

Potassium Channels as a Target for Cancer Therapy: Current Perspectives

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Abstract: Potassium (K⁺) channels are highly regulated membrane proteins that control the potassium ion flux and respond to different cellular stimuli. These ion channels are grouped into three major families, Kv (voltage-gated K⁺ channel), Kir (inwardly rectifying K⁺ channel) and K2P (two-pore K⁺ channels), according to the structure, to mediate the K⁺ currents. In cancer, alterations in K⁺ channel function can promote the acquisition of the so-called hallmarks of cancer – cell proliferation, resistance to apoptosis, metabolic changes, angiogenesis, and migratory capabilities – emerging as targets for the development of new therapeutic drugs. In this review, we focus our attention on the different K⁺ channels associated with the most relevant and prevalent cancer types. We summarize our knowledge about the potassium channels structure and function, their cancer dysregulated expression and discuss the K⁺ channels modulator and the strategies for designing new drugs.

Keywords: K⁺ channels, potassium channel blockers, K⁺ channels expression, cancer

Introduction

Potassium Channels Structure and Function

K⁺ channels are membrane proteins that facilitate the selective potassium ion flow under an electrochemical gradient. Besides the voltage-dependent gating, K⁺ channels are activated by several intracellular and extracellular stimuli,^{1–3} including extracellular and intracellular pH, kinases, SUMOylation, G protein-coupled receptors, stretch, and lipid regulation among others.^{1,2,4} These channels can be grouped into three major families according to their subunit structure: the Kv (voltage-gated K⁺ channel), Kir (inwardly rectifying K⁺ channel), and K2P (two-pore K⁺ channels)^{1,2,4} (see Figure 1A–C). K⁺ channels need four pore-forming domains, which together, generate a functional and selective ion pathway. Thus, the Kv and Kir channels need four subunits to form a functional pore in a tetramer architecture.^{2,4} On the other hand, the K2P family forms a functional channel in a dimer architecture (see Figure 1C).^{1,5} For each K⁺ channel, subunit is also clearly identifiable in this pore-forming P domain, characterized by the amino-acid signature GYG that confers the high selectivity to K⁺ ions observed in potassium channels.⁶ The Kv channels present a topology model with six transmembrane domains (TM1-6) and one pore-forming domain (P) (Figure 1A). This Kv family represents the most numerous K⁺ channel group, with 40 genes encoding for K⁺ subunits in humans. The transmembrane domain (TM4) into Kv channels present positive charged amino acids (Arg and Lys) which act as voltage sensors generating the channel opening in response to changes in voltages^{7,8} (Figure 1A).

For the Kir channel family, each subunit has one P domain and two transmembrane domains (Figure 1B), and this family is integrated by 15 different genes grouped into 7 subfamilies (Kir1.x to Kir7.x), identified in mammals.^{2–4} Kir potassium channels present a gating governed by a voltage-dependent blocked process by Mg²⁺ and polyamines.^{3,4} Moreover, the gating voltage-dependence for Kir channels defines their characteristic K⁺ inward rectification (movement into the cell).^{3,4}

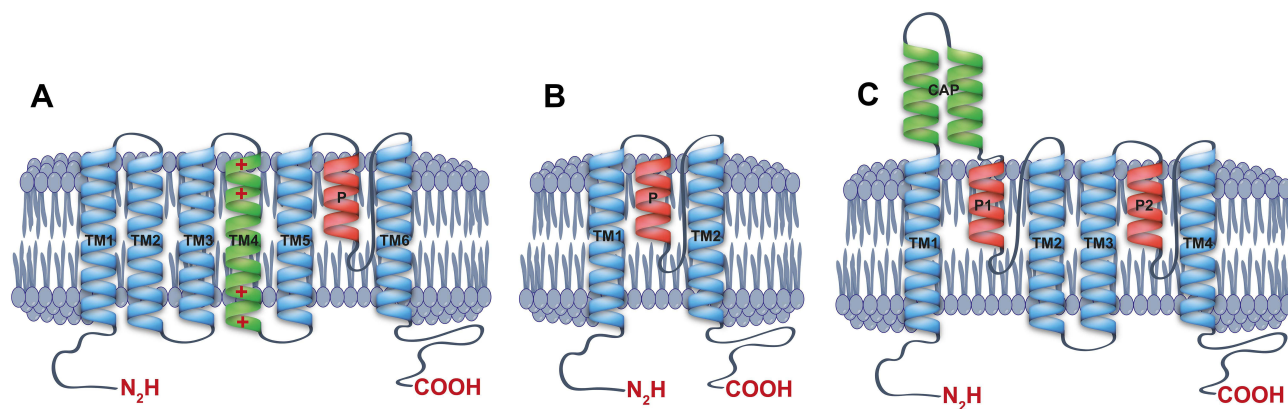


Figure 1 Schematic structure of potassium channels. Lateral view of monomers of a (A) voltage-gated potassium channel (Kv), (B) inward rectifier potassium channel (Kir) and (C) two-pore domain potassium channel (K2P), showing the transmembrane segments, the cap and their corresponding pore-forming loops (P-loops).

K2P family has a two-pore forming domain and four transmembrane domains, whose subunits assemble as dimers (Figure 1C). Fifteen different genes found in mammals encode these family subunits and are grouped into 6 subfamilies according to their homology and functional properties.^{1,5,9,10} The K2P channels are voltage-independent and highly modulated channels, playing key roles in the maintenance of the resting membrane potential in the cells. These channels are recognized as the leak or background potassium channels.^{1,5}

Potassium Channels in Cancer

Cancer condition is a major non-infectious public health problem and affects millions of people worldwide. Cancer is also the second most common cause of death after cardiovascular disease, with 10.0 million deaths (9.9 million excluding nonmelanoma skin cancer) in 2020,¹¹ with estimated 28.4 million cases in 2040, a 47% rise from 2020.¹¹ The Americas' accounts 20.9% of cancer incidence and 14.2% of mortality worldwide,¹¹ and for Latin America and the Caribbean region, it has been estimated that 1.7 million cancer cases will be diagnosed by 2030, whereas more than one million of the cases will die per year.¹² Currently, more than 100 types of cancer have been identified, being breast (24.5%), colorectal (9.4%), lung (8.4%), cervix (6.5%), and thyroid (4.9%) most frequent types of cancer in women.¹¹ Meanwhile, lung cancer (14.3%), prostate (14.1%), colorectal (10.6%), stomach (7.1%) and liver (6.3%) are the most common type of cancers among men.¹¹

In recent years, ion channels, and particularly potassium (K^+) channels, have emerged as relevant molecular targets for the development of cancer treatments.^{13–16} The association between potassium (K^+) channels and cancer disease is mainly due to the participation of those proteins in the cancer progression mechanisms.^{13,16–18} Potassium channels are complex proteins that form selective pores for K^+ conduction in biological membranes, which are critical in K^+ homeostasis, cell volume regulation, setting of resting membrane potentials, the neurotransmitters release, and regulating the excitability of neurons and muscle tissue.^{1,2,19}

For instance, overexpression of different potassium channels, such as Kv, Ca^{2+} -activated (K_{Ca}), ether go-go human (hEg), ATP-sensitive (K_{ATP}), and K2P has been reported in prostate cancer cells, colon, lung, breast, and other organs.²⁰ It has been hypothesized that there is a relationship between K^+ channel overexpression and the generation and growth of malignant tumors,^{14,17,18,21} being involved in cell proliferation, apoptosis, and differentiation.^{14,18,21} Studies performed with pharmacological drugs that specifically block K^+ channels have shown antitumor effects by inhibiting tumor growth directly or enhancing the effectiveness of chemotherapeutics or cytotoxic drugs as a combined therapeutical strategy.^{18,22} On the other hand, several studies have exhibited the impact of Kv channels (Eag1, HERG, and Kv1.3), Kir (Kir3.1), and Ca^{2+} -activated potassium channels ($K_{Ca1.1}$ and $K_{Ca3.1}$) in cancer cell proliferation and their association with tumorigenesis process in patients and animal models.^{17,18,21–23}

A relatively minor amount of research has focused on the relationship between K^{2P} channels and cancer.^{18,24} Those studies suggested that TASK-3 is involved in tumor formation in several types of human cancer.^{14,18,24,25} Moreover, other investigations showed that breast cancer cells' metastatic properties depend on TASK-3 expression levels.²⁰

By contrast, the Kir channels have been related to different cancer conditions, such as lung, gastric, prostate, stomach, breast, and choroid plexus.^{26–32}

Voltage-Gated Potassium Channels Involved in Cancer

The Kv channel is the most numerous K⁺ channel family, playing relevant functions in various cellular and physiological processes.² Additionally, these channels have been implicated in cancer hallmarks, such as cell proliferation, cancer progression, and migration^{14,15,33–35} (Figure 2 and Table 1).

The Kv1.1 (*KCNA1*) channel is relevant for potassium transport in the central nervous system and kidney.^{36,37} Moreover, it is overexpressed in cervical cancer tissues and medulloblastoma.^{38,39} Additionally, the Kv1.1 depletion suppressed growth, proliferation, migration and invasion of HeLa cells.³⁸

Kv1.3 channels also have been reported as overexpressed in the breast, lung, colon, prostate, pancreas, smooth muscle, skeletal muscle, and lymph node of some types of cancers.^{40–44} However, its relevance as a therapeutic target has been evidenced in glioblastoma, melanoma, and pancreatic adenocarcinoma models,^{45–47} where Kv1.3 suppression induces apoptosis.

Another related channel is Kv1.5. This channel shows a correlated expression pattern with glioma entities and malignancy grades, with a high expression in astrocytomas, moderate in oligodendrogliomas, and low in glioblastomas.⁴⁸ For the Kv1.5 channel, an overexpression was detected in some gastric cancer cell lines.⁴⁹ Furthermore, Kv1.5 plays a role in the activation and proliferation of cells in the immune system, is remodeled during carcinogenesis, and has shown an abundance that inversely correlates with clinical aggressiveness in human non-Hodgkin lymphomas.⁵⁰ In the same way that Kv1.3, this channel is overexpressed in human smooth muscle tumors.⁴⁰ Kv1.5 has been involved in tumor cell proliferation of gastric cancer cells, where this channel is overexpressed.⁴⁹

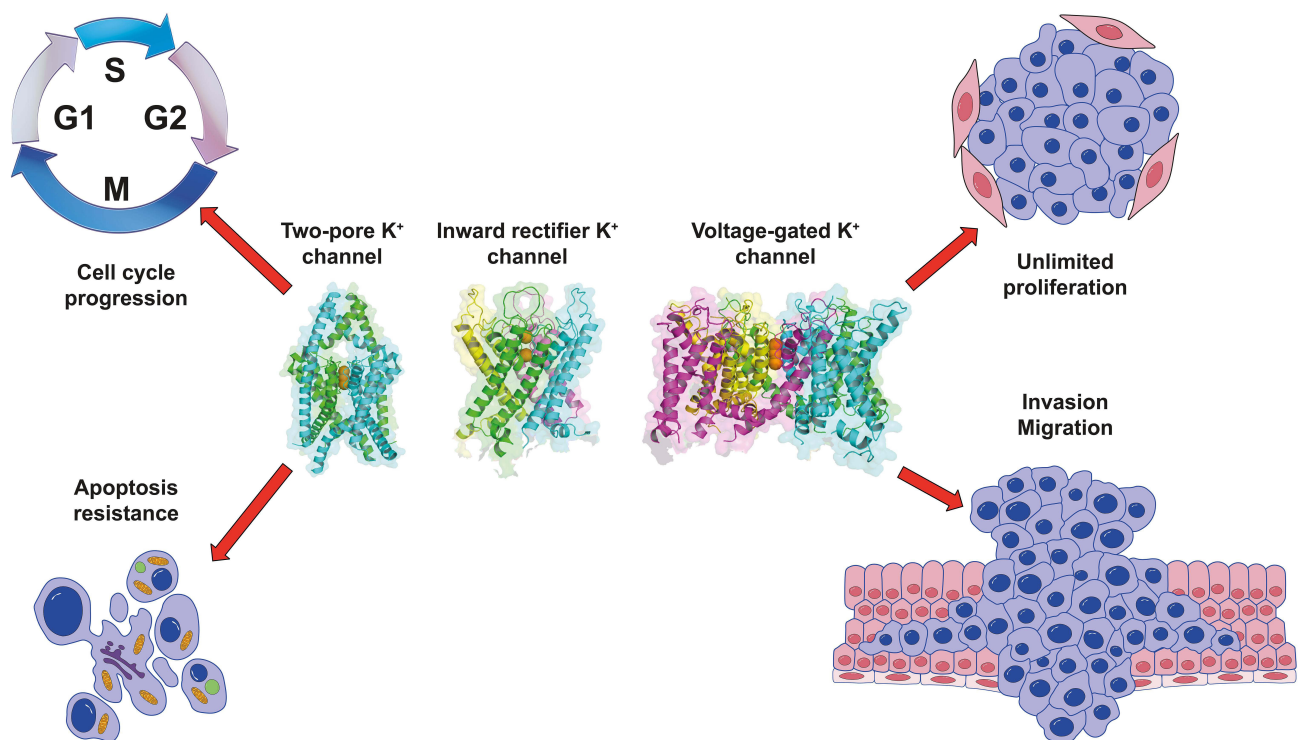


Figure 2 Roles of K⁺ channels in cancer hallmarks. Cellular processes associated with changes in expression and increased activity of the two-pore domain K⁺ channel (K^{2P}), the inward rectifier K⁺ channel (Kir), and the voltage-gated K⁺ channel (Kv) in cancer. K⁺ channels structure in ribbon representation were generated with the PDB 6RV2, 7s5z and 7wf4.

Table 1 Potassium Channels Associated with Cancer

Protein (Gene)	Cancer Hallmark	Tumor or Cancer Type	Reference
Kv1.1 (<i>KCNA1</i>)	Cell proliferation, apoptosis, migration and invasion	Cervical cancer, medulloblastoma	[38,39]
Kv1.3 (<i>KCNA3</i>)	Cell proliferation, apoptosis and migration	Breast, lung, colon, prostate, pancreas, smooth muscle, skeletal muscle, and lymph node cancers, glioblastoma and melanoma	[40–47]
Kv1.4 (<i>KCNA4</i>)	Cell proliferation and cell cycle	Neuroblastoma cells	[52]
Kv1.5 (<i>KCNA5</i>)	Cell proliferation and apoptosis	Glioma, astrocytomas, gastric cancer cells, human non-Hodgkin lymphomas, smooth muscle tumors	[40,48–50]
Kv2.1 (<i>KCNB1</i>)	Cell cycle progression and migration	Prostate cancer cells, neuroblastoma cells	[51,52]
Kv3.1 (<i>KCNC1</i>)	Proliferation, migration and invasion	Lung and breast cancer cells]	[55]
Kv3.4 (<i>KCNC4</i>)	Proliferation, migration and invasion	Oral squamous cell carcinoma, head and neck squamous cell carcinomas, lung and breast cancer models	[53–55]
Kv4.1 (<i>KCND1</i>)	Cell cycle progression	Breast cancer and gastric cancer cells	[56,57]
Kv4.2 (<i>KCND2</i>)	Cell proliferation and cell cycle	Neuroblastoma cells	[52]
Kv7.1 (<i>KCNQ1</i>)	Cell proliferation	Colon cancer cells, neuroblastoma cells	[52,58,59]
Kv9.3 (<i>KCNS3</i>)	Cell proliferation	Colon carcinoma, lung adenocarcinoma and cervical adenocarcinoma cells	[60,61]
Kv11.1 (<i>KCNH2</i>)	Cell cycle, apoptosis, migration and cell proliferation	Leukemia, ovarian, lung, pancreatic, colorectal and breast cancer cells	[74,79–81]
K _{Ca} 1.1 (<i>KCNMA1</i>)	Cell proliferation and migration	Prostate, glia, breast, pancreas, and endometrium cancer cells	[82–87]
K _{Ca} 2.3 (<i>KCNN3</i>)	Migration	Melanoma cells	[96]
Kir2.1 (<i>KCNJ2</i>)	Cell proliferation, invasion, cell cycle and apoptosis	Small-cell lung cancer and gastric cancer	[28,97]
Kir2.2 (<i>KCNJ12</i>)	Cell proliferation and cell cycle	Small-cell lung cancer, prostate, stomach, and breast	[31,98,99]
Kir3.1 (<i>KCNJ3</i>)	Cell proliferation and invasion	Pancreatic ductal adenocarcinoma, breast carcinomas, and non-small cell lung cancers	[26,100–102]
Kir3.4 (<i>KCNJ5</i>)	Cell proliferation	Adrenal aldosterone-producing adenomas	[29,103]
Kir4.1 (<i>KCNJ10</i>)	Cell proliferation, cell cycle and apoptosis	Brain tumors, astrocytomas and oligodendrogliomas	[32,104]
Kir6.1 (<i>KCNJ8</i>)	Cell proliferation, invasion, apoptosis and cell cycle	Leiomyoma cells, breast cancer cells (MDA-MB-231) and hepatocellular carcinoma	[30,105,106]
Kir6.2 (<i>KCNJ11</i>)	Cell proliferation, invasion, apoptosis and cell cycle	Leiomyoma cells, breast cancer cells (MDA-MB-231), hepatocellular carcinoma, cervical cancer and glioma cells	[30,105–108]

(Continued)

Table 1 (Continued).

Protein (Gene)	Cancer Hallmark	Tumor or Cancer Type	Reference
Kir7.1 (<i>KCNJ13</i>)	Cell proliferation	Choroid plexus tumors	[27,109–111]
TASK-1 (<i>KCNK3</i>)	Cell proliferation, invasion and apoptosis	Medulloblastoma, Ehrlich ascites tumor cells, osteosarcoma, non-small cell lung cancers and adenomas adrenals	[121–123,125]
TASK-2 (<i>KCNK5</i>)	Cell proliferation, invasion and apoptosis	Breast cancer, and pancreatic ductal adenocarcinoma	[126–128]
TASK-3 (<i>KCNK9</i>)	Cell proliferation, migration, invasion, apoptosis and cell cycle	Melanoma, ovarian carcinoma, breast tumors, colorectal cancers, lung and gastric cancer	[24,117,129–132,135,139,140]
TREK-1 (<i>KCNK2</i>)	Cell proliferation, apoptosis and cell cycle	Prostate cancer, osteosarcoma and ovarian cancer	[116,118,141,142,182]
TREK-2 (<i>KCNK10</i>)	Cell proliferation and cell cycle	Bladder cancer cells	[119]
TWIK-1 (<i>KCNK1</i>)	Cell proliferation	Pancreatic ductal adenocarcinoma	[115]
TWIK-2 (<i>KCNK6</i>)	Cell proliferation, invasion and migration	Breast cancer	[120]

The expression of the Kv2.1 channel recently was reported to be higher in the metastatic prostate cancer cells (PC3), and their blockade with stromatoxin-1 or siRNA significantly inhibits the migration of malignant prostate cancer cells.⁵¹ This channel as Kv1.4, Kv4.2, Kv7.1 and large-conductance Ca²⁺-activated K⁺ channel (BK_{Ca}) also showed a high expression in the CD133⁺ subpopulation of SH-SY5Y neuroblastoma cells.⁵²

Increased levels of Kv3.4 channel expression were identified in OSCC (oral squamous cell carcinoma).⁵³ In addition, the expression and clinical significance of this channel in the development and progression of head and neck squamous cell carcinomas was reported.⁵⁴ The Kv3.4 and Kv3.1 are known as oxygen sensors, and their function in hypoxia has been well investigated.⁵⁵ These channels, Kv3.1 and Kv3.4, are tumor hypoxia-related channels involved in cancer cell migration and invasion in A549 and MDA-MB-231 cells (lung and breast cancer models, respectively).⁵⁵

Another set of experiments showed a varied expression of Kv4.1 mRNA depending on the tumor stage in human breast cancer tissues.⁵⁶ Recent studies have demonstrated that Kv4.1 channels are expressed in the human gastric cancer cell lines.⁵⁷ Moreover, the suppression of Kv4.1 induces a G1-S transition blockade affecting the cell cycle progression.⁵⁷

Interestingly, together with the expression profile of Kv7.1 in neuroblastoma cells,⁵² this channel was also found to be up-regulated in human colonic cancer cells.⁵⁸ Conversely, Kv7.1 and Kv7.5 expression in vascular cancers was reported to be down-regulated.⁵⁹ In this case, the proposed role of Kv7 channels is related to cell proliferation rather than controlling vascular tone.⁵⁹

A particular case is a Kv9.3 channel, an electronically silent subunit, which forms heterotetramers with Kv2.1.⁶⁰ The Kv2.1/Kv9.3 heterotetramers are overexpressed in colon carcinoma, lung adenocarcinoma, and cervical adenocarcinoma cells.^{60,61} Moreover, the knockdown of Kv9.3 inhibits proliferation in colon carcinoma and lung adenocarcinoma models.⁶⁰

The Ether à go-go (Eag (hERG); Kv10.1) K⁺ channel expression is typically restricted to the adult brain and the heart, but it has been detected in several cancer cell lines and tumor tissues from patients,^{62,63} showing it to influence cell proliferation. This channel is overexpressed in 71% of tumors and cancer cell models of neuroblast, glial, liver, lung, breast, ovary, cervix, prostate, gastrointestinal tract, myeloid leukemia, and retinoblastoma.^{34,63–68} The Kv10.1 channel suppression generates apoptosis, inhibition of cell proliferation, and decrease in cancer cell migration.^{63,69–72}

Additionally, the inhibition of Kv10.1 channels sensitizes the mitochondria of tumor cells to antimetabolic treatments, improving the efficacy of the metabolic inhibitors.⁷³

Kv11.1 is overexpressed in leukemia, ovarian, lung, pancreatic, colorectal, and breast cancer cells, among others.^{74–79} The Kv11.1 channels have a key role in the cell cycle, acting as regulators for apoptosis and cell proliferation in cancer cells.^{74,79–81} However, blockers of Kv11.1 channels also retard the cardiac repolarization.⁸⁰

Another subgroup of potassium channels involved in cancer corresponds to the calcium-activated potassium channels. These channels are activated by rise in cytosolic calcium ions, allowing the K⁺ ion to flow under an electrochemical gradient. As a member of this subgroup, the K_{Ca}1.1 channel is overexpressed in prostate, glia, breast, pancreas, and endometrium cancer cell types.^{82–86} K_{Ca}1.1 channel regulates the proliferation and migration of prostate cancer condition.⁸³ In breast cancer, K_{Ca}1.1 channel overexpression has been associated with advanced tumor stage, cell proliferation, and poor prognosis.⁸⁷

On the other side, the K_{Ca}3.1 (intermediate conductance Ca²⁺-activated K⁺ channel) is overexpressed in 32% of glioma patients and correlates with poor patient survival.⁸⁸ In addition, these channels are overexpressed in breast cancer, non-small cell lung cancer, melanoma, leukemia, renal and hepatocellular carcinoma.^{89–94} The inhibition of K_{Ca}3.1 channel activity reduces the cancer cell motility, proliferation and induces apoptosis.^{91,94,95}

A less associated channel to a cancer condition corresponds to K_{Ca}2.3 (SK3), with a report of overexpression in melanoma cell lines, and their knockdown led to plasma membrane depolarization and decreased cell motility.⁹⁶

Inward Rectifying Potassium Channels in Cancer

The Kir channel family is integrated by 15 different genes grouped into seven subfamilies. Among these channels, different subunits have been associated with cancer conditions (Kir2.1, 2.2, 3.1, 3.4, 4.1, 6.1, 6.2)^{26,27,29–32,94} (Figure 2 and Table 1).

Kir2.1 (*KCNJ2*) is overexpressed in 44.23% of small-cell lung cancer (SCLC) tissues, and it correlates with the clinical stage and chemotherapy response in SCLC patients. Additionally, the Kir2.1 knockdown in H69AR and H446AR cells inhibited cell growth and was sensitized to chemotherapeutic drugs by increasing cell apoptosis and cell cycle arrest.²⁸ Kir2.1 channel also promotes the invasion and metastasis of human gastric cancer by enhancing MEKK2-MEK1/2-ERK1/2 signaling by interaction with Stk38.⁹⁷

Similarly, Kir2.2 is found in human SCLC cells.³¹ Kir2.2 knockdown induced growth arrest and senescence by a mechanism involving reactive oxygen species (ROS) accumulation in cell lines derived from tissues of the prostate, stomach, and breast.⁹⁸ Kir2.2 plays a role as an unconventional activator of RelA and increases the expression level of NF-κB targets, including cyclin D1, matrix metalloproteinase (MMP)9, and vascular endothelial growth factor (VEGF)⁹⁹ in cancer cells.

Another inward potassium channel associated with cancer is the Kir3.1 which is found within lymphocytes and in resected human pancreatic ductal adenocarcinoma (PDAC), overexpressed in 80% of tumor specimens. However, no associations were found between metastasis and Kir3.1 expression.²⁶ On the other hand, the gene encoding the Kir3.1 channel was found to be aberrantly overexpressed in invasive breast carcinomas.¹⁰⁰ In addition, the Kir3.1 overexpression correlates with lymph node metastasis, and this overexpression is greater in tumors with more than one positive lymph node.¹⁰⁰

Kir3.1 gene overexpression is detected in tissue specimens from patients with non-small cell lung cancers (NSCLCs).¹⁰¹ In addition, the expression of Kir3.1 has been shown in tissue samples from approximately 40% of primary human breast cancers and in breast cancer cell lines.¹⁰²

Also, the inwardly rectifying K⁺ channel Kir3.4 (*KCNJ5* gene) (or GIRK4 channel) have been identified in adrenal aldosterone-producing adenomas (APAs), where several ion channel gain-of-function mutants are associated with the APA condition.^{29,103}

In human brain tumors (low- and high-grade astrocytomas and oligodendrogliomas), mislocalization (redistribution) of the Kir4.1 channel has been reported and suggests a compromised buffering capacity of glial tumor cells.³² Furthermore, in human astrocytic tumors, Kir4.1 channel expression markedly increases with the pathologic grade of cancer¹⁰⁴ and suggests that Kir4.1 activation could promote proliferation and inhibit apoptosis in the tumors.¹⁰⁴

The subunits of ATP-sensitive Kir potassium channels (Kir6.1, Kir6.2) are highly expressed in leiomyoma cells.³⁰ The estrogen-induced proliferation of the leiomyoma cells is inhibited by treatment with glibenclamide (K_{ATP}-channel

inhibitor).³⁰ These two channels are expressed in MDA-MB-231 cancer cells, and the cytostatic effect of glibenclamide is mediated through K_{ATP} channels (Kir6.1 and 6.2), associated with the inhibition of the G1-S phase progression.¹⁰⁵ In hepatocellular carcinoma (HCC), the *KCNJ11* (Kir6.2) gene was identified as a key dysregulated K^+ channel and is associated with a poor prognosis in HCC patients.¹⁰⁶ In agreement, the knockdown of Kir6.2 inhibited cell proliferation, promoted cell apoptosis, and reduced cell invasive capacity.¹⁰⁶ The Kir6.2 overexpression was observed in cervical cancer cell lines and cervical tumor tissues.¹⁰⁷ In particular, the increased Kir6.2 channel expression was observed in high-grade, poorly differentiated and invasive human cervical cancer biopsies.¹⁰⁷ Moreover, an inhibitory effect of glibenclamide on the proliferation of cervical cancer cell lines is associated with Kir6.2 channel.¹⁰⁷

Kir6.2 channel activity plays a critical role in the proliferation of glioma cells where the expression is greatly increased.¹⁰⁸ Moreover, the treatment with tolbutamide (a Kir6.2 inhibitor) suppressed the proliferation of glioma cells and blocked the cell cycle.¹⁰⁸ The Kir6.2 knockdown obtained a similar result in glioma cell proliferation.¹⁰⁸

Finally, a less studied channel corresponds to Kir7.1 (*KCNJ13*) with a high expression linked to choroid plexus epithelium or choroid plexus tumors (CPTs)^{27,109,110} and it has been considered a sensitive and specific diagnostic marker for choroid plexus tumors.^{27,109,111}

Two-Pore Domain Potassium Channels in Cancer

The two-pore domain K^+ channels (K2P), encoded by the *KCNK* genes, are a family of fifteen members that form the leak or background channels.^{1,5,9} K2P channels display K^+ outward rectifying currents, constitutively open, that control the neuronal excitability. Thus, activation of K2P channels stabilizes the cell membrane potential below the firing threshold, whereas the K2P channels inhibition facilitates membrane depolarization and cell excitability.

The K2P family can be divided into six subfamilies based on structural and functional properties.^{1,5,9} Regarding protein structure, each K2P channel subunit has four transmembrane domains (TM1-TM4) and two pore-forming domains (P1 and P2) (Figure 1C). Moreover, two subunits are required to form a functional channel.^{112,113} K2P channels display an exclusive extracellular cap domain formed by the extracellular loop that connects the first transmembrane domain and the first pore-forming sequence (TM1-P1 loop) (Figure 1C). The extracellular cap covers the upper selectivity filter (SF) pore,¹¹⁴ and this structure is responsible for the poor sensitivity of K2P channels to classical K^+ channel blockers.¹¹⁴

From the K2P family, seven members are confirmed to be involved in cancer (TASK-1, TASK-2, TASK-3, TREK-1, TREK-2, TWIK-1, and TWIK-2)^{15,115–120} (Figure 2 and Table 1). Among these, TASK-1 (K2P3, encoded by *KCNK3* gene) has been detected in medulloblastoma and Ehrlich ascites tumor cells.^{121,122} Also, in MG63 osteosarcoma cells, the overexpression of TASK-1 was reported.¹¹⁸ Additionally, TASK-1 is overexpressed in a subset of non-small cell lung cancers, promoting proliferation and inhibiting apoptosis. TASK-1 knockdown enhances apoptosis and reduces the proliferation of lung cancer cell-line A549.¹²³ In these cells, A549, the overexpression of TASK-1 promoted epithelial mesenchymal transition (EMT), a pivotal event in lung cancer cell invasion and metastasis.¹²⁴ Moreover, the expression of TASK-1 has been associated with aldosterone production in both aldosterone-producing adenomas and normal adrenals.¹²⁵

The second K2P channel associated with cancer is TASK-2 (K2P5; encoded by *KCNK5* gene), a member of the TALK subfamily. TASK-2 plays a role in the proliferation of estrogen α receptor positive breast cancer cells being highly upregulated in response to 17β -estradiol (E2) in MCF-7 and T47D breast cancer cell lines.^{126,127} In these cells, the knockdown of the TASK-2 channel reduces the estrogen-induced proliferation of breast cancer cells.¹²⁷ Also, the overexpression of TASK-2 has found in HPAF cells, a human pancreatic ductal adenocarcinoma cell line, but the role in cancer progression has not been further studied.¹²⁸

Among the K2P channels, the most studied in cancer correspond to TASK-3 (TWIK-related acid-sensitive K^+ channel 3). This channel has been shown to localize in both the plasma membrane and mitochondrial inner membrane.¹¹⁷ The TASK-3 channel overexpression occurs in several types of cancer, such as melanoma, ovarian carcinoma, and breast cancer.^{24,117,129–132}

Also, TASK-3 (*KCNK9*, located in chromosomal region 8q24.3) gene expression is enhanced by 10–44% in human breast tumors and 35% in lung tumors.²⁴ Additionally, overexpression of *KCNK9* has been reported in over 90% of ovarian tumors.¹³⁰ In most cases studied, TASK-3 is associated with the acquisition of malignant characteristics, including hypoxia

resistance or serum deprivation conditions.^{24,25} Consistently, a monoclonal antibody (Y4) against the cap domain of TASK-3 inhibits the growth of human lung cancer xenografts and breast cancer metastasis in mice.¹³³ Further studies showed that TASK-3 gene knockdown in breast cancer cells is associated with an induction of cellular senescence and cell cycle arrest.¹³² Furthermore, TASK-3 is overexpressed in colorectal cancers and gastric cancers.^{134–136} In gastric adenocarcinoma cells, the TASK-3 gene knockdown causes changes in migration and reduces cell proliferation and viability by increasing apoptosis without affecting cell cycle checkpoints.¹³⁶

TASK-3 is highly expressed in melanoma,^{117,129,137} being identified in the inner mitochondrial membrane of melanocytes, WM35 and B16F10, and keratinocytes.^{117,129,137,138} In WM35 and A2058, human melanoma cells, the knockdown of TASK-3 resulted in compromised mitochondrial function, mitochondrial membrane depolarization, and reduced cell survival inducing apoptosis.^{139,140}

Another K2P channel related to cancer is TREK-1 (K2P2, encoded by *KCNK2*). This channel has been shown to play a pro-proliferative role in the human prostate cancer cell-line PC3.¹¹⁶ In MG63 osteosarcoma cells, overexpression of TREK-1 was reported¹¹⁸ and it is correlated with the proliferation of the osteoblast cells.¹⁴¹ TREK-1 is also overexpressed in prostate cancer tissues¹⁴² and epithelial ovarian cancer.¹³⁰ For TREK-1 channel, the exact role of cancer development is still unclear. However, TREK-1 overexpression is associated with a poor prognosis for patients with prostate cancer.¹⁴² In prostate cancer, inhibition or knockdown of TREK-1 inhibits proliferation by inducing cell cycle arrest at the G1/S checkpoint.¹⁴² On the other side, the treatment with TREK-1-blocking agents, such as curcumin, has shown reduced ovarian cancer cells proliferation and increased late apoptosis processes.¹³⁰

Among the TREK subfamily, the TREK-2 channel (K2P10, encoded by *KCNK10*) was present in bladder cancer cell lines and contributed to cell cycle-dependent growth.¹¹⁹ The sixth K2P channel involved in cancer is TWIK-1 (K2P1, encoded by *KCNK1*). The TWIK-1 was detected as an upregulated channel in pancreatic ductal adenocarcinoma (PDAC) compared to normal tissue.¹¹⁵ Recently, TWIK-2 (K2P6, encoded by *KCNK6* gene) was reported as a significantly overexpressed channel in breast cancer.¹²⁰ Moreover, the overexpression of TWIK-2 increases the capacity of proliferation, invasion, and migration of breast cancer cells.¹²⁰

Strategies for Designing New K⁺ Channels Blockers

The rational design and development of selective blockers is a dynamic field of study that includes diverse methods such as high-throughput screening, bioengineering techniques, and chemical modification, among others.^{143,144} Fortunately, we count on several software and computational tools that allow us to explore innovative approaches based on the molecular interaction of potassium channels structural data from the ligands and molecules, and the physicochemical and pharmacological properties of K⁺ channels interacting with drugs.

Some computational tools used for the rational design of specific modulators (blockers and activators) examine the three-dimensional structure of the target (K⁺ channels, in this case), previously solved by X-ray crystallography, cryoelectron microscopy¹⁴⁵ or comparative modeling. Following this, it is necessary to study the binding sites and affinity of the ligand.¹⁴³ This approach has been particularly helpful for the identification of ligands, targeting membrane proteins.^{146,147}

Additionally, the multidisciplinary work among different areas, such as biochemistry, bioinformatics, bioengineering, medical chemistry, genomics, proteomics, and metabolomics, has contributed to the development of new computational tools for the rational design of ion channel modulators.¹⁴³ Thus, the combinatorial strategy including docking, virtual screening, de novo drug design, molecular simulations and the experimental validation by electrophysiological measures have allowed the development and a successful search for small modulators.^{146,147} For the K⁺ channels, a three-dimensional structure of representative K⁺ subunits (Kv, K2P, and Kir) has been reported, providing insights into how these channels can be used to design specific modulators for cancer treatment.

Moreover, ion channels with limited background expression in normal tissues and strong overexpression in tumors due to their cell-surface accessibility constitute a preferential target for the development of antibody-based therapies.^{148–152} Antibodies recognizing ion channels represent a strategy effective in modulation of ion channel activity. The mechanisms of action include direct block of ion permeation pathway, modulation of ion channel gating, and internalization and degradation upon surface clustering.^{152–154} For example, systemic administration of specific mouse monoclonal antibodies

generated in the human channel K2P9 (KCNK9) using its M1P1 loop fused into the Fc domain of IgG2a, effectively inhibits the growth of human lung cancer xenografts and murine breast cancer metastasis in mice.¹³³ In addition, a specific monoclonal antibody which inhibits the function of highly oncogenic Kv10.1 potassium channel can effectively restrict cancer cell proliferation and reduce tumor growth in animal models with no significant side effects.¹⁵⁵ However, currently, only one polyclonal antibody (BIL010t; Biosceptre) targeting a non-functional form of P2X7 (nfP2X7) has reached the level of clinical trials for the treatment of basal cell carcinoma.^{156,157}

Other developing innovative strategies consist of the rational design of specific short peptides (less than 50 amino acid residues), which have acquired widespread interest as tools to address challenging protein–protein interactions (PPIs).^{158,159} These short peptides can form complexes, and structures, mimicking critical motifs of proteins,¹⁶⁰ which allow them to inhibit PPIs or functional activities with high specificity and affinity, emerging as a promising alternative to small molecules and biopharmaceuticals (>5000 Da). Furthermore, short peptides are easy to produce and modify¹⁶¹ and present low off-target side-effects given their higher specificity and reduced immunogenicity.¹⁶¹ All those attractive features make short peptides exceptional candidates to serve as therapeutics, even more considering that more than 100 peptide-based drugs are available in the market for AIDS, Cancer, and other medical conditions.^{162,163} Some examples of therapeutic drug-based peptides include oxytocin (8 aa), calcitonin (32 aa), teriparatide (34 aa), Fuzon (36 aa, antiretroviral), corticotropin-releasing hormone (41 aa), and growth-hormone-releasing hormone (44 aa).¹⁵⁹

Additionally, animal venoms are a natural and affluent source of peptides.^{164–166} These peptide sources (from different animals such as cone snails, scorpions, sea anemones, snakes, spiders, among others) have been widely used as a starting point to develop toxin-based drugs, and some of them have currently reached clinical trials.¹⁶⁵ Captopril was the first toxin-based drug approved for humans (1981). It is a nonapeptide that acts by blocking the angiotensin-converting enzyme (ACE) activity inhibiting the production of angiotensin II and was developed from *Bothrops jararaca* snake venom.¹⁶⁷ Captopril is currently suitable and widely used for hypertension treatment.¹⁶⁸ Among the different approved toxin-based drugs marketed, the ziconotide is obtained from cone snails, exenatide and lixisenatide are obtained from lizards. Bivalirudin and desirudin from leeches and Batroxobin and cobratide are purified from snake venoms.¹⁶⁵ Desirudin, on the other hand, is a recombinant peptide derivated from snake. Other drugs (bivalirudin, enalapril, eptifibatide, exenatide, tirofiban, and ziconotide) are synthetic molecules from the same source.¹⁶⁵

Currently, a large number of ionic channel blocking peptides (for Ca²⁺, K⁺ and Na⁺ channels) have been reported and obtained from different origin.^{166,169–173} For instance, some peptides with antitumor effect are κ-hefutoxin 1 and analogues, APETx4, purpurealidin analogs, KAaH1 and KAaH2 among others.^{174–177}

There is no doubt that the specific short peptide blockers can inhibit the functional activity of K⁺ channels and show an antitumor effect, impacting the hallmark of cancer and representing a novel strategy for the rational design of new cancer drugs.

Conclusion

Compelling evidence indicates that the upregulation of the majority of K⁺ channels is associated with current cancer hallmarks (Figure 2 and Table 1). Thus, these channels have emerged as alternatives to develop new cancer treatments. K⁺ channel subunits are diverse and highly regulated proteins that respond to different stimuli. In different cancer conditions, where K⁺ channels are overexpressed, K⁺ channel blockers have been shown to reduce the tumorigenic properties and reverse the cancer progression in cell lines and animal models. However, K⁺ channels are critical regulators in several cellular and physiological processes; therefore, the search for selective K⁺ channel blockers becomes restrictive in developing future cancer treatments. Fortunately, the 3D structure of representative K⁺ channels^{178–180} opens new possibilities for the rational design of highly selective K⁺ modulators.

The research for these highly selective potassium channel blockers must also include natural products (eg, plant extracts), bioinformatics search using the database (eg, Zinc¹⁸¹), venoms peptides, and the design of cyclic peptides (CPs) as modulators of protein–protein interactions. Indeed, there is no doubt that rational design, search, and development might increase the therapeutic arsenal of drugs against cancer conditions associated with K⁺ channels. Nevertheless, the design, search, and development of selective K⁺ channel blockers remains a challenge that must be addressed in a multidisciplinary manner, including chemistry, bioinformatics, bioengineering, and biophysics groups.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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