New insights into the physiological, pathological and pharmacological roles of voltage-gated potassium channel Kv10.1 in cancer (Review)

YUXIAO ZHEN[1*], WEIBO HU[2*], SHANSHAN DONG[1], BOCHANG WANG[3], JIAN SHEN[4], LEYUAN DING[5], LIFENG LI[6], HAILONG AN[1], XUZHAO WANG[7] and YAFEI CHEN[1]

[1]Key Laboratory of Molecular Biophysics of Hebei Province, Institute of Biophysics, School of Health Sciences and Biomedical Engineering, Hebei University of Technology, Tianjin 300401, P.R. China; [2]Department of Oncology, The People's Hospital of Leling, Leling, Shandong 253600, P.R. China; [3]Department of Breast Cancer, Tianjin Cancer Hospital Airport Hospital, National Clinical Research Center for Cancer, Tianjin 300308, P.R. China; [4]Department of Bioengineering, School of Chemical Engineering, Hebei University of Technology, Tianjin 300401, P.R. China; [5]Department of Applied Statistics, School of Science, Hebei University of Technology, Tianjin 300401, P.R. China; [6]Department of Otolaryngology-Head and Neck Surgery, Beijing Tongren Hospital, Capital Medical University, Beijing 100730, P.R. China; [7]School of Medicine, Hebei University of Engineering, Handan, Hebei 056038, P.R. China

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Abstract. Kv10.1, also known as Eag1 or KCNH1, is a voltage-gated potassium ion channel, which exists in cell membrane and is closely associated with cancer and multiple precancerous lesions. Emerging experimental evidence shows that Kv10.1 is essential for the occurrence, growth, metastasis, proliferation and death of various malignant tumors. The pathogenesis of Kv10.1 and the signal pathways involved in its regulation are different in different cancers. The present review explored the origin, structure, distribution in normal and tumor cells, physiological and pathological characteristics, roles in cancer and tumor regulation mechanisms of Kv10.1. Finally, Kv10.1 related signaling pathways and its current use as a pharmacological modulator are summarized, aiming to provide new insights into the pharmacological research of Kv10.1 in cancer.

Correspondence to: Dr Xuzhao Wang, School of Medicine, Hebei University of Engineering, 19 Taiji Road, Economic and Technological Development District, Handan, Hebei 056038, P.R. China
E-mail: wangxuzhao@hebeu.edu.cn

Professor Yafei Chen, Key Laboratory of Molecular Biophysics of Hebei Province, Institute of Biophysics, School of Health Sciences and Biomedical Engineering, Hebei University of Technology, 5340 Xiping Road, Beichen, Tianjin 300401, P.R. China
E-mail: chenyafei@hebut.edu.cn

*Contributed equally

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Contents

1. Introduction to tumor related potassium channels

Ion channels are pore-forming transmembrane proteins, which regulate the life activities of organisms by controlling the ion transport, not only participating in the remodeling of cytoskeleton and the interaction between cells, but also regulating the processes of cell migration and invasive growth. Moreover, it has been shown that abnormal expression or activity change of ion channels can regulate the proliferation and apoptosis of tumor cells (1).

Voltage-gated potassium channels (Kv) are a type of protein channels formed on the cell membrane, which can be turned on or off according to the voltage change of the cell membrane. They can regulate the transmembrane flow of potassium ions, thus maintaining the normal physiological functions of cells, such as nerve conduction, muscle contraction and cell excitability (2). The human genome contains 40 voltage-gated potassium channels, which are involved in a number of physiological processes, including the repolarization of neuron or cardiac action potential, the regulation of calcium signal and cell volume and the promotion of cell proliferation and migration. The Kv channel has shown promising research potential

in cancer, autoimmune diseases, metabolic, neurological and cardiovascular diseases. It has been found that several voltage-gated potassium channels are closely associated with tumors: KCa3.1 (KCNN4) (3), Kv10.1 (EAG1, KCNH1) (4), Kv1.3 (KCNA3) (5) and HERG (Kv11.1, KCNH2) (6).

Among the potassium ion channels, Kv10.1 has become a focus of current anti-cancer research due to its high expression characteristics in tumors and close association with tumor occurrence and development.

2. Kv10.1 potassium channel: An overview

Kv10.1 (potassium voltage-gated channel subfamily H member 1/KCNH1, known as Ether-à-go-go-1 or EAG1) is a voltage-gated potassium channel (4). Kv10.1 has been found to be expressed in a number of different cancer cell lines, including gastric cancer (7), liver cancer (8) and lung cancer (9), but its expression in normal tissues is limited (10,11). It has been proved that it is highly expressed in a number of tumors and plays an important role, which makes it a potential marker and target for tumor diagnosis and treatment (7-9,12-16).

The origin of Kv10.1. The discovery of Kv10.1 channel can be traced back to the study of voltage-gated potassium ion channels. Kv10.1 was first discovered by Kaplan *et al* (2) in 1969 in the mutant X chromosome of *Drosophila*. Its name 'ether-a-go-go' comes from the irregular leg tremor phenotype exhibited by *Drosophila* mutants under ether anesthesia, which is caused by a functional defect in voltage-gated potassium channels due to gene locus mutations (17). Studies have shown that molecular cloning technology confirms that the protein encoded by the *Eag* gene belongs to the Kv superfamily and reveals its direct association with the regulation of neural excitability in *Drosophila* (17). Kv10.1 is located in chromosome 1, band q32.1-32.3 and comprises 457,343 bases and 12 exons (18).

The molecular structure of Kv10.1. Kv10.1 is encoded by *KCNH1* gene, which encodes a 989 amino acid protein with an estimated molecular weight of 111,423 Daltons. The overall structure of Kv10.1 channel is similar to these of the other Kvs. The core region contains six transmembrane domains (transmembrane helices S1-S6), including voltage sensor domains (transmembrane helices S1-S4) and potassium ion selective permeability channels (transmembrane helices S5, pore helices S6) and the N-terminal and C-terminal of this channel protein (Fig. 1). The single-hole channels of these six transmembrane regions (S1-S6) are activated by depolarization (19-21). The N-terminal contains Per-Arnt-Sim (PAS) domain. C-terminal contains cyclic nucleotide binding homology domain (CNBHD), C-linker, ciliary localization signal and tetrameric coiled helix domain (19,22).

Although the structure of Kv10.1 has a number of similarities with other Kvs, based on the three-dimensional structure of the rat Kv10.1 obtained by single-particle cryoelectron microscopy, it was found that Kv10.1 has a number of unique structural features compared with other Kv channels. The S2-S3 connector of Kv10.1 extending into cytoplasm is different from those of other voltage-gated potassium channels. This connector is a conservative feature of Kv family and the only other Kv subfamily member containing the similar connectors is Kv7 (19,23). In Kv10.1, S4 region is the main positive charge concentration region, usually with 5-7 positive charges distributed. As a voltage receptor, this region can respond to the electric field force when the membrane potential changes and drive the conformational change of the channel. In addition, other transmembrane regions (such as S1, S2 and S3) may also contain a small amount of positively charged amino acid residues, but the positive charge density is relatively low and the sensitivity to voltage change is not as significant as that of S4 region. S1-S4 constitute positively charged amino acids in the field of voltage sensors, which move membrane potential with the depolarization of cerebral cortex (24-26). The S4-S5 linker in Kv10.1 is a short loop composed of five amino acid residues, which contrasts with the helical structure formed by 15 residues parallel to the membrane in domain exchange potassium channels (such as Kv1.2) (19,27). The segments S5-S6 form the pore domain of the channel, while the ring P (between S5-S6) is responsible for the K^+ selectivity. These local structural features determine that Kv10.1 has a different voltage gating process compared with other types of Kv channels. S4 in Kv10.1 directly interacts with the carbon terminal C-linker to close the channel, that is, the channel can realize voltage-dependent activation gating without covalent connection between S4 and S5 (27,28).

Kv10.1 also has unique N-terminal and C-terminal domains, which are necessary for subfamily-specific channel assembly (17,29,30). Kv10.1 has a large N-terminal and a C-terminal in cells, accounting for ~70% of its molecular weight. In addition, there are several regulatory domains at the ends of cells. N-terminal contains a PAS domain, which is usually involved in the detection of redox reaction. It is considered as an oxygen sensor, which can induce the production of hypoxia inducible factor hypoxia-inducible factor 1 (HIF-1) in hypoxic environment, thus causing the increase of glycolysis rate and angiogenesis, which is beneficial to the growth of tumor cells in hypoxic environment. The C-terminal contains a CNBHD, which is a calmodulin binding site (31). The fragment between CNBHD and S6 is called C-linker. S6 spirally extends to the intracellular region and is connected to C-linker, forming an intracellular ring above CNBHD. The C-linker couples the movements of S6 and CNBHD and CNBHD is connected to the pore region through C-linker (32). As with other ion channels, Kv10.1 undergoes nitrogen chain glycosylation at N388 and N406 sites, which is very important for the correct transport of the channel to the membrane. Three-dimensional structural analysis by cryo-electron microscopy showed that the PAS domain of Kv10.1 channel in rats was located in the intracellular region and mainly interacted with CNBHD, a neighboring subunit. In addition, Kv10.1 channel contain amino acid residues carrying glycosylation regions of polymers, among which glycosylation of N406 is a necessary condition to maintain the normal structure and function of Kv10.1 and deglycosylation will lead to weakening of channel current and slow activation (19,33).

The distribution of Kv10.1

The distribution of Kv10.1 in normal tissues. Kv10.1 channel is a protein embedded in plasma membrane, but it can also be found in subcellular structural membrane including

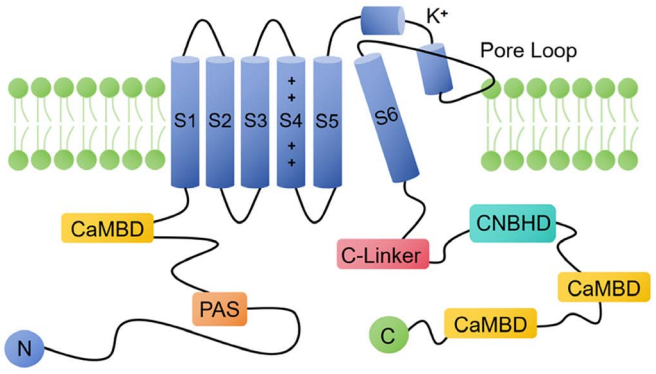

Figure 1. Structure of Kv10.1. Kv10.1 comprises six transmembrane domains (transmembrane helices S1-S6), including a voltage-sensing domain (formed by transmembrane helices S1-S4, with S4 bearing positive charges) and a potassium ion-selective permeation pathway (formed by transmembrane helix S5 and the pore helix S6), along with the N-terminus and C-terminus of the channel protein. The N-terminus contains a PAS domain. The C-terminus is connected to the CNBHD regulatory domain via a C-Linker and multiple CaMBDs are involved in the regulation of channel activity mediated by calcium signaling. PAS, Per-Arnt-Sim; CNBHD, cyclic nucleotide-binding homology domain; CaMBDs, calmodulin-binding domains.

the inner nuclear membrane, intracellular vesicles and close to the primary cilia. Under normal physiological conditions, Kv10.1 is almost undetected in peripheral tissues, except for a few peripheral tissues, such as pre fusion myoblasts (34) and Kv10.1 shows abundant expression in specific brain regions. Previous studies have shown that Kv10.1 mainly exists in the brain, locates at the presynaptic terminal and regulates the release of neurotransmitters, which can be used as a regulator of local action potential (35).

The distribution of Kv10.1 in malignant tumors and precancerous lesions. Kv10.1 potassium channel is the first voltage-dependent potassium channel proved to be closely associated with tumor growth (36-39). In recent years, a large number of studies have shown that Kv10.1 potassium channels are abnormally expressed in malignant tumors and precancerous lesions (7,40-55). Kv10.1 was highly expressed in the primary tumor of head and neck squamous cell carcinoma and was detected in 10 of 12 cell lines derived from head and neck squamous cell carcinoma (40,41). Kv10.1 was positively expressed in breast cancer cell lines, such as MCF-7 (12), T-47D (12) and MDA-MB-231 (42). Kv10.1 is highly expressed in lung cancer. A549 and NCI-H1975 are common lung cancer cell lines (9). In liver cancer, Kv10.1 inhibitor can inhibit the proliferation and migration of liver cancer cells HuH-7 cells and HepG2 cells (13). By immunohistochemical methods, >70% colon cancer tissues showed positive expression of Kv10.1, which was markedly higher than that of normal tissues adjacent to cancer. Kv10.1 was also highly expressed in colon cancer cell line SW480 (14). The primary tissue samples of gastric cancer were detected by immunohistochemistry and it was found that 70.5% of tumor tissues showed positive expression of Kv10.1 protein, which was markedly higher than that of normal tissues adjacent to cancer. Compared with normal gastric mucosal cells, the expression of Kv10.1 in gastric cancer cell lines (SGC-7901, BGC-823) is also higher (7,43). The expression of Kv10.1 in cervical cancer tissue was markedly higher than that in normal cervical tissue and the expression content of Kv10.1 in cervical cancer cells HeLa, Siha and Casci was higher than that in normal cervical cells (15,44). Studies have shown that Kv10.1 can be expressed in cervical intraepithelial neoplasia and the expression level is associated with the level of cervical intraepithelial neoplasia (16,45,46). Kv10.1 is highly expressed in ovarian cancer and atypical adenoma hyperplasia of precancerous lesions (16). The high expression of Kv10.1 may be a potential prognostic marker of prostate cancer, which is associated with the poor prognosis of patients. Kv10.1 is highly expressed in prostate cancer tissues and tumor cell lines, but almost not in normal prostate tissues (47-49). The abnormally high expression of Kv10.1 in neuroblastoma is not only driven by the transcription level, but also depends on the fine regulation of post-translational modifications (such as ubiquitination and phosphorylation) (50). Kv10.1 is also expressed in melanoma, which also affects the proliferation of melanoma cells (51-53). Kv10.1 is highly expressed in bone marrow primordial cells of acute myeloid leukemia patients, but hardly expressed in normal hematopoietic stem cells and benign blood diseases (54). The expression level of Kv10.1 in patients with soft tissue sarcoma has been detected by immunohistochemistry. Kv10.1 was expressed in 71% tumors and the frequency ranged from 56% in liposarcoma to 82% in rhabdomyosarcoma (55). Kv10.1 is also expressed in osteosarcoma, which also affects the proliferation of osteosarcoma cells (56). The aforementioned results are listed in Table I. The abnormal expression of Kv10.1 in a number of malignant tumors and precancerous lesions will provide a certain molecular basis for the diagnosis and treatment of corresponding diseases. Different experimental techniques are used to analyze its mechanism of action from multiple levels in studying the expression and function of Kv10.1. Fresh patient samples can be quantified for protein and mRNA expression levels through western blotting and quantitative (q) PCR. In cell lines in good condition, channel current characteristics can be directly measured through electrophysiological recording, while wax blocks can be used for immunohistochemistry and *in situ* localization of protein expression. Nevertheless, each method has its limitations. Western blotting involves semi-quantitative detection following protein separation by electrophoresis, allowing precise measurement of protein molecular weight and relative expression level. However, it cannot provide protein localization information and requires tedious experimental steps, with strict control of parameters such as sample loading volume and antibody concentration to avoid errors. qPCR reflects gene expression levels by detecting mRNA levels, which is simple to operate and has high throughput. However, it cannot directly reflect protein function and results may be affected by factors such as RNA quality and primer specificity. Inappropriate primer design may lead to PCR reactions with low specificity or efficiency. Immunohistochemistry localizes target proteins in tissue sections through antigen-antibody reactions, visually displaying their distribution in the cell membrane, cytoplasm, or nucleus. However, staining intensity is easily affected by factors such as antibody concentration and incubation time. Antibodies from different manufacturers have varying binding abilities to target proteins, leading to differences in results. Electrophysiological experiments directly measure the current characteristics of ion channels to reflect their functional activity. However, they require extremely high cell states and

Table I. Cell lines with high expression of Kv10.1.

Cancer type	Cell line	(Refs.)
Head and neck cancer	SCC29, SCC40, SCC42B, SCC040, SCC041, SCC078, SCC094, SCC096A, SCC120, SCC147	(33,36)
Breast cancer	MCF-7, T-47D	(12)
	MDA-MB-231	(42)
Lung cancer	A549, NCI-H1975	(9)
Liver cancer	HuH-7, HepG2	(13)
Colon cancer	SW480	(14)
Gastric cancer	SGC-7901, BGC-823	(7,43)
Cervical cancer	HeLa, SiHa, CaSki	(15,46)
Ovarian cancer	SKOV3, OVCAR3	(16)
Prostatic cancer	DU-145, PC-3	(47-49)
Neuroblastoma	SHSY-5Y	(50)
Melanoma	IGR1, IPC298, IGR39, A375	(51-53)
Acute Myeloid Leukemia	HL-60, K562, PLB-985, HEL, CMK, KASUMI, UT-7	(54)
Rhabdomyosarcoma	TE-671, A-204	(55)
Fibrosarcoma	HT-1080, Hs633t	(55)
Osteosarcoma	SaOS-2, MG-63	(56)

have long experimental cycles, making them difficult to apply on a large scale. In practical applications, selection should be based on research objectives and combined with the biological characteristics of the samples.

In addition, the ectopic expression of Kv10.1 is associated with the phenotype of chemotherapy-resistant cells. Therefore, the inhibition of Kv10.1 channel can improve the response of cells to commonly used therapeutic drugs in chemotherapy. *In vitro* experiments on ovarian cancer cells showed that the expression of Kv10.1 was associated with the chemotherapy resistance to cisplatin. Compared with cells treated with cisplatin alone, the combination of down-regulation of Kv10.1 and cisplatin increased the apoptosis of ovarian cancer cells (44).

3. Physiological and pathological functions of Kv10.1

Physiological characteristics of Kv10.1. Kv10.1 is a voltage-gated potassium channel, which is highly expressed in nervous system and some cancer cells. It has unique electrophysiological characteristics and plays an important role in cell excitability regulation, tumor occurrence and development.

Kv10.1 channel is voltage-dependent and its activation degree changes with the membrane potential. This characteristic makes Kv10.1 channel play an important role in regulating cell excitability. In addition, the gating characteristics of Kv10.1 channel are also different from other potassium channels, with a slow activation and deactivation process. The activation characteristics of Kv10.1 can be associated with Cole-Moore shift observed in squid axons published by Cole KS and Moore JW in 1960 (57). This effect was originally used to describe the potassium current in squid axons, which is characterized by a significant delay in current activation when hyperpolarized resting membrane potential channels are activated (58,59). The Cole-Moore shift of Kv10.1 is ~10s of milliseconds, while that of other members of the voltage-gated potassium channel family is close to 1 msec and the Cole-Moore shift of Kv10.1 is steeper than that of Kv10.2 (60). This electrophysiological feature can be used as a marker to identify the expression of Kv10.1 in cells and ectopic expression. The activation of Kv10.1 depends on cell membrane resting potential and extracellular Mg^{2+} concentration and low extracellular pH can slow its activation (61,62). Cole-Moore shift can be enhanced by increasing extracellular Mg2+ concentration in physiological range (63). The Cole-Moore shift of Kv10.1 can be inhibited by using amiodarone and mibefradil (64,65).

Kv10.1 is mainly expressed in the nervous system and its electrophysiological characteristics are closely associated with the function of the nervous system. In adult rats, the mRNA of Kv10.1 can be mainly detected in olfactory bulb, cerebral cortex, hippocampus and cerebellum and it is consistent with its protein expression level (66). Further research found that Kv10.1 was mostly expressed on dopaminergic cells in physiological state, which may be associated with its electrophysiological function (67). In the nervous system, Kv10.1 can be used as a regulator of local action potential, especially when other potassium channels suffer from high-frequency bursts of cumulative inactivation. Part of the function adjustment of Kv10.1 channel involves its detergent resistant membrane part (also called fat raft) (68,69).

The pathological function of Kv10.1 in cancer. Kv10.1 channel is highly expressed in 70% of tumors and its expression level is closely associated with the malignant degree, metastatic ability and clinical prognosis of tumors. Kv10.1 is highly expressed in head and neck cancer, breast cancer and acute myeloid cells (54,70-72) and inhibiting or knocking out Kv10.1 can reduce tumor growth (73-76). Therefore, Kv10.1 is considered as a potential target for cancer treatment.

Kv10.1 channel affects the production of resting potential and action potential by regulating the potassium ion

permeability of cell membrane. This electrophysiological change may further affect the intracellular signal transduction pathway, thus regulating the cell proliferation process. In tumor cells, the high expression of Kv10.1 channel may lead to uncontrolled cell proliferation and promote tumor growth. In addition to regulating cell proliferation, Kv10.1 channel may also participate in tumor metastasis by regulating cell migration and invasion.

Kv10.1 is very important for the proliferation of tumor cells. In 1997, Brüggemann *et al* first discovered the function of Kv10.1 in cell proliferation in *Xenopus* oocytes (77). Kv10.1 leads to abnormal proliferation of cells, including enhanced metabolic activity and reduced dependence of cells transfected with Kv10.1 on growth factors in the medium. Cells transfected with Kv10.1 can continue to grow in the medium with low concentration of serum, even without matrix indicating the loss of contact inhibition characteristics (17). *In vitro*, inhibiting the expression of Kv10.1 can reduce the cell proliferation, migration and invasion of cancer cells. *In vitro* experiments, injecting exogenous CHO cells expressing Kv10.1 into immunosuppressed mice induced the occurrence of invasive tumors (78), while using specific monoclonal antibodies to inhibit Kv10.1 can inhibit the growth of tumors *in vitro* (79) and similar effects were also observed in animal experiments (80-85). In recent years, the closed state wild-type channel model of cryoelectron microscope structure based on HERG and Kv10.1 channels has been constructed by using Rosetta software and cryo-electron microscope structure. These models were then used in molecular docking studies to explore the mechanism of drug channel interaction (86-89).

Generally, Kv10.1 channel plays an important role in the occurrence and development of cancer and its high expression is closely associated with the clinical prognosis of a number of tumors. In-depth study on the pathological function and regulation mechanism of Kv10.1 channel is expected to provide new theoretical basis and therapeutic strategies for cancer prevention and treatment.

4. Tumor regulation mechanisms of Kv10.1

In the process of carcinogenesis, Kv10.1 may play a role through various mechanisms. First, as a potassium ion channel, Kv10.1 can regulate the potassium ion permeability of cell membrane, thus affecting the generation of cell resting potential and action potential. This electrophysiological change may further affect the signal transduction pathway in cells and then regulate the gene expression associated with carcinogenesis. Second, Kv10.1 may also interact with other signal pathways to jointly promote the occurrence and development of tumors. Kv10.1 is highly expressed in a number of tumor cells and tissues, but its specific mechanism of action is not very clear. At present, there are only some explorations about Kv10.1 in cell cycle regulation, cell hyperpolarization, signaling pathway, epigenetic regulation mechanism.

Cell cycle regulation. In 2006, it was found that the expression activity of Kv10.1 was associated with the cell cycle (90). Cell cycle regulates the progress of mitosis. During mitosis, if progesterone or mitotic promoter exists, the activity of Kv10.1 channel will be inhibited, which also proves its cell cycle sensitivity (91).

The research after 2016 gave more specific results. That is, Kv10.1 is located in centrosome and primary cilia (92) and promotes the decomposition of primary cilia in G_2/M phase, which is beneficial to the progress of cell cycle (93). Following Kv10.1 knock-out, ciliary decomposition is inhibited and proliferation is delayed. Therefore, the regulation of Kv10.1 on ciliary development can explain the influence of Kv10.1 expression on normal cell proliferation and may be a main mechanism of its tumorigenesis (94). Kv10.1 affects Ca^{2+} entry through hyperpolarization and Ca^{2+} inhibits EAG1 function through calmodulin (3). Ca^{2+} is associated with the cell cycle and cell replication. Calcium influx is considered necessary for the transition from G_1 phase to S phase in the cell cycle. This hyperpolarization also facilitates the entry of a large amount of nutrients into the cell, thereby promoting cell proliferation (10,95).

Similar research also support the aforementioned view. Urrego *et al* (96) reported that Kv10.1 could be detected only in G_2/M phase. As the E2F transcription factor 1 (E2F1) coordinates cell division and induces the expression of Kv10.1 in G_2 phase, Kv10.1 can only be detected in G_2/M phase and downregulation of Kv10.1 will prolong the duration of G_2/M phase. However, Kv10.1 will be diluted in G_0/G_1 phase, so it cannot be detected in other stages of cell cycle (97). Some studies also hypothesize that the strong influence of Kv10.1 channel in cell cycle progress is also associated with ciliary disintegration, which usually provides the signal transduction needed to start proliferation (96,97). Cyclic expression of Kv10.1 has been proved to exist at the base of primary cilia of hTERRPE-1 cells, which may lead to significant disposability of microtubules in the subsequent process (10).

Regarding microtubule activity, the upregulation of Kv10.1 is closely associated with a significant increase in microtubule dynamics, characterized by assembly and disassembly rates. Therefore, there is an important association between Kv10.1 overexpression and certain processes including cellular variability (96,97). It has been proved that the mobility of MDA-MB-231 cells decreased markedly when Kv10.1 was exposed to a specific blocking agent such as astemizole. Some hypotheses suggest that cell migration caused by Kv10.1 channel is mainly due to the change of microtubule dynamics caused by hyperpolarization of action potential, which has been proved to induce calcium to enter through Ca^{2+} release and activates ORAI calcium release-activated calcium modulator 1(ORAI1). ORAI1 association with Ca^{2+} ATPase seems to be associated with the proliferation and survival of cancer cells (98).

Hyperpolarization mechanism. The outflow of K^+ through Kv10.1 channel makes cells hyperpolarized, thus promoting the influx of Ca^{2+}, leading to the proliferation of non-invasive cells (10,99,100). However, the relationship between Kv10.1 and intracellular Ca^{2+} is complicated. Although Kv10.1 is beneficial to Ca^{2+} influx under hyperpolarization, high intracellular Ca^{2+} reversibly inhibits the overexpression of Kv10.1 in a number of tumors (101,102). Overexpression of Kv10.1 can lead to membrane potential hyperpolarization and affect cell cycle progression. Potential changes in the

cell cycle are much slower, smoother and less pronounced than rapid action potentials. Due to membrane hyperpolarization, the driving force for calcium influx is enhanced. Ca^{2+} is a major second messenger involved in cell proliferation, migration, survival and apoptosis (103). Depletion of extracellular calcium ions can arrest cells in the early G_1 and G_1/S phase transition. Normal cell proliferation relies on intracellular and extracellular calcium ions, especially during the G_1 phase. However, cancer cells can bypass this requirement and continue to proliferate in calcium-deficient media (104,105). This mechanism exhibits high similarity across various types of cancer. Calcineurin is one of the main regulators of intracellular Ca^{2+} signaling. Calcineurin inhibits the degradation of cyclin D1 through dephosphorylation of T286 residue, promoting cell cycle progression (106). Ca^{2+} can also form a dynamic interaction network with the Hippo pathway, jointly regulating cell proliferation, differentiation and tissue homeostasis (107). Although there are currently no specific studies directly elucidating the role of Kv10.1 in the interaction with Ca^{2+} regulation of cyclin D1 and the Hippo pathway, based on the existing understanding of the complex regulatory relationship between Ca^{2+} and cyclin D1 and the Hippo pathway, it is reasonable to speculate that Kv10.1 may play a role in this regulatory network. Cell hyperpolarization is very sensitive to the activation of Kv10.1, which can regulate cell hyperpolarization through the interaction between N-terminal of PAS domain and S4-S5 connector (28).

When the cell membrane is hyperpolarized, the Kv10.1 channel can sense this potential change and open, allowing potassium ions to flow from the inside of the cell to the outside (17). Therefore, drug development for Kv10.1 channel has become a potential cancer treatment strategy, aiming at inhibiting the growth and spread of tumor by blocking its hyperpolarization mechanism.

Epigenetic regulation mechanism. Epigenetic regulation mechanism is a mechanism that changes biological phenotype without involving DNA sequence changes, but including DNA methylation, histone modification and non-coding RNA-mediated regulation. These modifications can affect the transcription activity of genes, thus regulating gene expression (108). For example, the DNA methylation status in the promoter region of Kv10.1 gene may affect its transcription activity, thus regulating the expression level of Kv10.1. In addition, histone modification may also regulate the transcription process of Kv10.1 gene by affecting the position and arrangement of nucleosomes. Studies have shown that several abnormally methylated genes, including Kv10.1, have been found in gastric cancer tissue and the methylation level of Kv10.1 in the samples is more than three times higher, suggesting that the hypermethylation of Kv10.1 may play a role in the occurrence and development of gastric cancer (17,35). Some have suggested that epigenetic changes in early life may alter lung cell function and lead to asthma risk (109). In mouse models, early exposure to house dust mite allergens alters DNA methylation and the expression of different genes detected, up to three consecutive generations and is associated with airway hyperresponsiveness and inflammation (109). In mice exposed to allergens, the Kcnh1 gene was hydroxymethylated and upregulated, indicating a susceptibility to asthma (109). In head and neck squamous cell carcinoma (HNSCC), histone acetylation, rather than DNA methylation, is hypothesized to be involved in the regulation of Kv10.1 (40).

Reversal of drug resistance. Simultaneous drug resistance to multiple drugs with different chemical structures and targets is the main obstacle to effective cancer treatment (110-114). Multidrug resistance (MDR) is an acquired resistance of microorganisms and tumor cells to chemotherapeutic drugs, which is characterized by different chemical structures and mechanisms of action. MDR is the result of overexpression of a number of protein and these protein drugs squeeze chemotherapy drugs out of cells to make their concentration lower than the effective concentration (115). MDR in cancer treatment causes tens of thousands of deaths every year and it can be endowed by a number of transporters that pump drugs out of cells. They can transport various substrates, including amino acids, peptides, ions, sugars, toxins, lipids and drugs and are associated with several serious human diseases (116). First-line therapy is usually followed by the proliferation of a small number of surviving cancer cells, which leads to the development of secondary tumors, which are insensitive to initial drugs. This may lead to tumor progression after stabilization or significant regression, because successful chemotherapy in the first stage becomes ineffective (117,118).

Platinum drugs (such as cisplatin and carboplatin) are one of the commonly used chemotherapy drugs in clinic and are widely used to treat various tumors. However, the resistance of tumor cells to platinum drugs limits their clinical application. As aforementioned, the ectopic expression of Kv10.1 is not only associated with the proliferation of tumor cells, but also associated with the phenotype of chemotherapy-resistant cells. *In vitro* experiments in ovarian cancer cells showed that the expression of Kv10.1 was associated with the chemotherapy resistance of cisplatin. Compared with the cells treated with cisplatin alone, the downregulation of Kv10.1 combined with cisplatin increased the apoptosis of ovarian cancer cells (16). Similar results were also observed in the chemotherapy-resistant glioblastoma cell line U251AR, which showed a high level of Kv10.1 (mRNA and protein). Notably, when the expression of Kv10.1 is downregulated, U251AR cells are more sensitive to chemotherapy drugs (119). Therefore, the inhibition of Kv10.1 channel can improve the response of cells to commonly used therapeutic drugs in chemotherapy.

Other mechanisms. The tumorigenic mechanism of Kv10.1 is associated with the fact that calcium-dependent calmodulin kinase-II is always activated, which can cause imbalance of cell proliferation and apoptosis even at low calcium ion concentration (120). Kv10.1 also promotes tumor progression by increasing the activity of hypoxia sensor hypoxia-inducible factor-1 alpha (HIF-1α), stimulating the secretion of vascular endothelial growth factor (VEGF) and increasing angiogenesis under hypoxia (78). The tumor microenvironment usually shows changes in extracellular matrix (ECM). ECM products, such as type 1 collagen and fibronectin, promote tumor progression by increasing cell movement (121).

Ion channels are highly fine-tuned protein necessary for cell physiology. Therefore, the synthesis and degradation of

ion channels should be a quality control process, which is necessary for correct cell function. However, the knowledge about the synthesis and degradation of Kv10.1 is limited. A study has shown that protein degradation of Kv10.1 depends on the protein ligase cullin 7 (Cul 7) (122). Cul7 degrades Kv10.1 protein on plasma membrane through proteasome and lysosomal pathways respectively (122).

5. Signaling pathway

In the field of tumor biology, abnormal regulation of cell signaling pathway is recognized as the core mechanism driving tumor occurrence, progress and metastasis. In recent years, because of its unique molecular structure, specific expression in tumor tissues and its regulation on cell proliferation, migration and invasion, Kv10.1 has become a typical example in the study of connecting ion channels with tumor signal pathways (Fig. 2).

p53-miR34-E2F1-hEAG1 signaling pathway. Studies have shown that the tumor suppressor gene regulatory network includes the p53-miR-34 pathway and E2F1 transcription factor, which can regulate the expression of Kv10.1 (96,123). The expression of Kv10.1 may be regulated by the negative feedback of this signal pathway (124,125). This negative regulation may be achieved through two mechanisms: direct inhibition of Kv10.1 at the post-transcriptional level and negative regulation of Kv10.1 through negative feedback mechanism through the p53-miR-34-E2F1 pathway. Studies have also shown that estrogen and human papillomavirus (HPV) regulate the level of Kv10.1 protein (126). As estrogen receptor interacts with p53 (125), HPV inhibits p53 and activates E2F1 (127), suggesting that EAG1 may affect downstream gene transcription by regulating E2F1. In addition, insulin-like growth factor 1 can also increase the expression of EAG1 by activating kinase AKT1 (128). Studies have shown that AKT1 can overcome the apoptosis-inducing effect of p53 (129), suggesting that p53 and Kv10.1 can act in opposite directions along the axis of apoptosis and proliferation (130).

HIF-1α/signal transducer and activator of transcription 3 (STAT3)/VEGF signaling pathway. The influence mechanism of silent Kv10.1 on HIF-1α/STAT3/VEGF pathway is a multi-level and multi-step process. As a potassium channel, the abnormal expression of Kv10.1 may regulate the activity of intracellular signal transduction pathway by affecting the balance of potassium concentration inside and outside the cell. Kv10.1 can upregulate the expression of HIF-1α by interacting with intracellular hypoxia homeostasis system. HIF-1α is a key transcription factor to regulate the expression of VEGF, which promotes the transcription of VEGF under hypoxia, thus inducing angiogenesis (131). In osteosarcoma cells, the phosphorylation level of STAT3 decreased markedly after Kv10.1 silencing, which indicated that Kv10.1 might regulate the expression of STAT3-VEGF downstream by influencing its activation state (84,132).

PI3K/AKT signaling pathway. The PI3K/AKT signaling pathway is an important signal transduction pathway with multiple biological functions mediated by enzyme-linked receptors in mammals. The PI3K/AKT pathway plays an important role in the occurrence and development of tumors. When stimulated by upstream signals, PI3K activates AKT, which further activates downstream signal molecules and regulates cancer cell proliferation, invasion and metastasis, angiogenesis and carbohydrate metabolism. In osteosarcoma, tumor growth and angiogenesis in osteosarcoma can be inhibited by downregulating VEGF/PI3K/AKT signaling pathway to silence Kv10.1 (133). The Kv10.1 channel and PI3K/AKT signaling pathway form a cancer-promoting signal axis through functional correlation and Kv10.1 is the key target of Nutlin-3 regulating PI3K/AKT through p53 (81). Therefore, it is of great significance to study PI3K/AKT signaling pathway and develop targeted drugs for tumor treatment.

The mitogen-activated protein kinase (MAPK) signaling pathway. The nuclear localization signal at the C-terminal of Kv10.1 potassium channel can activate the MAPK pathway to cause changes in cell morphology (134). The Kv10.1 channel plays the role of oncogene, such as promoting the proliferation of human osteosarcoma cells. The high expression of Kv10.1 in osteosarcoma cells is regulated by p38MAPK/p53 pathway (135). Inhibition of p38MAPK activation by p38 MAPK inhibitor SB203580 or short interfering RNA also decreased the level of Kv10.1 protein, but increased the level of p53 protein. In addition, the activation of p53 will lead to the growth stagnation of osteosarcoma cells and decrease the level of Kv10.1 protein, while the inactivation of p53 will promote the cell growth and increase the expression of Kv10.1 protein. This suggests that Kv10.1 may affect the proliferation of osteosarcoma cells by regulating p53 (136).

Cancer type specificities in the anti-tumor mechanisms of Kv10.1. Although Kv10.1 exhibits mechanistic similarities across various malignancies, namely, influencing tumor proliferation through hyperpolarization, exerting effects via the PI3K/AKT signaling pathway and inhibiting apoptosis (81), its downstream signaling network still demonstrates significant cancer type specificity. For instance, the expression of Kv10.1 in endometrial cancer tissues is markedly higher than that in normal endometrial tissues. Kv10.1 can be regulated by cyclin D1, p53 and other factors, thereby affecting the proliferation, migration and invasion of tumor cells (137). Kv10.1 may form different complexes or interaction networks with other molecules in various cancers, thereby influencing its function. For example, in osteosarcoma and hepatocellular carcinoma, Kv10.1 enhances tumor angiogenesis by upregulating the expression of hypoxia-inducible factor HIF-1α and promoting the secretion of VEGF. This effect is not dependent on its ion transport function but is achieved through interaction with the cellular hypoxia homeostasis system (133,138). Different mechanisms predominate in various cancers; for instance, in breast cancer, the PI3K/AKT pathway is central, driving cell proliferation and metabolic reprogramming; in hepatocellular carcinoma, the HIF-1α/VEGF pathway is predominant, promoting angiogenesis and tumor progression; in endometrial cancer and head and neck cancer, it may affect tumor behavior through cell cycle regulation and cytoskeleton dynamics (137-139). Drug targets are critical in drug discovery and therapy, as their identification is essential for achieving

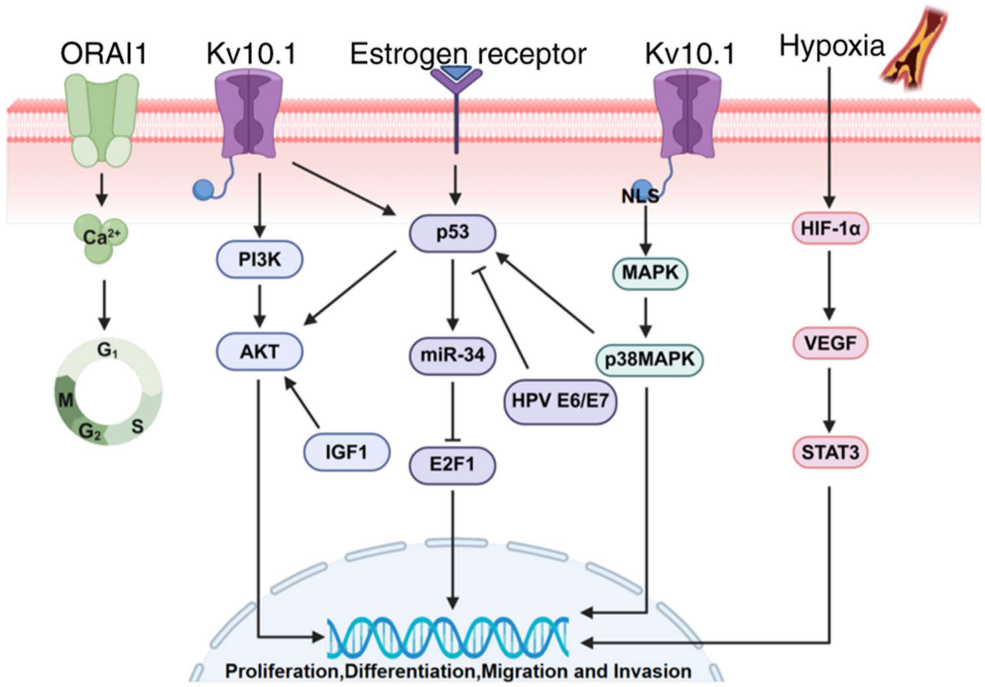

Figure 2. Kv10.1 activates multiple signaling pathways. Kv10.1 has become a typical example of the connection between ion channels and tumor signaling pathways due to its unique molecular structure, specific expression in tumor tissues and regulation of cell proliferation, migration and invasion. Kv10.1 is negatively regulated by the negative feedback mechanism of p53-miR-34-E2F1 pathway. P53 is regulated by a number of factors, such as estrogen receptor, HPV and E6/E7. Kv10.1 can upregulate the expression of HIF-1α by interacting with the intracellular hypoxia homeostasis system and promote the transcription of VEGF under hypoxia. In osteosarcoma cells, Kv10.1 regulates the expression of STAT3-VEGF by affecting the activation of stat3-vegf downstream. Kv10.1 channel and PI3K/AKT signaling pathway form cancer promoting signal axis through functional correlation and regulate cancer cell proliferation, invasion and metastasis, angiogenesis and glucose metabolism. The NLS in the C-terminal domain of Kv10.1 activates the MAPK signaling pathway. For example, the high expression of Kv10.1 in osteosarcoma cells is regulated by p38MAPK/p53 pathway. The increase of ORAI1 in plasma membrane can regulate intracellular calcium ion and mediate cell cycle. miR, microRNA; E2F1, E2F transcription factor 1; HPV, human papillomavirus; HIF-1α, hypoxia-inducible factor-1 alpha; VEGF. vascular endothelial growth factor; STAT3, signal transducer and activator of transcription 3; NLS, nuclear localization signal; MAPK, mitogen-activated protein kinase; ORAI1, ORAI calcium release-activated calcium modulator 1.

precision treatment (140). Therefore, Kv10.1 is considered a potential therapeutic target in various cancers.

6. Regulators and inhibitors

According to the activation mechanism of Kv10.1, its regulators are mainly divided into two categories: activators and inhibitors. Validation of Kv10.1 as a therapeutic target requires specific modulators and can be used as a basic tool for understanding channel pharmacology. Therefore, it is necessary to find more selective and effective modulators, especially inhibitors. According to the structure of Kv10.1, this section introduces its regulators and inhibitors and their applications in cancer (Table II).

PAS domain. The Kv10.1 channel is formed by assembling tetramer subunits and each subunit contains N-terminal PAS domain and C-terminal cyclic nucleotide binding homology domain. Small molecular ligands can inhibit Kv10.1 channels by binding to their PAS domains. Deleting PAS domain can cancel the inhibitory effect of chlorpromazine (141). At low voltage, chlorpromazine can inhibit mouse Eag1 by binding with PAS domain, but when the channel is open at high voltage, it will be inhibited by blocking the channel (142). Chlorpromazine, a small molecule binding agent of PAS domain, changes the interaction between PAS and CNBH domain and reduces the coupling between tetramer ring and channel hole in cells, while the coupling between PAS and voltage sensor domain (VSD) domain has little effect. In addition, the combination of chlorpromazine and PAS domain does not change the Cole-Moore shift characteristics of Kv10.1 channel, which further indicates that chlorpromazine has no effect on the movement of VSD from deep closed state to open state (143). Chlorpromazine inhibits the proliferation of oral cancer cells by regulating the PI3K/AKT/mTOR signaling pathway and effectively suppresses tumor growth in zebrafish and mouse models. Given that chlorpromazine can act on Kv10.1, it is hypothesized that it regulates tumor proliferation by modulating the PI3K/AKT signaling pathway through Kv10.1. Based on the mechanism of action of chlorpromazine on oral cancer cells and its potential association with Kv10.1, it is reasonable to hypothesize that chlorpromazine may regulate the PI3K/AKT signaling pathway through Kv10.1, thereby affecting tumor proliferation (144).

VSD. VSD has a small molecule binding site as a gating regulator and extracellular VSD allows molecules to regulate channels without transmembrane, as with toxins. Most of the known small molecules that regulate Kv10.1 activity first cross the cell membrane and bind to the inner side of the channel. Most of these compounds are physically closed pore blocker ion permeation pathways, such as mibefradil (65,145), Purpurealidin analog 5 (146), 20 (s)-Ginsenoside Rg3 (147,148), APETx4 (149) and Corydaline (150).

Table II. Kv10.1 inhibitors.

Compound name	Binding domain	Cell line	IC_{50}	(Refs.)
Chlorpromazine	PAS	*Xenopus* oocytes	3.7±0.7 μM	(143)
Mibefradil	VSD	293	Kd 1.3 μM, nH0.8	(65,145)
Purpurealidin analog 5	VSD	*Xenopus* oocytes	7.7±1.0 μM	(50)
20(S)-ginsenoside Rg3	VSD	*Xenopus* oocytes	1.18 μM	(1547,148)
APETx4	VSD	*Xenopus* oocytes	1.1μM	(149)
Corydaline	VSD	HepG2	11.3±0.6 μM	(150)
Tetrandrine	Selectivity filter	CHO	70±5.2 μM	(155)
ProcyanidinB1	Selectivity filter	293	10.38±0.87 μM	(13)
Tetraethylammonium	Pore domain	*Xenopus* oocytes	1.2±0.1 μM	(156)
Amiodarone	Pore domain	293	Kd 203 nM, nH0.9	(157)
Astemizole	Pore domain	293	196 nM	(157)
		Xenopus oocytes	2.8±0.1 μM	
Imipramine	Pore domain	*Xenopus* oocytes	40.2±0.3 μM	(157)
Dronedarone	Pore domain	293	Kd 9 μM, nH0.9	(76)
Quinidine	Pore domain	CHO	1.4±0.1 μM	(60)
Haloperidol	Pore domain	CHO	590±121 nM	(67)
κ-Hefutoxin 1	Pore domain	-	26±2 μM	(158)
Heme	C-linker	*Xenopus* oocytes	4nM	(161)

PAS, Per-Arnt-Sim; VSD, voltage sensor domain.

Mibefradil has been reported to alter the gating of Kv10.1 by binding to the VSD (65,145). When the hyperpolarizing potential acts outside the cell, mibefradil induces obvious open inactivation, but not from inside the cell. In addition, mibefradil also inhibited the Cole-Moore shift. It is also not used as a pore size blocker because it does not compete with the known pore size blocker, quinidine. Mibefradil 1 also inhibits other potassium channels and L-type and T-type calcium channels (65).

Purpurealidin is considered to be a gating modifier, which binds to the mibefradil binding site near the voltage sensor Kv10.1. Mibefradil is a Ca^{2+} channel antagonist and a Kv10.1 door control regulator. As with purpurealin, mibefradil moves the activation curve to the left. Studies have shown that the binding site of purpurealidin on Kv10.1 overlaps with that of mibefradil (65,145,146).

Ginsenoside is a steroidal glycoside that inhibits the KCNH family at sub μM concentrations. Its function is not limited to Kv channels. Studies have shown that ginsenosides can markedly inhibit the voltage dependent activation curves of Kv10.1 and HERG channels and increase their opening probability at more negative potentials (147,148). When combined with cisplatin, it can enhance chemotherapy sensitivity and reverse drug resistance by blocking the PI3K/AKT pathway (151).

Apetx4 is a new toxin isolated from sea anemones, which can inhibit the Kv10.1 channel. APETx4 inhibits its current by binding to Kv10.1 channel and the inhibitory effect is concentration dependent. APETx4 is a gating modifier that presumably binds to the S3b-E2-S4 region (voltage sensor paddle) of Kv10.1 (149). Corydaline is a novel natural product that selectively inhibits Kv10.1 channels, while being insensitive to other KCNH channels. Corydaline can inhibit the proliferation and migration of liver cancer cells by targeting Kv10.1. This previously unidentified new site can specifically bind to the medicinal pocket of Corydaline, providing possibilities for drug screening against diseases associated with abnormal Kv10.1 channels (150).

Selectivity filter. The selectivity filter of Kv10.1 consists of a highly conserved amino acid sequence, forming a structure similar to the 'potassium channel signature sequence' (152). Through the spatial arrangement of carbonyl oxygen atoms and threonine hydroxyl oxygen atoms, this region mimics the hydration layer mechanism of water molecules surrounding K^+, forming a series of K^+ binding sites (153,154).

Tetrandrine, a natural compound used in traditional Chinese medicine, can inhibit Kv10.1 in a concentration dependent manner with an IC_{50} of 69.97±5.2 μM (155). Tetrandrine specifically inhibited Kv10.1 channel, blocked potassium outflow, induced cell cycle arrest in G_1/S phase and enhanced cisplatin sensitivity by downregulating PI3K/AKT signaling pathway (44). Tetrandrine may also have the same binding site as procyanidin B1, a natural compound present in grape seeds, which inhibits Kv10.1 in a concentration dependent manner with an IC_{50} value of 10.4±0.9 μM (13). Procyanidin B1 directly inhibits channel activity and blocks tumor cell proliferation by hydrogen bonding to i550, t552 and q557 amino acids in the filter. Similar to tetrandrine, 100 μM procyanidin B1 did not markedly inhibit Kv7.1, Kir2.1, or HERG (13).

Pore domain. The pore region of Kv10.1 is composed of S5 and S6 transmembrane helices and intermediate pore rings, which is the core domain of ion selective permeation. In recent years, in the development of targeted drugs for the Kv10.1 channel, the pore domain has become the core target in the design of small molecular inhibitors because of its unique structural characteristics and functional importance. Tetraethylammonium is a commonly used potassium channel blocker, which can physically block ion passage (156). Tetraethylammonium can combine with aromatic amino acid residues on the inner wall of the channel, which hinders the selective filtration function of potassium ions, thus inhibiting the channel current. The mechanism of quinidine and tetraethylammonium is similar and does not depend on the voltage gating state of the channel, so it belongs to non-competitive inhibition (60). The blocking effect of quinidine on Kv10.1 channel is concentration-dependent and the inhibitory effect is more obvious at high concentration. Astemizole competitively binds to Kv10.1 channel with tricyclic antidepressants imipramine and tetraethylammonium (157). The blocking effect of imipramine is voltage-dependent and can be antagonized by intracellular tetraethylammonium. Amiodarone and dronedarone both act through the pore region, but their blocking effects on Kv10.1 are different and dronedarone cannot inhibit the Cole-Molar displacement characteristics of Kv10.1 channel (76). Haloperidol also inhibited the Kv10.1 channel through the pore region and the inhibition was associated with the drug concentration and membrane potential (67). κ-Hefutuxin 1, as the first peptide inhibitor of Kv10.1 channel, inhibits its activity by binding to Kv10.1 channel (158). As the first peptide inhibitor of Kv10.1 channel, κ-hefutuxin 1 inhibits its activity by binding to Kv10.1 channel and may act on or near the pore area of Kv10.1 channel. Channel residues met397 and asp398 may be the anchors to stabilize its binding (158).

Studies have investigated the effects of Haloperidol on the PI3K/AKT signaling pathway in PC12 cells (a neuroblastoma cell line) (159). The research found that Haloperidol can induce the nuclear translocation of PI3K, generating phosphatidylinositol-3,4,5-trisphosphate (PIP3) in the nucleus, effectively inhibiting the phosphorylation of AKT, leading to a decrease in AKT activity. Furthermore, Haloperidol can effectively suppress the expression of Kv10.1 (159,160). Although no studies have yet explored the direct relationship between these factors, it is possible that Haloperidol exerts its anticancer effects by indirectly influencing the PI3K/AKT signaling pathway through the inhibition of Kv10.1 expression (159).

Other binding sites. At present, the mechanism of action of Kv10.1 inhibitors is complex and diverse and the binding sites of some inhibitors are not yet clear. Heme is an endogenous regulator of the Kv10.1 channel, which inhibits its activity by binding to the CxHxH motif in the C-Linker region (161). The aforementioned results are listed in Table II.

Inhibitors with clear binding sites are beneficial for the development of new drugs for treating diseases, while inhibitors with unknown binding sites reveal the complexity and diversity of channel regulation. Future research should further strengthen the exploration of the mechanism of action of inhibitors with unknown binding sites and reveal the molecular mysteries of their interaction with Kv10.1 channels. Meanwhile, based on the mechanism of action of inhibitors, more efficient and specific Kv10.1 inhibitors have been developed, providing new strategies and means for the treatment of related diseases.

7. Clinical status

From a clinical perspective, Kv10.1 is highly expressed in various malignant tumor tissues, markedly higher than in normal tissues, thus possessing the potential to become a diagnostic marker for tumors. Currently, little is known about the mechanism of Kv10.1 in tumorigenesis and most data on Kv10.1 inhibitors are derived from *in vitro* cell lines or simple animal models. This lack of accurate targeting in drug development makes it difficult to design highly effective and specific targeted drugs. The metabolic process of drugs in the body, potential toxic effects and how to effectively deliver drugs to tumor tissues have become major obstacles in the clinical translation of Kv10.1 targeted drugs.

The clinical value of Kv10.1 as a diagnostic marker. Kv10.1 is expressed in a variety of malignant tumors, including clear cell renal cell carcinoma, breast cancer, cervical cancer, gastric cancer, colon cancer and cervical intraepithelial neoplasia (14,42,43,162-165). According to clinical data analysis reported in relevant literature, a total of 68 clinical samples were tested in the study of esophageal squamous cell carcinoma. The results showed that 51 cases showed positive expression, with a positive rate of 75%. Further analysis showed that the positive expression was closely associated with the depth of tumor infiltration and the survival time of positive patients was generally shorter (166). In clinical data of ovarian cancer, there were 336 samples, of which 249 showed positive results, with a positivity rate of 65%. The expression of Kv10.1 is associated with tumor size, differentiation degree, staging and metastasis (167). In the clinical data of head and neck squamous cell carcinoma, there were a total of 54 clinical samples, of which 45 samples showed positive results, with a positive rate as high as 83.00%. It is worth noting that Kv10.1 plays a key role in this head and neck squamous cell carcinoma and has been proven to be a tumor marker and potential therapeutic target. The expression of Kv10.1 is associated with important clinical pathological features such as tumor size, differentiation degree, staging and metastasis (40).

A research group has conducted in-depth predictive analysis of the clinical correlation between cancer-related genes and renal cell carcinoma cell lines using the Cancer Genome Atlas database. The research results indicate that Kv10.1 is a key biomarker and potential therapeutic target in clear cell renal cell carcinoma (ccRCC) (162). The widespread abnormal expression of Kv10.1 in numerous tumors suggests that it may be intrinsically associated with the occurrence and development of tumors and has potential value as a tumor marker for tumor screening and diagnosis. However, most of the data on Kv10.1 inhibitors to date have been derived from *in vitro* cell lines or simple animal models and there is no systematic patient-derived xenografts (PDX) model data to clearly demonstrate the quantitative indicators of tumor inhibition rate and survival extension effect of representative inhibitors. Due to the lack of such data, it is difficult to directly support

the conclusion that Kv10.1 inhibitors have significant clinical translational value in PDX models. Kv10.1 is highly expressed in brain tissue and involved in regulating neuronal excitability, neurotransmitter release and synaptic plasticity. When treating brain tumors, Kv10.1 inhibitors need to penetrate the blood-brain barrier (BBB) to target tumor cells. At this time, increased permeability of the BBB (such as through hyperosmotic solutions or nanocarrier technology) may facilitate drug entry into the brain, but it also increases the risk of exposure to normal brain tissue. When treating non-brain tumors, the BBB can prevent Kv10.1 inhibitors from entering the brain tissue, thereby avoiding neurotoxicity. Studies have shown that knocking out Kv10.1 did not result in significant abnormalities in multiple behavioral tests in mice and its function may have a redundant compensation mechanism with other channels. Therefore, Kv10.1 inhibitors have less interference with normal tissue, especially brain tissue function (67). Therefore, at present, it can only be concluded that Kv10.1 is a potential therapeutic target.

Bottleneck of clinical transformation of targeted drugs. The BBB is a selective barrier between the central nervous system and the circulatory system. Its unique structural characteristics, such as tight junction, stability of cytoskeleton and active efflux of transmembrane proteins, together constitute the physical and chemical barrier for drugs to enter the brain tissue. Kv10.1 is highly expressed in brain tumors (such as glioma), but the existence of the blood-brain barrier makes it difficult for most drugs to penetrate effectively, resulting in low treatment efficiency of brain tumors. Even if drugs can break through the blood-brain barrier for a short time, its action time is often not enough to play a lasting effect (168,169).

The molecular weight of peptide inhibitors is relatively small and the structure is relatively simple. It is generally considered to have low immunogenicity potential and it is easy to be degraded and excreted in the body, reducing the contact time with the immune system, thus reducing the immunogenicity. In addition, in the production process of peptide inhibitors, some impurities may be introduced, such as pollutants, solvents, enzymes, impurities formed by amino acid side chain modification, truncation, duplication, oxidation, insertion or deletion in the active pharmaceutical ingredient sequence. These impurities may have potential immunogenicity and can trigger the immune response of the body, thus affecting the safety and effectiveness of drugs.

Kv10.1 combination therapy reverses drug resistance. Kv10.1 inhibitors combined with chemotherapeutic drugs can act on tumor cells simultaneously through different mechanisms to produce synergistic killing effect. This combined strategy is expected to improve the therapeutic effect and prolong the survival time of patients. For example, Kv10.1 can participate in metabolic adaptation to cancer cells by regulating mitochondrial dynamics and inhibit Kv10.1 expression or function, resulting in mitochondrial fragmentation, increased reactive oxygen species and increased autophagy. Kv10.1 endogenous overexpression cells were also more sensitive to mitochondrial metabolic inhibitors than low expression cells, indicating that they were more dependent on mitochondrial function. Therefore, the combined treatment of Kv10.1 functional monoclonal antibody and mitochondrial metabolism inhibitor leads to the enhanced efficacy of the inhibitor (31). Kv10.1 specific scFv was fused with soluble TNF-related apoptosis inducing ligand. The combination of ligands and different chemotherapeutic drugs can overcome drug resistance and selectively induce apoptosis (170).

8. Summary

The Kv10.1 channel is overexpressed in 70% of tumor cells and has carcinogenic characteristics, regulates cell proliferation, survival, angiogenesis, migration and invasion and is associated with the formation and progress of invasive tumors. However, although Kv10.1, as a potential target for cancer treatment, has been confirmed *in vivo* and *in vitro* experiments and some carcinogenesis mechanisms have been proved, the specific mechanism of Kv10.1 participating in the occurrence and development of tumors is not completely clear.

However, several specific Kv10.1 inhibitors have been used in animal models and achieved good results, which can inhibit the proliferation of tumor cells, induce tumor cell apoptosis, preserve normal cells and make cancer cells more sensitive to chemotherapy drugs. If these specific Kv10.1 inhibitors are combined with the current routine clinical treatment, it will be a potential therapeutic strategy to make them really useful tumor targets.

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Authors' contributions

Investigation was by YX, SD, BW, JS, LD, LL, XW and YC. Writing the original draft was by YX and WH. Data curation was by YX, SD, BW, JS, LD, XW and YC. Conceptualization was by YX. Writing, reviewing and editing was by WH, LL, HA, XW and YC. Methodology was by SD. Resources were provided by BW, HA, XW and YC. Supervision was by HA, XW and YC. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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