Potassium channels as novel molecular targets in hepatocellular carcinoma (Review)

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Abstract. Hepatocellular carcinoma (HCC) poses a serious health burden worldwide. It is often not diagnosed until the patient is at an advanced stage of the disease, when treatment options are limited and the prognosis is poor. Therefore, novel treatment strategies are urgently required. Potassium (K^+) channels have an important role in HCC, including regulating the proliferation, migration, invasion and drug resistance of HCC cells. The aim of the present review was therefore to survey the relevant publications that have investigated K^+ channels not only as markers for the early diagnosis of HCC, but also as potential therapeutic targets for the treatment of HCC. Several of these channels have been indicated to be the sites of action for natural products previously known to inhibit HCC; however, more systematic studies are required to determine which K^+ channels may be utilized for the clinical treatment of HCC, particularly in the advanced stages of the disease and in cases where patients are resistant to the existing drugs.

Contents

1. Introduction

Hepatocellular carcinoma (HCC) is a chronic disease and one of the most significant causes of cancer-associated death; furthermore, the clinical prognosis is usually poor (1). The etiology of liver cancer is diverse, including viral infection, alcoholic and non-alcoholic fatty liver disease, aflatoxins, genetic and metabolic factors and infection, among which viral infection [via hepatitis B virus (HBV) and hepatitis C virus (HCV)] is the most important factor (2,3). In recent years, with the prevalence of obesity, diabetes and various metabolic syndromes increasing, the incidence of HCC has also been shown to be on a clear upward trajectory (1,4,5). Liver cancer is divided into primary and secondary HCC, and the most important type of HCC is primary HCC (cancer originating from mutations in hepatocytes or other cell types in the liver), which accounts for ~80% of all cases of HCC; other types of HCC include intrahepatic cholangiocarcinoma and mixed hepatocellular cholangiocarcinoma (3,6). Although various types of liver cancer are significant, the present review will focus mainly on primary HCC. Clinically, the majority of cases of HCC are identified at a nearly advanced stage, in part due to the fact that HCC is not generally associated with obvious physical signs or symptoms in the early stages. By contrast, early HCC can usually only be detected either by ultrasound imaging or by measuring the blood α-fetoprotein concentration, although its specificity is not high (2,6). As a result, HCC is not easily detected in the early stages, resulting in only a small number of, and poor, options of therapy being available. It is worth noting that the treatment of HCC is complex and several years of study have demonstrated that treatment of patients with HCC depends on the clinical manifestation, liver function and tumor staging, although multidisciplinary treatments exist, which mainly include surgical resection and liver transplantation, radiofrequency ablation, chemical drug targeting inhibition and immune suppression (3,7,8). However, due to its high invasiveness and high metastasis rate, the prognosis for patients with HCC continues to be poor (9,10). Therefore, there is an urgent need to identify novel early markers and therapeutic targets to prevent, diagnose and treat the disease.

Ion channels are specialized proteins found in cell membranes, which facilitate the movement of specific ions across the plasma membrane. These are involved in fundamental cellular processes, such as nerve impulse transmission, cell proliferation, apoptosis, hormone secretion and sensory transduction (11,12). The aberrant expression and function of ion channels leads to impairment of these processes, allowing normal cells to transform into malignant derivatives

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that exhibit uncontrolled proliferation and spread, which are hallmarks of cancer (13). Previous studies have confirmed that ion channels fulfill an important role in the development and progression of cancer, including the infinite proliferation of cells and their invasion and metastasis (14-16), and ion channels have been approved as effective drug targets for cancer therapy (17,18). As the most widely distributed type, K^+ channels regulate a variety of biological processes by controlling the flow of K^+ across cell membranes. The K^+ channel family has a total of 78 members, which can be divided into four major groups based on their domains and activation mechanisms: i) Voltage-gated K^+ (Kv) channels, ii) calcium-activated K^+ (KCa) channels, which themselves are divided into large conductance (BK), medium conductance (IK) and small conductance (SK) channels, iii) inward recirculated K^+ channels and iv) two-pore domain K^+ channels (15,19) (Fig. 1). As important contributors to the resting membrane potential, K^+ channels affect a variety of physiological processes (including regulating the heart rate, muscle contraction, neurotransmitter release, neuronal excitability, cell volume regulation, cell proliferation and differentiation, as well as cell cycle progression, apoptosis and metabolism) through regulating the intracellular K^+ concentration (20). There is an increasing body of evidence to suggest that a wide variety of K^+ channels are expressed on tumor cells, and dysregulation of their expression has been identified at the genomic, transcriptional, post-translational and epigenetic levels (15). In general, K^+ channels have been shown to regulate cell proliferation through four mechanisms: i) Establishment of oscillating membrane potentials; ii) control of cell volume dynamics; iii) regulation of calcium signaling; and iv) promotion of malignant growth through atypical non-ionic osmotic functions (15). Therefore, these channels have been shown to fulfill important roles in regulating tumor cell proliferation, cell cycle progression and apoptosis (21,22) (Fig. 2). For instance, upregulation of Kv1.1 has been demonstrated to be a marker for a subgroup of medulloblastomas (23); elevated levels of Kv1.3 expression are detected in numerous human malignancies, including breast, colon and prostate cancer (24); a high expression level of Kv11.1 [or human ether-a-go-go-related gene (hERG)] was shown to serve as a marker for solid and blood cancers (25); and the overexpression of Kv10.1 [or Ether-a-go-go-1 (EAG1)] has been identified in cancers of various human organs (26). In addition, K^+ channel modulators exert antitumor effects primarily as regulators of various types of cancer cell behaviors, including proliferation and migration (27). Furthermore, the abnormal expression and dysfunction of specific K^+ channels may lead to the development of various diseases. In addition, the expression and activity of K^+ channels have been indicated to be significantly correlated with the grade of malignancy of tumors. Targeting K^+ channels may therefore have great therapeutic potential in terms of the treatment of a wide range of human diseases (27,28). Certain studies have indicated that targeting the inhibition of K^+ channels may either directly inhibit tumor growth or improve the efficacy of chemotherapy or cytotoxic drugs, and this may be used as a combined treatment strategy for exerting anti-tumor effects (29,30). However, to date, to the best of our knowledge, the role of K^+ channels in HCC has rarely been studied.

Therefore, the aim of the present review was to provide an overview of the dysregulation of K^+ channels in HCC, also discussing their role in the proliferation, invasion and migration of HCC. The latest progress that has been made in terms of research on drugs targeting K^+ channels for the treatment of HCC is also discussed, as well as the existing limitations and future research directions in this field. These research efforts are geared towards providing novel opportunities for the early detection and treatment of HCC.

2. Role of K^+ channels in regulating metabolism, proliferation and injury of liver cells

The liver is a complex organ composed of a variety of different types of cells, which fulfills crucial roles in the body's metabolism. The roles of liver cells mainly comprise carbohydrate, lipid, protein and amino acid metabolism, bile acid intake, synthesis and output, as well as the metabolism of drugs and other foreign substances and the excretion of biological molecules (31). Therefore, damage sustained to the liver cells has an adverse effect on human health. K^+ channels fulfill an important role in acute and chronic hepatocyte injury. For instance, margatoxin (MgTX), a Kv1.3-specific blocker, has been shown to reduce the serum levels of TNF-α, IL-6, alanine transaminase and aspartate transaminase to reduce the expression ratio of C-C motif chemokine receptor 2/glutathione reductase 1 double-positive cells and ionized calcium binding adaptor molecule 1/c-type lectin domain family 4 member F positive cells in peripheral mononuclear macrophages, as well as reducing the infiltration rate of peripheral mononuclear macrophages into the liver (32). MgTX has also been shown to markedly protect the liver from acute liver injury. In addition, it is a novel target for the prevention and treatment of alcoholic fatty liver disease, precisely since it is able to regulate the function of macrophages. Further studies have indicated that the Kv1.3 pathway may alleviate the development of liver fibrosis by reducing the expression of TGF-β (32). It has been reported that KCa3.1 expression is increased in hepatocytes with liver fibrosis and that these increases coincide with the progression of liver injury. In addition, the inhibition of KCa3.1 has been shown to lead to cell apoptosis and increase the level of DNA damage, and also to stimulate the proliferation of hepatic stellate cells and aggravate liver fibrosis, which demonstrates that KCa3.1 channels exert a protective role in liver injury (33). The activity of two-pore domain K^+ (KCNK2) channels determines resting membrane potential and Ca^{2+} levels, thereby fulfilling a role in extracellular matrix production and the cell proliferation of hepatic stellate cells, providing a potential therapeutic target for hepatic fibrosis (34).

In recent years, the role of K^+ channels in the pathogenesis and treatment of HCC has been gradually uncovered. Several studies have shown that K^+ ions are a key regulator of hepatocyte function, which is manifested in inhibiting hepatocyte proliferation and inducing apoptosis, thereby preventing the metastasis of hepatocytes during the process of carcinogenesis. First, K^+ has been shown to inhibit the proliferation of hepatocytes, particularly HepG2 cells. In addition, the results of cell-cycle analysis experiments have indicated that K^+ is able to block the S-phase of the cell cycle and inhibit the growth of L02 and HepG2 cells via preventing normal DNA

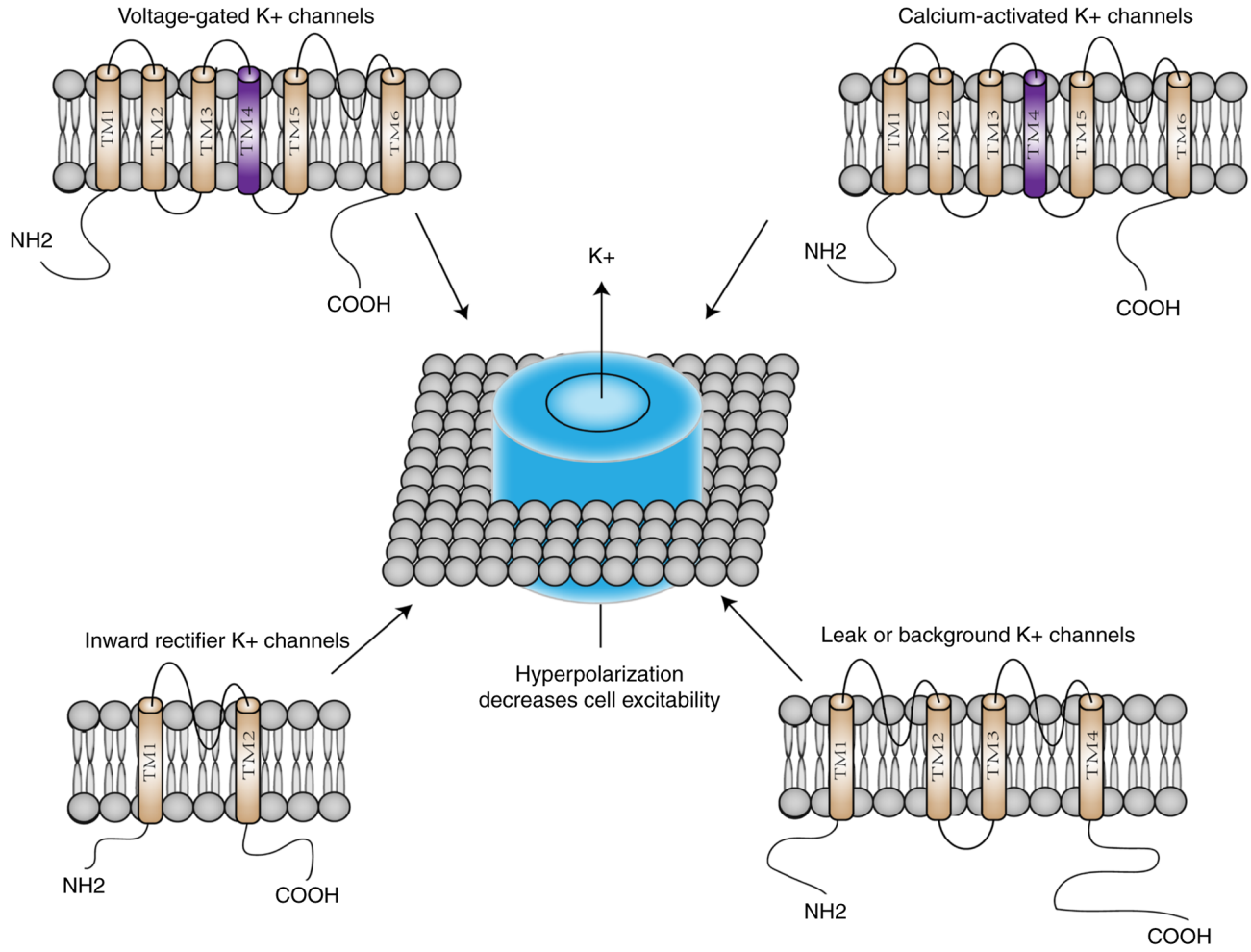

Figure 1. Schematic indicating the structure of potassium channels. A lateral view of monomers of an inward rectifier potassium channel, a two-pore domain potassium channel, a voltage-gated potassium channel and a calcium-activated potassium channel.

replication (35). Furthermore, it is well-established that the pro-apoptotic protein Bax and the anti-apoptotic protein Bcl-2 fulfill a key role in the regulation of cell apoptosis, and that a decrease in the Bcl-2/Bax ratio can promote cell apoptosis. K^+ ions promote the expression of the channel protein hERG in a dose-dependent manner, possibly by upregulating the expression of voltage-dependent anion-selective channel protein 1 or through disrupting the balance of the Bcl-2/Bax ratio, which prevents cells from being transferred to the precancerous pathway, leading to the imbalance of the mitochondrial membrane potential, thereby inducing mitochondria to release cytochrome c and to activate caspase proteins (35). These steps consequently result in an imbalance of the caspase-3/7 ratio, eventually leading to apoptosis. In conclusion, targeted activation or inhibition of K^+ channels can be a potential therapeutic approach to inhibit the development and progression of HCC.

3. K^+ channels in the development, migration, proliferation and invasion of HCC

Although a large number of ion channels associated with the proliferation, invasion and metastasis of HCC have been reported, the number of specific biomarkers and therapeutic targets available remains limited (36). As one of the most extensive ion channels, various studies have confirmed that K^+ channels have an important role in the development, migration, proliferation and invasion of HCC and may be recruitable as novel tumor markers and targeted therapeutic targets (Table I). Although the underlying mechanisms involved have yet to be fully elucidated, this may help to provide a foundation upon which further research can be based.

BK channels. Large-conductance calcium-activated potassium channels, i.e. BK channels, belong to the Ca^{2+}-activated K^+ channel family, which also contains two other members, namely IK and SK Ca^{2+}-activated K^+ channels (37). BK channels were first identified in chromaffin cells in 1981 (38), and were later found to be expressed in neurons of the vibratory nervous system, where they can be activated by membrane depolarization and increased cytosolic Ca^{2+} levels (39). Previous studies have reported a variety of functions of BK channels; for instance, BK channels are involved in the regulation of the cell cycle and proliferation, and they have also been shown to be involved in the migration of cancer cells (40). Previous studies have reported on disorders of BK channels in various types of cancer cells, including triple-negative breast cancer cells, neuroblastoma cells, glioblastoma and human astrocytoma cells (40). The patch-clamp technique has also been used

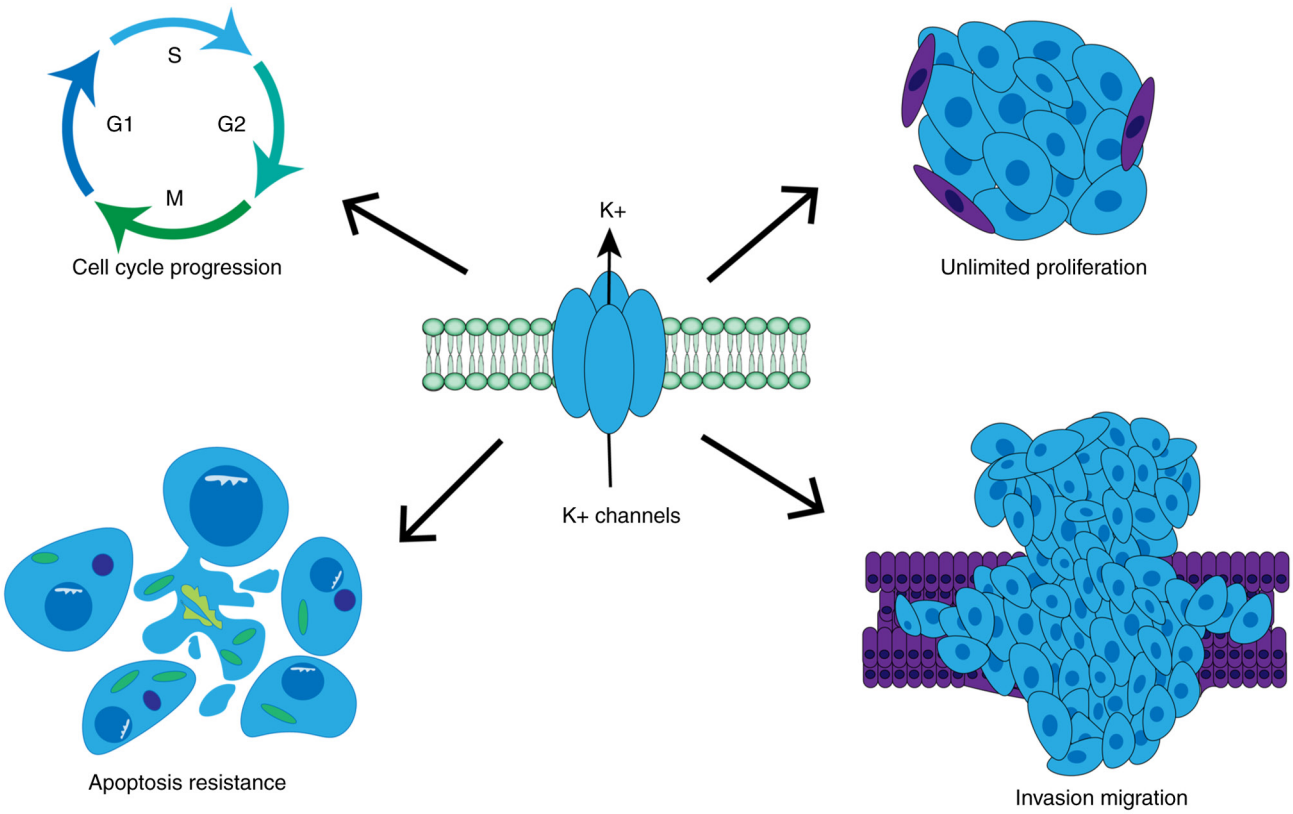

Figure 2. Roles of K+ channels in cancer, highlighting how they regulate cell proliferation, apoptosis, migration and invasion.

to identify BK channels in SMMC-7721 and Huh7 cells. The results obtained indicated that BK channels were functionally expressed in both HCC cells and normal stem cells (40). At the same time, the expression of BK channels in patients with HCC was detected, and it was found that the expression of BK channels in tumor tissues was higher compared with that in non-tumor tissues. More interestingly, the prognosis of patients with a high expression of BK channels was found to be significantly lower compared with that of patients with low BK channel expression (40). A significant role has been identified for BK channels in terms of promoting cancer cell migration and two possible explanations have been proposed: i) Through reducing the expression of epithelial-to-mesenchymal transition (EMT)-associated proteins, such as E-cadherin, vimentin and N-cadherin, and cell-cell contact is thereby reduced, which promotes cancer cell migration; and ii) through reducing cell volume to promote tumor cell migration (40).

KCa3.1 channels. The IK Ca^{2+}-activated K^+ channel (KCa3.1) belongs to a medium-conductance calcium-activated K^+ channel family and is a potential tumor-targeting molecule, which regulates intracellular ion homeostasis and cell volume under physiological conditions (41). It has been confirmed that this channel is overexpressed in a variety of different types of cancer and regulates the migration, invasion, proliferation and treatment resistance of cancer cells (42,43). It is well-known that HCC stem cells fulfill an important role in tumorigenesis, tumor recurrence and metastasis. A previous study found that KCa3.1 is highly expressed in liver cancer stem cells. KCa3.1 has also been shown to promote the proportions of $CD133^+$ and $CD44^+$ cell subsets, the expression of stem cell transcription factors and the ability of pellet formation *in vitro*, and to increase the incidence of tumor and tumor growth *in vivo* (44). Several studies have used immunohistochemical analysis to observe that the expression of KCa3.1 in HCC tissues is significantly upregulated, and this upregulation of gene expression is not only associated with the serum α-fetoprotein level, but it is also associated with an increased risk of recurrence in patients with early HCC (45,46). A number of studies have investigated the potential underlying mechanism(s) governing how KCa3.1 exerts a role in HCC. On the one hand, silencing the expression of KCa3.1 has been shown to lead to a reduction in the levels of extracellular signal-regulated kinases 1 and 2 (ERK1/2) and matrix metalloproteinase 9 (MMP-9) (47). Both ERK1/2 and MMP-9 are considered important biomarkers in the MAPK/ERK signaling pathway. MMP-9 is able to induce the degradation of the extracellular matrix, thereby reducing the stability of cancer cells and making them more prone to metastasis. Activation of ERK1/2 may lead to the transcriptional activation of downstream target genes that are associated with cell proliferation, migration and metastasis (47). In addition, it has been conclusively shown that KCa3.1 promotes the migration of HCC cells through the MAPK/ERK signaling pathway, thereby promoting tumor migration and invasion. Knockdown or inhibition of KCa3.1 expression has also been shown to reduce the migratory and invasive capabilities of HCC cells (46). Alternatively, other studies have found that KCa3.1 can promote the proliferation, invasion and migration of HCC cells via regulating the S-phase kinase-associated protein 2 (SKP2)/P27/P21 signaling pathway. The possible underlying

Table I. Role of K+ channels in the development of HCC.

Name	Role	Therapeutic strategy	(Refs.)
BK	Exhibits high expression in HCC Promotes the migration of HCC cells	Inhibition	(37)
KCa3.1	Exhibits high expression in HCC Promotes the proliferation, migration and transfer of HCC and ICC cells	Inhibition	(38-40)
EAG1	Exhibits high expression in HCC Promotes the proliferation, migration and invasion of HCC	Inhibition	(41)
KCCN2, KCNK15, KCNK17	Low expression in HCC Utility as diagnostic markers and predictors of prognosis	Requires further research	(42)
KCNK9	Exhibits high expression in HCC Utility as a diagnostic marker	Requires further research	(42)
KCNQ1	Shows low expression in HCC Promotes the invasion of cells	Activation	(43)
KCNQ1OT1	Exhibits high expression in HCC Promotes the proliferation and transfer of HCC cells, and inhibits apoptosis	Inhibition	(44-46)
ATP1A1FXYD6	Exhibits high expression in HCC Promotes the occurrence, proliferation and migration of HCC cells	Inhibition	(47-49)
Kv1.3	Exhibits high expression in PBC Promotes cell proliferation and apoptosis	Inhibition	(50)

HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; BK, large-conductance calcium-activated potassium channel; KCa3.1, intermediate-conductance Ca^{2+}-activated K^+ channel; EAG1, Ether-a-go-go-1 channel; KCCN2, KCCN15, KCCN17, KCCN9, two-pore domain K^+ channels; KCNQ1, potassium voltage-gated channel, KQT-like subfamily, member 1 channel; KCNQ1OT1, long non-coding RNA K+ voltage-gated channel subfamily Q member 1 overlapping transcript 1 channel; ATP1A1FXYD6, Na^+/K^+-ATPase channel; Kv1.3, voltage-gated potassium channel 1.3.

mechanism is that upregulation of KCa3.1 expression changes the half-life of the SKP2 protein, which subsequently mediates the degradation of P21/P27 to promote HCC cell cycle progression. By contrast, knockdown of KCa3.1 was found to significantly reduce the migratory or invasive potential of LM3 and Huh7 cells (45). These results corroborated that KCa3.1 may be a potential molecular target for the treatment of HCC. In HCC, KCa3.1 channels have also been implicated in the development of intrahepatic cholangiocarcinoma (ICC). The expression of the KCa3.1 channel is significant in ICC and this was found to be correlated with the age, lymph node metastasis and TNM stage of the patients. Finally, pharmacological inhibition or knockdown of KCa3.1 was also shown to reduce the proliferative and invasive capabilities of ICC cells (43).

Eag1 channel. The Eag1 channel, also known as Kv10.1, is a voltage-gated K^+ channel that is mainly distributed in the cell membrane and participates in various physiological processes of the body, including cell action-potential repolarization, Ca^{2+} signal transduction and cell volume regulation, thereby promoting cell proliferation and migration (27). It is worth noting that this channel has been found to have carcinogenic properties and that it has therefore garnered great interest among cancer researchers (48). A previous study reported that Eag1 is expressed at a low level in normal tissues, with the exception of the central nervous system and abnormal expression in tumor cells of different origins (26). A previous study also reported that, the mRNA and protein expression of Eag1 in cirrhotic tissues and pretumor lesions was significantly higher compared with that in normal liver (49). To investigate the role of Eag1 in HCC, the authors found that the colony-formation capabilities and proliferation rates of the LM3 and Huh7 cell lines were significantly decreased following downregulation of Eag1. On the other hand, Eag1 overexpression promoted the colony-formation capability and proliferation of the cells. In addition, macroscopic observations of the tumor volume showed that the tumors with Eag1 overexpression were larger compared with those in the control group with normal expression of Eag1 (50). In the same study, the authors identified the putative mechanism to account for the above effects: On the one hand, Eag1 is able to regulate SKP2 through ubiquitination to improve cell proliferation, and the expression of Eag1 was shown to be positively correlated with SKP2. Overexpression of Eag1 led to a prolongation of the half-life of SKP2, which subsequently stimulated the degradation of P21/P27, thereby accelerating the cell cycle progression of HCC. On the other

hand, Eag1 has also been shown to promote the migration and invasion of tumor cells via promoting the formation of pseudopodia (50). In conclusion, downregulation of Eag1 expression may be used as a therapeutic strategy for HCC.

KCNK channels. KCNK channels are K^+-selective channels. The majority of KCNKs act as outward rectifying channels, or are almost voltage-independent at physiological K^+ concentrations to maintain the resting membrane potential, thereby regulating biological metabolism and apoptosis (51-53). It is worth noting that KCNKs are able to contribute to oncogenes in various cancers. For instance, in ovarian cancer, certain regulators of KCNK2 have been shown to inhibit apoptosis and to promote cell proliferation (54). The expression level of the long non-coding RNA (lncRNA) KCNK15-antisense 1 was found to be downregulated in pancreatic cancer, which consequently inhibited the invasiveness of tumor cells (55). By contrast, KCNK9 is upregulated in breast and colorectal cancer, and increases tumor tolerance via its anti-apoptotic activity on the cancer cells (56,57). In HCC, different KCNK channels have been demonstrated to have different expression levels. Through analyzing the UALCAN database, researchers observed that the expression levels of KCNK2, KCNK15 and KCNK17 were decreased in HCC, whereas the expression level of KCNK9 was increased, and these trends were associated with poor prognosis for patients with HCC. Additionally, the receiver operating characteristic curve analysis suggested that the levels of KCNK2, KCNK9, KCNK15 and KCNK17 levels may be used as biomarkers for the diagnosis and prognosis of HCC (52). This study provided important information for the early diagnosis of HCC.

Potassium voltage-gated channel, KQT-like subfamily, member 1 (KCNQ1) channels. KCNQ1 channels, as a class of voltage-gated K^+ channels, are usually expressed in a variety of tissues, including the heart, stomach, intestine and pancreas, which mediate the outflow of K^+ ions from cells and regulate ion homeostasis in tissues (58). Previous studies have confirmed that the expression of KCNQ1 is markedly downregulated in human HCC cell lines compared with non-malignant cells or normal human liver tissues (59,60). On the other hand, overexpression of KCNQ1 inhibited the invasion of HCC, and the same study revealed that pharmacological activation of KCNQ1 channels inhibited tumor metastasis of HCC in nude mice. The putative underlying mechanism may be that KCNQ1 affects the cellular distribution of β-catenin, thereby inhibiting the activity of the Wnt/β-catenin signaling pathway, which acts as one of the main pathways involved in both the initiation and progression of HCC (59) and in the mRNA expression of its downstream targets, ultimately fulfilling a tumor-suppressor role (60). In conclusion, it has been demonstrated that the KCNQ1 channel may be used as both a biomarker and potential therapeutic target for HCC.

Long non-coding RNA (lncRNA) K^+ voltage-gated channel subfamily Q member 1 overlapping transcript 1 (KCNQ1OT1) channels. The lncRNA KCNQ1OT1 is a chromatin-regulatory lncRNA that has been shown to participate in the regulation of various types of cancer as an oncogene, including rectal cancer and lung cancer (61). However, at present, little is known concerning the mechanism via which KCNQ1OT1 promotes carcinogenesis. However, certain studies have found that the short-strand repeat polymorphism in KCNQ1OT1 contributes to the initiation of HCC, which may affect the expression of KCNQ1OT1 and cyclin-dependent kinase inhibitor 1C (CDKN1C) through a structure-dependent mechanism (62). Previous studies have also reported that the expression of KCNQ1OT1 is associated with the development of HCC. Several studies have reported that KCNQ1OT1 is able to affect the growth of HCC; for example, by inhibiting the expression of microRNA (miR-504) (61), through targeting miR-338-3p (63), by regulating the miR-506-3p/forkhead box (Fox)Q1 axis (64) and through regulating the miR-146A-5p/alkaline ceramidase 3 signaling axis (65). Of note, the latter study (65) reported that the expression of KCNQ1OT1 is significantly upregulated in HCC; furthermore, it was found that silencing KCNQ1OT1 inhibited cell proliferation, improved the sensitivity to radiotherapy and promoted cell apoptosis, as well as hindering the metastasis of HCC cells. In terms of treatment strategies, a previous study (66) reported that KcNQ1OT1 knockdown enhanced the sensitivity of sorafenib through targeting miR-506, induce cell apoptosis and inhibit the metastasis of sorafenib-resistant HCC cells. In conclusion, KCNQ1OT1 may also provide novel therapeutic strategies and opportunities for HCC.

Na^+/K^+-ATPase (NKA) channel. NKA channel, as a member of the P-type ATPase family, is composed of three peptides: The α and β subunits and FXYD protein (a type of small molecule single transmembrane protein, which regulators of Na+/K+-ATPase). It pumps three Na^+ ions out and two K^+ ions in for each ATPase hydrolyzed, acting as a multifunctional protein, which fulfills roles in cell attachment, adhesion, motility and signal transduction (67,68). In recent years, it was shown that NKA is abnormally expressed and has abnormal activity in various types of cancer, which signified that it may be anticipated to become a novel target for tumor therapy. Of note, the dysregulation of NKA subunits has been shown to vary among different types of cancer. Previous studies have found that the expression of ATPase Na^+/K^+ transporting subunit α1 (ATP1A1) in HCC is significantly higher compared with that in adjacent non-tumor tissues (69,70). ATP1A1 has been shown to have the following roles: i) Knockdown of ATP1A1 in HepG2 and MHCC97H cells significantly reduced their proliferation *in vitro* and inhibited the tumorigenicity of MHCC97H cells *in vivo*; ii) downregulation of ATP1A1 expression in of HepG2 cells led to cell-cycle arrest in G_2/M phase and apoptosis, and in Hep3B, it increased cell migration; and iii) downregulation of ATP1A1 expression led to the production of excessive reactive oxygen species (ROS), which led to DNA damage and cell-cycle arrest, and prevented the replication of damaged and defective DNA (69). In addition, in non-alcoholic steatohepatitis (NASH)-associated malignancies, α1-NKA signaling was shown to activate the PI3K/Akt signaling pathway, which simultaneously inhibited the FoxO3 circuit, leading to the downregulation of the anti-apoptotic survival protein and pro-apoptotic protein, second mitochondria-derived activator of caspase/direct inhibitor of apoptosis-binding protein with low pI, a process that is conducive to cell division and the development of HCC (71).

Table II. Drugs targeting K+ channels in HCC.

Drugs	Mechanism	(Refs.)
IbTX	Blocks the BK channel Inhibits migration and invasion	(37)
Astemizole	Blocks the Eag1 channel Inhibits proliferation and promotes apoptosis	(82)
Procyanidin B1	Blocks the Eag1 channel Inhibits proliferation and promotes apoptosis	(79)
TRAM-34	Blocks the KCa3.1 channel Inhibits proliferation and promotes apoptosis	(38,83)
Berberine and Ouabain	Combined with Na+/K+-ATPase enhances the anti-liver cancer effect of sorafenib	(47,84)
Sodium orthovanadate	Inhibition of ATPase reverses sorafenib resistance of HCC cells	(85)

HCC, hepatocellular carcinoma; Eag1, Ether-a-go-go-1; IbTX, iberiotoxin; TRAM-34, 1-[(2-chlorophenyl) diphenylmethyl]-1H-pyrazole.

Therefore, ATP1A1 not only serves as a potential biomarker for the diagnosis and prognosis of HCC (72), but it may also offer a therapeutic path for HCC. FXYD proteins are regulators of Na^+/K^+-ATPase that are located in the cell membrane, which regulate the kinetic properties of Na^+/K^+-ATPase by changing the rate and affinity of Na^+ and K^+ transport (73). FXYD6 was shown to be upregulated in HCC, promoting the migration and proliferation of HCC cells (74). The upregulation of FXYD6 is also positively correlated with an increase of Na^+/K^+-ATPase activity and it mainly exerts its antitumor activity through activating the downstream SrC-ERK signaling pathway. In addition, the blocking of FXYD6 by self-produced anti-FXYD6 functional antibody was shown to significantly inhibit the growth of mouse xenograft tumors, indicating that FXYD6 can act as a novel therapeutic target for HCC (74). Taken together, these results demonstrated that FXYD6 fulfills a key role in the progression of HCC, suggesting that FXYD6-targeting therapy may be of benefit for the clinical treatment of patients with HCC. Therefore, each subunit of NKA may be used as a novel potential therapeutic target for HCC, offering further options for the treatment of HCC.

Kv1.3. Kv1.3, an important regulatory protein of the immune response, has been found in lymphocytes and is mainly involved in immune regulation of the body's immune system (75). Kv1.3 protein on cell membranes is involved in cell proliferation, whereas Kv1.3 channels located on mitochondria are involved in cell apoptosis, and therefore, Kv1.3 located on mitochondria is considered to be a novel tumor biomarker (32,76). It has been reported that the Kv1.3 channel is involved in the proliferation and apoptosis of a variety of different types of tumor. It is noteworthy that the expression of Kv1.3 has been shown to vary with the tumor stage and downregulation of Kv1.3 may significantly inhibit cell proliferation and increase cell apoptosis (77). However, to date, only a small number of studies have been published on the role of this channel in HCC, although a previous study reported that Kv1.3 blocker can regulate the hyperreactivity of B lymphocytes and inhibit the abnormal hypersecretion of antimitochondrial antibodies in primary biliary cirrhosis to achieve the purpose of treating HCC (78). However, the precise role of Kv1.3 in HCC requires further study.

4. Targeted therapeutic agents for HCC

At present, the treatment of HCC mainly includes surgery, radiotherapy and chemotherapy, although HCC is not sensitive to radiotherapy and conventional chemotherapy drugs, such as doxorubicin, fluorouracil and cisplatin, have serious side effects (7,79). Sorafenib is the first-line drug in the treatment of HCC supported by the currently available data, although the efficacy varies among different patients and the sensitivity to the drug is typically reduced following long-term treatment (80); therefore, it is urgent to identify novel therapeutic strategies. With this as the aim, molecular targeted therapy has been attracting increasing attention. Research confirming that the abnormal expression of certain K^+ channels serves an important role in the development and progression of HCC, has also found several drugs able to target and inhibit the ion channels, thereby exerting antitumor effects (Table II). For instance, pharmacological inhibition of voltage-gated K^+ channels has long been reported to reduce the adhesion and proliferation of HCC cells, thereby exerting their antitumor effects (81).

Iberiotoxin (IbTX). IbTX, a BK channel antagonist, selectively binds to the pore-forming α-subunit of the BK channel (40). It has been reported that blockade of BK channels inhibits both hypoxia-induced migration and chemotherapy resistance to cisplatin in human glioblastoma cells (82). In HCC, the authors of a previously published study (40) experimentally found that blocking BK channels with IbTX led to a marked inhibition of the migration and invasion of HCC cells under hypoxic conditions (40). Subsequently, the same authors identified that the mechanism of its action was to induce G_2 phase arrest of HCC cells, thereby inhibiting their migration and invasion, and

regulating the growth of the tumor (40). This finding provided a novel strategy for the treatment of HCC.

Astemizole. Astemizole is an antihistamine that penetrates lipid bilayers and binds to channels inside cell membranes (83). Owing to its inhibitory effects on several cancer-associated proteins, including K^+ channels, histamine receptors and P-glycoproteins, research has focused on its potential therapeutic role in cancer. A previous study identified that astemizole was able to inhibit the proliferation and increase the apoptosis of HepG2 and Huh-7 cells (84). Although astemizole has diverse targets, exploration of the mRNA and protein expression levels of Eag1 in these cells has revealed that the inhibition of Eag1 channels mediated by astemizole in HCC may potentially be the mechanism that accounts for its anti-proliferative and pro-apoptotic effects (49,85). Treatment with astemizole was also shown to reduce the mRNA and protein expression levels of Eag1 in diethylnitrosamine-treated mice, resulting in both improved histological features and appearance of the liver (85). It was thereby determined that astemizole may have clinical utility in terms of the prevention and treatment of HCC. Another study reported that serious adverse reactions to the use of astemizole as a therapeutic agent only occur in excessive use of the drug with HCC (84), and thus, it holds promise as a selective agent both to prevent the risk of HCC and as a promising therapeutic agent for patients with HCC.

Procyanidin B1. Procyanidin B1, a natural compound derived from grape seed, not only induces the apoptosis of cells, but also inhibits tumor growth (86,87). A previous study reported that procyanidin B1 directly binds to the Eag1 channel, thereby inhibiting its current, whereas its effect on other K^+ channels was negligible, and this provided the putative underlying mechanism to account for its inhibition of the migration and proliferation of HCC cells (79). Of note, procyanidin B1 was found to not exert any adverse effects on normal metabolism in mice compared with conventional antitumor drugs. In conclusion, procyanidin B1 was demonstrated to be a significant potential antitumor drug for HCC.

1-[(2-Chlorophenyl)diphenylmethyl]-1H-pyrazole (TRAM-34). A previous study reported that inhibition of KCa3.1 via genetic and pharmacological means led to a significant reduction in the proliferation of tumor cells and the susceptibility of tumors to certain therapeutic interventions was also changed (88). TRAM-34, a specific KCa3.1 blocker, has been reported to be effective in inhibiting cell proliferation and motility in a variety of different types of cancer, including glioblastoma and lung cancer (89,90). Of note, long-term treatment with TRAM-34 for atherosclerosis therapy at therapeutic concentrations did not lead to any significant side effects (91). TRAM-34 has also been shown to inhibit the proliferation and induce the apoptosis of HepG2 cells. On the one hand, TRAM-34 can inhibit cell proliferation by mediating decreases in both the mRNA expression of estrogen receptor-α and nuclear factor-κB activation (92); on the other hand, the apoptosis of HCC cells was found to be promoted by regulating the intracellular level of ROS and through promoting p53 activation. In addition, treatment with TRAM-34 also led to a marked inhibition of the migration of HepG2, thereby reducing the development of HCC (93). In addition to fulfilling a role in HCC, inhibition of KCa3.1 channels by TRAM-34 was also shown to inhibit hepatocyte fibrosis (94) and ICC tumor growth (43). Taken together, these results indicated that TRAM-34 may potentially be a drug for the treatment of HCC.

Berberine and ouabain. Berberine, a natural dibenzyl isoquinoline alkaloid isolated from Berberis (common name: Barberry), has been studied as a drug against a variety of different types of cancer, including HCC. It was demonstrated that berberine could induce the phosphorylation of Src in a Na^+/K^+-ATPase-dependent manner, leading to activation of p38-MAPK and the epidermal growth factor receptor (EGFR)/ERK signaling pathway (95). In addition, the Na^+/K^+-ATPase ligand ouabain has also been shown to induce the phosphorylation of Src, EGFR, insulin-like growth factor 1 receptor, ERK1/2 and p38-MAPK in HCC cells, leading to the inhibition of cell growth and migration through inhibiting EMT in HCC cells both *in vivo* and *in vitro* (69). It was found that treatment of HCC with sorafenib led to a significant induction of cell death and inhibition of the growth of HCC xenografts *in vivo* (95). Therefore, targeting the Na^+/K^+-ATPase with berberine and ouabain is a novel strategy to enhance the effects of sorafenib. In addition to the drugs that have already been studied, it would be useful to identify other drugs that target this channel in future studies.

Sodium orthovanadate (SOV). It has been reported that Na^+/K^+-ATPase activity is increased in drug-resistant tumors and its enhanced activity contributes towards the biological behaviors observed in, and drug resistance of, cancer, such as prostate, breast and lung cancer or leukemia (96). Blocking Na^+/K^+-ATPase through the use of specific inhibitors has been shown to re-sensitize cancer to chemotherapy drugs (97,98). It was found that the sorafenib resistance of HCC cells was associated with higher levels of Na^+/K^+-ATPase activity. SOV, a phosphate analogue, is a recognized ATPase inhibitor and treatment of sorafenib-resistant HCC with SOV has been shown to re-sensitize the cancer to sorafenib, enhancing its antitumor effects (99). Although the exact mechanism underlying its inhibition of ATPase requires further study, what has been discovered to date is at least sufficient to demonstrate that SOV may be an effective candidate drug to overcome sorafenib resistance in the treatment of HCC.

5. Conclusions and prospects

A large number of studies have demonstrated that the regulation of ion channels is associated with the development and progression of HCC (77). In the present review, the abnormal expression of K^+ channels in HCC was discussed. These K^+ channels are known to be involved in the development, proliferation and invasion of HCC, and so they may serve as novel tumor markers and potential therapeutic targets for HCC. Although an increasing body of evidence has indicated the abnormal expression and function of K^+ channels in HCC, research on ion-channel-targeted therapy in cancer remains in its infancy and the mechanisms of action have yet

to be fully elucidated. Therefore, further systematic exploration of the mechanisms involved is required to help improve the quality of life of patients with HCC. Although certain K^+ channels have been shown to be abnormally expressed in HCC, whether they can be selectively targeted in tumor cells remains to be determined. Although the expression levels of K^+ channels in tumor and non-tumor tissues have been compared, the differences in K^+ channel expression at the different stages of HCC remain poorly understood. The majority of channels studied so far have been confined to the plasma membrane, but these ion channels may also fulfill important roles in other organelles, such as the mitochondria, and these may be useful as novel targets for tumor therapy in the future. The majority of studies performed to date have been laboratory-based and further studies are required. In the future, it is expected that these targeted drugs will be tested in clinical trials and their efficacy either alone or in combination with other antitumor drugs in patients with HCC or at risk of developing HCC may be further tested. To date, differences between K^+ channels in HCC and other tumors have not been reported, and whether K^+ channels may be used to distinguish different cancers by comparing the expression levels or expression sites requires further research.

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Authors' contributions

XC made substantial contributions to the conception and design of the study, as well as writing the manuscript and performing the literature search. LZha, LHe, LZhe and BT were involved in revising the manuscript critically for important intellectual content. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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