Review

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Transient receptor potential (TRP) channels, promising potential diagnostic and therapeutic tools for cancer

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Summary **Despite the advances in detection of and therapies for various tumors, high rates of treatment failure and mortality still exist throughout the world. These high rates are mainly due to the powerful capability of tumor cells to proliferate and migrate. Recent studies regarding the transient receptor potential (TRP) have indicated that TRP channels are associated with tumors and that TRP channels might represent potential targets for cancer treatment. TRP channels are important calcium-selective ion channels in many different tissues and cell types in mammals and are crucial regulators of calcium and sodium. TRP were first discovered in the photoreceptors of Drosophila with gene defects or mutations. TRP channels can be divided into seven subfamilies: TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPML (mucolipin), TRPP (polycystin), TRPA (ankyrin transmembrane protein), and TRPN (NomPC-like). TRPC proteins are conserved across organisms since they are most homologous to Drosophila TRP. TRP superfamilies have been linked to many physiological and pathological functions, including cell differentiation, proliferation, apoptosis, and ion homeostasis. This review focuses on the properties of TRP in oncogenesis, cancer proliferation, and cell migration.**

Keywords: Ion channels, transient receptor potential (TRP), cancer, proliferation, migration

1. Introduction

Most of life's activities cannot function properly without ion channels (*1*). Likewise, many studies have found that tumor proliferation, invasion, and metastasis are always accompanied by changes in ion channels, and particularly changes in the expression of transient receptor potential (TRP) channels. TRP channels are Ca^{2+} entry channels. They are ubiquitously expressed in a wide variety of tissues and have an extraordinarily diverse set of functions. Tumor formation and metastasis are complex processes involving multiple genes and multiple steps, including oncogenesis, basement membrane degradation, matrix permeability, cell adhesion, and vessel formation. During these processes, many genetic alterations induce changes in TRP channels expression, and the abnormal expression of these channels may promote the growth, proliferation, and metastasis of tumor cells (*2*). A growing amount of evidence from both *in vitro* and *in vivo* studies has implicated TRP channels in these processes. For example, TRPM8 is highly expressed in prostate cancer (*3*) and TRPM7 channels influence the growth and proliferation of head and neck tumor cells (*4*).

2. TRP

TRP genes were first described in *Drosophila melanogaster* in studies related to the fruit fly's visual system, but the genes were not recognized until Montell and Rubin's work in 1989 (*5*). As their research progressed, TRP channels were further understood, but the original study did not go far enough. About thirty TRP channels have currently been identified, and they are grouped into seven main

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subfamilies depending on their homology and channel function: TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPML (mucolipin), TRPP (polycystin), TRPA (ankyrin transmembrane protein), and TRPN (NomPC-like). With the exception of TRPN proteins, the other TRP proteins have been detected in mammals; TRPN proteins have been detected in fruit flies and zebra fish (*6,7*). According to in silico sequence analysis, all of the TRP proteins contain six transmembrane segments (S1-S6) and a pore-forming loop between segments S5 and S6. The major differences between TRP channel subfamilies are found in the N- and C-terminal cytosolic domains, which contain putative protein interaction and regulatory motifs (*8*) (Figure 1). Most TRP channels are non-selective cation channels, and they are widely expressed in almost all tissues and cell types. These channels also perform various functions, including taste transduction, temperature sensation, muscle contraction, and cell death (*9,10*).

3. TRP channels and cancer

TRP channels are increasingly recognized as playing roles in the growth, proliferation, migration, and invasion of cancer cells (Table 1 and Figure 2).

3.1. *TRP channels and lung cancer*

Of all cancers, lung cancer has the highest mortality rate. It is a major public health problem and causes death worldwide. More than 1.3 million new lung cancer cases and over one million deaths due to lung cancer occur every year (*11*). In 2013, the US had approximately 228,190 new lung cancer cases and approximately 159,480 deaths due to lung cancer-related disease (*12*). The median survival time for patients with advanced lung cancer is only 8-12 months (*13,14*). Invasion, metastasis, and recurrence are common biological characteristics of lung cancer, and they are also the major obstacles hampering therapeutic interventions and prognosis.

Recent studies have implicated TRPC1, TRPC3, TRPC4, TRPC6, TRPM7, and TRPM8 as playing a role in lung cancer.

TRPC1 regulates cell proliferation and migration. In non-small cell lung cancer cell lines, siRNA-mediated TRPC1 depletion inhibits cell proliferation and induces G_0/G_1 cell cycle arrest, resulting in a dramatic decrease in cell growth. TRPC1 might mediate these processes *via* epidermal growth factor receptor (EGFR) phosphorylation and the activation of EGF-induced signaling pathways (*15*). Jiang *et al.* found that the expression of TRPC1, TRPC3, TRPC4, and TRPC6 was correlated with the grade of NSCLC differentiation; no correlation was observed between TRP channel expression and age, sex, smoking history, or cell type. The blocking of TRPC channels inhibited A549 cell proliferation, while over-expression of TRPCs led to increased proliferation. Additionally, all-trans-retinoic acid (ATRA) induced the up-regulation of TRPC3,

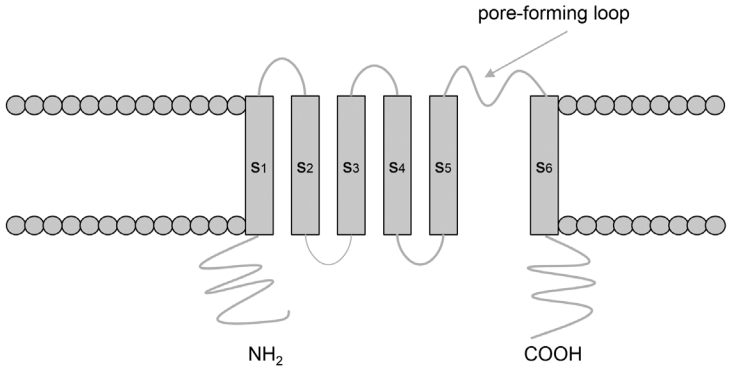

Figure 1. TRP channels contain six transmembrane segments and a pore-forming loop between S5 and S6.

Table 1. TRP channels involved in cancer proliferation and migration

Cancer	Proliferation		Migration		*Ref.*
	Positive correlation	Negative correlation	Positive correlation	Negative correlation	
Lung cancer	TRPC1,C4,C6	--	TRPC1,M7	--	*15-20*
Breast cancer	TRPC1,C3,C6,V6,M7,M8	--	TRPM7,V6	--	*22-31*
Prostate cancer	TRPM8,V2,V6,M2,C6	--	TRPM8,V1,V2	--	*3,33-46*
Ovarian cancer	TRPC1,C3,C4,C6	--	--	--	*48-49*
Gastric cancer	TRPC6,M7,V6	--	--	--	*53-57*
Liver cancer	TRPC1,C3,C6,M4,M7	--	TRPV1,V4	--	*60-64*
Nasopharyngeal cancer	TRPM7	--	TRPC1,M7	--	*4,68-70*
Glioblastoma	TRPC1,C3,C4,C5,C6	TRPV1,V2	TRPV4	--	*73-76*
Melanoma	TRPM2,M8	TRPV2,M7	--	TRPM1	*78-86*

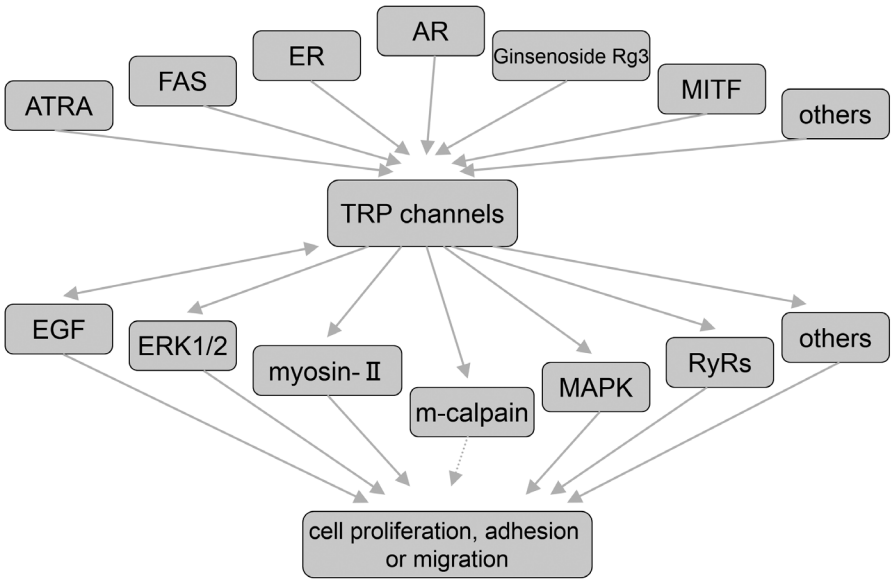

Figure 2. TRP channels mediated signal transduction pathways and cellular behaviors. ATRA can stimulate TRPC3, 4, and 6. EGF and some TRP channels may interact with each other. Stimulation of Fas receptors could induce TRPM7 to regulate apoptosis and may induce the negative control of TRPV2. ER could affect the expression of TRPM8 and TRPV6. AR changes could lead to the expression of changes in TRPM8. Ginsenoside Rg3 could block TRPM7 to induce cell death. The up-regulation or down-regulation of MITF could cause corresponding changes in TRPM1. Some TRP channels may induce cell proliferation, adhesion, or migration *via* ERK1/2, myosin-II, MAPK, RyRs, and unknown signaling pathways while other TRP channels may inhibit those processes *via* pathways such as m-calpain. ATRA, all-trans-retinoic acid; EGF, epidermal growth factor; ER, estrogen receptor; MITF, microphthalmia transcription factor; ERK1/2, extracellular signal-regulated kinases 1 and 2; MAPK, mitogenactivated protein kinase; RyRs, ryanodine receptors.

TRPC4, and TRPC6 expression and enhanced Ca^{2+} influx in A549 cells (*16*). Conversely, Saito *et al.* suggest that TRPC3 expression is related to the progression and the clinicopathological characteristics of lung cancer (*17*). The 5-year overall survival (OS) and disease-free survival (DFS) rates for patients with higher levels of TRPC3 mRNA expression are significantly higher than the rates for patients with lower levels of TRPC3 mRNA. Higher levels of TRPC3 expression in tumor cells are an independent predictor of a better prognosis for patients with lung adenocarcinoma.

In A549 lung cancer cells, the depletion of TRPM7 expression *via* RNA interference inhibited cell migration, and TRPM7 is positively correlated with EGF expression (*18*). TRPM8 is the predominant thermoceptor for cellular and behavioral responses following exposure to cold temperatures (*19*). This thermoceptor has been studied in different contexts, including breast adenocarcinoma, lung adenocarcinoma, melanoma, and prostate cancer (*20*).

3.2. *TRP channels and breast cancer*

Breast cancer is the most frequently diagnosed cancer (excluding skin cancers) and has the second highest mortality rate of all cancers, following lung cancer, in the US. An estimated 39,510 deaths were expected to occur in the US in 2012. Notably, the incidence of breast cancer has increased in developing countries; about half of the new breast cancer cases and 60% of breast cancer-associated deaths occur in developing countries (*21*).

TRPC1, TRPC3, TRPC6, TRPM7, TRPM8, and TRPV6 expression are correlated with breast cancer. Dhennin-Duthille *et al.* observed high levels of TRPC1, TRPC6, TRPM7, TRPM8, and TRPV6 expression in human breast ductal adenocarcinoma (hBDA) tissue in comparison to adjacent non-tumor tissue. A study reported that TRPC1, TRPM7, and TRPM8 expression a strongly correlated with the Scarff-Bloom-Richardson (SBR) grade, Ki67 proliferation index, and tumor size (*22*). Moreover, the activation of TRPC1 enhanced the proliferation of MCF-7 cells, a human breast cancer cell line with low metastatic potential, by stimulating phosphorylation of extracellular signal-regulated kinases 1 and 2 (ERK1/2) and Ca^{2+} entry (*23*).

Previous studies reported that TRPC3 and TRPC6 are involved in the control of the growth of polarized epithelial cells (*24*). Recently, TRPC6 was found to be expressed and to be the predominant TRPC channel in biopsied breast cancer tissue, and TRPC3 appears to be significantly up-regulated in breast cancer tissue (*25*).

The level of TRPV6 expression is higher in invasive tissue compared to corresponding non-invasive tissue and TRPV6 expression has been assessed using laser capture microdissection. TRPV6 silencing can inhibit MDA-MB-231 migration and invasion in addition to MCF-7 cell migration (*22*). Moreover, limited estrogen receptor (ER) signaling reportedly leads to lower levels of TRPV6 expression, and the antitumor effect of Tamoxifen may be related to the inhibition of TRPV6 expression (*26*).

TRPM7 plays an important role in breast cancer. TRPM7 is both an ion channel and a protein kinase that is ubiquitously expressed in various tissues; these proteins are also called "channels plus enzymes" or "chanzymes". Studies have found that the TRPM7 channel regulates breast cancer cell proliferation, and TRPM7 is over-expressed in breast carcinoma tissue and is positively correlated with the Ki67 mitosis marker (*27*). Some studies have found that TRPM7 influences cell adhesion and migration *via* the regulation of myosin-IIA filament stability and that it influences protein localization by phosphorylating the heavy chain (*28*). However, one study found that mitogen-activated protein kinase (MAPK) signaling pathways are involved in the TRPM7-mediated migration and invasion of MDA-MB-435 breast cancer cells. Silencing of TRPM7 caused a significant reduction in the migration and invasion potential of MDA-MB-435 breast cancer cells in addition to a decrease in the levels of phosphorylated Src and MAPK (*29, 30*).

TRPM8 channels are highly expressed at both the mRNA and protein levels in the MCF-7 breast cancer cell line. These channels are over-expressed in breast adenocarcinomas and are correlated with estrogen receptor positive (ER^+) tumors according to immunohistochemical analysis (*31*).

3.3. *TRP channels and prostate cancer*

Prostate cancer is the second leading cause of internal malignancy in men worldwide, and approximately 29,720 men die from the disease each year in the US (*12*). Furthermore, data indicate that prostate cancer mortality is increasing in Asia, and particularly in China and Japan (*32*).

A number of TRP channels have been implicated in prostate cancer, including TRPV1, TRPV2, TRPV6, TRPM8, TRPM2, and TRPC6. Among these, TRPV6 and TRPM8 are the most studied and characterized.

The expression of TRPV6 may be a predictor for prostate cancer progression because levels of TRPV6 mRNA and protein are both substantially elevated in prostate carcinoma compared to normal tissue or cells. Lehen *et al.* first found that Ca^{2+} entry *via* the TRPV6 channel controls proliferation directly and promotes apoptosis resistance in prostate cancer cells (*33*). TRPV6-targeted siRNA has been reported to effectively inhibit the transcription of TRPV6 mRNA, inhibit the proliferation of human prostate cancer LnCaP cells, arrest the LnCaP cell cycle in the G0 and G1 phases, and induce LnCaP apoptosis (*34*). Moreover, the expression of TRPV6 in lymph node metastases and androgen-insensitive tumors is markedly and significantly decreased in comparison to untreated tumors. Furthermore, TRPV6 expression is significantly correlated with the Gleason score, the pathological stage, and extraprostatic extensions (*35*).

Tsaveler *et al.* originally identified TRPM8 in 2001 by screening a prostate cDNA library; the gene was described as a novel prostate-specific gene with expression that increased during the transformation of prostate cancer (*20*). In normal prostate cells, there is a slight level of TRPM8 expression. In prostate cancer, however, the expression of TRPM8 increases dramatically (*36*). A similar result has been reported by Fuessel *et al.*, who analyzed multiple tumor markers in primary prostate cancers *via* quantitative real-time PCR (*37*). One potential mechanism for the action of TRPM8 in prostate carcinoma is through the inhibition of the migration of prostate cancer cells by inactivating focal adhesion kinase. Furthermore, the over-expression of TRPM8 is independent of changes in the level of androgen receptor (AR) mRNA expression (*38*). Henshall *et al.* found that the expression of TRPM8 decreased markedly following anti-androgen therapy. They also showed that TRPM8 expression decreased when prostate cancer cells became androgen-independent, supporting the hypothesis that TRPM8 is regulated by androgens (*39*). Indeed, the androgen dependence of TRPM8 expression is related to the stage of differentiation of prostate epithelial cells. Affymetrix gene chip experiments have been conducted to determine whether TRPM8 expression was correlated with the Gleason grade or the TNM stage. Results of those experiments indicated that TRPM8 mRNA expression increases with the Gleason score and TNM stage (*40*).

TRPC6 is also up-regulated in prostate cancer and is associated with the histological grade, Gleason score, and extra-prostatic cancer extension. However, there is no significant difference between androgen-independent and androgen-dependent tumors (*41*). In addition, TRPV1 and TRPV2 are up-regulated in patients with metastatic cancer (*42-44*). Levels of TRPM2 mRNA are elevated in both prostate cancer tissue and in LnCaP and PC3 cell lines (*45,46*). This suggests that these channels could play an important role in the diagnosis and treatment of prostate carcinoma.

3.4. *TRP channels and ovarian cancer*

Ovarian cancer (OC) is one of the most common gynecological cancers. It poses a great challenge because it is a heterogeneous, rapidly progressing, and highly lethal group of malignancies (*47*). According to estimates, approximately 22,240 women will be diagnosed with OC and 14,030 women will die from this disease in 2013 in the US (*12*). The etiology of OC is still poorly understood.

TRPC1, TRPC3, TRPC4, and TRPC6 channels were identified by Western blotting and immunostaining in human ovarian adenocarcinoma tissue and in ovarian adenocarcinoma-derived SKOV3 cells. In 2009, Yang *et al.* found that the protein expression of TRPC3 increased markedly in human OC tissue compared to

normal ovarian tissue (*48*). The down-regulation of TRPC3 expression in SKOV3 cells led to a reduction in proliferation, suppression of epidermal growth factor-induced Ca^{2+} influx, dephosphorylation of Cdc2 and CaMKIIα, and prolonged M phase progression in these cells. Furthermore, decreased expression of TRPC3 suppressed tumor formation when SKOV3 cells were injected into nude mice. A 2013 study by Zeng *et al.* reached similar conclusions with RT-PCR, whole-cell patch recording, Western blotting, and immunostaining (*49*). Additionally, they also found that several spliced variants of TRPC1, TRPC3, TRPC4, and TRPC6 were expressed in ovarian cancer. TRPC channel activity was blocked using 2-APB, SKF-96365, or TRPC isoform-specific functional antibodies or by transfecting cells with TRPC siRNAs; blocking of the channel significantly inhibited cancer cell proliferation. Furthermore, the level of TRPC expression is reportedly correlated with the grade of cancer differentiation, and the over-expression of *TRPC* genes could also increase ovarian cancer colony growth. An interesting fact is that the expression of *TRPC* genes in undifferentiated human ovarian cancer is significantly lower than their level in normal ovarian tissue. Further study is required to elucidate the role of TRPC channels in ovarian cancer.

3.5. *TRP channels and gastric cancer*

Gastric cancer continues to be a leading cause of cancer death worldwide (*50*). In East Asia, including South Korea, Japan, and China, the morbidity due to gastric cancer is the second highest among common cancers while and the mortality due to that cancer is the third highest among common cancers. In more than half of gastric cancer cases, cancer recurs after curative surgery, and the median survival time for these patients is only 6-9 months (*51,52*). The prognosis for these patients is poor mainly because there are limited diagnostic measures for early detection and because of the clonal hyperplasia that is characteristic of gastric cancer cells. The discovery of TRP channels may help to improve the diagnosis and treatment of gastric cancer.

TRPC6, TRPM7, and TRPV6 are the main TRP channels associated with gastric cancer. TRPC6 is not only associated with lung cancer, breast cancer, prostate cancer, and ovarian cancer as mentioned earlier, but it also over-expressed in gastric cancer epithelial cells compared to normal gastric epithelial cells. When the TRPC6 channel was inhibited with SKF96365, the growth of gastric cancer cells was suppressed and cells were arrested in the G2/M phase. Cai *et al.* found that the histamine-mediated Ca^{2+} elevation in MKN45 human gastric cells was inhibited by SKF96365 and DNC6, and that inhibition of TRPC6 suppressed the formation of gastric tumors in nude mice (*53*).

The activation of TRPM7 is associated with the growth and survival of human gastric adenocarcinoma cells. Kim *et al*. examined the expression and potential role of TRPM7 channels in the growth and survival of AGS cells, the most commonly used line of human gastric adenocarcinoma cells (*54*). Abundant expression of TRPM7 messenger RNA and protein were observed in AGS gastric cancer cells. Transfection of AGS cells with TRPM7 siRNA significantly reduced the expression of TRPM7 mRNA and protein levels as well as the amplitude of the TRPM7-like currents. Blocking of TRPM7 channels with La^{3+} and 2-APB or suppression of TRPM7 expression with siRNA inhibited the growth and survival of these cells. Kim *et al*. later found that TRPM7 channels are over-expressed in HEK 293 cells undergoing Rg3-induced cell death. Ginsenoside Rg3 inhibits the growth and survival of gastric cancer cells, which occurs due to the blocking of TRPM7 channel activity (*55,56*).

Moreover, the up-regulation of TRPV6 levels has been observed in gastric cancer cells. Over-expression of TRPV6 in normal cells increased capsaicin-induced apoptosis, and knockdown of TRPV6 in cancer cells suppressed this activity (*57*).

3.6. *TRP channels and liver cancer*

Liver cancer (696,000 deaths, 9.2% of all cancer deaths) is the third most common cause of cancer death after lung cancer (1.38 million, 18.2% of all cancer deaths) and gastric cancer (738,000 deaths, 9.7% of all cancer deaths) worldwide (*58*). There are two common types of cancer affecting the liver, hepatocellular carcinoma (HCC) and liver metastases from colorectal cancer (LM-CRC). Liver cancer greatly impacts people's health, and this is particularly true in China (approximately 350,000 incident cases per year) (*59*).

Numerous studies have shown that several TRP channels are present in liver cancer tissue, including TRPC1, TRPC3, TRPC6, TRPV1, TRPV2, TRPV4, TRPM4, and TRPM7.

TRPC1, TRPC3, TRPC6, TRPM4, and TRPM7 mRNAs are expressed in both rat hepatocytes and in H4-IIE cells (derived from rat liver tumor cells); immunofluorescence was used to directly compare these cells to hepatocytes isolated from normal rat liver (*60*). TRPC6 is very weakly expressed in hepatocytes isolated from healthy patients and is expressed at much higher levels in human liver tumor tissue. Over-expressing TRPC6 or silencing TRPC6 *via* siRNA revealed that increased expression of TRPC6 is associated with increased thapsigargin-initiated Ca^{2+} entry and an increased rate of cell proliferation (*61*).

TRPV1 and TRPV4 are reported to be involved in modulating cell migration (*62*). In addition, high levels of TRPV1 expression have been noted in hepatocarcinoma tissue in comparison to normal liver tissue. Clinicopathologic examination indicated a

significant correlation between TRPV1 expression and histopathologic differentiation. Moreover, univariate analysis revealed that low levels of TRPV1 expression were associated with increased disease-free survival (*63*).

Quantitative PCR, Western blotting, and immunofluorescence analyses revealed increased levels of TRPV2 mRNA and protein expression in moderately and well-differentiated human hepatocarcinoma tissues compared to poorly differentiated tumors. Clinicopathologic assessment suggested a significant association between TRPV2 expression and portal vein invasion and histopathologic differentiation (*64*).

3.7. *TRP channels and nasopharyngeal carcinoma*

Compared to the malignant cancers mentioned earlier, nasopharyngeal carcinoma (NPC) is a rare malignancy in most parts of the world. However, the incidence of NPC is relatively high in Asian countries, and China accounts for almost 80% of all NPC cases. An annual incidence of more than 20 cases per 100,000 has been reported in southern China. Men are twice as likely to develop NPC as women (*65*). NPC is a confusing, misdiagnosed, and poorly understood disease. Radiotherapy is a primary treatment for nasopharyngeal carcinoma and has significantly improved clinical outcomes. The median survival time for patients receiving radiotherapy is approximately 52 months, and the 5-year survival rate is 50-80% (*66,67*). Although many patients with NPC had a good clinical prognosis, some still died of recurrence or metastatic disease. Furthermore, related risk factors play an important role during the development of the tumor type.

TRPM7 warrants mention when considered the relationship between NPC and TRP channels. TRPM7 is a bifunctional protein consisting of a Ca^{2+} and Mg^{2+} permeable TRP channel that is fused to a C-terminal α-kinase domain, and this channel plays an important role in regulating cell adhesion and directional migration. A pro-migratory role of TRPM7 was noted in NPC cells, in which impaired TRPM7 channel function significantly reduced cellular migratory potential. Conversely, increased TRPM7 activity promoted migration. Moreover, activation of TRPM7 resulted in a global increase in $[Ca^{2+}]_i$ (intracellular calcium influx) due to both Ca^{2+} entry and calcium-induced calcium release (CICR) involving ryanodine receptors (RyRs) (*68*).

Jiang *et al.* studied TRPM7 expression in the FaDu and SCC25 human head and neck tumor cell lines (*69*). They suggested that activation of the TRPM7 channel was critical to the growth and proliferation of human head and neck carcinoma cells. Additionally, low levels of extracellular Ca^{2+} induced the TRPM7 current, which was inhibited by Gd^{3+}, 2-APB, or intracellular Mg^{2+}.

Recently, the current authors have provided evidence demonstrating that TRPM7 plays a role in NPC cell migration by mediating Ca^{2+} influx. This role of TRPM7 in potential migration was examined in 5-8F and 6-10B human nasopharyngeal carcinoma cells using RT-PCR, Western blotting, immunofluorescence, calcium imaging, siRNA silencing, and a transwell chamber migration assay. The migratory potential of 5-8F cells was significantly reduced by the addition of an extracellular Ca^{2+} chelator (EGTA), TRPM7 inhibitors (La^{3+} and 2-APB), and TRPM7 knockdown. Conversely, addition of a TRPM7 activator (Bradykinin) and overexpression of TRPM7 promoted the migration of 5-8F and 6-10B cells. Furthermore, the sustained Ca^{2+} influx regulated by TRPM7 activated release of Ca^{2+} stores *via* RyRs and a calcium-induced mechanism of calcium release (*4*).

In addition, studies by colleagues have indicated that TRPC1 is involved in nasopharyngeal carcinoma cell migration. Those researchers used RNAi technology or the addition of 2-APB, an inhibitor of the inositol 1,4,5-trisphosphate (IP3) receptor and store-operated Ca^{2+} channel-mediated Ca^{2+} entry, to down-regulate TRPC1 in CNE2 cells. Down-regulation of TRPC1 significantly attenuated the adhesive and invasive abilities of NPC cells (*70*).

3.8. *TRP channels and glioblastoma*

Glioblastoma is the most common malignant primary brain tumor, and it accounts for almost 80% of all primary brain tumors. Despite advances in surgical and adjuvant radiation and chemotherapy strategies, glioblastoma continues to be associated with a poor prognosis (*71*). Patients with glioblastoma multiforme have a median survival of approximately 12 months. Approximately 10,000 new cases are diagnosed each year in the US (*72*).

Only two factors have thus far been shown to conclusively affect glioma risk: exposure to high doses of ionizing radiation and inherited mutations in highly penetrant genes associated with rare syndromes. Therefore, additional factors that correlate with glioblastoma occurrence and development should be studied (*71*).

Different studies have suggested that TRP channels (*e.g.*, TRPC1, TRPC3, TRPC4, TRPC5, TRPC6, TRPV1, TRPV2, TRPV4, TRPM2, and TRPM8) are likely to play a role in glioma progression, growth and/or invasion.

The TRPC1 channel is associated with lipid rafts and is essential for glioma chemotaxis in response to stimuli such as epidermal growth factor (EGF). Gliomas are attracted to EGF in a chemotactic manner. Stimulation with EGF results in TRPC1 channel localization at the leading edge of migrating D54MG glioma cells. Chemotaxis toward EGF was lost when TRPC channels were pharmacologically inhibited or

knocked down with TRPC1-specific shRNA (*73*).

The TRPC6 channel is involved in the growth of glioblastoma. Some studies suggest that TRPC6 is more abundant at both the protein and mRNA levels in human glioma tissue. The increased expression of TRPC6 is also associated with the grade of glioma malignancy. Inhibition of TRPC6 activity or decreased expression of the channel led to an increase in intracellular Ca^{2+} *via* platelet-derived growth factor, which suppressed cell growth and clonogenic ability and induced cell cycle arrest in the G2/M phase (*74*).

Moreover, TRPV1 has been implicated in the capsaicin-induced apoptosis of glioma cells. TRPV2 negatively controls glioma cell survival and proliferation and protects the cells from Fas-induced apoptosis in an ERK-dependent manner (*75,76*).

3.9. *TRP channels and melanoma*

Among skin diseases, malignant melanoma is the leading cause of death and accounts for approximately 75% of deaths attributed to skin disease due to its propensity to metastasize. Localized melanoma is curable by surgical techniques and immunotherapy, whereas there are limited therapeutic options for metastatic melanoma or melanoma with metastatic potential. Once diagnosed with metastatic melanoma, most patients will die from the disease within 2 years (*77*). Moreover, current diagnostic methods are limited in their ability to diagnose early disease and to accurately predict an individual's risk of disease progression and outcome (*78*). Thus, melanoma diagnosis and therapy are great clinical challenges.

TRPM1 (also called melastatin) is known to be involved in melanoma, and TRPM2, TRPM7, TRPM8 (also known as Trp-p8), and TRPV2 also play a role. TRPM1 was first discovered by differential display analysis in the B-16 mouse melanoma cell line. The gene is steadily lost during the progression of primary cutaneous and vertical growth phase melanomas (*79*). Many studies suggest that the *TRPM1* gene is a tumor suppressor. TRPM1 mRNA is partially absent or completely absent in approximately 80% of invasive primary melanomas (*78*).

In their study involving murine cell lines, Duncan *et al.* reported that TRPM1 was expressed at high levels in poorly metastatic variants of the B16-F1 melanoma cell line and expressed at very low levels in the highly metastatic B16-F10 melanoma cell line (*80*).

In similar human melanomas experiments, Deeds *et al*. examined TRPM1 mRNA expression in nevi, primary melanoma, and melanoma metastases. They found high levels of TRPM1 mRNA in melanocytic nevi, but radioactive *in situ* hybridization was unable to detect levels of TRPM1 mRNA in melanoma metastases (*81*). Decreased expression of TRPM1 has been shown to correlate with the melanoma cell transition from a low to a high metastatic phenotype (*80*). Moreover, TRPM1 mRNA is reported to correlate with patient prognosis. Patients with American Joint Committee on Cancer stage I tumors diffusely expressing TRPM1 mRNA have an 8-year disease-free survival rate of 100% while patients with stage I tumors with no TRPM1 expression have an 8-year disease-free survival rate of 77 ± 15%. Furthermore, patients with stage II disease in which tumors diffusely express TRPM1 mRNA have an 8-year disease-free survival rate of 90 ± 7% while patients with stage II disease with no TRPM1 expression have an 8-year disease-free survival rate of 51 ± 8% (*82*). Some studies suggest that TRPM1 transcription is regulated by the binding of microphthalmia transcription factor (MITF), which is an essential transcription factor for the development of melanoma. Levels of MITF and TRPM1 mRNA are high in several human melanoma cell lines. Endogenous TRPM1 expression may be regulated by MITF up- or down-regulation, and TRPM1 promoter-driven reporters yielded similar patterns (*83*).

The TRPM8 channel is expressed in the G-361 human melanoma cell line, and the channel is activated by menthol, a naturally occurring ligand for TRPM8. Menthol-induced activation caused prolonged increases in both the intracellular Ca^{2+} concentration and the amplitude of the current in melanoma cells. The most interesting finding is that exposure to menthol drastically reduced the survival of melanoma cells (*84*). TRPV2 mRNA is found in benign astrocyte tissues, and its expression progressively decreased in high-grade glioma tissues as the histological grade increased (*76*).

Moreover, TRPM2 is cited as a factor that can induce melanoma apoptosis and necrosis, while TRPM7 is regarded as a protector and detoxifier in both melanocyte physiology and in melanoma cells (*85,86*).

3.10. *TRP channels and other cancers*

Several TRP channels have been identified in other cancers. For example, TRPC6 has been observed in esophageal carcinomas, and TRPM7 and TRPM8 have been identified in pancreatic adenocarcinoma (PDAC). TRPV1, TRPV3, and TRPV6 have been noted in colon cancer, and TRPC1, TRPC4, TRPC6, and TRPC7 have been observed in renal cell carcinoma.

4. Conclusion

In summary, cancer continues to be a public health problem worldwide. Different TRP channels exist in normal tissues and tumors, and some play important roles in the processes of tumorigenesis, migration, and metastasis. Differences in expression of TRP channels may provide a new basis for tumor diagnosis and might be a new target for cancer therapy. Tumor treatment may become more diverse and more accurate. Although

many studies have examined TRP channels and cancer, this area of research is still in its infancy. Current data are not sufficient to ascertain the specific action of TRP since there are no highly selective inhibitors or agonists of TRP. Not all TRP channels have been investigated, and most of the completed research is still inadequate. An inspiring fact is that associations between TRP proteins and various cancers are still being discovered thanks to rapid advances in molecular biology, genetics, and other disciplines. TRP channels may play an important role in the diagnosis and targeted treatment of tumors.

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