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The Emerging Roles of TRPV4 in Cancer

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ABSTRACT

Cancer is a disease with marked heterogeneity in both response to therapy and survival. Malignant neoplasm or cancer is a type of genetic disease in which a group of cells display uncontrolled growth, invasion and sometimes metastasis. Cancer progression is not only associated with changes in the cell cycle that inactivate pathways leading to cell death or senescence but also enhanced cell proliferation. Usually, these changes are associated with alterations in Ca^{2+} homeostasis in cells. The transient receptor potential (TRP) channels play a role as cell sensors and are involved in a plethora of Ca^{2+}-mediated cell functions. TRP vanilloid 4 (TRPV4) is a member of the TRPV ion channel family which is permeable to both Ca^{2+} and Na^{+}. TRPV4 is expressed in various types of tissues such as kidneys, airway smooth muscle and lungs. As other TRPV channels, TRPV4 may also be involved in cancer cell proliferation, apoptosis, angiogenesis, migration and invasion. Previous studies have demonstrated that TRPV4 plays a role in the proliferation of several types of cancer cells. Moreover, TRPV4 also contributes to cancer cell angiogenesis via arachidonic acid-induced migration of breast tumour-derived endothelial cells. TRPV4 is also able to regulate angiogenesis via mechanotransduction. Recent studies have also reported a significant role of TRPV4 in breast cancer metastasis and induction of breast cancer cell death. In this review, the emerging roles of TRPV4 in cancer will be discussed which further supports the potential of TRPV4 as a promising drug target for cancer therapy.

Keywords: TRPV4; cancer; proliferation; angiogenesis; metastasis; apoptosis.

INTRODUCTION

The transient receptor potential (TRP) ion channel family constitutes a diverse group of mostly non-selective cation channels that are further divided into seven subfamilies, namely TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPP (polycystin), TRPML (mucolipin), TRPA (ankyrin) and TRPN (this subfamily is not found in mammals)[1,2]. TRP ion channels exhibit differences in

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ion selectivity, modes of activation and physiological functions (2). The TRPV subfamily consists of six distinct members, denoted as TRPV1-6 (2). TRPV4 is a member of the TRPV ion channel family which is permeable to both Ca^{2+} and Na^{+} (3). TRPV4 has been implicated in various physiological processes such as osmoregulation, thermoregulation, and mechanosensation, to name a few[2,4,5]. The mechanism of activation of TRPV4 is found to be polymodal, since it is responsive to multiple stimuli including heat, cell swelling, phorbol esters and arachidonic acid[2,4-8].

The involvement of TRP channels in carcinogenesis is increasingly recognised, as evidenced by the growing number of studies assessing the consequences of aberrant expression of TRP ion channels in different aspects of cancer progression such as proliferation, apoptosis, angiogenesis, migration, invasion and metastasis[9-14]. Among the TRPV ion channels, TRPV4 has recently captured a great attention in the fields of calcium signalling and cancer.

Thus, we aim to highlight the reported roles of TRPV4 and its involvement in cancer hallmarks: i) self-sufficiency in growth signals, ii) insensitivity to growth-inhibitory signals, iii) resistance towards apoptosis, iv) infinite ability to replicate, v) sustained angiogenesis (induction of new blood vessels), and vi) tissue invasion and metastasis[15,16].

TRPV4 and cancer

As a group, TRPV channels have been implicated in the regulation of cancer-related processes such as proliferation, apoptosis, angiogenesis, migration and invasion[17]. Despite the well-documented roles of other TRPV channels (such as TRPV6) in various types of cancer[9,10,18-21], studies assessing the involvement of TRPV4 in cancer remain limited.

TRPV4 and cell proliferation

Evidence from previous studies supports a role for TRPV4 in regulating cell proliferation in several cell types including human brain capillary endothelial cells[22] and esophageal epithelial cells[23]. In the context of cancer, Thoppil and his colleagues[24] showed that reduced expression of the mechanosensitive ion channel TRPV4 in tumour endothelial cells (TEC) causes an increase in proliferation which may contribute to abnormal tumour angiogenesis. In addition, pharmacological activation of TRPV4 with a selective TRPV4 activator GSK1016790A showed decreased TEC proliferation *in vitro*. Compared to TEC proliferation, GSK1016790A-activated TRPV4 displayed no effect on the proliferation of normal endothelial cells. The reduced TEC proliferation by TRPV4 activation was correlated with a decrease in high basal ERK1/2 phosphorylation[24]. The authors proposed that TRPV4 channels are able to regulate tumour angiogenesis by selectively inhibiting TEC proliferation via modulation of the ERK pathway[24].

Recent evidence from independent studies by Lee and co-researchers[25] found that TRPV4 is dispensable for breast cancer cell proliferation since there was no effect on the proliferation of 4T07 breast cancer metastasis model cell line (which highly expressed TRPV4) compared to control cells when TRPV4 was silenced in this study model. This finding is also consistent with the results obtained by Peters *et al*[26] where pharmacological inhibition of TRPV4 using RN 1734 (1-10 µM) is not anti-proliferative in both MDA-MB-231 (moderate levels of TRPV4) and MDA-MB-468 (high levels of TRPV4) basal-like breast cancer cell lines.

In the case of colorectal cancer, recent studies suggest that TRPV4 may be involved in colorectal cancer cell proliferation[27]. Using MTT cell proliferation assay, Wasilewski *et al*[27] observed that co-incubation of fatty acid amide hydrolase inhibitor PF-3845 with the non-classical cannabinoid receptor antagonist RN 1734 yielded the highest potency in reducing the viability of human colon adenocarcinoma Colo-205 cells compared to the other cannabinoid receptor antagonists being tested. However, this observation warrants further investigations since their work did not involve the assessment of TRPV4 expression levels in Colo-205 cells. Using gastric cancer cells, recent work by Xie and his co-workers[28] discovered a co-localisation of calcium-sensing receptor (CaSR) and TRPV4 and that activation of CaSR promotes Ca^{2+} entry via TRPV4 channel. They also demonstrated a functional coupling of CaSR and TRPV4 which is implicated in the proliferation of gastric cancer cells. This is evidenced by attenuation of CaSR-induced

Table 1: Studies on TRPV4 and cancers

Cancer type	Changes in TRPV4 expression levels	Possible role of TRPV4 and mechanism proposed
Breast cancer	Upregulated in basal breast cancers (25, 26), in BTEC (32), in breast cancer metastasis model cell lines (25) and in the metastatic lesions of breast cancer clinical samples (36)	Pharmacological activation of TRPV4 promotes cell death via oncosis and apoptosis in breast cancer cells overexpressing TRPV4 and also suppresses tumour cell growth in vivo (26) Inhibition of TRPV4 in breast cancer cell lines with endogenous expression of TRPV4 has no effect on cell proliferation (25, 26) TRPV4 is important for the migration of breast tumour-derived endothelial cells (32) TRPV4 is required for breast cancer metastasis by regulating cancer cell stiffness via Ca2+-dependent activation of AKT and downregulation of E-cadherin cell cortex protein (25, 36)
Tumour endothelial cells (TEC)	Downregulated in TEC	TRPV4 regulates tumour angiogenesis by inhibiting TEC proliferation via modulation of ERK pathway (24) TRPV4 is a critical regulator of TEC mechanosensitivity, tumour angiogenesis and tumour vessel maturation by modulating Rho signalling pathway (33, 34)
Skin cancer	Downregulated from a healthy to a skin cancer phenotype	The loss of TRPV4 expression in skin cancer implicates that TRPV4 may represent an early biomarker of skin carcinogenesis (39)
Colorectal cancer	Upregulated (TRPV4 expression was obtained from the ICGC data)	No mechanism assessed (40)
	Downregulated in patient tissue samples	No mechanism assessed; however, the authors postulated that epigenetic influence may be involved in the downregulation of TRPV4 in colorectal cancer (41)
	No assessment of TRPV4 expression in human colon adenocarcinoma Colo-205 cells	TRPV4 may be important for colorectal cancer cell proliferation since co-incubation of FAAH inhibitor PF-3845 with the TRPV4 antagonist RN 1734 remarkably decreased the viability of Colo-205 cells (27)
Liver cancer	Downregulated (TRPV4 expression was obtained from the ICGC data)	No mechanism assessed (40)

	Functionally expressed in human hepatoblastoma HepG2 cells	TRPV4 provides a Ca2+ entry pathway in HepG2 cells and is implicated in the migration of this cell line (37, 42)
Gastric cancer	Expressed in both normal gastric and GC cells	TRPV4 provides a Ca2+ entry route upon activation of CaSR in GC cells which in turn stimulates proliferation and migration of GC cells through Ca2+/AKT/?-catenin signalling pathway (28)
Cervical cancer	Upregulated (TRPV4 expression was obtained from the ICGC data)	No mechanism assessed (40)

BTEC = breast tumour-derived endothelial cells; TEC = tumour endothelial cells; ICGC = International Cancer Genome Consortium; FAAH = fatty acid amide hydrolase; CaSR = calcium-sensing receptor; GC = gastric cancer.

proliferation of gastric cancer cells in the presence of TRPV4 inhibitor RN 1734[28]. Taken together, current lines of evidence suggest that TRPV4 appears to play some roles in the proliferation of cancer cells; however, this role may be cancer cell type specific.

TRPV4 and apoptosis

The role of TRPV4 in apoptosis has been reported in some study models, for example, the involvement of TRPV4 in apoptosis of mouse retinal ganglion cells[29] and mouse pancreatic beta cells[30]. Recent studies have begun to suggest a role for TRPV4 in inducing cell death, particularly in breast cancer cells which overexpress TRPV4. Peters *et al*[26] demonstrated that there was a reduction in the viability of two basal breast cancer cell lines, MDA-MB-468 and HCC1569 as a result of pharmacological activation of TRPV4. These two cell lines showed an overexpression of TRPV4. Results from their studies have provided new insights into the role of TRPV4 in inducing breast cancer cell death via two distinct pathways: apoptosis and oncosis[26]. Apoptosis was related to PARP-1 cleavage while oncosis was corresponded to a rapid decline in intracellular ATP levels[26]. The researchers also observed that TRPV4 activation leads to decreased tumour growth *in vivo* (26), suggesting that targeting TRPV4 may be relevant for breast cancers that overexpress this specific Ca^{2+} channel.

TRPV4 and angiogenesis

Angiogenesis is the formation of new blood vessels which is important for cancer cells in order to receive sufficient oxygen and nutrients and also for waste products removal[31]. The early evidence to link TRPV4 with breast cancer in the context of angiogenesis is demonstrated by Fiorio Pla *et al* [32] who discovered the importance of TRPV4 in mediating arachidonic acid (AA)-induced migration of breast tumour-derived endothelial cells (BTEC), which is one of the key events in tumour angiogenesis. The authors found that endogenous expression of TRPV4 was significantly higher in BTEC than the corresponding 'normal' endothelial cells (HMVEC). They also confirmed that TRPV4 is functional in both cell types since stimulation with AA and the TRPV4 activator 4±-phorbol 12,13-didecanoate (4±-PDD) produced increases in $[Ca^{2+}]_{CYT}$, which is more pronounced in BTEC compared to HMVEC cells[32]. Further functional studies using the widely used non-specific TRPV4 antagonist ruthenium red and short hairpin RNA against TRPV4 completely abolished AA-induced BTEC migration, indicating that TRPV4 is involved in the migration of BTEC. The pro-migratory effect of TRPV4 upon stimulation with 4±-PDD or AA on BTEC further illustrates a direct association between TRPV4 and AA-mediated cell migration[32].

Subsequent studies by Adapala and co-researchers[33] have provided further evidence on the role of TRPV4 in regulating TEC mechanosensitivity, tumour angiogenesis and tumour vessel maturation. The team uncovered that TEC express lower levels of

TRPV4 than normal endothelial cells. The observed downregulation of TRPV4 has been associated with altered mechanosensitivity and abnormal tumour angiogenesis in TEC and also enhanced tumour growth in TRPV4-deficient (TRPV4 KO) mice[33]. All of the aforementioned effects are reversed upon stimulation with TRPV4 pharmacological activator or restoring TRPV4 expression[33], reiterating the role of TRPV4 in tumour angiogenesis. They also demonstrated that TRPV4 activation combined with a chemotherapy drug cisplatin, significantly suppresses tumour growth *in vivo* by normalising tumour vasculature which improves the effectiveness of cisplatin therapy[33]. Indeed, findings by Adapala *et al*[33] strongly support the rationale for targeting TRPV4 particularly for anti-angiogenic and vascular normalisation therapies.

Further work by Thoppil *et al*[34] have elucidated the molecular mechanism by which TRPV4 may regulate tumour angiogenesis. Their investigations were focused on the Rho/Rho kinase pathway which is essential for tumour growth and progression[35]. The researchers identified that, compared to wild type endothelial cells, the loss of TRPV4 in TRPV4 null endothelial cells (TRPV4KO EC) is associated with enhanced proliferation, migration and abnormal angiogenesis[34]. Furthermore, their analysis of Rho activity revealed that treatment with the Rho/Rho kinase pathway inhibitor Y-27632 is able to normalise abnormal mechanosensitivity and angiogenesis displayed by TRPV4KO EC, suggesting that TRPV4 regulates tumour angiogenesis by modulating endothelial cells mechanosensitivity through the Rho/Rho kinase pathway[34]. Collectively, based on the evidence outlined above, TRPV4 is indeed an attractive drug target for therapeutic intervention in the context of angiogenesis.

TRPV4 and metastasis

In addition to the reported role of TRPV4 in tumour angiogenesis[24, 32-34], recent studies by Lee and co-workers[25] highlighted a novel role of TRPV4 in breast cancer metastasis. Using phosphoproteomics analysis, the researchers detected a significant upregulation of TRPV4 in breast cancer metastasis model cell lines, where its upregulation has been associated with the acquisition of the extravasation trait. Their assessment of TRPV4 expression in human clinical samples using public databases revealed that TRPV4 expression is also enriched in basal subtype of breast cancer and is associated with a more aggressive phenotype and poor survival. Both TRPV4 siRNA-mediated knockdown and pharmacological inhibition of TRPV4 lead to suppression of migration and invasion of the TRPV4-high 4T07 breast cancer cell line, further confirming the involvement of TRPV4 in metastatic processes[25]. Further functional experiments unravelled that TRPV4 is vital for regulating cancer cell stiffness and cell cortex dynamics required for cancer cell metastasis[25]. Subsequent studies by the same research group attempted to establish the precise mechanism for the pro-migratory and pro-metastatic effects of TRPV4 in breast cancer[36]. They reported that TRPV4 mediates breast cancer metastasis by regulating cancer cell softness via Ca^{2+}-dependent AKT-E-cadherin signalling axis as well as the expression of extracellular proteins involved in cytoskeleton and extracellular matrix remodelling[36].

The mechanosensitive ion channel TRPV4 has also been documented to be implicated in the migration of human hepatoblastoma HepG2 cells[37], which is one the multiple steps involved in cancer metastasis[38]. A study by Waning and colleagues[37] showed that application of a TRPV4 agonist 4±-PDD results in an increase in lamellipodial dynamics in HepG2 cells pre-treated with hepatocyte growth factor, indicating that functionally expressed TRPV4 channel does play a role in mediating Ca^{2+} influx required for the migration of HepG2 cells.

Apart from reports on TRPV4's function in breast cancer metastasis[25, 36], TRPV4 has also been recently shown to be involved in gastric cancer metastasis[28]. The researchers observed that CaSR activation induces human gastric cancer growth and metastasis, which is achieved by TRPV4-evoked increases in Ca^{2+} influx which in turn, activates AKT/²-catenin signalling pathway[28]. Altogether, although studies assessing the potential role of TRPV4 in cancer metastasis are still in their infancy, current findings should prompt further research on the likelihood of TRPV4 as a drug candidate for cancer therapy, especially in the case of metastatic cancers.

CONCLUSIONS

TRPV4 ion channel is Ca^{2+}-permeable and it is one of the TRPV members which is implicated in cancer progression. This review has provided compelling evidence for the emerging roles of TRPV4 in several aspects of cancer progression, with a focus on the cancer hallmarks. As discussed above, it is clear that there is involvement of TRPV4 in cancer progression particularly in the context of cell proliferation, apoptosis, angiogenesis and metastasis. Table 1 summarises all studies assessing TRPV4 and its potential role in various cancer types. Given the essential roles of TRPV4 in cancer progression and aberrant expression of TRPV4 in some cancer tissues compared to their normal counterparts, it is very likely that TRPV4 will emerge as a potential drug target with therapeutic benefits in various cancer types such as breast cancer.

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