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The role of ion channels in high-grade glioma (HGG)

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Abstract

High-grade glioma (HGG) is an aggressive brain cancer with an overall 5-year survival rate of less than 10% in adults and less than 2% in children. Despite significant research efforts, surgery combined with chemo- and radiotherapy is the only treatment option available for these patients. New targeted therapies such as kinase inhibitors, and combined modalities fail in clinical trials due to the inability of drugs to cross the blood-brain barrier, and HGG pathway rewiring. *In vitro* studies suggest that ion channels contribute to HGG pathway rewiring and tumor survival. There are several United States Food and Drug Administration-approved neurological drugs that readily cross the blood-brain barrier and target ion channels. These drugs are readily available on the shelf and can be easily repurposed to treat HGG. A systematic understanding of the oncogenic roles of ion channels in patients with HGG will help us to repurpose ion channel drugs to treat HGG. The study of the oncogenic potential and therapeutic targeting of ion channels in HGG is still in the early stage. This review summarises the findings that elucidate the expression and oncogenic potential of ion channels in HGG patients. We have identified the research gaps to translate ion channels as therapeutic targets for HGG. Finally, we highlight the potential to use ion channel drugs as a single agent or as part of combination therapy for the treatment of patients with HGG.

Keywords: High-grade glioma, Ion channels, Ion channel drugs, Tumor resistance, Drug repurposing

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Introduction

Glial cells form 50% of the cells in the central nervous system where they support and protect neurons, form myelin, and facilitate cellular homeostasis (1). About a third of all brain cancers originate from glial cells and are known as gliomas. Gliomas are grouped based on their region of origin, grades/pathological features, and aggressiveness. Based on the region of origin, gliomas are subdivided as; diffuse intrinsic pontine glioma (DIPG), astrocytoma, oligodendrogliomas, brain stem glioma, optic nerve glioma, oligoastrocytoma, ependymoma (EPN) and glioblastoma multiforme (GBM) (2). Gliomas are classified as grades based on their pathological features (grade I, II, III and IV). Highly diffusive and invasive gliomas that belong to grades III and IV are collectively known as high-grade gliomas (HGG) and they invade through the extracellular space in the brain and central nervous system (3, 4).

The diffusive nature of HGG makes complete surgical resection impossible (2, 5, 6). Hence, surgery followed by chemo- and radiotherapy is the only treatment option for HGG patients, resulting in a very low 5-year survival rate of <10% (7). As HGGs belong to stage III and IV, most patients die within 18 months of diagnosis despite advances in treatment. Therefore the only way to measure the therapeutic effectiveness of drugs is via the increased survival rate of patients (8). HGG plasticity enables the tumor to rewire and adapt its pathways for tumor growth and drug resistance (8–10) however, the key regulators that drive HGG plasticity are not fully understood. This emphasises the need to identify novel therapeutic targets to prevent HGG plasticity and increase the survival of patients with HGG.

Recent advances in the field of HGG demonstrate a role for ion channels in both HGG proliferation and invasion (11–13). Ion channels are membrane structures that regulate the movement of ions across the cellular membrane to control various physiological functions including brain cell function (14–18). Normal brain cells maintain a high degree of plasticity to cope with continuous brain remodelling during memory formation and to recover from various forms of brain cell injury (19–21). Ion channels are the key regulators of brain cell plasticity that contribute to pathway rewiring in brain cells through their structural and functional alterations (22). Research suggests that cancer cells hijack this dynamic nature of ion channels to support their oncogenicity (23, 24). The role of ion channels in HGG tumors has been demonstrated primarily through retrospective correlational studies of ion channel aberrations and patient survival with genomic and proteomic studies (101, 102). While *in vitro* studies demonstrate that ion channel gene mutation and abnormal pore formation can drive HGG tumorigenicity (reviewed in (25–28), (12, 29–31), some studies suggest that kinase pathways activates ion channels in HGG (32). However, the functionality and oncogenic potential of many ion channels remain unknown.

Repurposing ion channel drugs for HGG treatment may represent an attractive therapeutic option for patients with HGG, as most clinically approved ion channel drugs are used to treat neurological disorders, and can easily cross the blood-brain barrier (BBB) (reviewed in (33)), (34). While literature does summarize the ability to target ion channels as cancer therapy using laboratory models (reviewed in (35), there are few studies that discuss ion channel expression patterns in HGG clinical/patient samples and correlate them with therapeutic options (36). Therefore, this review will discuss: 1) ion channel biology and its role in cancer, 2) expression and function of ion channels in HGG clinical samples, 3) ion channel therapeutics to treat cancer, including HGG and 4) areas for future research. We also briefly discuss ion channel expression patterns identified in HGG clinical samples and their correlation with patient prognosis and survival with relevance to the various types of ion channels.

Overview of ion channel biology and its role in cancer

Ion channels are integral membrane proteins that maintain an electrochemical gradient for ion transport across cellular membranes (37). Each ion channel comprises of multiple protein subunits that are assembled together to form a pore-forming structure. This process is known as ion channel biogenesis (38–40). The concentration of different intracellular ions such as calcium, sodium, potassium and chloride play a key role in regulating ion channel biogenesis (Figure 1) (41). Ion channel expression and function is highly

cell-type specific (37, 42, 43) (44). Ion channel expression is highly dependent on biological processes including transcription, translation, protein processing, subunit assembly and transportation of ion channel genes. Each cell type may express more than ten different types of ion channels (45).

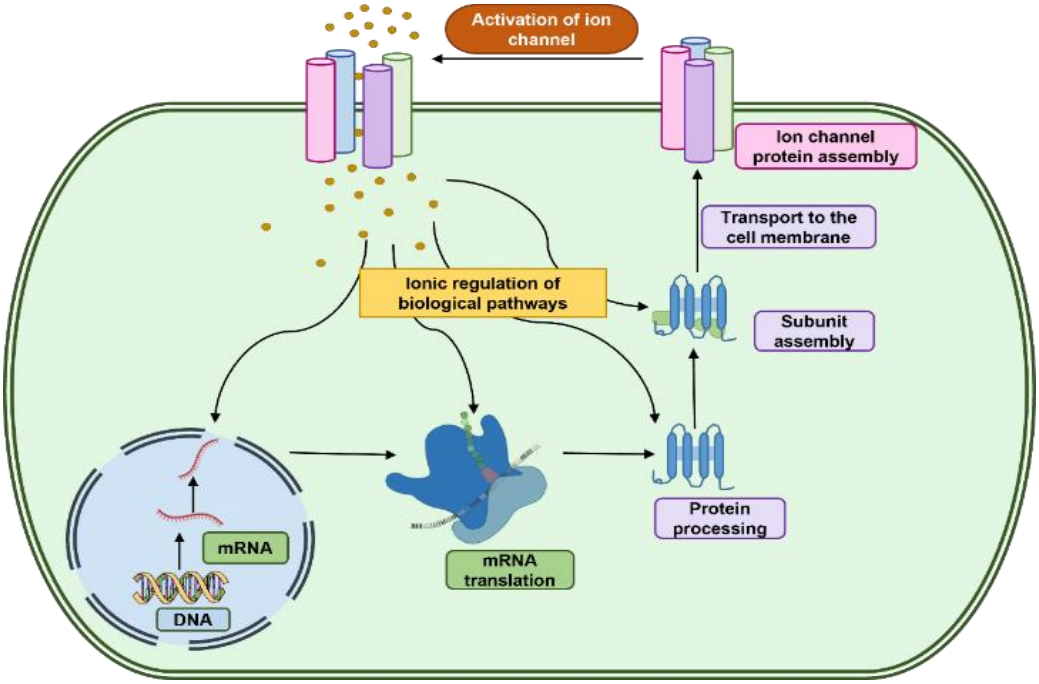

Figure 1. Regulation of ion channel expression. Ion channel biogenesis is a multistep process and is regulated by intracellular ionic concentration. Extracellular ionic concentration is responsible to keep an ion channel either in the open or closed state (41).

The function of an ion channel is dependent on its activation state (reviewed in (44)) and ion channels can swing between both active and inactive states (46). The activation state is regulated by multiple factors including gating strategy and the channel orientation across the cell membrane (reviewed in (47–51)). Multiple ion channels share common roles and possess complementary and compensatory functions to effectively maintain the cellular membrane potential (52). The ability of ion channels to constantly change between their activation states make them particularly susceptible to malignant transformation (53). For example, changes in the extracellular ionic concentration results in an acidic tumor microenvironment that is demonstrated to increase cell proliferation and invasion (38, 54), (reviewed in (55–57)). Genomic instability or protein dysfunction of ion channels (58), (reviewed in (56, 59)) is the most common malignant transformation that alters the activation state of ion channels. Their functions include altering key intracellular processes such as transcription, cellular secretion and cell volume to regulate cell proliferation, autophagy and cell cycle (60–62), (reviewed in (63–68) 69–72). Thus, ion channels are dynamic in their function and undergo constant structural, functional, and activation changes to coordinate and maintain an electrochemical gradient. Ligand binding, electrical flux or voltage alterations or a combination of these maintains the activation state of ion channels (73). Collectively, ion channels regulate the functioning of vital organs such as cardiac muscles (reviewed in (74)) and synaptic transmission across neurons (reviewed in (75)). Recent evidence demonstrates a role for ion channels in cancer progression (Table 1) (76, 77) (reviewed in (56, 78, 79)). Cancer cells hijack ion channels for cellular proliferation, invasion, metastasis, and drug resistance (80–82). Whole genome Pan-cancer analysis demonstrated ion channel gene dysregulation in almost all cancer types with particularly high expression of many ion channel genes seen in most cases (83).

In the context of HGG, *in vitro* proliferation and invasion assays demonstrate a role for ion channels in HGG progression (reviewed in (13)). For instance, calcium (84–86) and calcium-induced potassium channels are involved in HGG proliferation (87–90), (reviewed in (12)); potassium, chloride (91–93) and

calcium-activated intermediate (IK) potassium channels regulates HGG migration (4, 94) and sodium and chloride channels play a key role in HGG drug resistance (31, 95, 96).

Table 1. Role of ion channels in cancer progression.

Cancer type	Ion channel type	Genes involved	Oncogenic phenotype	Reference
Nasopharyngeal	Transient Receptor Potential Cation Channel Subfamily M	TRPM7	Cell migration	(202)
	Calcium-sensitive chloride channel	CIC-3	Cell proliferation	(175)
Esophageal squamous cell	voltage-dependent potassium channel (Kv)	hERG1	Proliferation, stem cell growth	(203)
	Transient Receptor Potential Cation Channel Subfamily V	TRPV2	Proliferation and drug resistance	(204)
	Transient Receptor Potential Cation Channel Subfamily C	TRPC6	Poor patient prognosis	(203)
	calcium release-activated calcium channel protein 1	Orai1	Cell proliferation	(205)
Thyroid	Transient Receptor Potential Cation Channel Subfamily C	TRPC1	Cell proliferation and migration	(206)
	voltage-dependent potassium channel (Kv)	hERG1	Cell migration	(206)
Breast	Transient receptor potential melastatin channel	melastatin channels	cellular invasion	(207)
	voltage-sensitive calcium-activated chloride channel	TMEM16A	Cell proliferation	(208)
	Transient Receptor Potential Cation Channel Subfamily V	TRPV2	Revert drug resistance	(209)
	voltage-gated sodium channel	Nav1.5	Tumor Metastasis	(164)
	Potassium voltage-gated channel	Kv10.1 (EAG)	Cell proliferation and migration	(210)
	small conductance calcium-activated potassium channel	KCa 2.3	Cell migration	(211)
Renal cell	Transient Receptor Potential Cation Channel Subfamily M	TRPM3	Promotes cell growth	(212)
	Transient Receptor Potential Cation Channel Subfamily C	TRPC6	Cell proliferation and aggressiveness	(213)
	calcium release-activated calcium channel protein 1	Orai1	Cell proliferation and migration	(214)
	small conductance calcium-activated potassium channel	KCa3.1	Highly metastatic and reduced progression-free survival	(215)
Colon	Intracellular chloride channel	CLIC1	Cell invasion and migration	(216)
	Transient Receptor Potential Cation Channel Subfamily C	TRPC1, Orai1	Cell migration	(203)
	voltage-gated sodium channel	Nav1.5	Poor patient prognosis	(217)
	small conductance calcium-activated potassium channel	KCa3.1	Proliferation and invasion	(218)
Ovarian	Intracellular chloride channel	CLIC1	Intraperitoneal metastasis	(219)
	Transient Receptor Potential Cation Channel Subfamily C	TRPC3	Cell growth	(220)
	voltage-gated sodium channel	Nav1.5	Cell metastasis	(221)
Cervical	voltage-dependent potassium channel (Kv)	hERG1	Cell proliferation	(222)
	voltage-gated sodium channel	NaV 1.6	Higher invasive potential	(223)
Melanoma	voltage-dependent potassium channel (Kv)	hERG1	Tumor metastasis	(224)

Bladder	Transient Receptor Potential Cation Channel Subfamily M	TRPM7	Proliferation, recurrence, metastasis and invasion	(221,225)
Prostate	Transient Receptor Potential Cation Channel Subfamily M	TRPM4, 8	Enhanced survival, proliferation, cellular invasion	(207)
	Intracellular chloride channel	CLIC1	Cell proliferation and metastasis	(226)
	Potassium channel subfamily K member 2	TREK-1	Reduced castration resistance-free survival	(227)
	voltage-gated sodium channel	Nav1.7	Tumor metastasis	(228)
	Intracellular chloride channel	CLIC1	Cell migration and proliferation	(229)
	Transient Receptor Potential Cation Channel Subfamily M	TRPM8	Tumor proliferation and growth	(230,231)
Gastric	voltage-dependent potassium channel (Kv)	hERG1	Survival and cell invasion	(203)
	Transient Receptor Potential Cation Channel Subfamily M	TRPM7	Cell proliferation	(184)
	Intracellular chloride channel	CLIC1	lymphatic invasion, lymph node metastasis and perineural invasion	(232)
	calcium release-activated calcium channel protein 1	Orai 1	Cell metabolism, migration and invasion	(233)
	voltage-gated sodium channel	Nav1.7	Cell proliferation and invasion	(234)
	voltage-dependent potassium channel (Kv)	hERG1B (Kv11.1)	Reduced survival, metastasis	(235)
Hepatocellular	Transient Receptor Potential Cation Channel Subfamily C	TRPC1	Cell proliferation	(236)
	Intracellular chloride channel	CLIC1	Poor prognosis	(237)
	small conductance calcium-activated potassium channel	KCa3.1	Cell proliferation and migration	(238)
Glioma	small conductance calcium-activated potassium channel	KCa3.1	Tumor invasion	(239)
	Transient Receptor Potential Cation Channel Subfamily C	TRPC6	Hypoxia-induced aggressive tumor and angiogenesis	(240)
	Transient Receptor Potential Cation Channel Subfamily C	TRPC1,3,5	Cell proliferation	(241)
	Intracellular chloride channel	CLIC1	Reduced patient survival	(180)
	voltage-dependent calcium channel L-type, alpha 1C subunit	Cav1.2	Cell Proliferation	(242)
	P/Q voltage-dependent calcium channel	Cav2.1	Progression of tumor growth	(216)
	Voltage-gated potassium channel	Mitochondrial Kv1.3	Cell survival	(243)
	ATP driven potassium channel	Katp	Radio resistance	(244)

Additionally, *in vitro* models demonstrate a distinct role for calcium, potassium, sodium, and chloride ion channels in regulating HGG progression and cellular homeostasis compared to glial cells (reviewed in (97, 98)) (Figure 2). Multiple ion channels coordinate together to balance ionic flux, making it complicated to tease apart their mechanism of oncogenesis. For example, Ca2+-activated K+ (BK) channel co-localize with ClC-3 Cl^- channels to initiate brain metastasis (4). However, there is limited pre-clinical evidence to demonstrate the oncogenic potential of ion channels and the anti-tumor efficacy of ion channel drugs in HGG tumors (99,100). On the other hand, ion permeating proteins are a common drug target. A pan-cancer analysis identified ion permeating proteins are highly expressed in a group of cancer samples of HGG (83).

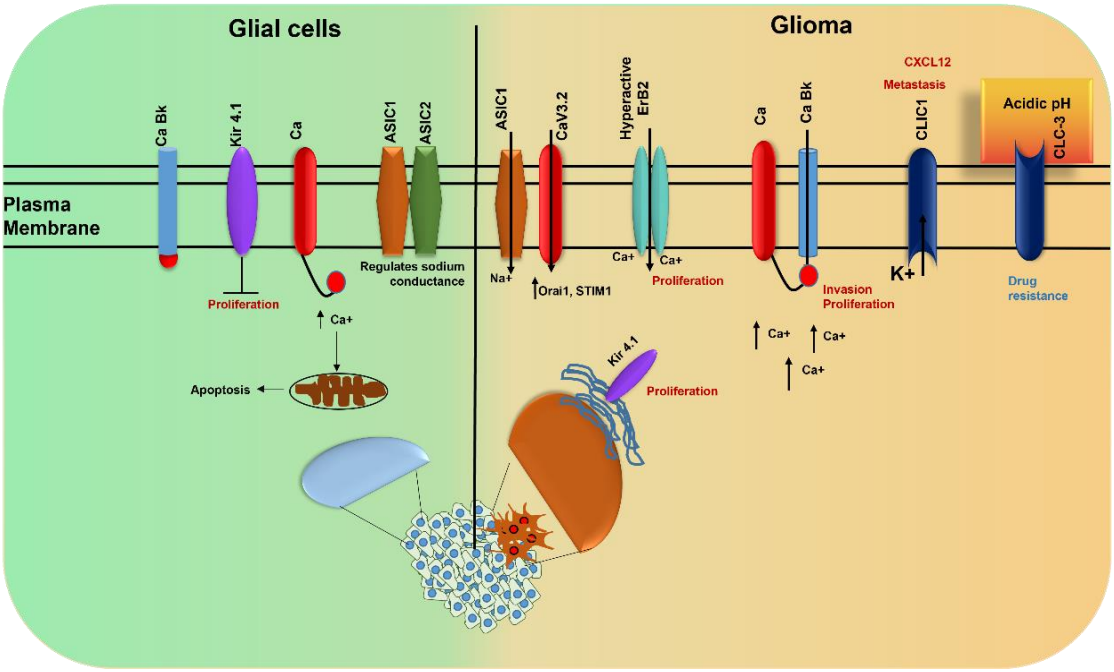

Figure 2. Expression and function of ion channels in normal brain cells and glioma cells. The pictorial representation shows the expression of some distinct ion channels and their role in glioma progression. Glioma cells have distinct ion channel expression and localization patterns compared to normal glial cells. The key oncogenic channels in glioma include calcium-activated potassium channel that results in increased intracellular calcium which then facilitates cell invasion and proliferation. Cell proliferation is also facilitated by increased calcium influx through the ErB2 receptors that act as temporary ion transporters. Acid-sensing ion channel 2 (ASIC2) is absent in glioma cells which otherwise would inhibit the Acid-sensing ion channel 1 (ASIC1) in the glial cells to regulate sodium conductance. Chemotactic metastasis and drug resistance are driven by the expression of chloride channels on HGG cell membrane.

Expression and function of ion channels in HGG

The success of translational research depends on its ability to mimic clinical conditions in the research environment. Ion channel abnormalities in HGG patient samples have been demonstrated by genomic and proteomic analyses. Genome-wide analysis of HGG tumor samples reveals that up to 90% of all HGG tumors harbour mutations in ion channel genes (29). These findings are in line with evidence from genome-wide analysis of HGG stem-like cell exon sequencing, which also identified distinct ion channel gene mutations in HGG tumor-derived stem-like cells (101). The Repository of Molecular Brain Neoplasia Data (REMBRANDT) is a comprehensive database that has mapped the gene expression and copy number arrays of HGG alongside clinical phenotypic of HGG tumor samples. A dataset study on REMBRANDT revealed a HGG-specific ion channel gene expression signature (56 genes overexpressed out of a panel of 251 genes) which included genes from a range of different families of ion channels (102). This gene signature was validated in an independent *in vitro* study using pharmacological knock-down or genetic knock-down mouse models. This study demonstrated that the expression of the identified ion channel gene signature enhanced HGG growth in culture (101). In addition, whole-genome HGG tumor analysis has identified a range of ion channel abnormalities including mutations across different families of ion channels in calcium, sodium, potassium, and chloride channels (101). The below section discusses studies that correlate ion channel gene expression with HGG progression.

Calcium channels

Calcium channels were one of the first identified oncogenic ion channels to play a role in the pathogenesis of HGG (59). *In vitro* studies demonstrate that an increase in intracellular calcium contributes to an increase in HGG proliferation, and inhibition of the T-Type Calcium channel prevents HGG growth and metastasis (103). $Ca_v3.2$ is a gene that codes for the T-type calcium channel and increases intracellular calcium levels by opening T-type calcium channels

during membrane depolarization. Zhang and colleagues (104) analysed HGG patient data from both The Cancer Genome Atlas (TCGA) and REMBRANDT databases and identified that 11% of patients either had a mutation, or mRNA upregulation or amplification in the $Ca_v3.2$ genes (102,104). Suggesting, potential aberrations within $Ca_v3.2$ may have driven the oncogenicity of T-Type calcium channel and contributed to poor patient survival in this cohort of patients (104).

Sodium Channels

Joshi et al used tumor genome sequencing information and correlated the presence of sodium channel mutations with a decreased median survival of HGG patients (30). This finding validates other studies that identify a role for activated sodium channels in HGG tumor progression (101). Acid-sensing ion channels (ASIC) are a type of sodium channel that are voltage insensitive in both neuronal and glial cells and can detect ionic alterations in the extracellular environment (105). ASIC expression maintains HGG cells in a depolarised state, making them susceptible to malignancy (reviewed in (106)).

Co-expression of ASIC1 and ASIC2 suppressed sodium influx in normal brain astrocytes. However, the sodium influx suppression was absent in HGG tumor samples. mRNA expression analysis of the HGG tumor samples showed the absence of ASIC2 genes led to the increase in sodium influx (107). Similarly, an independent study by Tian and colleagues identified high expression of ASIC1, and ASIC3, in addition to low expression of ASIC2 in the HGG patient tumor dataset from REMBRANDT (108). Further *in vitro* testing on HGG stem cells demonstrate that the co-expression of ASIC2 and ASIC3 resulted in the suppression of the oncogenic potential of ASIC3 (108). Na_v 1.6 is a sodium channel membrane protein mainly concentrated in the sensory and nervous systems (109). Recent drug screening analyses identified oncogenic potential for Na_v 1.6 in HGG cells *in vitro* and targeting these channels have shown effective reduction in cell proliferation. However, further *in vivo* analysis is needed to validate the oncogenic role of Na_v 1.6 (110). Taken together, these studies suggest that increase in sodium influx could be oncogenic in HGG, making sodium channels an appealing target for therapeutic intervention.

Potassium channels

Evidence in exploring the oncogenic role of potassium channels in neurological cancer are starting to emerge (111). Potassium channels can co-assemble with multiple other channels and form the most complex class of ion channels (112). In normal astrocytes, voltage-gated potassium channels, Kv1.5 and Kv1.3, have been shown to have a role in cell proliferation and growth (113,114). This is demonstrated in a 2017 study, where novel Kv1.3 inhibitors (PAPTP or PCARBTP) induced massive cell death in HGG cells. Another study investigating the expression of these channels in HGG samples demonstrated differential expression of Kv1.5 in HGG according to subtype and malignancy grade, while Kv1.3 did not (113). Interestingly, Arvind and colleagues (115) identified overexpression of Kv1.5 protein, a voltage-gated potassium channel, in low-grade gliomas directly correlated with better patient survival. Thus, Kv1.5 protein expression has been identified as a good prognosis marker for low-grade gliomas.

Another potassium channel, Kir4.1, is specifically located on the cell membrane of astrocytes, attaching to blood vessels and forming synapses. A study found that Kir4.1 expression is decreased in HGG and resulted in increased cell invasion, however, the mechanism by which this occurs has not been elucidated (116). It is hypothesized that Kir4.1 expression may favour the assembly of cytoskeletal proteins in the filopodia and hence, increase cell invasion. Kir4.1 also facilitates cellular differentiation in normal astrocytes. These channels are upregulated in terminally differentiated astrocytes and are downregulated in immature proliferative astrocytes ((117) 113). Therefore, it is suggested that the downregulation of these channels in HGG may contribute to unrestrained growth and proliferation. Kir4.1 facilitates cellular differentiation in normal astrocytes, and is not expressed in proliferative astrocytes as this prevents cells from post-mitotic transition (118). In contrast, Kir4.1 channels in HGG cells are localised on the nuclear membrane and are absent in the cell membrane, which may be indicative of tumor cell proliferation. Ca^{2+}-activated K^+ (BK)

channels co-localize with ClC-3 Cl− channels for the formation of brain metastasis (4). These studies demonstrate an oncogenic role for the potassium channels that are expressed on the internal membrane of brain cells.

Chloride channels

Chloride transportation is critical for normal cellular functioning (119). Chloride flux contributes to cell proliferation and cell division via cell volume regulation (120). In HGG, chloride channels have been identified to increase proliferation and drug resistance (96). Increased expression of chloride channels in HGG tumor samples correlated with reduced patient survival (96). Wang and colleagues compared tumors from grades I-IV and identified two chloride channel genes (chloride intracellular channel 1 (CLIC1) and chloride intracellular channel 4 (CLIC4)) to be upregulated in grade IV tumors and in paediatric brain cancer (121). This suggests oncogenic roles for CLIC1 and CLIC4 in aggressive HGG and its contribution to radio-resistance (122). Similarly, in an independent study, upregulation of mRNA transcript levels of CLIC1 in HGG patient tumors correlated with poor patient survival (123). Furthermore, the expression of CLIC1 and CLC3 in HGG tumors correlated with chemotactic metastasis and drug resistance (123).

In vitro mechanistic knockdown studies suggest a role for CLIC3 in HGG proliferation and metastasis. Activation of CLC-3 by the Ca2+/calmodulin-dependent protein kinase II enhanced the HGG cellular condensation during cell division, suggesting a role for CLC-3 in HGG proliferation (124). NF-κB is an oncogenic transcription factor that increases the transcription of matrix metalloproteinases MMP-3 and MMP-9 for cell migration in HGG (125). CLIC3 interacts with Ca2+/calmodulin-dependent protein kinase II to enhance the oncogenic transcriptional activity of NF-κB for cell migration (126). NKCC1 is a form of cotransporter protein that facilitates active transport of chloride, sodium, and potassium ions. In HGG, NKCC1 accumulates high concentrations of intracellular Cl− which is known to be utilised by HGG cells during invasion (127) suggesting a role for chloride channels and transporters in regulating HGG cell volume for oncogenesis (128).

Miscellaneous channels

Besides the four major ion channels, there are other minor channels including transient receptor potential melastatin (TRPM) (129), transient receptor potential canonical (TRPC), purinergic receptors (PRX) and human ether-a-go-go related gene (hERG). These minor channels have distinct expression patterns in HGG patient cohorts which correlate with patient survival. For example, a recent study concluded that overexpression of TRPM3 and P2RX4 directly correlated with reduced survival of patients with HGG (101). In contrast, Alptekin and colleagues (130) analyzed the survival of 33 patients with HGG and identified that patients who survived longer than 12 months expressed high transcripts of TRP channel genes (*TRPC1, TRPC6, TRPM2, TRPM3, TRPM7, TRPM8, TRPV1*, and *TRPV2*). This suggests that the expression of some of the transient channels in patients with HGG may be indicative of a good prognosis (130). Similarly, P2X7R, an ATP-gated cation-permeable receptor, was highly expressed in a subset of HGG patient tumor biopsies. The expression of these receptors were correlated with disease-free overall patient survival, and a positive response to radiotherapy (131). In addition, over-expression of gamma-aminobutyric acid type A receptor subunit gamma (GABRG3) in HGG tumors is suggestive of an increased mean patient survival (101). Overall, these findings suggest that ion channels can also be used as biomarkers for positive prognoses (increased patient survival). Knockdown studies suggest a role for mechanosensitive ion channel Piezo2 in glioma chemo resistance (132). Piezo2 is also identified to be overexpressed in patient fatality caused by peritumoral brain edema (133). Table 2 summarizes the different ion channel families, their roles in HGG, along with potential targeting strategies.

Table 2. Clinically approved ion channel drugs.

Ion channel targeting	Drug	Treatment	Reference
Sodium channel blockers	Tetrodotoxin (TTX)	Pain relief	(304)
voltage-dependent sodium channel	Lidocaine, lignocaine and Novocaine	Anaesthetics	(305,306)
voltage-dependent sodium channel	Lidocaine, Flecainide, Propafenone	Antiarrhythmic drugs	(307)
voltage-dependent sodium channel	Phenytoin, fosphenytoin, Lacosamide, Valproate, Zonisamide	Antiepileptic	(308)
voltage-dependent sodium channel	Lacosamide	Anticonvulsant	(309)
Sodium potassium channel blockers	phenytoin, topiramate, lamotrigine and carbamazepine	Antiepileptic	(310–312)
Voltage-gated L-type calcium channel blockers	verapamil, diltiazem, nimodipine, nifedipine and amlodipine	Angina	(313)
Potassium ATP channel agonist	vasodilator, and nicorandil	Angina	(314)
sodium and potassium channels	Amiodarone	Antiarrhythmic	(315,316)
Voltage-gated calcium channel blockers	verapamil, amlodipine and nifedipine	Hyertension	(317)
potassium channel activator	diazoxide	Vasodilation during hypertension	(314)
Regulator of intracellular calcium levels	Nicotinic acid (NA)	Atherosclerosis.	(318)
K ATP channels blocker	sulphonyl urea drugs – glibenclamide	Diabetes	(319)
selective inhibitor of Kv1.3	Margatoxin (MgTX),	Non-small cell lung cancer cell	(320)
antagonist of TRPM8	cannabigerol (CBG)	Colon cancer cells	(321)
VGSC-blocking drug	phenytoin	Breast cancer *in vitro*	(164)
potassium channel blocker	Oxaliplatin	Anti-proliferative effects on HGG, colorectal cancer *in vitro*	(322)
Kv channels blocker	PAPTP and PCARBTP	Glioma cells *in vitro*	(243)
InaP blockers	ranolazine and riluzole	Metastatic breast and prostate cancer	(197,233,23)
Multi-channel blocker, Potassium channel modulator	Hydroquinidine	Currently used to treat short-QT and Brugada arrhythmia syndromes Significant antiproliferative and pro-apoptotic effect on TMZ-sensitive and -resistant HGG cells	(325)
Sodium channel blocker	Oxcarbazepine	FDA-approved antiepileptic drug Anti-proliferative and pro-apoptotic in IDH mutant glioma stem cells	(326)
EAG2-Kvβ2 complex blocker	Designer peptide against EAG2-Kvβ2 complex	Anti-proliferative in patient-derived xenograft and syngeneic mouse models	(327)
SK2 channel blocker	P01 scorpion toxin	Anti-proliferative in U87 glioma cells	(328)
hERG channel opener and potassium modulator	NS1643 – small molecule inhibitor	Combinations of Pantoprazole with TMZ, retigabine and NS1643 had anti-proliferative in U87 cells	(182)
Potassium channel opener	Retigabine - FDA-approved epilepsy drug		

proton-pump inhibitor	Pantoprazole - FDA-approved proton-pump inhibitor		
Calcium channel blocker	Flunarizine - Not FDA-approved. Used to treat migraines	Anti proliferative effect and inhibit invadopodium	(329)
Calcium channel blocker	Econazole nitrate - Anti-fungal drug		
Potassium channel blocker	Quinine hydrochloride - Anti-malarial drug		
Potassium channel Kv1.3 blocker	PAPTP/PCARBTP	Anti-proliferative in HGG cells	(243)
T-type/L-type calcium channel blocker	Mibefradil was used to treat hypertension. Currently withdrawn from market	Suppressed HGG growth and stemness	(104)
Potent TRPC antagonist (TRP3-7)	Compound 15g	Anti-proliferative effects in HGG	(254)
hERG antagonist/ligand	Doxazosin - Treatment for benign prostatic hyperplasia	Anti-proliferative effects in HGG	(269)
hERG antagonist/ligand	letrozole - Phase I clinical trial	Anti-proliferative effects in HGG	(270)
AMPAR (calcium permeable channels)	Fluoxetine - FDA approved antidepressant	Anti-proliferative effects in HGG	(238)
Sodium/potassium/chloride co-transporter isoform 1 (NKCC1)	STS66 Bumetamide derivative	Anti-proliferative, reduced cell growth in HGG	(330)
TRPV4 antagonist	Cannabidiol	Anti-proliferative in HGG	(331)

Collectively, there is evidence demonstrating ion channel aberrations in HGG tumors. Some ion channels play an oncogenic role while others may be tumor suppressive and each of the ion channel family members can contribute to a particular hallmark of cancer. For example, inhibiting sodium channels can prevent tumor cell invasion while inhibiting calcium channels may trigger an anti-proliferative effect. However, ion channel aberrations have only been retrospectively correlated with the survival of patients with HGG and an in-depth mechanistic understanding of their oncogenic roles in HGG is lacking. The current research gap between pre-clinical testing and the clinical understanding of HGG tumors has limited the effective translation of research findings for HGG treatment and will be discussed below.

Overview of ion channels therapeutics in cancer

Every cell has ion channels and ion transporters along their plasma membrane to transport ions across the cells. Each type of cell possesses specific ion selectivity and permeability making their ionic composition different from one another and from their microenvironment (134). This ionic difference creates a membrane potential (V_m) to the cell membrane (135). The change in V_m in turn regulates the movements and function of the cellular proteins to drive cellular activities such as proliferation, invasion and differentiation. The ionic exchange is necessary to regulate cellular volume, a critical factor in cell cycle and cell invasion (136). Cardiovascular, anaesthetic and many psychiatric drugs target ion channels (74,137–139). A faster approach to translational medicine is to repurpose drugs. Drug repurposing is a process that has been largely used for neurological disorders. Ion channel drugs have been used to treat various neurological disorders at different treatment regimens (140). The recent developments in high-throughput assays and technologies such as flux-based assays, fluorescence-based assays and automated electrophysiological assays have drastically changed the outlook of using ion channel drugs to treat “channelopathies” such as Bartter Syndrome, seizures and cystic fibrosis through ion-channel-specific assays (47,141,141–146). There are many clinically approved ion channel drugs to treat neurological disorders (147), neuronal damage (148), cardiovascular damage, cardiac disease, hypertension, diabetes, epilepsy, spinocerebellar ataxia type-13, infectious diseases (149), and brain defects (150). These drugs can effectively cross the blood-brain barrier and the majority are classified as anticonvulsant drugs or

calcium and sodium channel blockers (33,151). As a result, ion channel drugs are being tested to treat a range of diseases, disorders and cancers, including HGG (Table 3).

Table 3. Role of ion channels in HGG and potential targeting strategies.

Ion channel name	Ion channel type	Genes involved	Oncogenic Phenotype	Potential targeting strategy	Reference
Cav3.1	Voltage-gated calcium channels T-type, alpha 1G subunit	CACNA1G	Increased proliferation and regulation in autophagy	Cardiac arrhythmia, epilepsy, hypertension drugs can be used	(245)
Cav3.2	Voltage-gated calcium channels T-type, alpha 1G subunit	CACNA1H	Increased proliferation through AKT/mTOR pathways	Pain, and epilepsy drugs can be tested	(104,246,247)
Cav2.1	Voltage-dependent P/Q type	CACNA1A	Increased proliferation	Epilepsy, and migraine drugs can be used to target	(241)
Cav1.2	Voltage-dependent L-type	CACNA1C	Increased proliferation	Cardiovascular drugs	(248)
TRPC1, 5	Transient receptor potential cation channel, subfamily M, member 1 and 5	TRPC1, TRPC5	Increased proliferation through regulation of calcium signalling and increased migration	Riluzole TRPC5 agonist approved drug for the treatment of amyotrophic lateral sclerosis can be used in HGG	(249–251)
TRPM8	Transient receptor potential cation channel, subfamily M, member 8	TRPM8	Increased proliferation, and migration mediated by BK activation	Anti-inflammatory drugs targeting TRPM8 can be used to target HGG	(252,253)
TRPM7	Transient receptor potential cation channel, subfamily M, member 7	TRPM7	Increased, proliferation, migration and invasion		(253–255)
TRPC6	Transient receptor potential cation channel subfamily C member 6	TRPC6	Increased proliferation, regulation of cell cycle, hypoxic migration		(203,256)
CLIC1	Chloride intracellular channel protein 1	CLIC1	Increased proliferation	Biotin conjugated analog of MTI-101 can target CLIC1 to reduce HGG proliferation	(180,257)
CLC3	Chloride voltage-gated channel 3	CLCN3	Increased migration and invasion	Inducible gene deletion strategies can help target CLCN3 to reduce HGG migration and invasion	(124,126,258)
TRPML2	Mucolipin-2 transient receptor potential cation channel	MCOLN2	Increased proliferation and decreased apoptosis	TRP channel inhibitors such as Capsaicin, SKF-96365 and 2-APB can target MCOLN2 in HGG	(259–262)
TRPV4	Transient receptor potential vanilloid 4	TRPV4	Increased migration and invasion, cytoskeletal remodelling	Orally active pulmonary edema drug targeting TRPV4 can reduce HGG migration	(263–265)
Kv1.3, Kv1.5	Voltage-gated potassium channel	KCNA3, KCNA5	Increased proliferation	Kv1.3 specific toxins such as charybdotoxin and margatoxin can be used to prevent HGG proliferation	(266–268)

Kv2.1	Voltage-gated potassium channel	KCNB1	Increased proliferation, regulation of autophagy	Antiarrhythmic drugs such as Quinidine, 4-Aminopyridine (4-AP) and potassium channel blocker, Tetraethylammonium, are specific blockers of Kv2.1	(70,113,126)
Kv11.1 (hERG)	Ether-a-go-go potassium channel	KCNH2	Increased proliferation	Dofetilide an anti-arrhythmic drug and E-4031 a well known hERG channel blocker may reduce proliferation in HGG	(224,269–271)
VRAC	Volume-regulated anion channel	LRRC8A	Hypoxia-related proliferation and survival	Small molecule inhibitors such as DCPIB or LRRC8A specific antibodies are good therapeutic opportunities for HGG	(27,272–274)
Nav1.6	Voltage-gated sodium channel	SCN8A	Increased proliferation, migration and invasion	Small molecules like PF-06372865 and GS967 have been shown to selectively inhibit SCN8A.	(110,275)
Nav1.5	Voltage-gated sodium channel	SCN5A	Increased invasion with NHE1	Multiple antiarrhythmic and antianginal drugs such as Amiodarone, Ranolazine, Quinidine, Mexiletine, Lidocaine, Flecainide can target SCN5A in HGG	(51,276,277)
AMPAR	Calcium permeable channels	GLUA1 and GLUA4	Increased proliferation and invasion	Selective GLUA1 inhibitor - LY3130481 and GLUA4 inhibitor such as CX614 and Cyclothiazide	(238,278–280)
ANO1, TMEM16A	Anoctamin 1 voltage-gated calcium-activated anion channel	TMEM16A	Increased proliferation, supports maintenance of stemness in GSCs	Anoctamin 1 inhibitors such as T16Ainh-A01 and CaCCinh-A01 can reduce GSC stemness	(281–283)
ASIC1 and ENaC	Acid-sensing ion channel 1a	ASIC1	Increased migration and lamellipodium expansion	Amiloride is a well-known diuretic that blocks epithelial sodium channels	(284–286)
Kir4.1	ATP-sensitive inward rectifier potassium channel 10	KCNJ10	Decreased proliferation	Baicalein is a flavonoid compound that effectively inhibit KCNJ10 can be used to treat HGG	(118,287,288)
KATP, Kir6.2	ATP-sensitive potassium channels	KCNJ11	Increased proliferation	Glyburide, a KATP channels blocker currently in the clinic to treat neonatal diabetes caused by KCNJ11 mutations can be used to reduce HGG proliferation	(289–291)
KCa1.1, BK	Calcium-activated potassium channel subunit alpha-1	KCNMA1	Increased proliferation and migration	Clinically available epileptic drug such as Paxilline blocks KCNMA1	(292–294)
KCa3.1	Intermediate-conductance calcium-activated potassium channel	KCNN4	Increased migration and invasion	Senicapoc (ICA-17043) is a KCa3.1 channel blocker, that reduces hemolysis and improving red blood cell survival in patients with sickle cell anemia. This drug may reduce HGG migration by blocking KCa3.1 with minimal side effects	(97,292,295)

PIEZO1	Mechanosensitive non-specific cation channel	PIEZO1	Increased proliferation, regulation of tissue stiffness and aggression	There are no clinically approved drugs to treat PIEZO1 channel. GsMTx4 is a peptide toxin derived from tarantula venom and is potent to inhibit PIEZO1.	(296–298)
NHE5	Na+/H+ exchanger 5	SLC9A5	increased proliferation, metastasis, cell adhesion and invasion	There are no selective inhibitors for NHE5. NHE1 inhibitors such as Amiloride and its derivatives can be used to reduce HGG growth and metastasis.	(57,299)
NHE9	Endosomal pH regulator	SLC9A9	Increased proliferation, stemness	There are no selective inhibitors for NHE5. NHE1 inhibitors such as Amiloride and its derivatives can be used to reduce HGG growth and metastasis.	(57,300,301)
NKCC1	Na+K+/Cl- cotransporter isoform 1	SLC12A2	Increased proliferation, migration, invasion	Bumetanide and Furosemide are loop diuretic that inhibits NKCC1 and is used primarily to treat edema and hypertension. This can be tested on HGG for anti-cancer effects.	(302,303)

Electrophysiological analysis of cancer cells demonstrate depolarization of the cancer cell membrane which contributes to the stemness of cancer cells and attribute to the cellular proliferation, invasion and migration (109, 135, 152). Studies using hepatoma and adenocarcinoma demonstrates increased intracellular sodium concentration compared to normal cells, suggesting a role for cancer cell depolarisation (153, 154). More recently, ion channels have been identified as a target for cancer therapy with a few reviews summarising their role as a therapeutic target for cancer (55,155,156). Ion channel drugs modulate ion channels by either blocking or opening them, altering the ionic concentration and in turn, reducing the function of oncogenic proteins across cancer cells (157,158). However, the drugs may have different modes of action in different types of cancer due to their diverse oncogenic function and their complex interactions between other ion channels and oncogenes (159,160). Once the altered channels are identified in any given cancer, treating the alteration using modulators will recalibrate the ionic balance and alter the V_m to reduce the oncogenic potential (161). Some of these drugs have been used in pre-clinical models to demonstrate their anti-cancer effects (162–164). Based on drug repository screening *in silico, a* study screened over 100 United States Food and Drug Administration (FDA) approved drugs against small cell lung cancer (SCLC) (165). Of the top 100 drugs identified, many were ion channel modulators such as imipramine, promethazine and verapamil, that significantly inhibited the growth of SCLC both as a single agent (165) and in combination (166). However, these drugs were specific to SCLC and did not add any survival benefit in a phase III study in patients with multidrug-resistant multiple myeloma (167). This suggests that ion channels may interact with other pathways specific to the cellular context and hence, studying ion channel drugs in the presence of other oncogenic drivers may be a greater determinant of drug efficacy. Further, the clinical availability of multiple ion channel drugs means a shorter translation time and a higher rate of clinical success, underlining the need for additional research to identify roles of ion channels in HGG tumors. However, there is limited literature exploring the opportunity of repurposing ion channel drugs for cancer therapy (36).

Therapeutic targeting of ion channels in HGG

HGGs are commonly treated with alkylating agents (such as temozolomide) (168,169) and ionizing radiation (168,170) that causes DNA damage and

induce apoptotic cell death (168). However, HGG tumors develop resistance to standard treatments due to pathway rewiring, resulting in mortality. Chemo- and radiotherapy-induced DNA damage triggers a series of tumor-cell survival mechanisms including alterations in calcium-activated potassium channels and calcium-permeable non-selective cation channels (95). Ion channels are active in excitable cells such as neurons and possess cell-specific functions (133). *In vitro* analyses demonstrate that activated ion channels induce both intrinsic and acquired resistance to radiotherapy in HGG stem-like cells (95) (171). Current combination treatment with alkylating agents and ionising agents are ineffective and additional research is required to urgently identify alternate therapies (172). Apart from conventional drug treatments, the use of alternative electric fields known as Tumor Treating Fields has been recently used to treat paediatric HGG by targeting ion channels (173). Currently, this technique is being used in combination with ion channel blockers to induce cell death, demonstrating oncogenic role for ion channels in HGG (122). Based on the functions of ion channels in brain cells, it is proposed that targeting aquaporin (water channels) together with ion channels can limit HGG invasiveness, however this is yet to be tested *in vivo* (174).

Ion channel drugs as single-agent therapy in HGG

CLC-3, a voltage-gated chloride channel, is present in the plasma and intracellular membrane of HGG cells (175) and is predicted to drive drug resistance (96). Chlorotoxin (Cltx) preferentially inhibits HGG cell invasion by binding to CLC-3/matrix metallopeptidase 2 (MMP2) membrane complex and inhibits the enzymatic activity of MMP2 to reduce the cell surface expression levels of MMP2 to inhibit cell invasion. Cltx has recently entered phase I and II clinical trials for patients with HGG (176). Similarly, I-TM-601, a synthetically labelled Cltx, has also entered phase I and II clinical trials for patients with HGG tumors (177). Besides its therapeutic potential, radiolabelled I-TM-601 has also been used as a diagnostic marker in identifying tumor burden in patients with HGG. Radiolabelled I-TM-601 can be effectively detected using whole-brain single-photon emission computed tomography scans (178) and immunohistochemistry of brain tissue (179). Another study tested the efficacy of a therapeutic antibody against CLIC1 in a pre-clinical study using HGG derived progenitor cells where the antibody significantly increased survival in mouse models (180).

Ion channel drugs as part of combination therapy in HGG

Multiple independent oncogenic pathways combine to trigger the hallmarks of cancer. Combination therapy is, therefore, the gold standard for cancer treatment (181). Ion channel drugs that failed as a single-agent treatment have been shown to increase survival benefits when used as combination therapy in HGG clinical trials (182). Amiodarone, an anti-arrhythmic drug, targets multiple ion channels and increases the risk of certain types of cancers when administered for neurological disorders (183). However, in combination with a therapeutic recombinant human protein, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), amiodarone impeded HGG growth *in vitro* through the induction of calcium influx associated apoptosis (184). This apoptotic effect was selectively in HGG cells and did not affect normal astrocytes, highlighting the potential utility of amiodarone as part of combination therapy for patients with HGG with minimal side effects. This evidence together demonstrates that the pharmacodynamics of ion channel drugs could be completely different in a cancer setting as opposed to neurological disorders. As a result, ion channel drugs should be treated as novel compounds for cancer treatment and stresses the importance of rigorous pre-clinical and clinical testing. Bepridil and cibenzoline are two calcium channel drugs that were previously used only as anti-arrhythmic agents. These two drugs impeded HGG cell growth as part of combination therapy with TRAIL (185). The dual calcium and G-protein coupled receptor inhibitor, pimozide, has been shown to reverse resistance to the chemotherapeutic drug, temozolomide and sensitize HGG cells to radiation treatment (186). Furthermore, nifedipine, a calcium channel blocker, sensitized resistant HGG cells to cisplatin and inhibited tumor growth both *in vitro* and in pre-clinical mouse models (187). *In vitro* and *in vivo* studies demonstrate that mibefradil, a nonspecific calcium channel blocker sensitizes HGG stem-like cells (GSC) to temozolomide by inhibiting the AKT/mTOR pathways and reversing stemness. Mibefradil sensitized HGG to

temozolomide and stimulated apoptotic proteins such as survivin and BAX (103). Similarly, Krouse and colleagues repurposed mibefradil to sensitize HGG tumors to conventional chemotherapy in a phase 1b clinical trial (188). The results from the clinical trial demonstrated a positive outcome in patients with HGG (188–190). However, despite the positive outcome in patients with HGG, the trial could not progress further as mibefradil was withdrawn from the market following multiple reports of drug-drug interactions (191).

Although these studies are preliminary and not all drugs have been tested in pre-clinical animal models, the findings highlight the potential in repurposing ion channel drugs as a treatment for patients with HGG. However, to date, studies investigating the role of ion channels in HGG survival have been associational, not mechanistic and further studies are necessary to identify the mechanistic role for ion channels as a potential therapeutic target for HGG. Pre-clinical testing of ion channel drugs on clinically relevant HGG models will expedite the clinical translation of FDA-approved ion channel drugs as both single and in combination with conventional therapies, in both adult and paediatric patients with HGGs, which may otherwise cause severe neurological side effects (192).

Research gaps in repurposing ion channel drugs for cancer therapeutics – preclinical model development

Historically, limitations of both *in vivo* animal studies and 2D *in vitro* models have delayed progress in this field (193). 2D immortalized monolayer cell culture have been used due to their cost effectiveness and reproducibility. However, they do not accurately reflect the tumor environment, the highly heterogeneous nature of HGG nature. Since the announcement by the United States Food and Drug Administration in 2022 to abolish the mandate to test on animals, *(*through the *FDA Modernization Act 2.0) in vitro* methods and models are rapidly advancing in this area (193–195). Non-animal models include 2D cell culture, 3D spheres (or neurospheres), organoids, bio printing, tissue-slice cultures and tumor-on-chip methods, all which have advantages and disadvantages (194,195). To account for the highly heterogeneous nature of HGG and for *in vitro* studies to be reflective of clinical outcomes, it is important to use patient-derived cell lines. Development of 3D *in vitro* models that can incorporate vasculature and immune cell components will advance this field (194). Tumor-on-chip is both dynamic and can incorporate vasculature by joining multiple organ (organ-on-chip) systems. Alternatively, culturing 3D spheroids in a chip environment provides a more dynamic and physiologically accurate model, which has already been used to test certain FDA approved drugs for repurposing (196). More complex models have been developed since, integrating biosensor enhanced on-chip models (197). Complex scaffolding models utilising biomaterials have been developed to overcome some of the limitations of current models (195). Bio-banking will be essential to advance these preclinical models. The use of preclinical models using patient-derived cell lines can help investigate the mechanism of action and thereby, improve the translation of research findings. Further improvements must focus on the accurate recapitulation of the tumor microenvironment (including electrical stimulation) and the range and plasticity of cellular states of HGG among others (198). Combining the knowledge gleaned from computational simulation of ion channel biology can further improve *in vitro* models, particularly for tissue engineering and microfluidic (tumor-on-chip) approaches (193,198). It is evident that ion channels play an oncogenic role in HGG and additional research in clinically relevant models is required for the development of effective treatments.

Future directions

Compelling evidence on the prevalence of ion channel aberrations in patients with HGG is starting to accumulate. However, while ion channels are emerging as promising oncogenic targets across many different cancers, very few ion channel inhibitors have been tested in patients with HGG (177,199).

Clinical failure is largely due to an oversight on the interaction of ion channels with other oncogenes such as tyrosine kinases and other ion channel family members. However, these complex interactions may be key contributors to the cellular and pharmacological response to ion channel drugs. For example, the same ion channel drug may induce completely different outcomes in a patient with a kinase mutation as

compared to a patient with a transcription factor mutation. Thus, ion channels need to be studied under the influence of other oncogenic genes in patients with HGG and administered as personalized medicine based on the tumor pathology. Additionally, ion channels compensate for each other's function (52). This may explain why some drugs can effectively impede cancer growth while others do not. Hence, it is critical to study ionic alterations as an orchestra of multiple cellular ion channels that maintains an electric gradient on the cell membrane to regulate cellular processes. To achieve this, appropriate *in vitro* models are necessary (194,200). Testing ion channel drugs in patient derived HGG neurospheres (201) recapitulates the clinical phenotype and hence, will significantly increase the success of ion channel drugs in the clinic. Patient-derived cell line mouse models will help us understand the drug's mechanism of action in the presence of the tumor microenvironment to bridge the knowledge gap between the clinic and laboratory research of HGG. Personalized approaches are essential for treating HGG due to their significant heterogeneity. These tumors exhibit vast genetic, epigenetic, and phenotypic diversity between both patients and within the same tumor. This variability impacts treatment responses and outcomes, making standardized therapies less effective. By tailoring personalized treatment strategies to the unique characteristics of each patient's tumor, we can improve the efficacy and outcomes of patients with HGG. With many ion channel drugs on the shelf, molecular profiling of tumor biopsy samples to identify ion channel aberrations, can address the complex nature of HGG more effectively with ion channel drugs.

It is important to understand the level of deviation between the effects of ion channel drugs *in vitro* and *in vivo* compared to the effects they will have in clinic. Furthermore, it is necessary to undertake studies in clinically relevant models through multi-omic approaches to better understand the distinct oncogenic roles of ion channels in HGG. These studies will enrich our knowledge on the molecular mechanism of ion channel drugs on HGG tumors and help us understand drug induced resistance. These findings will facilitate identifying a targeted therapy to treat patients with HGG with minimal side effects.

Conclusion

The highly plastic, diffusive, and heterogeneous nature of HGG tumors results in very low patient survival, which has been improved only minimally with current therapeutic options due to the development of drug resistance. The current landscape of HGG treatment is characterized by a combination of surgery, radiotherapy, and chemotherapy, yet these approaches often fail to extend the patient survival. Ion channels have been identified as a promising target for HGG therapeutics, due to strong evidence of ion channel pathologies (abnormalities/mutations) in HGG proliferation, and drug resistance. The distinct patterns of ion channel expression observed in HGG compared to normal brain tissues suggest that these channels play a crucial role in HGG progression. Notably, the upregulation of certain ion channels, such as those involved in calcium, potassium, and chloride transport, underscores their potential as biomarkers for HGG prognosis and as targets for therapeutic intervention. The same ion channels identified as therapeutic targets could also be used as biomarkers for disease or disease progression. Ion channel drugs have been repurposed for a host of neurological conditions, and although these drugs cross the blood-brain barrier, only a few have been tested for their anti-cancer effects. In addition, their complex mode of action is not well understood. There is growing evidence of the potential to use ion channel drugs for cancer therapy, particularly in combination with conventional therapy, but differences in the pharmacodynamics of ion channel drugs need further mechanistic investigation. The integration of ion channel-targeting drugs into clinical protocols offers a promising avenue to enhance therapeutic efficacy. Preclinical studies have already demonstrated the potential of ion channel modulators in reducing HGG growth and sensitizing tumors to conventional treatments. For instance, drugs targeting specific potassium and chloride channels have shown encouraging results in pre-clinical models by impairing HGG growth and inducing apoptosis.

Future research should focus on elucidating the precise roles of various ion channels in HGG pathophysiology and identifying ion channel-targeting compounds for clinical use. Personalized medicine approaches, leveraging the unique ion channel expression profiles

of individual tumors, could further refine treatment strategies, ensuring maximal therapeutic benefit while minimizing adverse effects. New 3D *in vitro* models using patient-derived cells, tissue engineering and microfluidic approaches are improving the accurate recapitulation of the tumor environment and the range and plasticity of cellular states of HGG, showing promise to elucidate oncogenic mechanisms of HGG. Targeting ion channels represents a novel and promising therapeutic strategy in the fight against HGG, with the potential to significantly improve patient outcomes and advance the current standard of care. Clinically relevant and physiologically accurate models will improve testing of ion channel drugs, offering a personalized medicine approach that can be combined with multi-omics to improve our understanding of HGG, HGG drug resistance and create enhanced therapeutics with minimal side effects.

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PJM conceptualizing, drafting, editing and reference collection. **NA** conceptualizing and overall editing, **CR** drafting and editing.

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