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Mini Review

KCNA1 in Glioblastoma: Biological Functions and Therapeutic Implications

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Abstract

KCNA1 encodes Kv1.1, a voltage-gated potassium channel primarily recognized for its role in neuronal excitability. Evidence from glioma models has expanded its biological relevance to membrane potential regulation, tumor invasion, ferroptosis-associated responses, and mitochondrial homeostasis. Early electrophysiological experiments established functional Kv1.1 currents in glioma-derived cells, while subsequent transcriptomic studies identified heterogeneous KCNA1 expression across glioblastoma samples and invasive tumor regions. Pharmacological and genetic interventions further associated KCNA1 with malignant cellular behavior, and recent findings implicated SLC7A11-related antioxidant defense in its effects on ferroptosis susceptibility. Together, these observations suggest that KCNA1 participates in multiple aspects of glioblastoma cell biology. However, the relationship between its ion-conducting activity and tumor-associated phenotypes remains incompletely defined. Moreover, the physiological importance of Kv1.1 in neuronal function complicates therapeutic targeting. This mini-review summarizes current experimental evidence and examines the mechanistic and translational questions that must be addressed to determine the therapeutic relevance of KCNA1 in glioblastoma.

Keywords: *KCNA1, Kv1.1, Glioblastoma, Invasion, Ferroptosis, Potassium channels*

Introduction

Glioblastoma (GBM) is characterized by extensive infiltration into surrounding brain tissue and resistance to conventional treatment. Recent studies have demonstrated that glioblastoma cells integrate into local and long-range neuronal circuits, with neuronal activity and synaptic interactions influencing tumor invasion, progression, and treatment responses [1,2]. Electrophysiological investigations have further identified distinct electrical properties among tumor cells at the infiltrative brain–tumor interface, highlighting the functional heterogeneity of glioblastoma [3]. Together with growing evidence implicating potassium channels in glioblastoma biology [4], these findings provide a framework for examining the contribution of individual ion channels to malignant cellular behavior.

KCNA1 encodes Kv1.1, a member of the Shaker-related voltage-gated potassium channel family. Although Kv1.1 is best known for regulating neuronal excitability, its expression and electrical activity have also been documented in glioma-derived cells [5]. Subsequent studies have identified KCNA1-associated expression patterns in glioblastoma, including enrichment in invasive tumor populations, and have linked its genetic manipulation to changes in tumor growth, invasion, and ferroptosis-related responses [6-9].

These findings have expanded interest in KCNA1 beyond its established neurological functions. This mini-review examines the evidence connecting KCNA1 to glioblastoma biology, with particular emphasis on its functional expression, involvement in malignant cellular behavior, and potential relevance to therapeutic intervention.

KCNA1 Expression and Function in Glioma

Functional Expression and Spatial Distribution

Early electrophysiological investigations demonstrated endogenous Kv1.1 expression in C6 glioma cells, where dendrotoxin-I-sensitive potassium currents contributed substantially to the resting membrane potential. Elevation of intracellular cyclic AMP accelerated KCNA1 mRNA degradation, followed by reduced Kv1.1 protein expression and potassium conductance [5]. These findings established a relationship between KCNA1 expression and the electrical properties of glioma-derived cells.

Subsequent transcriptomic investigations identified KCNA1 among genes associated with glioblastoma [7,9]. Integrated bioinformatic analyses included KCNA1 within a group of candidate genes related to neuronal signaling and glioblastoma-associated molecular alterations [9]. Another study reported reduced KCNA1 expression in glioblastoma tissues and cell lines compared with non-tumor controls, identifying it among several potential molecular markers of the disease [7].

Spatial analyses revealed additional heterogeneity in KCNA1 expression within glioblastoma. In six pediatric glioblastoma-derived orthotopic models, matched tumor-core and invasive-front cell populations were isolated and compared. KCNA1 mRNA expression was elevated in invasive populations in four models, while increased protein staining was observed in invasive regions in five models [6]. These findings demonstrated that KCNA1 expression can differ between spatially distinct tumor populations, adding a regional dimension to its expression profile in glioblastoma.

KCNA1-Associated Invasion and Tumor Progression

The identification of KCNA1 in invasive tumor populations was accompanied by functional evidence linking potassium channel activity to glioblastoma invasion. Treatment with ADWX-1, Agitoxin-2, or 4-aminopyridine (4-AP) reduced the invasive capacity of patient-derived glioblastoma cells. In an orthotopic model, systemic administration of 4-AP also suppressed intracranial tumor infiltration and prolonged animal survival [6].

Genetic manipulation provided complementary evidence for the involvement of KCNA1 in malignant cellular behavior. KCNA1 knockdown reduced glioblastoma cell proliferation, migration, and invasion, whereas its overexpression enhanced these phenotypes [8]. Intracranial experiments further demonstrated reduced tumor progression following KCNA1 depletion. These observations extended the functional association of KCNA1 from spatially invasive tumor populations to broader growth- and invasion-related phenotypes.

Together, electrophysiological, transcriptomic, and functional studies establish a foundation for investigating KCNA1 in glioma biology. They encompass several distinct dimensions of the gene, including its contribution to membrane electrical properties, heterogeneous expression within tumors, and association with malignant cellular behavior.

KCNA1, Ferroptosis, and Mitochondrial Dysfunction

Ferroptosis is a regulated form of cell death characterized by iron-dependent lipid peroxidation [10,11]. Its regulation involves the balance between oxidative damage to membrane phospholipids and cellular antioxidant defenses. The SLC7A11–glutathione (GSH)–GPX4 pathway is a major protective system, in which cystine uptake supports GSH synthesis and GPX4-dependent detoxification of lipid peroxides [12,13].

KCNA1 has been implicated in this antioxidant network in glioblastoma cells. KCNA1 expression was positively associated with SLC7A11, and KCNA1 knockdown decreased SLC7A11 and GPX4 protein expression, reduced intracellular GSH, and increased reactive oxygen species and lipid peroxidation [8]. Conversely, KCNA1 overexpression attenuated several ferroptosis-associated alterations following erastin exposure. These results linked KCNA1 expression to the cellular response to ferroptotic stress and suggested an association with SLC7A11-dependent antioxidant regulation.

Changes in mitochondrial function were also observed following KCNA1 manipulation. KCNA1 depletion was associated with reduced mitochondrial membrane potential and ATP production, increased mitochondrial reactive oxygen species, and alterations in mitochondrial ultrastructure [8]. Immunofluorescence analyses further demonstrated overlapping KCNA1 and TOMM20 signals, indicating a spatial association between KCNA1 immunoreactivity and mitochondria. Outside glioblastoma, KCNA1 silencing has also been associated with mitochondrial damage and suppression of malignant phenotypes in cervical cancer cells [14].

These observations extend the biological profile of KCNA1 from electrical regulation and tumor invasion to cellular redox balance and mitochondrial function. In glioblastoma, the reported changes in SLC7A11 expression, lipid peroxidation, and mitochondrial activity provide a basis for considering KCNA1-associated cellular stress responses alongside its established invasion-related phenotypes.

Mechanistic Questions and Therapeutic Implications

The available studies identify several KCNA1-associated phenotypes, but their mechanistic relationships remain to be resolved. A central distinction concerns KCNA1 expression and Kv1.1-mediated potassium conductance. Functional Kv1.1-associated currents have been demonstrated in C6 glioma cells [5], whereas the more recent evidence for glioblastoma progression comes largely from pharmacological inhibition and genetic manipulation [6,8]. Whether the effects of KCNA1 depletion on invasion, proliferation, and ferroptosis susceptibility require channel conductance remains an important question. Electrophysiological characterization combined with rescue experiments using channel-function-deficient KCNA1 variants would help establish the contribution of ion transport to these phenotypes.

The relationship between KCNA1-associated invasion and ferroptosis regulation also warrants closer examination. Although KCNA1 manipulation influences both invasive behavior and SLC7A11-related antioxidant responses, these observations do not establish that ferroptosis resistance mediates the invasive phenotype. The two processes may share upstream regulation or represent distinct consequences of KCNA1 activity. Similarly, mitochondrial dysfunction following KCNA1 depletion does not establish direct mitochondrial ion channel activity or identify mitochondria as the initiating site of ferroptotic signaling. Functional rescue, time-resolved analyses, and compartment-specific measurements could distinguish these possibilities.

Another consideration is the heterogeneous expression of KCNA1 across experimental settings. Reduced expression relative to non-tumor controls and enrichment within invasive tumor regions describe different biological comparisons [6,7]. Their interpretation requires attention to tumor cellular composition, anatomical location, and molecular subtype. Spatially resolved analyses combined with functional studies in molecularly characterized patient-derived models would help determine whether KCNA1 dependence is associated with particular glioblastoma cell populations.

From a therapeutic perspective, potassium channel inhibition offers an experimentally accessible means of modifying glioblastoma invasion. Among the compounds evaluated, 4-AP is of particular interest because its extended-release formulation, dalfampridine,

is approved for improving walking performance in patients with multiple sclerosis [15]. Nevertheless, 4-AP blocks multiple voltage-gated potassium channel subtypes, and the peptide inhibitor ADWX-1 exhibits greater potency against Kv1.3 than Kv1.1 [16]. Accordingly, the anti-invasive effects observed with these agents cannot be assigned exclusively to Kv1.1 inhibition. The development or application of more selective pharmacological tools, supported by genetic target validation, would strengthen the rationale for KCNA1-directed intervention.

Neurological safety and drug delivery present additional challenges. Kv1.1 has an established role in neuronal excitability, and KCNA1 dysfunction is associated with neurological manifestations, including episodic ataxia [17]. Dalfampridine treatment also carries a recognized risk of seizures, particularly with increased systemic exposure [15]. These considerations are relevant to patients with intracranial tumors, in whom seizure susceptibility may already be elevated. In addition, effective targeting of infiltrative glioblastoma cells requires sufficient drug exposure in brain regions where the blood–brain barrier may remain relatively intact. Therapeutic development must therefore balance tumor activity, channel selectivity, brain penetration, and preservation of normal neuronal function.

The translational value of KCNA1 ultimately depends on establishing a reproducible functional dependence in glioblastoma cells and identifying a pharmacological approach capable of exploiting that dependence within an acceptable neurological safety margin.

Conclusions

Research on KCNA1 in glioma has progressed from the characterization of functional potassium currents to the identification of invasion-associated expression patterns and links with cellular antioxidant responses. These findings broaden the biological relevance of Kv1.1 in glioblastoma, while highlighting the complexity of interpreting ion channel expression in a heterogeneous tumor.

The next stage of investigation should move beyond expression-based associations toward defining the cellular contexts and molecular functions that make KCNA1 relevant to glioblastoma progression. Such evidence will determine whether KCNA1 remains primarily a marker of particular tumor phenotypes or develops into a therapeutically actionable vulnerability.

Declarations

Conflict of Interest

The authors declare that they have no competing interests.

Authors' Contributions

Yutong Mei: Conceptualization, Writing – original draft.

Yi Jin: Writing – original draft.

Yuhan Liu: Literature review, Writing – original draft.

Siyuan Zhao: Literature review, Validation.

Runze Han: Literature review, Validation.

Yucheng Shen: Literature review, Validation.

Zongqi Wang: Conceptualization, Supervision, Writing – review & editing.

Jiangang Liu: Supervision, Funding acquisition, Writing – review & editing.

All authors reviewed and approved the final version of the manuscript.

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