

## Review Article

# Ion channels as targets for cancer therapy

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**Abstract:** Cancer is a leading cause of death in the world. Conventional treatments have severe side effects and low survival rate. It is important to discover new targets and therapeutic strategies to improve the clinical outcomes of cancer patients. Ion channels are specialized membrane proteins that play important roles in various physiological processes. Recent studies have shown that abnormal expression and/or activity of a number of ion channels e.g. voltage-gated K<sup>+</sup>, Na<sup>+</sup>, Ca<sup>2+</sup> channels, TRP channels, and epithelial Na<sup>+</sup>/degenerin family of ion channels, are involved in the growth/proliferation, migration and/or invasion of cancer cells. In this review, we summarize the present knowledge about the roles of different ion channels in the development of cancer.

**Keywords:** Ion channels, cancer, therapeutic targets, voltage-gated K<sup>+</sup>, Na<sup>+</sup>, Ca<sup>2+</sup> channels, TRP channels, epithelial Na<sup>+</sup>/degenerin family of ion channels

### Introduction

Cancer, one of the leading causes of mortality in the world, is a devastating disease involving many steps of complex signaling pathways. Conventional treatments for cancer include surgery, chemotherapy and radiation. In addition to severe side effects, current available treatments have low survival rate and limited clinical outcomes for many cancers. It is essential to discover new targets and therapeutic strategies to increase the survival rate and improve the clinical outcomes of cancer patients. Collective studies have shown that ion channels, the specialized membrane proteins that conduct ion fluxes, are involved in the development of many diseases including cancers [1]. The roles of various ion channels in the growth/proliferation, migration and/or invasion of cancer cells, for example, have been well documented [2-8].

Ion channels can be divided into two major categories based on their gating mechanism: (1) Voltage-gated channels, which are opened by membrane potential changes. These channels conduct specific ions when they are activated. (2) Ligand-gated channels, which are opened by

ligands, conduct cations or anions without high selectivity. Both voltage-gated and ligand-gated ion channels play important roles in physiological conditions such as electrical signaling, gene expression, hormone secretion, learning and memory [3,4]. In pathological conditions, the property or activity of ion channels may change. The abnormal property/activity of certain ion channels is able to promote the growth and proliferation of tumor cells [7].

In this review, we summarize the present knowledge about the roles of different ion channels in the growth/proliferation, migration, and invasion of tumor cells.

### Voltage-gate ion channels (VGICs)

VGICs are widely expressed in excitable and non-excitable cells. In addition to be involved in a variety of physiological processes, VGICs are known to be involved in the development of a number of diseases, such as cardiac arrhythmias, epilepsy, hyperkalemia, and some hereditary diseases, etc. [3]. In addition, recent studies have shown that VGICs are involved in the onset, proliferation, migration and survival of

various types of cancers [3].

According to the ion selectivity, VGICs are divided into three major types: voltage-gated potassium, voltage-gated sodium and voltage-gated calcium channels. All these sub-types share similar structural topology. The essential structure feature in VGICs is a tetrameric association of a series of six transmembrane  $\alpha$ -helical segments, numbered S1-S6, connected by both intracellular and extracellular loops, the interlinkers of  $\alpha$ -helical segments [1]. In addition to essential  $\alpha$ -subunit, voltage-gated channels also have multifunctional accessory proteins called  $\beta$ -subunits, which modulate gating properties and assist in associations between different ion channels [3].

### *Voltage-gated potassium channels (VGKCs or Kv)*

VGKCs are a large heterogeneous family of channels distributed widely throughout excitable cells such as neurons and cardiac myocytes, in which they control the membrane potential, and in non-excitable cells, in which they are involved in a number of physiological processes including volume regulation, apoptosis, immunomodulation and differentiation. In addition to physiological processes, Kv channels have been shown play a pivotal role in the proliferation, progression, and apoptosis of various cancer cells and have been considered as new targets for designing cancer treatment strategies [9].

Kv channels are divided into different subfamilies (Kv 1.1-1.8) based on their difference in the  $\alpha$ -subunit [1], the subunit that contains essential voltage-sensor and pore-forming region. Accessory proteins  $\beta$ -subunits also exist in potassium channels. Their functions are thought to be independent of  $K^+$  channel conductance, but are involved in protein recruitment/scaffolding and cell adhesion with extracellular matrix proteins. One of well-studied Kv channels associated with cancer development is human ether-a-go-go potassium channel (EAG1, KCNH1, Kv10.1). Lines of studies have shown that EAG1 is associated with the development of tumors both in patients and in animals [5,6,10-21]. Human EAG1 mRNA is almost exclusively expressed in normal brain. However, its ectopic expression has been linked to oncogenesis and tumor progression. The overexpression of EAG1

channels leads to uncontrolled cell proliferation. Over 75 % of tumors, including cell lines and primary tumors, for example, have been found to have overexpression of EAG1 proteins [16,18]. Farias and coworkers were the first to study the EAG channel activity in human tumors. They demonstrated the expression of EAG1 mRNA in several somatic cancer cell lines, and EAG1 protein in primary cultured cervical cancer cells and in cervical cancer biopsies [14]. Knockdown of EAG1 expression with siRNA and inhibition of EAG mediated currents decreased cell proliferation in cancer cell lines [14]. Studies by Mello and coworkers have shown that the expression level of EAG1 depends on the histological type, but no association was seen between expression of this protein and grade or tumor size [18]. Based on the high frequency of expression of EAG1 in primary tumors and the restriction of normal expression of the channel to the brain, EAG1 appears to be a promising cancer target either for diagnostic or therapeutic purposes [5,18]. Since normal cells expressing EAG1 are either protected by the blood-brain barrier or represent the terminal stage of differentiation, EAG1 based therapies are expected to produce only minor side effects [17].

The mechanism(s) of Kv mediated tumor progression and invasion remain unclear. Studies by Downie group suggest that EAG1 interferes with the cellular processes for maintaining oxygen homeostasis, increasing HIF-1 activity, and thereby VEGF secretion and tumor vascularization [19]. In MCF-7 breast cancer cell line, Kv are involved in both proliferation control and cell cycle progression according to the "membrane potential" model [22-24]. It has also been shown that Kv, like BK channels, are involved in glioma invasion and the formation of brain metastasis [25]. It is believed that activation of these channels, in concert with  $Cl^-$  currents, affects net salt fluxes. Water is obliged to accompany these net salt fluxes, leading to cell shrinkage/flattening, conditions permissive to movement through the extracellular space of tissues.

In addition to EAG1 channels, other Kv channels have been found in tumor cells (**Table 1**). For example, the expression of Kv 2.1-Kv 9.3 channels has been found in uterine cancer cells and that these channels are involved in the proliferation of uterine cancer cells [26]. Similarly,

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**Table 1.** Involvement of VGKCs in the pathology of cancer/tumor cells

Major Kv channels	Cancer type (cell line)	Reference(s)
Kv 1.1	MCF -7 human breast cancer cell line	[22]
Kv 2.1-2.9	Uterine cancer cells	[26]
Kv 1.3	Breast cancer cells	[27,28]
Kv 4.1	Human breast epithelial cells	[30]
KATP channel	glioblastoma multiforme; allogeneic brain tumor model; uterine leiomyoma.	[32,33]
G-protein coupled inwardly rectifying potassium channel 1(GIRK1)	Breast carcinoma	[22,35]
HERG K <sup>+</sup> channels	Leukemia cell lines K562, HL-60, and almost all the primary leukemia cells; gastric cancer cells	[36,37]
BKCa	Osteosarcoma; human glioma cells; human ovarian cancer cells; breast cancer (KCNMA1); MCF -7 human breast cancer cell line; LNCaP prostate cancer cells	[23, 25,28,31,32, 34, 38,39]
KCa3.1	Leukocytes, mitogen-induced endothelial cells, vascular smooth muscle cells; human colon cancer cells	[40,41]
TREK-1 ( two-pore domain (K (2P)) potassium channel)	Prostate cancer	[42]
TASK3 (TWIK-related acid-sensitive K <sup>+</sup> channel, KCNK9)	Human glioma cell lines; glioma specimens; breast tumors	[22,43]
Kir 4.1	Human astrocytic tumors	[44,45]

the expression of Kv 1.3 potassium channels and large conductance Ca<sup>2+</sup> and voltage-activated K<sup>+</sup> channels has been reported in breast cancer cells [27-29].

### *Voltage-gated sodium channels (VGSCs or Nav)*

VGSCs, gated by membrane depolarization, are primarily expressed in excitable cells, such as neurons and cardiac myocytes, in which they are responsible for the initiation of membrane depolarization by allowing rapid influx of Na<sup>+</sup>. The well known function of VGSCs is the generation of action potential in excitable tissues [1]. Mammalian VGSCs are composed of one single pore forming  $\alpha$ -subunit associated with one or two auxiliary  $\beta$ - subunit. While  $\alpha$ -subunits are responsible for current amplitude and density, the  $\beta$ - subunit modifies the kinetics and voltage-dependence of the channel gating [46]. So far, at least 9 functional members of VGSC $\alpha$  gene family have been studied in expression systems. They are designated Nav 1.1 - Nav 1.9 accord-

ing to their phylogeny [47,48]. The distribution of Nav subunits are tissue specific. For example, Nav 1.4, Nav 1.5, Nav, and SCN1  $\beta$ -subunit are expressed predominantly in the heart. Nav 1.1, Nav 1.2, Nav 1.3, Nav 1.8, SCN1 $\beta$ , and SCN3 $\beta$ -subunits are found predominantly in the brain [3]. According to the sensitivity to TTX, VGSCs are divided into TTX- sensitive (e.g. Nav 1.1-Nav 1.4, Nav 1.6 and Nav 1.7), which are blocked by nM TTX, and TTX- resistant (e.g. Nav1.5, Nav1.8 and Nav1.9), which are blocked by  $\mu$ M TTX [49]. In addition to producing action potentials in excitable cells, these channels also play important role in proliferation, migration, and adhesion of non-excitable cells including glia, fibroblasts, endothelial cells and T-lymphocytes [49-51]. It has been reported that VGSCs are associated with several channelopathies such as paralysis, epilepsy, multifocal motor neuropathy, hyperkalemia, long-QT syndrome and idiopathic ventricular fibrillation [1]. In addition, several lines of studies have demonstrated the role of sodium channels in several

strongly metastatic carcinomas in controlling various steps of the metastatic cascade [4,52]. For example, high expression levels of VGSCs have been found in several aggressive carcinomas including prostate cancer [53-56], breast cancer [52,57,58], lymphoma [59], small cell lung cancer [60], non-small cell lung cancer [61], mesothelioma [62], neuroblastoma [63,64], melanoma [65], and cervical cancer [66]. Therefore, VGSCs may represent promising new targets for developing novel therapeutics for metastatic cancers.

The mechanism(s) of VGSCs in metastatic carcinomas is still under investigation. One possible explanation is that  $\text{Na}^+$  flows into the cell by sodium channel activation. Increased intracellular  $\text{Na}^+$  may affect downstream pathways, such as intracellular  $\text{Ca}^{2+}$  and protein kinases which implicated in cellular mobility [4].

### *Voltage-gated calcium channels (VGCCs or Cav)*

VGCCs, expressed widely in excitable- and non-excitable tissues, are composed of five subunits:  $\alpha 1$ ,  $\alpha 2$ ,  $\beta$ ,  $\delta$ , and  $\gamma$ . The  $\alpha 1$  subunit contains voltage-sensor and channel pore, while  $\alpha 2$ ,  $\beta$ ,  $\delta$ , and  $\gamma$  subunits are regulatory in channel function. VGCCs are classified into six subtypes based on the channel characteristics and their sensitivity to certain drugs: L, N, P, Q, R, and T types. L-type channel are characterized by long lasting activation, slow inactivation and dihydropyridine sensitivity. Although expressed in a variety of excitable and non-excitable tissues, the L-type channels are found predominantly in the brain, and in skeletal and cardiac muscle, where they play a role in coupling the afferent excitation to muscle contraction. N-type channels are slow inactivation channels, which are located in the presynaptic nerve terminals, controlling neurotransmitter release. P-type channels, also slow in inactivation, are found in the presynaptic terminals of cerebellar neurons, and in neuromuscular junctions. These channels can also control the release of neurotransmitters. Q-type channels play a similar role in the control of secretagogue release from cerebellar granule cells and pyramidal neurons. R-type channels, exist in cerebellar granule cells and in the dendrites of pyramidal neurons, are characterized by their fast gating properties. T-type channels are activated by small membrane depolarizations and have rapid inactivation. These channels are widely expressed in the

brain, kidney, liver, bone, and heart. In addition to severe long QT syndromes, VGCCs are involved in other channelopathies including paralysis, Lambert-Eaton Myasthenic Syndrome, migraines, and epilepsy. VGCCs are also found in some cancer cells and play an important role in cancer progression. For example, T-type Cav was found in human prostate cancer and up-regulated during neuroendocrine differentiation [67]. The L-type calcium channel subunit, Cav 1.2, was found in colon cancer cells [68]. Cav 1.2 expression increases with the differentiation of colon cells to cancer cells. P- and L-type Cav was found in small lung carcinomas [69]. Calcium spikes, which are caused by unspecified T-type calcium channels and play a role in membrane depolarization [70], have been shown to alter the motility of fibrosarcoma cells [71].

In summary, voltage-gated ion channels (VGICs) play an important role in the progression of cancer cells although the detailed cellular processes are still uncertain. In addition to affecting cell proliferation and migration, voltage-gated ion channels also play major roles in cell specific differentiation program for neuronal and non-neuronal cell types. Additionally, in some types of cancers, the peptide hormones and other growth factors in the control of VGICs are also very important. For example, Nav in prostate cancer cells are regulated by steroid hormone [3]. On the other hand, VGICs may act dependently in the physiological conditions. The depolarization of membrane potential that opens the VGSCs can in turn result in the opening of VGCCs.  $\text{Ca}^{2+}$  entry into the cells from VGCCs and increased intracellular  $\text{Ca}^{2+}$  may have multiple functions within the cell. In addition, the membrane depolarization will also activate VGICs, which could then repolarize the membrane, effectively blocking activation of VGSCs or VGCCs. Normal cell growth and differentiation need the synchronization of VGICs. If this synchronization of VGICs is disturbed, cancer cell may be produced. A better understanding of these channels, their distribution and downstream effectors may help develop new therapeutic strategies through modulations of the channel activity in a selective manner.

### **Transient receptor potential (TRP) channels**

Transient receptor potential (TRP), six-transmembrane cation-permeable channels, are widely expressed in mammalian tissues.

They regulate intracellular  $\text{Ca}^{2+}$ ,  $\text{Na}^{+}$  concentrations and membrane voltage in both excitable and non-excitable cells. These channels, as signal integrators, can be activated by multiple distinct stimuli. When TRP channels open,  $\text{Ca}^{2+}$  and  $\text{Na}^{+}$  ions flow into the cell, which couple their activity to downstream cellular signal amplification via calcium permeation and membrane depolarization [72]. Based on the amino acid sequence homology, mammalian TRP channels can be divided into 7 subfamilies: TRPA, TRPC, TRPM, TRPML, TRPN, TRPP, and TRPV [73,74]. Because  $\text{Ca}^{2+}$  is an essential regulator for cell cycle and proliferation [75], TRP channels play important roles in many physiological processes. In addition, they have been shown to be involved in a variety of pathological processes including tumor formation and metastasis.

### *TRPM subfamily*

TRPM subfamily, also called melastatin-like transient receptor potential channels, comprised of eight members: TRPM1/3, TRPM4/5, TRPM6/7, TRPM2 and TRPM8 [72,76]. TRPM subfamily has important effects on various physiological and pathological processes through mediating cations entry and membrane depolarization.

**TRPM1:** TRPM1 is highly expressed in early stage melanomas but its expression declines with increases in the degree of aggressiveness of the melanoma [77,78]. Consistent with these results, several studies have suggested that TRPM1 may act as tumor suppressor [79-81]. Therefore, TRPM1 is identified as a prognostic marker for metastasis of localized melanoma [77]. Although its channel activity has not been described definitively, it has been proposed that TRPM1 may activate a  $\text{Ca}^{2+}$  permeable channel [82]. However, it is still not clear how TRPM1 reduces the growth rate of melanoma cells.

**TRPM 7:** Recent studies by our laboratory have demonstrated the expression of TRPM7 channels in FaDu and SCC25 cells, two human head and neck tumor cell lines [83]. In both cells, lowering extracellular  $\text{Ca}^{2+}$  induced a large non-desensitizing current with characteristics of TRPM7 channel currents inhibited by  $\text{Gd}^{3+}$ , 2-aminoethoxydi-phenyl borate (2-APB), or intracellular  $\text{Mg}^{2+}$ [84-87]. Consistent with the electrophysiological findings, the expression of

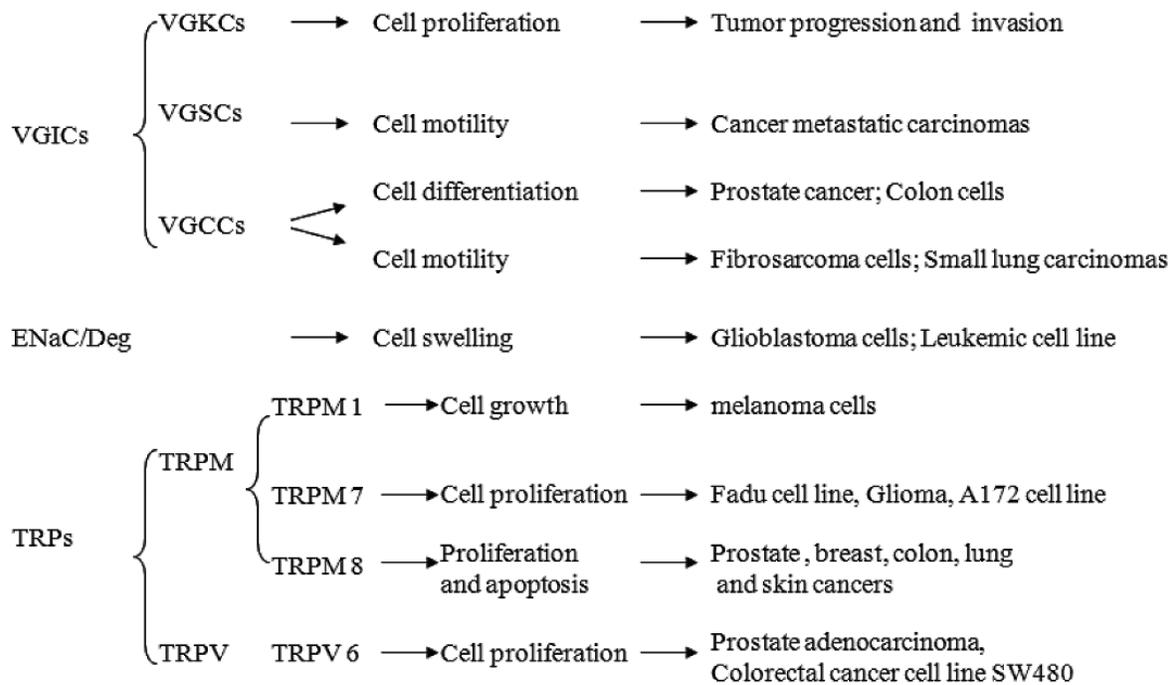
TRPM7 proteins and mRNA was confirmed by Western blot, immunocytochemistry and reverse transcription-PCR techniques. Suppressing the activities of these channels inhibited the growth and proliferation of FaDu cells [83]. Similar to human head and neck cancer cells, TRPM7 channels were detected in both primary human glioma cells and human glioma cell lines (e.g. A172 cells)[88]. Suppressing these channels e.g. by channel inhibitors and/or siRNA, also inhibited the growth and proliferation of these cells. Taken together, our results suggest that activation of TRPM7 channels play an important role in the growth and proliferation of tumor cells.

**TRPM 8:** TRPM 8, a non-selective cation channel activated by cold stimuli (17-25°C) and menthol (cooling compounds) is highly expressed in sensory neurons[89-92]. In addition to sensing cold, they play a broader role in both physiological and pathological conditions including cancer. For example, TRPM 8 was first identified in prostate epithelial cells by Tsavaler group [93]. In normal prostate, the TRPM 8 level is moderate. However, the expression level of TRPM 8 increases dramatically in prostate cancer [94]. Similarly, the expression level of TRPM 8 becomes highly enriched in other primary human tumors such as breast, colon, lung and skin cancers [93]. In addition to  $\text{Ca}^{2+}$  entry across the plasma membrane, TRPM 8 also facilitates  $\text{Ca}^{2+}$  release from  $\text{Ca}^{2+}$  stores. Increased intracellular  $\text{Ca}^{2+}$  potentiates sensory synaptic transmission, causing cell proliferation and apoptosis [95-97]. In addition to be activated by cold stimuli, TRPM8 channel can also be activated by membrane potential changes. TRPM8 has been considered to be a promising target for therapeutic interventions in prostate cancer [98].

### *TRPV subfamily*

TRPV (Vanilloid) channels have also been found to regulate cancer cell proliferation, apoptosis, angiogenesis, migration and invasion. TRPV6 gene is the first cloned TRPV subfamily from rat duodenum using an expression cloning strategy in *Xenopus laevis* oocytes [8]. Although it belongs to TRPV family, it is much less similar to other TRPVs [72]. TRPV6 channels show high  $\text{Ca}^{2+}$  selectivity and exhibit strong inward rectification in human embryonic kidney and rat basophilic leukemia cells [99-101]. The gating of

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**Figure 1** Ion channels involved in cellular processes vital to the progression and development of cancer cells.

TRPV6 channel is strongly dependent on the intracellular free  $Ca^{2+}$ , and extracellular divalent cations [99,102]. TRPV6 channels can be activated by removing extracellular divalent cations and /or by lowering the intracellular  $Ca^{2+}$  [99,102]. Several studies have reported that TRPV6 mRNA is expressed in prostate adenocarcinoma, and colorectal cancer cell lines [103-105]. Its expression has been considered as a general marker for neoplasms since the expression level of TRPV6 mRNA correlates with the tumor grade and aggressiveness [104-106]. Expression of TRPV6 is also increased in prostate cancer and in a number of other cancers.

The expression of TRPV1, TRPC1, TRPC6, TRPM4, and TRPM5 is also increased in some cancers. Studies in human cell line and patients' specimens have shown that there were correlations between TRP mRNA expression levels and cancer progression. However, the molecular mechanisms underlying the modulation of cell proliferation by these proteins may be different even though all of them are  $Ca^{2+}$  permeable. In addition to intracellular  $Ca^{2+}$ , physiological interaction with proteins may also be involved in cell proliferation [107,108]. In summary, TRP channels are novel targets for developing new diagnostics tools and therapeutic

strategies for the treatment of various cancers.

### Epithelial $Na^+$ channel /degenerin family (ENaC/DEG)

Epithelial sodium channel (ENaC)/Degenerin are widely expressed, from epithelial, endothelia, osteoblasts, keratinocytes, taste cells, to lymphocytes, and brain tissues [109].  $Na^+$  ions flow into the cell through ENaC via facilitated diffusion. The ENaC/DEG family usually has five subunits:  $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$  and  $\epsilon$ , although typical ENaC channels are composed of  $\alpha$ ,  $\beta$  and  $\gamma$  subunits [110,111]. All subunits share the same structural topology with short intracellular N and C termini, two transmembrane domains and a large extracellular cystein-rich loop [109,112]. In addition to diseases such as salt-sensitive hypertension [113,114], pseudohypoaldosteronism [113], cystic fibrosis, chronic airway disease [115,116] and flu [117], ENaC/DEG family of channels also play an important role in the pathology of cancers. Kapoor and colleagues have reported that the presence of ENaC/DEG in glioblastoma cells. Knockdown of  $\alpha$ ,  $\beta$  and  $\gamma$  subunits inhibited migration of glioblastoma cells [63,118]. One possible mechanism underlying the involvement of ENaC/DEG in glioblas-

toma cell migration is that, Na<sup>+</sup> flows into the cell via ENaC channel, which causes H<sub>2</sub>O into the cell resulting from the higher osmolality in the cell interior. This will cause cell swelling, a process required for lamellipodium expansion [119]. The presence ENaC has also been reported in human leukemic cell lines [120,121].

### Conclusion

Membrane ion channels are essential for many physiological processes. However, they can also play an important role in the development of cancer (Figure 1). Although the detailed molecular mechanism(s) underlying the involvement of ion channels in proliferation, apoptosis, invasiveness, and metastatic spread of cancer cells are still under investigation, ion channels represent promising targets for developing novel and effective cancer therapies.

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