, R. Wu, Z. Zhuo, X. Deng, W. Li, C. Liu, Identification of circATG9A as a novel biomarker for renal cell carcinoma, Cancer Gene Ther. (2023 Nov 9), https://doi.org/10.1038/s41417-023-00684-1.

[61] X. Hong, J.J. Yu, MicroRNA-150 suppresses epithelial-mesenchymal transition, invasion, and metastasis in prostate cancer through the TRPM4-mediated β-catenin signaling pathway, Am. J. Physiol. Cell Physiol. 316 (4) (2019 Apr 1) C463–C480, https://doi.org/10.1152/ajpcell.00142.2018.

[62] X. Liu, L. Gan, J. Zhang, miR-543 inhibits cervical cancer growth and metastasis by targeting TRPM7, Chem. Biol. Interact. 302 (2019 Apr 1) 83–92, https://doi.org/10.1016/j.cbi.2019.01.036.

[63] Y.S. Ha, Y.Y. Kim, N.H. Yu, S.Y. Chun, S.H. Choi, J.N. Lee, B.S. Kim, E.S. Yoo, T. G. Kwon, Down-regulation of transient receptor potential melastatin member 7 prevents migration and invasion of renal cell carcinoma cells via inactivation of the Src and Akt pathway, Investig Clin Urol 59 (4) (2018 Jul) 263–274, https://doi.org/10.4111/icu.2018.59.4.263.

[64] Z. Zhao, M. Zhang, X. Duan, Y. Chen, E. Li, L. Luo, W. Wu, Z. Peng, H. Qiu, G. Zeng, TRPM7 regulates AKT/FOXO1-Dependent tumor growth and is an independent prognostic indicator in renal cell carcinoma, Mol. Cancer Res. 16 (6) (2018 Jun) 1013–1023, https://doi.org/10.1158/1541-7786.MCR-17-0767.

[65] S. Guo, P. King, E. Liang, A.A. Guo, M. Liu, LncRNA HOTAIR sponges miR-301a-3p to promote glioblastoma proliferation and invasion through upregulating FOSL1, Cell. Signal. 94 (2022 Jun) 110306, https://doi.org/10.1016/j.cellsig.2022.110306.

[66] J. Wan, A.A. Guo, I. Chowdhury, S. Guo, J. Hibbert, G. Wang, M. Liu, TRPM7 induces mechanistic target of Rap1b through the downregulation of miR-28-5p in glioma proliferation and invasion, Front. Oncol. 9 (2019 Dec 17) 1413.

[67] Y. Zhang, K. Tian, E. Zhou, X. Xue, S. Yan, Y. Chen, P. Qiao, L. Yang, X. Chen, hsa_circ_0023305 enhances laryngeal squamous cell carcinoma progression and modulates TRPM7 via miR-218-5p sponging, BioMed Res. Int. 2021 (2021 Dec 2) 9968499, https://doi.org/10.1155/2021/9968499.

[68] X. Deng, Y. Qing, D. Horne, H. Huang, J. Chen, The roles and implications of RNA m6A modification in cancer, Nat. Rev. Clin. Oncol. 20 (8) (2023 Aug) 507–526, https://doi.org/10.1038/s41571-023-00774-x.

[69] S. Zaccara, R.J. Ries, S.R. Jaffrey, Reading, writing and erasing mRNA methylation, Nat. Rev. Mol. Cell Biol. 20 (10) (2019 Oct) 608–624, https://doi.org/10.1038/s41580-019-0168-5.

[70] K.D. Meyer, S.R. Jaffrey, The dynamic epitranscriptome: N6-methyladenosine and gene expression control, Nat. Rev. Mol. Cell Biol. 15 (5) (2014 May) 313–326, https://doi.org/10.1038/nrm3785.

[71] I. Barbieri, T. Kouzarides, Role of RNA modifications in cancer, Nat. Rev. Cancer 20 (6) (2020 Jun) 303–322, https://doi.org/10.1038/s41568-020-0253-2.

[72] Y. Feng, F. Wu, Y. Wu, Z. Guo, X. Ji, LncRNA DGUOK-AS1 facilitates non-small cell lung cancer growth and metastasis through increasing TRPM7 stability via m6A modification, Transl Oncol 32 (2023 Jun) 101661, https://doi.org/10.1016/j.tranon.2023.101661.

[73] T. Zhang, F. Su, Y.B. Lu, X.L. Ling, H.Y. Dai, T.N. Yang, B. Zhang, D. Zhao, X. M. Hou, MYC/MAX-Activated LINC00958 promotes lung adenocarcinoma by oncogenic transcriptional reprogramming through HOXA1 activation, Front. Oncol. 12 (2022 Feb 9) 807507, https://doi.org/10.3389/fonc.2022.807507.

[74] Cheng Tang, Xinyi He, Lintao Jia, Xiao Zhang. Circular RNAs in glioma: molecular functions and pathological implications. Non-coding RNA Res 9 (2024) 105–115.