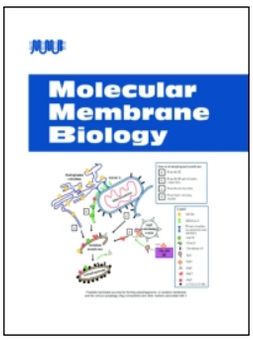

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Potassium channels and their role in glioma: a mini review

Jia Liu [1),2)], Chao Qu[2)] , Chao Han [3)], Meng-Meng Chen [4)], Li-Jia An [1)], Wei Zou [2),4)*]

[1)] *School of Life Science and Biotechnology, Faculty of Chemical, Environmental and Biological Science and Technology，Dalian University of Technology, Dalian 116024, China;*

[2)] *College of Life Science, Liaoning Normal University, Dalian 116081, China;*

[3)] *Regenerative Medicine Center, First Affiliated Hospital of Dalian Medical University, Dalian, 116011*

[4)] *Qingdao Re-Store Life Sciences, Qingdao 266000, China*

Jia Liu: liujia5708@163.com

Chao Qu: quchao__2006@163.com

Chao Han: hanchao0427@163.com

Meng-Meng Chen: qdjinchi@126.com

Li-Jia An: bioeng@dlut.edu.cn

Wei Zou: weizou60@126.com

*Corresponding author:

Dr. WeiZou, the Professor of Liaoning Normal University, China.

E-mail: weizou60@126.com; weizou60@hotmail.com

No. 1 The South Street of Liushu, Ganjingzi District,
Dalian, Liaoning Province,
China

Abstract:

K^+ channels regulate a multitude of biological processes and play important roles in a variety of diseases by controlling potassium flow across cell membranes. They are widely expressed in the central and peripheral nervous system. As a malignant tumor derived from nerve epithelium, glioma has the characteristics of high incidence, high recurrence rate, high mortality rate, and low cure rate. Since glioma cells show invasive growth, current surgical methods cannot completely remove tumors. Adjuvant chemotherapy is still needed after surgery. Because the blood-brain barrier and other factors lead to a lower effective concentration of chemotherapeutic drugs in the tumor, the recurrence rate of residual lesions is extremely high. Therefore, new therapeutic methods are needed. Numerous studies have shown that different K^+ channel subtypes are differentially expressed in glioma cells and are involved in the regulation of the cell cycle of glioma cells to arrest them at different stages of the cell cycle. Increasing evidence suggests that K^+ channels express in glioma cells and regulate glioma cell behaviors such as cell cycle, proliferation and apoptosis. This review article aims to summarize the current knowledge on the function of K^+ channels in glioma, suggests K^+ channels participating in the development of glioma.

Key words:

K^+ channel; Glioma; Cell cycle; Cell proliferation; Cell apoptosis

Ion channels have been shown to play a pivotal role in the origin of various cancers in the literature. They become a very useful and accessible target for modulation. K^+ channels are transmembrane proteins that are defined by their ability to selectively facilitate the permeation of K^+ between intracellular and extracellular environments (Pardo and Stuhmer, 2014). Under resting conditions, nearly all of the ions that move across the membrane (intracellular to extracellular) are K^+ ions, and these results in a negative membrane potential (Pardo and Stuhmer, 2014). According to conductance properties, structural criteria, and whether combine with stimulus, K^+ channels are divided into four classes: Kv channels (Voltage-gated K^+ Channels), KCa^{2+} channels (Calcium-activated K^+ Channels), Kir channels (Inward-rectifier K^+ Channel) and K_{2P} channels (Two-pore-domain K^+ Channel).

K^+ channels are one of the most widely distributed ion channels and play an important role in the development of many diseases (Zhorov, 2011). Recent studies found many K^+ channels subtypes abnormally expressed and regulated cell biological behaviors, such as the leiomyosarcoma aggressiveness (Bielanska et al., 2012; Jang et al., 2011), epilepsy evolution (Niday and Tzingounis, 2018), endometrial carcinoma migration and invasion (Zhang et al., 2019).Therefore some scholars have classified the malignant tumor into the "K^+ Channel Disease" category (Huang and Jan, 2014; Lastraioli et al., 2015; Tian et al., 2014), and regarded K^+ channels as the promising therapeutic target. Accumulating evidence has demonstrated that a variety of K^+ channels, including Kv channel (Cazares-Ordonez and Pardo, 2017; Ryland et al., 2015), KCa^{2+} channel (Abdullaev et al., 2010), K_{2P} channel (Zuniga and Zuniga, 2016) and Kir channel (Huang et al., 2009) are overexpressed in tumorous tissues compared with their healthy counterparts.

As a common CNS (Central Nervous System) tumor, glioma is a primary intracranial malignant tumor with a 5-year survival rate of less than 1%. At present, there is no effective treatment except for surgical resection. It has been found that that glioma may be related to the abnormal expression of various potassium ion channels in recent years. These K^+ channels were mainly (1) Kv channels such as EAG1 (*Ether à go-go* Channel)(Bai et al., 2013), hERG (human *Ether à go-go* Related Gene Channel)(Wang et al., 2015); (2) KCa^{2+} channels such as BK (Large Conductance Calcium-activated K^+ Channel)(Hoa et al., 2016; Rosa et al., 2017; Weaver et al., 2006a), IK (Intermediate-conductance Ca^{2+}-activated K^+ Channel)(Stegen et al., 2015; Weaver et al., 2006b), KCa3.1 (D'Alessandro et al., 2016) and SK (Small-conductance Ca^{2+}-activated K^+ Channel)(Weaver et al., 2006b); (3) K_{ATP} channels (ATP-sensitive K^+ Channel) such as Kir6.2 (Huang et al., 2009). They were highly correlated with the malignancy of gliomas. K^+ channels blockers such as 4-AP (4-aminopyridine, Kv blocker), tolbutamide (K_{ATP} channel blocker) could significantly influences the growth of glioma (Felipe et al., 2012; Huang et al., 2009). Therefore, K^+ channels play an important role in the development of gliomas.

1 Expressions of K^+ channels and Gliomas

K^+ channels selectively expressed in multiple types of tumor cells, and deeply influenced on biological behavior of tumors, such as proliferation, apoptosis, differentiations and invasions. However K^+ channels didn't expressed or down-expressed in normal tissues, such as mammary glands (Felipe et al., 2012), prostate glands

(Qi et al., 2014; Sharifi et al., 2016). This selective expression in tumor tissue indicates K^+ channel may be the potential therapeutic target, and has important clinical application value. Gliomas are the most common malignant brain tumors, and numerous studies have shown that there are many kinds of K^+ channel expressed in glioma cells, such as Kir channels (So et al., 2014), Kv channels (Arvind et al., 2012), BK channel (Debska-Vielhaber et al., 2009a), KCa^{2+} channels (Turner et al., 2014), K_{ATP} channels (Ru et al., 2014) and hERG channels (Staudacher et al., 2014) (Table 1).

A series of investigations utilizing genetic and pharmacological manipulations confirmed other K^+ channels also expressed in glioma. Preussat first found the levels of expression of Kv1.3 and Kv1.5 subtypes discriminated between various glioma groups, and a clear differential expression of Kv1.5 was observed according to malignancy grade (Preussat et al., 2003). Later, Debska-Vielhaber found that LN229 cell (human glioma cell line) expressed BK channel (Debska-Vielhaber et al., 2009a). What's more, Basrai reported that BK channel was found in the human glioma cell line STrG-1 (anaplastic astrocytoma, WHO grade III) and D54-MG (glioblastic glioblastoma, WHO grade IV) (Basrai et al., 2002). EAG channel has been shown to express in numerous tumor tissues, and may closely associate with tumor generation, malignant growth, invasion and metastasis (Jehle et al., 2011; Patt et al., 2004; Sales et al., 2016; Staudacher et al., 2014). hEAG channels belong to the family of Kv channels with delayed rectifier characteristics (Staudacher et al., 2014). Patt found a differential expression of hEAG1 and hERG1 in gliomas depending on the malignancy grade and nature of the tumor cells (Patt et al., 2004). Catacuzzeno demonstrated that K^+ ion flux was essential for the FCS-induced glioblastoma cell (U87-MG) migration (Catacuzzeno et al., 2011). Kir 4.1 channels have been inserted into the glial cell membrane during the first two years of life in human (Olsen et al., 2015) and second week in rodents (Kofuji et al., 2002; Schopf et al., 2004). After that time glioal cells Kir4.1 channels serve for the cessation of proliferative activity when glial cells are differentiated from the dividing progenitors (Bringmann et al., 2006). Zhu found that Kv1.3 and Kv1.6 channel could be observed in rat astrocytes (Zhu et al., 2014). And recently, Venturini report that Kv1.3 is expressed in mitochondria of human and murine GL261, A172 and LN308 glioma cells. Treatment with the novel Kv1.3 inhibitors induced massive cell death in glioma cells (Venturini et al., 2017).

Glial cells are key elements of the brain and play a vital role in maintaining a stable brain environment. They cooperate with neurons in the proper function of the neuron system, and beyond the early conception of their role as a structural "glue" for the tissue. These cells outnumber neurons >12 times in the brainstem and about 3.5 times in the cortex in human brains (Lent et al., 2012). There are many types of CNS cells arising from glial cells such as astrocytes, oligodendrocytes, Müller glia, ependymal cells, pituicytes, etc. Therefore, K^+ channels in glial cells have important implications for gliomas. Kir4.1 channels play a key role in providing the crucial prerequisite for most of the brain-supportive functions of mature glial cells (Bringmann et al., 2006; Djukic et al., 2007). As the major glial cell K^+ channels (Bringmann et al., 2006; Olsen et al., 2015), Kir4.1 channels are apparently necessary for glial cell normal function to support highly hyperpolarized membrane potential in healthy brain (Djukic et al., 2007; Kucheryavykh et al., 2007; Olsen et al., 2015). A loss of

functional Kir channels has been shown in a number of neurological diseases including temporal lobe epilepsy (Heuser et al., 2012), ALS (Bataveljic et al., 2012) and malignant gliomas (So et al., 2014). Olsen found during proliferative diseases in brains, Kir4.1 channels are nearly completely lost while BK channels became expressed greatly (Olsen and Sontheimer, 2008). Thuringer demonstrated that Kir4.1 as a miR-5096 targeted to promote invasion of glioblastoma cells (U87-MG and U251) (Thuringer et al., 2017). Kir4.1, therefore, represents a potential therapeutic target in a wide variety of neurological conditions (Thuringer et al., 2017).These studies have supported that K^+ channel may involve in the process of gliomas.

2 K^+ channels **and Cell Cycle of Gliomas**

The cell cycle is divided into defined phases, namely G_1 (first gap), S (synthesis), G_2 (second gap) and M (mitosis), while a post-mitotic cell in G_0 is considered to be in a non-dividing status (quiescent). While cancer cells generally maintain moderately depolarized membrane potential compared with nontransformed cells, transient hyperpolarization has been reported to be necessary for successful G_1/S cell cycle progression (Huang and Jan, 2014; Jehle et al., 2011).

Kir channels have also been shown to act as critical regulators of cell division whereby Kir function is correlated with an exit from the cell cycle. Conversely, loss of functional Kir channels is associated with re-entry of cells into the cell cycle and gliosis (Olsen and Sontheimer, 2008). In spinal cord astrocytes down-regulation of Kir accompanied with a depolarization was observed to promote cell cycle progression through the G_1/S checkpoint (MacFarlane and Sontheimer, 2000). This indicates depolarization to be necessary for entering the S phase. Using medicines blocking the Kv channels and K_{ATP} channels in U87-MG could inhibit the growth of tumor via an arrest in the G_0/G_1 transition during the cell cycle (Ru et al., 2014). Similarly, Huang reported that treating U251(glioma cell line) cells with the blocker of K_{ATP} channels blocked cell cycle in G_0/G_1 phase (Huang et al., 2009), while a block of delayed rectifier K^+ channel caused proliferating astrocytes to arrest in G_0/G_1. What's more, Klumpp recently reported that blocking the intermediate-conductance Ca^{2+}-activated K^+ channel KCa3.1 could force G_2/M cell cycle progression in GL261 glioma cells treated with the DNA-alkylating drug temozolomide, and then facilitates apoptotic cell death (Klumpp et al., 2018).

In summary, there are evidence suggesting that several different types of K^+ channel-ligand-as well as voltage-gated or combinations of these channels are necessary for cells to progress through the cell cycle. The reason for this effect was attributed to K^+ diffusion through K^+ channels out of the cells as shown in theoretical models resulting in hyperpolarization of the membrane potential (Shah and Aizenman, 2014; Tian et al., 2014).

3 K^+ channel **and Proliferation/Apoptosis of Glioma**

Given the important role of K^+ channels in tumors, it is necessary to clarify their role in proliferation. Accumulating evidence has indicated that K^+ channels are relevant players in controlling cell proliferation and apoptosis of various tumor cells, and pharmacological blockades of Kv channels lead to cell proliferation

inhibition (Hu et al., 2014).

Electrophysiological and pharmacological results demonstrated that quinidine inhibited cell (U87-MG cell (Hu et al., 2014) and C6 glioma cell (Weiger et al., 2007)) proliferation and apoptosis in the concentration range required to block Kv channel currents. This indicates that quinidine potentially inhibited cell proliferation and induced apoptosis by blocking Kv channel activities. Since K_{ATP} was found also involved in regulating numerous cellular functions. Ru (Ru et al., 2014) found that Kv and K_{ATP} channel blockers inhibited proliferation and tumorigenesis of U87-MG glioma cells. It was likely that K^+ channels activities modulated Ca^{2+} influx into U87-MG cells and therefore affected the proliferation and apoptosis. Huang studied the effect of K_{ATP} channels activity on glioma cells proliferation, which is mediated by ERK (extracellular signal-regulated kinase) activation (Huang et al., 2009). They found that activation K_{ATP} channel triggered ERK activation and inhibiting K_{ATP} channel depressed ERK activation. Abdullaev demonstrated that downregulation BK channels in U251 cells using gene-specific siRNA didn't affect the rate of proliferation, while paxilline (inhibitor of BK channel) reduced both U251 and U87-MG cells proliferation in an additive fashion (Abdullaev et al., 2010). Hao down-regulated TASK-1 (TWIK-related acid-sensitive K^+ channel-1, where TWIK stands for tandem pore domains in a weak inwardly rectifying K^+ channel) by the transfection of siRNA improved the proliferation rates of N2A cells, suggested that this channel was involved in the regulation of neuronal growth (Hao and Li, 2015). What's more, Staudacher found that suppression of hERG protein is a crucial molecular event in glioblastoma cell (LNT229 and U87-MG) apoptosis (Staudacher et al., 2014).

Recent study has shown that Kv channels are expressed in the inner mitochondrial membrane. Kv3.4 inhibition blocked MPP^+ (1-Methyl-4-phenylpyridinium ion)-induced cytochrome c release from the mitochondrial intermembrane space to the cytosol and mitochondrial membrane potential depolarization (Bednarczyk et al., 2010), which are characteristic features of apoptosis (Song et al., 2017). The finding of Szabo study demonstrated that mitochondrial Kv1.3 channel mediated Bax-induced (Bcl-2 associated protein X) apoptosis (Szabo et al., 2008), and Cheng found that mitochondrial K^+ channels play a central role in the induction of apoptosis by Bax (Cheng et al., 2011). Similar to these, Ru reported that blocking the Kv channels would induces glioma cell apoptosis by reducing expression of microRNA-10b-5p (Ru et al., 2018).

However, some studies hold the different opinion. Debska-Vielhaber showed BK channel openers CGS7181 and CGS7184 induced glioma cell death, and this effect was due to the modulation of calcium homeostasis by BK channel openers leading to activation of calpains (Debska-Vielhaber et al., 2009a). Li found that the blockage of Kv channels could improve the proliferation of N2A cells (Li et al., 2015).

K^+ channels may use several mechanisms to regulate cell proliferation. The induction of tumor growth via the abnormal expression of K^+ channel subtypes since Ca^{2+} acts as an activator involved in many cellular signal transduction pathways, including the cell growth and mitosis pathways (Shen et al., 2009). Hyperpolarization increases the driving force for Ca^{2+} into the cells according to the Nernst equation, which makes sense since Ca^{2+} is another major factor in cell-promoting proliferation (Weiger and Hermann, 2014). At low resting membrane potential, increased Ca^{2+} entry into cells via T-type Ca^{2+} channel (Capiod, 2011). Constitutive Ca^{2+}

entry also can activate KCa^{2+} Channels which will further hyperpolarize membrane potential with different outcomes, an increase in influx for SOCE (store-operated calcium entry) and NCCE (non-capacitative calcium entry) channels and a possible exit from the window for voltage-dependent calcium channels. KCa^{2+} channels like BK channels may serve as regulatory sensors by hyperpolarizing cells and in this way limit the action of voltage-operated Ca^{2+} channels. As K^+ conductance is the predominant regulator for setting up the resting membrane potential, K^+ channel composition in cancer cells should accommodate the necessity of maintaining a relatively depolarized state. Neuroblastoma cells exhibit hyperpolarization at G1-S transition and depolarization at G2-M transition, and the hyperpolarization phase correlates with increased K^+ effux (Boonstra et al., 1981).

Kir4.1 channel and Glutamate Transport. Extracellular glutamate and glutamine concentrations are related grades of glioblastoma (Tong et al., 2015). And Corbetta found that GLAST (glutamate-aspartate transporter) expression significantly correlates with shortened patient survival while glutamate was crucial in favoring glioma invasion of surrounding normal brain (Corbetta et al., 2019). Meanwhile, Campbell found that patient-derived glioma xenoline and D54 (human glioma cells) peritumoral reactive astrocytes had lower average RMPs (resting membrane potentials) with a subset of astrocytes being notably depolarized and a reduced K^+ uptake capacity (Campbell et al., 2019). After downregulating Kir4.1 channels, glutamate uptake collapsed consequently (Kucheryavykh et al., 2007) which induced high and early mortality in animal models (Djukic et al., 2007). The loss of Kir4.1 function is pathologically relevant and associated with other forms of epilepsy and neurological disorders that present with seizures (Campbell et al., 2019). Therefore, depletion of Kir4.1 channels in glial cells results in turn of cell functions in a severe pathology such as seizures, epilepsy, ataxia, which are also a common feature for glioma development.

Kir4.1 channel, PAs and Glioma. Polyamines (PAs), such as spermidine and spermine, are the major component of glial cells and are vital regulators of Kir channel, and involved in glial-neuronal communication, especially during periods of stress such as during ischemia and trauma (Sala-Rabanal et al., 2013; Skatchkov et al., 2014). A unique capability of healthy glial cells is to preferentially accumulate PAs without synthesis, which is the major feature of healthy glia, and they serve for normal Kir4.1 function (Biedermann et al., 1998; Skatchkov et al., 2000; Skatchkov et al., 2014). Proliferative glial cells start producing own PAs which play a fundamental role in functional rectification of Kir4.1 and Kir6.1 channels (Skatchkov et al., 2000; Skatchkov et al., 2002). Gioma, and other brain tumors such as astrocytoma, pituicytoma generate PAs by synthesis, but glioblastoma internalizes organic cation transporters (SLC22A) from the cell membrane to the cytoplasm. The PAs regulated Kir4.1 channels (Olsen and Sontheimer, 2004; Olsen and Sontheimer, 2008) and a PA transporter OCT (organic cation transporter) SLC22A subfamily, OCT3 are mislocalized (Kucheryavykh et al., 2014) in glial cells involved in gliomas. Normally, because of no synthesis of spermidine in astrocytes (Krauss et al., 2006), SLC22A subfamily served for PA uptake in healthy glial cells (Inyushin et al., 2010; Sala-Rabanal et al., 2013), and cancer cells need PAs for growth.

Kir4.1 channel, Cx43 and Glioma. Gap junctions are formed of connexins, a family of homologous

protein subunits, and their channels are connexin dodecamers formed of hexameric hemichanne, one from each of the coupled (Yeager and Nicholson, 1996). Although cortical astrocytes may also express Connexin (Cx) 26, Cx30, Cx40, and Cx45 in vivo or in vitro (Dermietzel et al., 2000; Rash et al., 2001), Cx43 in the brain is primarily expressed in glial cells (Contreras et al., 2002) in close proximity to Kir4.1 channels. Cx43 has higher permeability to K^+ ion than other monovalent cations (Wang and Veenstra, 1997), and this gap junction can be down-regulated by elevated $[Ca^{2+}]i$ and $[H^+]$ (Kucheryavykh et al., 2017), which is similar as Kir4.1 (Sala-Rabanal et al., 2010). And PAs can hold Cx43 gap junctions open for diffusion of ions and molecules to enhance cell survival (Kucheryavykh et al., 2017), while not Cx40 (Musa and Veenstra, 2003). Considering Cx43 mainly express in glial cells, while Cx40 is absent. Therefore, Cx43 play a vital role in potassium fluxes in glial cells. What's more, Cx43 hemichannels open to extracellular matrix under essentially normal conditions (Contreras et al., 2002), and can be served as ionic channel similar to Kir4.1, Kir6.1, BK, Kv and others in glia for potassium fluxes. Many studies focused on gap junctions between cells within solid tumors, with the data indicating that gap junctions between tumor cells act as tumor suppressors (Cronier et al., 2009; Mesnil et al., 2005). Hong found that lack of functional gap junctions between glioma cells promotes their invasiveness, and Cx43-mediated communication between glioma cells and the surrounding astrocytes in the brain parenchyma was involved in glioma invasion (Hong et al., 2015). Gliomas and other tumors deplete connexin gap junctions which normally are also necessary for macro-molecular signaling between cells making large astrocytic syncytium (Skatchkov et al., 2015). Peng showed that gap junctions composed of Cx43 significantly enhanced the inhibitory effect of miR-34a on cell proliferation in glioma cells (Peng et al., 2019). These results indicated that as the key factor that holds astrocytes together in the integrative syncytium, Cx43 of tumor is down-regulated, gap junctions that support cell structure and function are reduced, so the vital signaling including anti-proliferative signaling is stopped, and then cells may enter the proliferative mode. Interestingly, PAs such as spermine and spermidine can open Cx43 (Benedikt et al., 2012; Kucheryavykh et al., 2007; Skatchkov et al., 2015). When cells deplete Cx43 gap junctions in glioma, the PAs and Cx43 are disconnected. Therefore, such regulation is avoided, and glial syncytium may be revitalized for cell-to-cell communication and restoring healthy syncytial function. It indicate that Cx43 may be a novel target for glioma therapy.

The studies that whether K^+ channel blockers promote tumor cells' apoptosis are rarely published. But some believe that the activation of K^+ channel and the outflows of potassium and Cl^- are necessary to change cell volume before apoptosis, thus blocking K^+ channels cause the inhibition of apoptosis (Shah and Aizenman, 2014).

4 Blockers of K^+ channel and Treatments of Gliomas

The MDR (multiple drug resistance) of tumor cell associated with a variety of mechanisms is a significant obstacle in tumor therapy. Increased evidence showed that, K^+ channels were involved in the process of MDR in cancers. Liu demonstrated that Kir2.1 induced cell cycle arrested at the G0/G1 phase, modulated cell growth and drug resistance by regulating MRP1 (multidrug resistance protein 1) expression, and was simultaneously

regulated by the Ras/MAPK pathway (Liu et al., 2015). Bai found that over-expression of miR (short non-coding RNA molecules)-296-3p sensitised glioblastoma cells to anticancer drugs, whereas down-expression using antisense oligonucleotides conferred MDR (Bai et al., 2013). Meanwhile, it has been found that a large number of toxins and drugs have the ability to regulate K^+ channels, which can be used to block K^+ channels or change channels' sensitivities to voltage and calcium concentration (Vyas et al., 2019).

The development of the tumor requires the acceleration of proliferation and the weakening of apoptosis. The inhibition of K^+ channel blockers to cell proliferation is related to cell volume, transmembrane potential, and cell cycle. Yang found blocking K^+ channel using TEA (tetraethylammonium) could inhibit rat glioma cell lines (C6 and 9L) proliferation and induce apoptosis in both cell lines (Yang et al., 2009), and it might be associated with the increase in intracellular ROS (reactive oxygen species) production. Ru found that quinidine (a commonly used Kv channel blocker) significantly inhibited the proliferation of U87-MG cells and induced apoptosis in a dose-dependent manner (Ru et al., 2015). Sales demonstrated that silencing EAG1 is a promising strategy to improve glioma treatment (Sales et al., 2016). Newly, there is a compound, senicapoc which is made with KCa3.1 blocking tool, has previously been in Phase III clinical trials. And this medicine can cross the blood brain barrier, which means it would be available for repurposing, and could be used to quickly translate findings compounds into clinical trials (Brown et al., 2018).

The opening of K^+ channel could release voltage-insensitive Ca^{2+} ions, which activated Ca^{2+} channel. Increased Ca^{2+} ions participatd in Ca^{2+} signaling pathway, and accelerated the proliferation of cancer cells. K^+ channel blockers could inhibit this process, thereby inhibiting the growth of cancer cells (Bi et al., 2013). Blockage of K^+ channels not only can inhibit the growth of tumor cells, but also can induce the apoptosis of tumor cells (Ru et al., 2015; Szabo et al., 2008). Therefore, we could view this as a potential therapeutic target in cancer treatments. In the early stage of tumor cell generation, K^+ channel blockers were used to prevent excessive proliferation, while the tumor cells were killed by K^+ channel activators in the stage of terminal cancer (MacFarlane and Sontheimer, 2000; Taglialatela et al., 2001). Therefore, inhibition of glioma cells by K^+ channel blockers and its specific mechanism remains to be further studied.

5 Summary

The expression of K^+ channels of different subtypes has been confirmed in various glioma cells or tissues, and the blockade of K^+ channels often affects a variety of cellular activities. In addition, the K^+ channel can also as the gene therapy target of cancer treatment. Such as using knockout, antisense oligo nucleotide can inhibit the growth of tumor. The role of K^+ channel inhibitors in inhibiting glioma cell growth can provide new insights into the treatment of glioma. However, the cellular mechanism regulated by K^+ channels is extremely extensive and the role of K^+ channel blockade at the level of glioma tissue is still lacking in a large amount of experimental data. Therefore, further study of the role of K^+ channels in the development of gliomas and verify its effects at the tissue or even the individual, is necessary for the development of K^+ channel targeted drugs for glioma.

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Tables

Table 1 Expression of K^+ channels in glioma cells

Channel	Tumor	Reference
Kv Channel	Diffuse Astrocytoma, Glioma	(Arvind et al., 2012) **Kv1.5**, (Preussat et al., 2003) **Kv1.3 and Kv1.5**, (Venturini et al., 2017) **Kv1.3**
KCa^{2+} Channel	Glioblastoma	(Catacuzzeno and Franciolini, 2018; D'Alessandro et al., 2013; D'Alessandro et al., 2016; Kinboshi et al., 2019; Turner et al., 2014)**KCa3.1**, (Debska-Vielhaber et al., 2009b; Ge et al., 2014; Hoa et al., 2016; Rosa et al., 2017; Weaver et al., 2006a)**BK**, (Huang et al., 2015; Stegen et al., 2015; Weaver et al., 2006b) **IK**, (Weaver et al., 2006b) **SK**
Kir Channel	Glioblastoma	(Kinboshi et al., 2019; So et al., 2014; Thuringer et al., 2017)**Kir4.1**, (Veeravalli et al., 2012) **Kir4.2**
EAG Channel	Glioblastoma	(Bai et al., 2013)**EAG1**
hERG Channel	Glioblastoma	(Staudacher et al., 2014)
K_{ATP} Channel	Glioma	(Huang et al., 2015; Ru et al., 2014)