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REVIEW ARTICLE

Functional Roles of the Ca^{2+}-activated K^+ Channel, KCa3.1, in Brain Tumors

Giuseppina D'Alessandro[a,b], Cristina Limatola[b,c,*] and Myriam Catalano[a,b]

[a]*Department of Physiology and Pharmacology, Sapienza University of Rome, Rome, Italy;* [b]*IRCCS Neuromed, Pozzilli, Italy;* [c]*Department of Physiology and Pharmacology, Laboratory affiliated to Istituto Pasteur Italia-Fondazione Cenci Bolognetti, Sapienza University of Rome, Rome, Italy*

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Abstract: ***Background*:** Glioblastoma is the most aggressive and deadly brain tumor, with low disease-free period even after surgery and combined radio and chemotherapies. Among the factors contributing to the devastating effect of this tumor in the brain are the elevated proliferation and invasion rate, and the ability to induce a local immunosuppressive environment. The intermediate-conductance Ca^{2+}-activated K^+ channel KCa3.1 is expressed in glioblastoma cells and in tumor-infiltrating cells.

***Methods*:** We first describe the researches related to the role of KCa3.1 channels in the invasion of brain tumor cells and the regulation of cell cycle. In the second part we review the involvement of KCa3.1 channel in tumor-associated microglia cell behaviour.

***Results*:** In tumor cells, the functional expression of KCa3.1 channels is important to substain cell invasion and proliferation. In tumor infiltrating cells, KCa3.1 channel activity is required to regulate their activation state. Interfering with KCa3.1 activity can be an adjuvant therapeutic approach in addition to classic chemotherapy and radiotherapy, to counteract tumor growth and prolong patient's survival.

***Conclusion*:** In this mini-review we discuss the evidence of the functional roles of KCa3.1 channels in glioblastoma biology.

Keywords: Intermediate conductance Ca^{2+}-activated K^+ channel (KCa3.1), brain tumors, Glioblastoma Multiforme (GBM), invasion, microglia, proliferation, 1-[(2-Chlorophenyl)diphenylmethyl]-1H-pyrazole (TRAM-34).

1. INTRODUCTION

KCa3.1, the intermediate-conductance Ca^{2+}-activated K^+ channel, is a tetrameric trans-membrane protein, with all the subunits composed of six trans-membrane segments, with a pore between the fifth and sixth segments [1]. The Ca^{2+} sensitivity of the channel is due to the presence of a calmodulin binding site at the C terminus of each segment, being also responsible for assembly and surface expression of the channel [2]. K^+ efflux through the channel helps to maintain a negative cell membrane potential that permits an electrochemical driving force for Ca^{2+} influx into the cells [3]. These changes in ion equilibrium help the cells to modify their shape and volume, both events necessary for cell migration. KCa3.1 is expressed, in physiological conditions, in different body districts, by many cells, such as epithelial cells of the gastro-intestinal regions, the lung, the endocrine and exocrine glands, as well as by vascular endothelial cells, fibroblasts and vascular smooth muscle cells (reviewed in [4]) and by cells of the hematopoietic lineage, such as erythrocytes, platelets, lymphocytes, mast cells, monocytes and macrophages [5]. Physiologically, the main role of the channel has been described in cell movement. During migration, cells increase their volume in the leading edge for protrusion and reduce their volume in the trailing one for the retraction. This localized change of volume is due to specific local K^+ (mainly through BK channels), Cl^- (ClC-3 channels) and water fluxes in the invadopodia, the dynamic actin-rich membrane structures, permitting cell migration and invasion in the neighbouring tissue; BK and ClC-3 co-localize in the lipid-raft domains of invadopodia, both contributing to ions efflux [6]. Channels involved in this process are voltage-gated K^+ channels [7-9] and, mainly, Ca^{2+} activated K^+ channels [9-11]. This mechanism is further strengthened by the activity of a Na^+/H^+ pumps at the leading edge and of aquaporin channels at the trailing one [12]. Deletion of KCa3.1 gene, *KCNN4*, inhibits the ability of lymphocytes and red blood cells to sense osmotic changes in mice [13].

*Address correspondence to this author at the Department of Physiology and Pharmacology, Sapienza University of Rome, Piazzale Aldo Moro, 5; 00185 Rome; Tel: +390649690243 Fax: +390649910851;
E-mail: cristina.limatola@uniroma1.it

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KCa3.1 is also expressed in the brain, in particular, by CNS-resident immune cells (microglia/macrophages), where KCa3.1 regulates the activation state [14, 15]. Recently, KCa3.1 has been demonstrated to be expressed on amyloid beta oligomer treated astrocytes [16] and on human pyramidal neurons in brain edema [17] deducing an important role played by KCa3.1 in brain dysfunction. The most common brain tumors are gliomas; the high grade (IV) glioblastoma multiforme (GBM) leaves patients with a mean survival time of 14.6 months [18]. KCa3.1 channel is commonly expressed by GBM, and correlates with shorter patient survival [19]. KCa3.1 is necessary for GBM cell movement modulating cell invasion both *in vitro* and *in vivo*. This mini-review aims to recapitulate the evidence of the efficacy of KCa3.1 inhibition to counteract GBM progression.

1.1. KCa3.1 Roles in Brain Tumors

In the last few years, ion channels have been identified as promising therapeutic targets to reduce the invasiveness of brain tumor cells. Ion channels are indeed deeply involved in tumor cell functions such as migration, angiogenesis and proliferation [20-23]. Movement of ions causes cytoplasmic water to move across the membrane allowing for the robust shape and volume changes. Volume changes are necessary for migration and, if inhibited, block cell migration [24]. Calcium-activated potassium channels are involved in this process [25-29]. Several studies show that large conductance Ca^{2+}-activated potassium channels (KCa1.1 or BK), ubiquitously expressed in the body, are required for tumor cell migration in pleural mesothelioma, glioma and breast cancer [30-33]. One additional promising target for new therapeutic approaches to glioma is the intermediate conductance Ca^{2+}-activated K^+ channel (KCa3.1). This channel is functionally expressed in virtually all normal and transformed migrating cells [25-29, 34] and its calcium dependency was shown in human GBM [22]. GBM is a deadly brain tumor [35]; its malignancy is mainly due to a high infiltrative behavior that renders complete surgical resection difficult. In 1938, Hans Joachim Scherer [36] first described the invasive patterns of GBM cells into human brain parenchyma. He detected, in over one hundred human GBM specimens, specific cell invasion pathways, named secondary structures today referred to as i) perineuronal and perivascular satellitosis, ii) subpial spread, and iii) invasion along the white matter tracts [37]. In 2008, Newcomb's group [38] provided a possible explanation for the secondary Scherer' structures, investigating the role of CXCR4, a G-protein coupled chemokine receptor overexpressed in most GBM cells (for a review [39]). He described that CXCR4 and its ligand CXCL12 are highly expressed in the GBM, providing an autocrine stimulatory loop for tumor cell proliferation, invasion and angiogenesis. In addition, he showed that invading glioma cells, positive for CXCR4, were closely organized around and along CXCL12 positive Scherer' structures; this was demonstrated in mouse brain transplanted with the murine GL261 glioma cells. We have demonstrated [40] that KCa3.1 is involved in CXCL12-induced glioma cell migration. The role of KCa3.1 channels was confirmed by experiments in GBM cell lines and in cells obtained from patients, that were silenced for KCa3.1 channel expression. We showed the first *in vivo* evidence of KCa3.1 involvement in GBM cell invasion in severe combined immunodeficiency (SCID) mice xenografted with human GL-15 GBM cells [41]: these cells have a high infiltrative behavior and permit to study the effect of compounds affecting tumor spreading in the brain parenchyma [42]. Inhibiting KCa3.1 by shRNA or by pharmacological tools, significantly reduced the tumor infiltrated area, especially along the white matter tracts, and reduced the maximal antero-rostral spreading of GBM in cerebral parenchyma [41]. KCa3.1 inhibition also decreased astrogliosis and microglia/macrophages (M/Mϕ) activation at the boundary of the tumor, suppressing M/Mϕ phagocytosis and migration. In 2014, Turner *et al*. [19] also tested whether KCa3.1 channels contributed to glioma invasion using patient derived gliomas propagated in the flank of nude mice as well as GBM cell lines (U251 cells). They showed that the expression of KCa3.1 conferred an invasive phenotype to GBM, and its deletion significantly reduced tumor cell invasion both *in vivo* and *ex vivo,* in acute slices obtained from tumor bearing brain. Altogether these results confirmed a crucial role of KCa3.1 channels in tumor cell spreading. The current chemotherapeutic agent for newly diagnosed GBM is temozolomide (TMZ), which extends patient's survival of about three months [18]. TMZ is a cytotoxic imidazotetrazine that leads to the formation of O6- methylguanine, which mismatches with thymine in subsequent DNA replication cycles, with effects on several cellular functions, such as autophagy [43], apoptosis and mitotic catastrophe [44]. A role for KCa3.1 in chemo and radio resistance has been recently observed in melanoma cells and in GBM. Cells with a blockade of KCa3.1 function are sensitized to this drug, potentiating the anti-tumor effects [45-47]. We recently demonstrated that treating GBM cells or cancer stem cells freshly dissected and isolated from patients, or human and murine glioma cell lines (GL261, U87MG), with TMZ and the selective KCa3.1 inhibitor, TRAM-34, induces a co-adjuvant effect on different tumor cell parameters such as cell invasion, proliferation and cell cycle progression [46]. We showed that channel inhibition forces TMZ treated cells, arrested in the G2 phase of cell cycle, to move toward the G0/G1 phases [46], a process that induces apoptotic death [48]. We demonstrated that KCa3.1 function is involved in the modulation of cdc2 G2/M check point protein, through cdc25C phosphatase activity; and that TRAM-34 and TMZ co-treatments increased the frequency of apoptotic cells and the mean survival time in a syngeneic GL261 glioma mouse model in comparison with single treatments. In line with this evidence, Stegen and co-authors [47] showed that ionizing radiation activates KCa3.1 channels in human GBM cells (T98G, U87MG) and that the pharmacological inhibition or the mRNA silencing of KCa3.1 channels reduced cell arrest in the G2-M phase and DNA repair, and reduced the clonogenicity of irradiated glioblastoma cells. In addition, they reported that pharmacologic targeting of KCa3.1 channels radiosensitized GBM cells grown ectopically in mice during fractionated radiation therapy. These *in vitro* findings and the *in vivo* outcomes in different mouse models highlighted the role of KCa3.1 channels in cell cycle regulation and are in accordance with retrospective clinical data where high levels of KCa3.1 gene transcription are correlated with reduced patient survival [19]. KCa3.1 channel is an attractive

therapeutic target for brain tumors mainly because it is highly expressed in GBM cells [39] and tumor associated microglia [49] and is poorly expressed [50] in normal CNS. KCa3.1 targeting could be a ready to use therapeutic approach to treat GBM patients considering the strategy of drug repurposing. In fact a KCa3.1 inhibitor, structurally related to TRAM-34, named Senicapoc® already passed through clinical phase I to III trials for sickle cell disease and is considered safe and well-tolerated by patients [51].

1.2. KCa3.1 Role in Tumor Associated Microglia Cells

In many brain pathologies, such as Alzheimer disease, ischemia, traumatic brain injury, spinal cord injury, optic nerve transection and experimental autoimmune encephalomyelitis, the selective inhibition of KCa3.1 channel turned out to be beneficial [50, 52-59]. In all these cases, the effect of KCa3.1 inhibition results in an overall improvement and in the reduction of pathological symptoms. Glioma cells in the brain produce high level of glutamate that can produce local concentrations as high as 10 times more than normal [60]. This is induced by altered buffering by surrounding astrocytes [61], and dysfunction of the Na^+-independent cystine/glutamate transporters X_c, expressed on glioma cells, and represents the main cause of neuron death (by excitotoxicity) in case of brain tumors [62]. Neuronal loss creates free spaces in the brain parenchyma, enabling tumor expansion [63]. Intriguingly, TRAM-34, *in vitro*, protects neurons from glioma-induced toxicity [46], and *in vivo* reduces the tumor-associated gliosis [41]. Altogether, these data suggest that

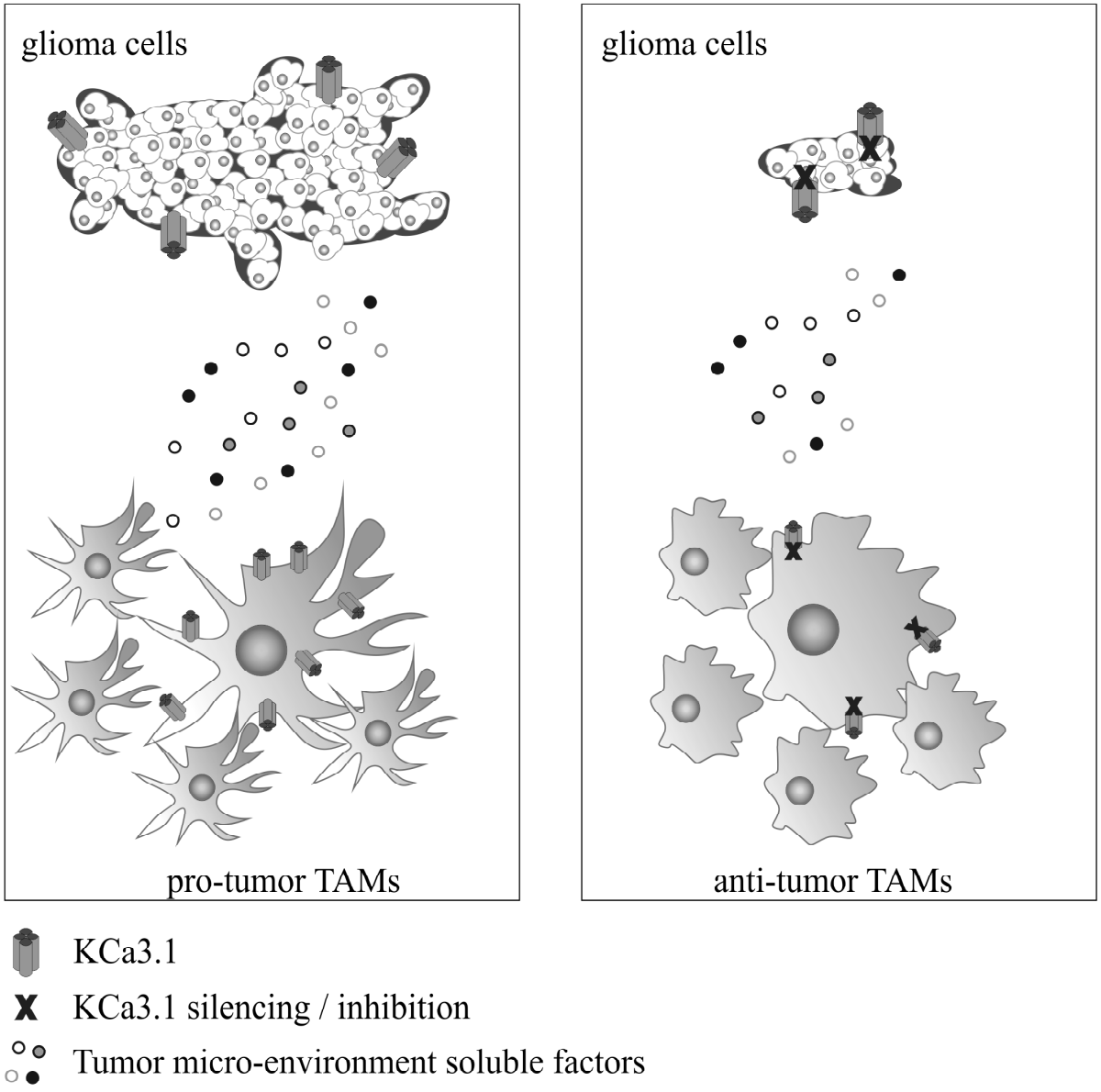

Fig. (1). A schematic representation of tumor microenvironment composed by glioma cells and tumor-associated microglia/macrophages (TAMs) is reported on the left, with high level of tumor growth and invasion and TAMs oriented toward a pro-tumor phenotype. Right: effect of KCa3.1 channel silencing/inhibition, with a reduction of tumor growth and invasion, and TAMs acquiring an anti-tumor phenotype.

KCa3.1 blockade might reduce tumor burden also reducing neuronal death induced by the presence of the tumor. KCa3.1 channels are functionally expressed in microglia, as shown by electrophysiological patch clamp experiments [64], by mRNA expression studies [65], that excluded the contribution of additional channels in Ca^{2+} activated K^+ currents recorded in these cells [66, 67]. In microglia, KCa3.1 channels are also involved in cell migration, with Ca^{2+}- [15, 68] and cAMP/PKA-dependent mechanisms. The effects of KCa3.1 channels in microglia also comprise the production of reactive oxygen species (ROS) through the p38/MAPK and cGMP/PKG pathways [69]. Migration and nitric oxide generation are closely associated with the inflammatory roles of these cells [70]; microglia exert both pro- and anti-inflammatory activities, in response to surrounding stimuli, that induce continuous shape and volume changes, enabling cells to monitor brain parenchyma. *In vitro* microglia stimulated with IL-4 assume an anti-inflammatory phenotype, producing cytokines such as IL-6 and TGFß [71, 72], and increasing the migratory ability by enhancing expression of MMP2, cathepsin S and cathepsin K [64]. This is often referred to as M2-like phenotype, in analogy with macrophages ([73], but see also [74]). IL-4 treatment of microglia also increased the functional expression of KCa3.1 channels, and channel inhibition blocks the intrinsic migratory ability of IL-4 stimulated cells [15, 68]. The M2-like phenotype is also induced *in vivo* by glioma, on tumor-associated myeloid cells (TAMs). Myeloid cells invading the tumor are mainly microglia and macrophages, and represent up to 30-50% of tumor mass [75, 76]. These cells are recruited in the tumor mass by cytokines and other soluble factors released by glioma [77-79]. In response to tumor factors, such as CXCL12, CCL2/MCP1, MCP3, GDNF, CSF-1 and GM-CSF [80-85], TAMs release a wide array of molecules that enhance tumor progression by multiple mechanisms that favour cell invasion [86]. Many of these factors, such as STI1, EGF, IL-6, TGFß, also stimulate migration of glioma cells [84, 87]. IL-6, in turn, increases CCL2 release by tumor cells, enhancing tumor invasion, while TGFß increases the expression of integrins on glioma cell lines, and favour the degradation of the extracellular matrix [88-90]. TAMs also increase the expression of membrane type 1–matrix metalloproteinase and reduce the expression of metalloproteinases inhibitors, further favouring extracellular matrix degradation, necessary for glioma invasion [91]. In murine glioma models, microglia depletion by clodronate treatment (*ex vivo)*, reduced glioma cell invasion in surrounding parenchyma [92]. Specific depletion of $CD11b^+$ cells in mice also decreased glioma cell proliferation in *in vivo* models [93, 94]. We demonstrated that KCa3.1 activity in TAMs (in cultures, as well as *in vivo*) reverts the pro-tumor phenotype toward a pro-inflammatory, anti-tumor state [49]. All these experiments demonstrated that TAMs are potentially appropriate therapeutic targets to fight against gliomas. Trying to interfere with the pro-tumor effects of TAMs, for example reverting the phenotype toward a pro-inflammatory one, could be a promising approach to counteract GBM progression [95-97].

CONCLUSION

GBM, the most common primary brain tumor, presents a high level of cell infiltration and proliferation. Inside and around tumor mass, M/Mϕ represent the major infiltrating cell population. These TAMs are forced to assume an anti-inflammatory phenotype necessary to maintain and promote tumor progression. Current standard therapy, that includes surgical resection, radiotherapy plus chemotherapy, is insufficient to eradicate the tumor. New therapies are necessary to reduce invasion and proliferation of tumor cells as well as to reprogram the immune response of microglia and macrophages towards a pro-inflammatory, anti-tumor phenotype. KCa3.1 channel blockade by mRNA silencing or by pharmacological tools acts on these two fronts. In fact, the selective inhibition of the channel reduces tumor invasion and growth with direct effects on glioma, and switches the activation state of TAM towards an antitumor phenotype. Fig. (**1**) summarizes the actions of KCa3.1 on tumor cells and TAMs. Data obtained in *in vitro* and *in vivo* models of glioma delineate the possibility to target KCa3.1 as innovative therapeutic approach for GBM.

LIST OF ABBREVIATIONS

cAMP	=	cyclic adenosine monophosphate
CCL2	=	C-C motif ligand 2
Cdc2	=	cell division control 2
Cdc25C	=	cell division control protein 25 C
cGMP	=	cyclic guanosine monophosphate
CNS	=	central nervous system
CSF-1	=	colony stimulating factor 1
CXCR4	=	C-X-C motif receptor 4
EGF	=	epidermal growth factor
GDNF	=	glial cell line-derived neurutrophic factor
GM-CSF	=	granulocyte macrophage colony stimulating factor
IL-4	=	interleukin 4
IL-6	=	interleukin 6
MAPK	=	mitogen activated protein kinase
MCP-1	=	monocyte chemoattractant protein-1
MCP3	=	monocyte chemoattractant protein-3
M/Mϕ	=	microglia/ macrophages
MMP2	=	matrix metalloproteinases 2
PKA	=	protein kinase A
PKG	=	protein kinase G
CXCL12	=	chemokine ligand 12
STI1	=	stress inducible protein 1
TGFß	=	transforming growth factor ß
TRAM-34	=	1-[(2-Chlorophenyl)diphenylmethyl]-1H-pyrazole

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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