TRPC Channels and Glioma

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Abstract

Glioma is the most common type of brain tumors and malignant glioma is extremely lethal, with patients' 5-year survival rate less than 10%. Treatment of gliomas poses remarkable clinical challenges, not only because of their particular localization but also because glioma cells possess several malignant biological features, including highly proliferative, highly invasive, highly angiogenic, and highly metabolic aberrant. All these features make gliomas highly recurrent and drug resistant. Finding new and effective molecular drug targets for glioma is an urgent and critical task for both basic and clinical research. Recent studies have proposed a type of non-voltage-gated calcium channels, namely, canonical transient receptor potential (TRPC) channels, to be newly emerged potential drug targets for glioma. They are heavily involved in the proliferation, migration, invasion, angiogenesis, and metabolism of glioma cells. Abundant evidence from both cell models and preclinical mouse models has demonstrated that inhibition of TRPC channels shows promising anti-glioma effect. In this chapter, we will give a comprehensive review on the current progress in the studies on TRPC channels and glioma and discuss their potential clinical implication in glioma therapy.

Keywords

Glioma • Drug targets • TRPC

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14.1 Introduction

Glioma is the most common tumor in the brain. It constitutes ~30% of all brain tumors and 80% of all malignant brain tumors [16]. Glioma has a yearly incidence of 3–5 per 100,000 population, and it occurs in all age groups but is most prevalent in adults over the age of 45. Studies on the tumor cell origin suggest that glioma could originate from neural stem cells, transit amplifying cells, neural/glial progenitors, astrocytes, or oligodendrocytes [54]. Based on their histological characters, glioma is classified into four main types: ependymomas, astrocytomas, oligodendrogliomas, and mixed gliomas [1]. Glioma is further classified according to their pathologic features (WHO grade I–IV), and glioblastoma multiforme (GBM) is the most aggressive glioma that accounts for more than 50% of gliomas [35]. Despite great progresses have been made in conventional therapeutic approaches, the overall 5-year survival rate of GBM is less than 5% and even worse for the elderly [12]. Therefore, it is fundamentally important to explore new molecular targets, and combination of those new treatments with conventional therapeutic approaches may improve the effects for patients with GBM.

Gliomagenesis and development are complex processes, which are only partially understood. Maintenance of intracellular Ca^{2+} homeostasis is essential for a large number of cellular processes [3]. The Ca^{2+} exerts biphasic effects on cellular growth. For example, a modest increase in intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) could promote cell proliferation, whereas high $[Ca^{2+}]_i$ would result in elevated mitochondrial Ca^{2+} levels and eventually the release of pro-apoptotic factors, leading to cell death [47]. To regulate the intracellular Ca^{2+} levels, cells have evolved multiple mechanisms, mainly by regulating the function of Ca^{2+} channels. Important players in this regulation are members of the TRP superfamily of ion channels (TRPC, TRPV, TRPM, TRPML, TRPP, TRPA, and TRPN). Cancer cells have abnormally regulated Ca^{2+} homeostasis [13], resulting in their abnormal biological behavior. Dysregulation of TRPC channels is one of the culprits leading to these malignancies.

14.2 Role of TRPC Channels in Glioma

Channels formed by the TRPC proteins are a subfamily of the TRP proteins, which are widely expressed in mammalian cells. It has been reported that the TRPC family consists of six members in human (TRPC1 and TRPC3-7) and seven in rodents (TRPC1-7) [55]. Diverse studies have suggested that TRPC channels are likely to play a role in glioma growth and development at different levels by regulating cellular metabolism, controlling cell proliferation, promoting angiogenesis, and triggering the migration and invasion during glioma progression (Fig.14.1).

In each square are the represented members of the TRPC family, which are involved in the main processes driving glioma progression.

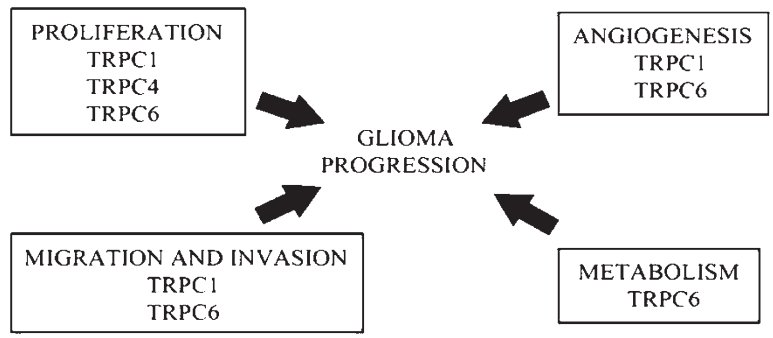

Fig. 14.1 TRPC and glioma progression

We are going to summarize the role of TRPC channels in glioma to deepen our understanding of glioma biology and help to find new and effective drug targets.

14.3 Role of TRPC Channels in Cell Proliferation in Glioma

The Ca^{2+} signaling plays a vital role in cell proliferation and is required at multiple stages of cell cycle [25]. The signaling involves receptors, channels, transducers, Ca^{2+} effectors, Ca^{2+}-sensitive enzymes, Ca^{2+} pumps, and Ca^{2+} exchangers [11]. These Ca^{2+} signaling proteins contribute to the proliferative capacity of cells.

Growth control of cancer cells has been studied extensively over the past decades, and some members of the TRPC family have been identified to affect the proliferation of many types of cancer cells [38]. Studies have demonstrated the expression of five TRPC channel proteins (TRPC1, 3, 4, 5, and 6) in glioma cell lines and patient-derived tissues [5]. Ca^{2+} influx through these channels activates intracellular Ca^{2+} effectors and Ca^{2+}-sensitive enzymes, which in turn mediate cellular activities necessary for cell cycle progression and proliferation [49].

Glioma, particularly the GBM, proliferates extensively and cells often undergo incomplete cell divisions, resulting in multinucleated cells. The recent study in D54MG glioma cells indicates that pharmacological or short hairpin RNA (shRNA)-mediated inhibition of TRPC1 channels, which are involved in agonist-induced Ca^{2+} influx and reloading of intracellular Ca^{2+} stores, leads to reduced cell proliferation and higher percentages of multinucleated cells. Moreover, decreased TRPC1 protein expression correlates with an increased percentage of multinucleated cells in GBM patient biopsies and impairs in vivo tumor growth in a xenograft tumor model. These results suggest that TRPC1 plays a critical role in glioma cell division by regulating Ca^{2+} signaling during cytokinesis [4].

In addition, a role for TRPC4 channels in glioma cell proliferation has been suggested. TRPC activation has been demonstrated as downstream signal of the epidermal growth factor receptor (EGFR) stimulation [44]. EGFR is the major growth factor receptor activated in malignant gliomas, as mutated or amplified EGFR is often observed in malignant gliomas and is associated with increased cell proliferation [7]. In Cos-7 cells, EGFR activation leads to TRPC4 phosphorylation and channel insertion into the plasma membrane [44]. Furthermore, knockdown of TRPC4 in human corneal epithelial cells suppresses EGF-induced cell proliferation, again linking proliferation to TRPC channels [62].

Another TRPC channel member, TRPC6, also plays a role in the control of glioma cell cycle and proliferation. Studies have shown that the mRNA and protein levels of TRPC6, among the TRPC family, are specifically enhanced in human glioma tissues compared to normal brain tissues. The increased expression of TRPC6 is associated with glioma malignancy grades. Moreover, functional TRPC6 channels are present in U251MG, U87MG, and T98G glioma cells. In these cells, inhibition of TRPC6 activity or expression by using a dominant-negative form of TRPC6 (DNC6) [21] or shRNA, respectively, causes a decrease in Ca^{2+} influx stimulated by platelet-derived growth factor (PDGF), which suppresses cell growth, induces cell cycle arrest at the G2/M phase, and enhances the anti-proliferation effect of irradiation. Further analysis shows that inhibition of TRPC6 suppresses the activation of cyclin-dependent kinase 1 (CDK1) via downregulation of cell division cycle protein 25C (CDC25C) expression, which is responsible for the cell cycle arrest. More importantly, inhibition of TRPC6 activity also significantly reduces tumor volumes in nude mice subcutaneous xenograft model and increases mean survival in nude mice intracranial xenograft model [11]. Besides, another study shows that TRPC6 channels could promote the proliferation and malignant growth of glioma during hypoxia by activating the calcineurin-nuclear factor of activated T-cell (NFAT) pathway [10]. Taken together, these findings strongly imply the reliance of glioma cell proliferation on TRPC6 channels.

14.4 Role of TRPC Channels in Angiogenesis in Glioma

Angiogenesis is recognized as a key event in glioma progression [2]. Glioma cells stimulate the growth of new blood vessels to support their energy demands, a process known as neovascularization. Neovascularization in the brain tumors is positively correlated with the biological aggressiveness, degree of malignancy, and clinical recurrence and negatively correlated with the postoperative survival of patients with glioma [48]. GBM is the most common form of malignant brain tumor, and the growth of these tumors is highly angiogenesis dependent, meanwhile higher-grade malignant astrocytomas have a higher degree of vascularity [57]. Tumor angiogenesis is not only resulted from adaptation to hypoxia in response to the increasing tumor mass but also resulted from genetic mutations that activate gene transcription for angiogenesis [31]. Ca^{2+} entry through plasma membrane affects angiogenesis, and several reports indicate that TRPC channels are activated during glioma angiogenesis.

Vascular endothelial growth factor (VEGF) is the most potent angiogenic factor implicated in tumor angiogenesis, whose expression is activated by hypoxia [34]. In U87MG cells, Ca^{2+} influx through TRPC channels plays a critical role in hypoxia-induced VEGF gene expression. Importantly, silencing of TRPC1, not other TRPC members, largely suppresses the upregulation of VEGF expression by hypoxia, suggesting the involvement of TRPC1 channels in glioma angiogenesis [57] Recently, it is reported that in zebra fish, knockdown of TRPC1 severely disrupts angiogenic sprouting of intersegmental vessels (ISVs), which is attributable to the impairment of filopodia extension, migration, and proliferation of ISV tip cells. Furthermore, TRPC1 acts synergistically with VEGF-A in controlling ISV growth and seems to be downstream of VEGF-A in controlling angiogenesis. Therefore, TRPC1 is essential for angiogenesis in vivo [63].

Other TRPC channels have also been found to be involved in glioma angiogenesis. Ca^{2+} entry through TRPC6 increases endothelial permeability and promotes angiogenesis [26]. TRPC6 can be activated by VEGF. Overexpression of a dominant-negative TRPC6 construct in human microvascular endothelial cells (HMVECs) suppresses the VEGF-mediated increase in intracellular Ca^{2+} levels, migration, sprouting, and proliferation. In contrast, overexpression of a wild-type TRPC6 construct promotes the proliferation and migration of HMVECs [19]. Additionally, inhibition of TRPC6 in human umbilical vein endothelial cells (HUVECs) by pharmacological or genetic approaches arrests cells at the G2/M phase and suppresses the VEGF-induced proliferation and tube formation, which are key steps in angiogenesis. Furthermore, inhibition of TRPC6 abolishes VEGF-induced angiogenesis in the chicken embryo chorioallantoic membrane (CAM) [15]. The above reports indicate that VEGF activates TRPC6 channels to regulate the angiogenesis. Conversely, TRPC6 activation in endothelial cells (ECs) may stimulate transcription and release of angiogenic growth factors such as VEGF, which stimulate angiogenesis. For example, hypoxia induces Notch1 activation, increases TRPC6 expression, and thus elevates $[Ca^{2+}]_i$ that is coupled to the activation of the calcineurin-NFAT pathway, resulting in glioma angiogenesis [10]. It remains to be determined whether Notch pathway directly or indirectly regulates TRPC6 expression [17, 52].

14.5 Role of TRPC Channels in Cell Migration and Invasion in Glioma

GBM is extremely invasive and thus the clinical prognosis for patients is desperate. Numerous studies have focused on understanding the molecular mechanisms of glioma cell invasion, and Ca^{2+} signaling has been shown to play a role in it [28].

TRPC1-mediated migration and chemotaxis have been demonstrated in different cell types such as myoblasts [36], renal epithelial cells [14], and nervous cells [58]. Recently, it has been reported that TRPC1 regulates glioma chemo-

taxis induced by EGF and the localization of TRPC1 in lipid rafts is essential for the function [6]. In response to EGF, TRPC1 is enriched in the leading edge of D54MG cells and co-localized with lipid raft proteins. Pharmacological or shRNA-mediated inhibition of TRPC1 channels abolishes EGF-induced cell migration, without affecting the motility of un-stimulated cells. Moreover, disruption of lipid rafts not only decreases chemotaxis but also decreases store-operated Ca^{2+} entry and impairs TRPC currents. These results indicate that TRPC1 association with lipid rafts is essential for glioma chemotaxis in response to specific stimuli.

As mentioned above, TRPC6 expression is markedly enhanced during hypoxia in a manner that is dependent on Notch activation [10]. Notch signaling is reported to mediate hypoxia-induced tumor migration and invasion [50]. TRPC6 is also required for the development of this aggressive phenotype because knockdown of TRPC6 decreases glioma invasion.

The last step of invasion requires cytoskeletal rearrangements and formation of lamellipodia and filopodia, where the Rho family of GTPases plays a critical role. The role of TRPC6 in Rho activation and actin cytoskeletal rearrangements has been indicated in several studies [51]. Therefore, the TRPC6-mediated Ca^{2+} influx likely contributes to glioma invasion by promoting actin-myosin interactions and the cell-substratum adhesion assembly and disassembly that are important for migration [39, 50].

14.6 Role of TRPC Channels in Cellular Metabolism of Glioma

Cellular metabolism influences survival and death decisions. In recent years, an emerging theme in tumor biology is that metabolic regulation is closely linked to tumor progression [42]. Interest has been renewed as it has become clear that many cancer-related pathways have significant impacts on tumor metabolism and that many tumors become dependent on specific metabolic processes.

It has been reported that all major tumor suppressors and oncogenes have intimate connections with metabolic pathways [29]. Genetic alterations (affecting HIF-1, AMPK, p53, Myc, and PI_3K) drive the metabolic inputs into multiple pathways that not only supply cellular energy (i.e., ATP) but also provide macromolecular precursors (i.e., ribose and acetyl-CoA) as well as the reducing power for biosynthetic processes and redox regulation (NADPH). More and more studies reveal that altered cellular metabolism could be one of the major routes by which oncogenes promote tumor formation and progression [23]. By far, there is no direct evidence existing about the role of Ca^{2+} in tumor metabolism, although being a key player in tumor progression. However, it should be mentioned that some key molecules (i.e., HIF-1, AMPK, p53, Myc) involved in tumor metabolism are sensitive to Ca^{2+} [8]. It is therefore possible that Ca^{2+} affects tumor metabolism by regulating these metabolic regulators.

A recent study confirmed this hypothesis [32]. Insulin-like growth factor 1 (IGF-1) is specifically released from human glioma cells during hypoxia. TRPC6, the specifically upregulated TRPC member in human glioma tissues, is then rapidly activated by IGF-1 receptor (IGF-1R)/phospholipase C (PLC)/IP_3 receptor (IP_3R) pathway. IGF-1 released in hypoxia stimulates IGF-1R, leading to the activation of PLC, which hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP_2) into diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP_3). IP_3 induces Ca^{2+} release from internal stores, which in turn activates TRPC6 to mediate Ca^{2+} influx. TRPC6 activation decreases α-ketoglutarate (α-KG) levels and inhibits HIF prolyl hydroxylase (PHD) activities, leading to HIF-1α accumulation. HIF-1 plays a critical role in tumor cell glucose metabolism via regulating the expression of the metabolic related genes [61]. And TRPC6 is shown to enhance glucose uptake through HIF-1α. Inhibition of TRPC6 by using DNC6 dramatically suppresses hypoxia-induced glucose transporter 1 (GLUT1, also known as SLC2A1) expression. Expressing exogenous HIF-1 indeed reverses DNC6 inhibition of GLUT1 expression. Importantly, express-

ing HIF-1 reversed DNC6 suppression on glucose uptake in hypoxia. Further, treatment of the cells with 1-oleoyl-2-acetyl-sn-glycerol (OAG), the membrane-permeable DAG analogue known to induce Ca^{2+} entry through TRPC6, increases GLUT1 mRNA and protein levels in hypoxia, which is significantly decreased by expressing DNC6 [10]. It should be mentioned that two other well-known genes involved in energy metabolism, lactate dehydrogenase A (*LDHA*) and lactate dehydrogenase B (*LDHB*), are not affected by TRPC6. Collectively, these results imply that activation of TRPC6 promotes glucose metabolism in hypoxia, yet however does not stimulate glycolysis to produce energy. Therefore, TRPC6 controls the metabolite levels to regulate the rapid hydroxylation and stability of HIF-1α and affect the consequent glucose metabolism during hypoxia. In this context, The Ca^{2+} influx via TRPC6 can act as an important metabolic regulator (Fig. 14.2). In addition, the inhibitory effect of DNC6 on GLUT1 expression may partially explain its suppression of glioma cell development [10, 11]. Therefore, studying the possible role of TRPC in the regulation of glioma metabolism likely has profound clinical significance.

TRPC6-mediated regulation of the metabolite levels promotes glucose uptake through an increase in HIF-1α stability in human glioma cells under hypoxia [32].

Based on the above findings, TRPC channels could be potential drug targets in glioma treatment. SKF96365, known as a selective inhibitor of receptor-mediated Ca^{2+} entry and voltage-gated Ca^{2+} entry, can inhibit many other types of Ca^{2+} channels besides TRPC channels, leading to strong nonspecific effects [40]. In the past decades, great effort was made to explore the agents specifically targeting Ca^{2+} channels including TRPC channels (Table 14.1). Recently, a potent and selective TRPC4/5 antagonist, ML204, is identified. Its selectivity is far superior to other pharmacological blockers currently used in TRPC research [41]. However, such agents for TRPC1 or TRPC6 channels have not yet been reported. Therefore, in order to facilitate the clinical treatment of glioma, the development of specific blockers targeting TRPC1 and TRPC6 channels is in urgent need.

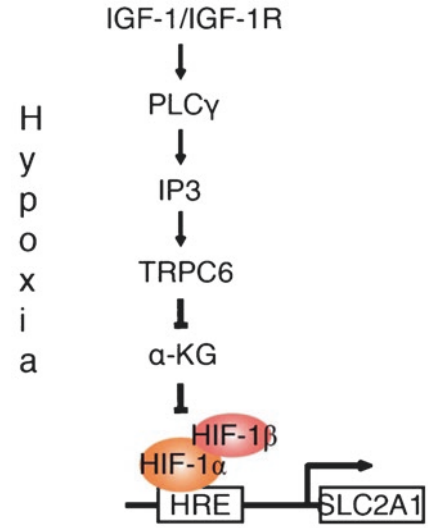

Fig. 14.2 TRPC6 and glioma metabolism

Table 14.1 Pharmacological antagonists of TRPC channels

TRPCs	Channel blockers
TRPC1	La^{3+}, Gd^{3+}, 2-APB, SKF96365, GsMTx-4 [53, 64]
TRPC3	Gd^{3+}, BTP2, La^{3+}, 2-APB, SKF96365, ACAA, Ni^{2+}, KB-R7943, Pyr3, [18, 20, 27, 33]
TRPC4	Niflumic acid, ML204, 2-APB, La^{3+}, SKF96365 [41, 56]
TRPC5	La^{3+}, KB-R7943, progesterone, ML204, bromoenol lactone, 2-APB, Mg^{2+}, chlorpromazine, BTP2, SKF96365, flufenamic acid, GsMTx-4 [9, 24, 30, 37, 41, 43, 59]
TRPC6	Gd^{3+}, La^{3+}, SKF96365, amiloride, Cd^{2+}, extracellular H^+, 2-APB, ACAA, GsMTx-4, KB-R7943, ML9 [22]
TRPC7	La^{3+}, SKF96365, amiloride, 2-APB [46]

14.7 Conclusion and Prospective

In this chapter, we have summarized the important role of TRPC channels in glioma growth and development and pointed out that TRPC channels are potential therapeutic targets for glioma. Although the link between TRPC and glioma becomes clearer, there are areas still relatively less explored. Until now, almost all the evidence comes from loss-of-function experiments. One interesting thing for the future is that whether

TRPC overexpression indeed contributes to gliomagenesis, which will deepen our understanding of TRPC in glioma biology. Another aspect of glioma biology where TRPC is going to be critical but has not been explored is the tumor epigenetics. "Epigenetics" is critical for gene regulation, where Ca^{2+} also has important roles. An increasing number of studies showed that the epigenetic differences could influence tumorigenesis [45, 60]. Further studies on the epigenetic differences resulting from TRPC dysfunction and thus the gliomagenesis are required. It is hoped that extensive knowledge about TRPC would offer effective therapeutic targets and specific chemotherapeutic agents and enable the use of TRPC channels as invaluable markers of diagnosis and prognosis in patients.

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