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Mini-review

TRPM4 channel and cancer

Yahui Gao[a], Ping Liao[a,b,c,*]

[a] Calcium Signalling Laboratory, National Neuroscience Institute, Singapore
[b] Duke-NUS Medical School, Singapore
[c] Health and Social Sciences, Singapore Institute of Technology, Singapore

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ABSTRACT

The TRPM4 channel has been extensively studied in cerebral diseases such as stroke, head injury and multiple sclerosis. In the heart, gain-of-function mutations of TRPM4 are a cause of familial cardiac block. Recently, evidence has emerged to support the role of TRPM4 in certain types of cancer, such as prostate cancer and large B cell lymphoma. The expression of TRPM4 could mediate certain behaviors of cancer cells such as migration and invasion. However, the mechanisms are largely unknown. As a nonselective monovalent cation channel, TRPM4 upregulation and activation enhance sodium entry, which leads to depolarization of the membrane potential. The membrane potential is critical in regulating calcium influx, and a disturbed calcium homeostasis is always associated with cancer cell behaviors. Research on TRPM4 channels in cancer is at a very early stage. In this review, we summarize the expression of TRPM4 in various cancers as well as our current understanding of TRPM4 in cancer. The potential mechanisms of the TRPM4 channel in regulating calcium homeostasis in cancer cells are further discussed in detail. Targeting the TRPM4 channel can be a novel way of managing cancer metastasis via disrupting calcium signaling pathways.

1. Introduction

Transient Receptor Potential melastatin subfamily member 4 channel (TRPM4) is a nonselective cation channel conducting monovalent ions and is impermeable to divalent cations [1]. TRPM4 can be activated by an increase in intracellular Ca^{2+} and depletion of ATP. Therefore, conditions such as ischemia that affect intracellular Ca^{2+} and ATP levels could enhance the channel activity. Even though TRPM4 does not conduct Ca^{2+} ions, it indirectly regulates intracellular Ca^{2+} levels via regulating the membrane potential. The Na^+ entry upon TRPM4 activation could depolarize the cellular membrane potential and reduce the driving force for Ca^{2+} influx [2]. The physiological functions of TRPM4 have been reviewed by Guinamard et al. TRPM4 could modulate immune response, insulin secretion, cerebral blood flow, and respiratory activity [3]. Recently, TRPM4 was revealed to be involved in hippocampal synaptic plasticity and learning [4]. TRPM4 also plays an important role in disease. Ectopic expression of TRPM4 has been identified in many disorders within the central nervous system [5] such as stroke, subarachnoidhemorrhage, traumatic head injury, spinal cord injury, and multiple sclerosis. TRPM4 upregulation together with a hypoxic microenvironment could greatly enhance TRPM4 activity, leading to excessive Na^+ entry. As water travels along with Na^+ ions, oncotic cell death occurs, causing tissue damage [6]. In the heart, mutations of TRPM4 have been reported in families with a history of cardiac block. These gain-of-function mutations could increase TRPM4 activity, disrupt action potential propagation and block cardiac conduction [7]. Recently, novel evidence has emerged to link the expression of TRPM4 with the invasion of certain cancers. In this review, we summarize the current understanding of the role of TRPM4 in cancer and, more importantly, provide clues for future research.

2. Expression of the TRPM4 channel in cancer

TRPM4 channel expression has been reported in a number of cancers, including prostate cancer [8–11], urinary bladder cancer [12], cervical cancer [13], colorectal cancer [14,15], and large B cell lymphoma [16,17]. It was also observed in liver cancer [18].

TRPM4 has been extensively studied in prostate cancer. Both benign and cancerous prostate tissues express the TRPM4 protein. Using cDNA microarray, increased TRPM4 transcripts were first reported in 2004 to be associated with malignant transformation from prostatic intraepithelial neoplasia to invasive prostate cancer [11]. Subsequent studies verified the upregulation of TRPM4 in prostate cancerous tissues [8,9,19–21]. Importantly, a higher level of TRPM4 protein correlates with a higher risk of recurrence following radical prostatectomy [9]. Another cancer that demonstrates an involvement of TRPM4 is diffuse

* Corresponding author. Calcium Signalling Lab, National Neuroscience Institute, 11 Jalan Tan Tock Seng, 308433, Singapore.
E-mail address: ping_liao@nni.com.sg (P. Liao).

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large B cell lymphoma. Two studies using microarray showed that TRPM4 transcripts were upregulated in human large B cell lymphoma [16,17]. Within lymphoid tissues (reactive tonsil, lymph node and appendix), the human normal B cells express a very low level of TRPM4, whereas in diffuse large B cell lymphoma, a higher TRPM4 protein level was detected in approximately 26% of all cases [16]. Similar to that in prostate cancer, TRPM4 expression in diffuse large B cell lymphoma is associated with more aggressive clinical parameters, conferring poorer outcomes [16]. Overexpression of TRPM4 was also reported in cervical cancer [13]. In a cervical cancer HeLa cell line, blocking TRPM4 could alter cell volume change in response to hypertonicity [22]. Interestingly, gain-of-function mutations of the TRPM4 gene were identified in a rare skin disease, progressive symmetric erythrokeratoderma [23]. Even though the pathological change was not cancerous, TRPM4 activity was reported to correlate with the enhanced proliferation of cultured keratinocytes.

It should be noted that not all cancers demonstrate a higher expression of TRPM4. In urinary bladder cancer, TRPM4 was found in both cancerous and control bladder tissues. However, real-time PCR revealed no difference between the two tissues [12]. In colorectal cancer, TRPM4 expression was reported to be either lower [14] or of no change compared to normal tissue [15].

3. Functions of TRPM4 in cancer

In healthy tissues, TRPM4 is important for cell migration. For example in immune cells, TRPM4 expression regulates the activation of T-lymphocyte and mast cells, as well as the migration of dendritic and mast cells [24–27]. Under inflammatory stimulation, TRPM4 is involved in vascular endothelial cell migration with the production of reactive oxygen species [28]. To achieve these physiological functions, TRPM4 was proven to mediate intracellular calcium levels in these cells [24,26,27]. Furthermore, TRPM4 can directly interact with a number of focal adhesion molecules and impact their disassembly during cell migration [29].

In cancer cells, TRPM4 upregulation is primarily associated with cancer cell migration, proliferation and invasion. In HeLa cells, TRPM4 silencing by short hairpin shRNA could promote GSK-3β-dependent degradation of β-catenin and inhibit β-catenin/Tcf/Lef-dependent transcription. As a result, cell proliferation is suppressed [30]. In prostate cancer, knockdown of TRPM4 by siRNA could reduce cell migration but not proliferation of the androgen-insensitive prostate cancer cell lines DU145 and PC3 [8]. Most recently, TRPM4 was shown to be regulated by mircoRNA-150 (miR-150) in prostate cancer (Fig. 1A) [19]. miR-150 directly targets the TRPM4 gene and suppresses TRPM4 expression. In prostate cancer tissues, the expression of miR-150 is inversely correlated with TRPM4 expression. In PC3 cancer cells, a lower miR-150 level enhanced TRPM4 expression, leading to activation of the β-catenin signaling pathway and epithelial-mesenchymal transition (EMT). Conversely, upregulation of miR-150 or knockdown of TRPM4 could suppress EMT, cell proliferation, migration and invasion, leading to an inhibition of tumor growth and metastasis [19]. This anticancer effect of miR-150 has also been identified in colorectal and pancreatic cancers [31,32]. The role of TRPM4 in prostate cancer cell migration and invasion was verified in a separate study using PC3 prostate cancer cells [10]. TRPM4 knockdown by shRNA reduced the expression of an EMT transcription factor Snail1 and a number of EMT markers including MMP9, E-cadherin/N-cadherin, and vimentin. Cell migration and invasion were thus inhibited accordingly. Interestingly, in androgen-sensitive LnCaP cells, the expression of TRPM4 is lower, and overexpression of TRPM4 resulted in an increase in Snail1 expression and promoted cell migration [10]. It is possible that in addition to miR-150, androgen may regulate TRPM4 expression in prostate cancer cells. This possibility is supported by studies on another TRP channel, TRPM8, in prostate cancer. Androgen has been reported to mediate the expression of the TRPM8 channel in LnCaP cells [33,34], whereas in androgen-insensitive PC3 cells, androgen has no effect on TRPM8 expression [33]. Therefore, it is important to further investigate the mechanism that regulates TRPM4 expression in androgen-sensitive cells, in particular, the role of androgen and miR-150.

Ca^{2+} signaling plays an important role in cancer proliferation and migration [35]. Major pathways for Ca^{2+} entry include store-operated Ca^{2+} entry (SOCE), voltage-gated calcium channels (VGCC), and transient receptor potential channels (TRP channels) (Fig. 1B). TRPM4 upregulation in cancer cells has the potential to affect all three pathways. As a monovalent cation channel, TRPM4 conducts Na^+ and K^+ ions without significant permeation of Ca^{2+} [1]. Although constitutively active, TRPM4 channel activity is greatly enhanced by ATP depletion and a higher intracellular Ca^{2+} level. As hypoxia is commonly associated with cancer, both activation factors could be present in cancer cells. Upon TRPM4 activation, Na^+ influx depolarizes the membrane potential, and subsequently, the driving force for Ca^{2+} entry is reduced [24]. Therefore, calcium influx through voltage-independent pathways such as SOCE and Ca^{2+}-permeable TRP channels is likely to be suppressed. Meanwhile, membrane depolarization could activate VGCC and enhance calcium influx via VGCC. The overall effect of

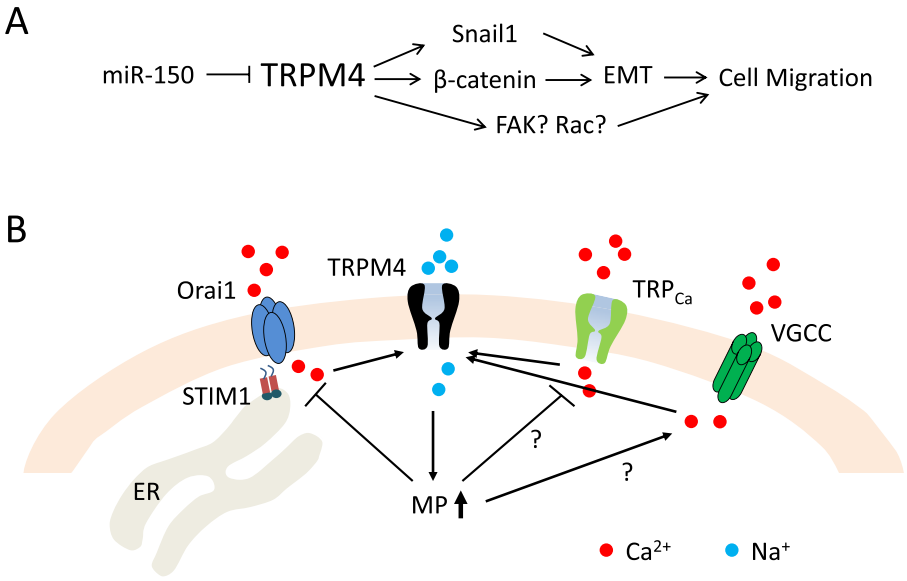

Fig. 1. Potential functions of TRPM4 in cancer pathophysiology. A, Current understanding of the signal pathway of TRPM4 in cancer cell migration. B, Potential role of TRPM4 in regulating intracellular calcium levels in cancer cells. Sodium influx via the TRPM4 channel depolarizes the membrane potential, leading to a reduction of the driving force for calcium entry via SOCC and calcium-permeable TRP channels. Conversely, increased intracellular calcium further enhances TRPM4 activity. Meanwhile, a depolarized membrane potential could activate VGCC and subsequently increase calcium entry. EMT: epithelial-mesenchymal transition; ER: endoplasmic reticulum; MP: membrane potential; TRP_{Ca}: calcium-permeable TRP channels; VGCC: voltage-gated calcium channel.

TRPM4 activation on intracellular calcium levels may vary among different cancers, depending on the predominance of individual Ca^{2+} conducting channels and transporters.

The detailed mechanisms of TRPM4 in regulating intracellular calcium signals have been described in non-cancer cells. In T lymphocytes, TRPM4 inhibition transforms agonist-mediated Ca^{2+} oscillations into a sustained elevation in intracellular Ca^{2+} concentration [24]. In this process, TRPM4-mediated membrane depolarization plays a key role in modulating Ca^{2+} entry via SOCE. A similar Ca^{2+} overload was observed in dendritic cells when TRPM4 was deleted, resulting in an impairment of cell migration [26]. In cancer, localized Ca^{2+} signals contribute to cell migration [36]. For example, localized Ca^{2+} flickers, which are highly localized (~5 μm diameter) and transient (10 ms–4 s), control the direction of cell migration [37]. It is unknown whether TRPM4 channel could affect Ca^{2+} flickers in cancer cells. However, evidence for the role of TRPM4 in regulating SOCE has emerged recently. In androgen-insensitive prostate cancer cells, TRPM4 inhibition by siRNA significantly increased SOCE activity, resulting in a reduction of cancer migration without affecting cell proliferation [8]. However, a hyperactive SOCE pathway and overexpression of SOCE proteins STIMs and Orais have been known to promote metastasis in many cancers [38]. Then why does SOCE play an opposite role in prostate cancers? A possible explanation could be that cancer cell migration requires a higher but carefully orchestrated intracellular calcium level, which varies among different cancers. Ca^{2+} concentrations above or below this optimal level could impair cancer cell functions. This duality of the Ca^{2+} signal has been reported in calcium-permeable TRPM8 channels, where both activation and inhibition of TRPM8 reduced the viability of cancer cells [33]. Therefore, in prostate cancer, TRPM4 may serve as a negative regulator of the intracellular calcium level via mitigating SOCE activity. Apart from SOCE, evidence on whether TRPM4 regulates VGCC and other calcium conducting TRP channels in cancer cells is largely unknown. However, some clues can be found in noncancerous cells. In mouse embryonic fibroblasts, blocking TRPM4 reduced calcium entry possibly via inhibiting the VGCC pathway [29]. Interestingly, TRPM4 inhibition in fibroblasts disrupted the turnover of focal adhesions, focal adhesion kinase (FAK) and Rac activities, and led to a reduction of cell spreading, migration and contractile behavior (Fig. 1A) [29].

4. Conclusion and perspectives

Upregulation of TRPM4 has been discovered in certain types of cancer. As a monovalent cation channel, enhanced TRPM4 activity could alter intracellular calcium levels in cancer cells via regulating the membrane potential. However, detailed mechanisms of calcium regulation by TRPM4 in cancer cells are largely unknown, in particular, mechanisms associated with VGCC and calcium-permeable TRP channels. It is noteworthy that the expression of TRPM4, as well as channels and transporters for calcium entry, varies among different cancers. Therefore, the functions of TRPM4 could be different, and future experiments are needed to address these concerns. It is well known that cancer cells grow rapidly. With more oxygen and nutrients consumed, hypoxia is induced, which in turn facilitates cancer proliferation and migration. The hypoxic environment not only affects cancer cell behavior but also may impact the functions of healthy tissues. TRPM4 upregulation has been well documented in ischemic stroke [39,40]. It has been reported that hypoxia stimulates transcription of Abcc8, which is the gene encoding SUR1, a subunit of the SUR1/TRPM4 complex. Within the Abcc8 promoter, the binding sites for specificity protein 1 (Sp1), but not for HIF, were required for stimulation of Abcc8 transcription by HIF1α [41]. SUR1 upregulation could enhance the expression of the SUR1/TRPM4 complex. The hypoxic condition surrounding the cancerous tissue may also induce TRPM4 and/or SUR1 expression in certain types of cells, such as the endothelium, similar to that in stroke. Elucidating the role of TRPM4 in the cancerous environment could help further understand the pathophysiology of cancer and may even alter cancer behavior. Additionally, TRPM4 is known to regulate immune response [3]. It will be interesting to know whether targeting TRPM4 could mediate immune cell functions on cancer cells.

A number of TRPM4 mutations have been reported in cardiac conduction disorders [7,42]. However, TRPM4 mutations in cancer have not been identified. The impact of TRPM4 on cancer behavior can be further studied in patients carrying TRPM4 mutations. In summary, research on TRPM4 channel in cancer is still at a very early stage. Deciphering the detailed roles of TRPM4 in various cancers would certainly pave the way for the development of novel therapies.

Conflicts of interest

The authors declare no conflict of interest.

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