REVIEW ARTICLE

Growth factors and kinases in glioblastoma growth

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Abstract: Glioblastoma multiforme (GBM) is the most aggressive type of brain cancer, having the highest invasion, migration, proliferation, and angiogenesis rates. Several signaling pathways are involved in the regulation of these processes including growth factors and their tyrosine kinase receptors, such as vascular endothelial growth factor (VEGF), transforming growth factor beta (TGFβ), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), and insulin-like growth factor–I (IGF–I). Different kinases and regulators also participate in signaling pathways initiated by growth factors, such as mitogen-activated kinases (MAPK), protein kinases C (PKC), phosphatidylinositol-3-kinases (PI3K), protein kinase B (PKB or Akt), glycogen synthase kinase 3β (GSK3β), the mTOR complex, and Bcl-2. In this review, we will focus on the role of these proteins as possible therapeutic targets in GBM.

Keywords: glioblastoma; growth factors; kinases


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Introduction

Gliomas are the most common type of brain tumor, representing approximately 50% of all neoplasia in the central nervous system[1]. Histopathologically, gliomas are classified as astrocytomas, oligodendrogliomas, oligoastrocytomas, and ependymomas[2]. Astrocytomas are the most common and malignant type of glioma, and can be caused by astrocytes, glial progenitors, and cancer stem cells[3-6]. According to the World Health Organization, gliomas are classified into four grades (I-IV), with glioblastoma (grade IV) being the most common and malignant grade[7].

Owing to the heterogeneity observed in glioblastoma (GBM)[8], its poor prognosis, and its diverse mechanisms for therapy resistance and progression[7], a number of studies have focused on understanding different signaling pathways that participate in these processes[9]. Genetic and histopathological studies have thoroughly described the important receptors and pathways involved in this disease. The importance and recurrence of some of these molecules have made them attractive biomarkers in understanding the tumor, as well as in choosing a more adequate and effective treatment[10-13]. One of the most studied markers is the epidermal growth factor receptor (EGFR), which plays a crucial role in the biology of GBM; in this regard, there is a lot of information about the EGFR signaling network, which has been significantly implicated in the initiation and progression of these kinds of tumors[14-16]. In this review, we are focusing on other markers and pathways besides EGFR that include growth factors and their tyrosine kinase receptors such as VEGF, TGFβ, FGF, PDGF, and IGF-I, as well as different kinases and regulators such as MAPK, PKC, PI3K, PKB, GSK3β, the mTOR complex, and Bcl-2 (Figure 1).

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Growth factors, receptors, and kinases involved in GBM. Color-coded lines connect the receptors to the most common kinases whereas the black lines further connect these kinases to the effects mentioned; in many cases, several different pathways are involved. EGF/R: epidermal growth factor/receptor; VEGF/R: vascular endothelial growth factor/receptor; PDGF/R: platelet-derived growth factor/receptor; TGF/R: transforming growth factor/receptor; IGFR/R: insulin-like growth factor/receptor; FGF/R: fibroblast growth factor/receptor; Shh: Sonic Hedgehog protein; P3K: phosphatidylinositol-3-kinase; Bcl-2: B-cell lymphoma 2; mTOR: mammalian target of rapamycin; GSK3β: glycogen synthase kinase 3 beta; IRS: insulin receptor substrate; PTC: Patched receptor; Smo: Smoothened receptor; PKC: protein kinase C; MAPK: mitogen-activated protein kinase.

Growth factors and receptors

Vascular endothelial growth factor (VEGF)

The two characteristics of glioblastoma that contribute to poor prognosis are recurrence and invasion, but angiogenesis has also been reported to be important for tumor growth\(^{17}\). Although GBM cells are capable of producing different factors that induce angiogenesis, VEGF and its receptor (VEGFR) are among the most studied and targeted as possible anti-angiogenic treatment\(^{17}\). The vascular endothelial growth factor family includes VEGF A, B, C, D, and placental growth factor (PLGF). These ligands bind to three known receptors that act as tyrosine kinases: VEGFR1, 2, and 3\(^{18,19}\). VEGF-A binds to VEGF receptor 2 and acts as the best-characterized angiogenic factor; both the growth factor and receptor tend to be highly expressed in cancer, particularly in GBM\(^{18,20}\).

Hypoxia is the most important factor that induces VEGF expression by hypoxia-inducible factor 1 alpha (HIF1α), but the secretion of other growth factors can also increase VEGF levels, such as epidermal growth factor (EGF), transforming growth factor (TGF), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), and fibroblast growth factor (FGF)\(^{21}\). After the ligand-receptor interaction, several signaling pathways can be activated to induce cell survival (phosphatidylinositol-3 kinase, or PI3K), proliferation (mitogen-activated protein kinases, or MAPK), and migration (cellular Src kinases, or c-Src)\(^{18}\). Moreover, a previous study indicated that radiation therapy induces the expression of VEGF, which then increases invasion and migration through the focal adhesion kinase (FAK) and Src activation\(^{22}\). Since VEGF is capable of activating several signaling cascades, blocking these effects through its receptor appears to be a good therapeutic strategy. One of these strategies is the use of antibodies that would antagonize the receptor and prevent its activation such as sunitinib and cediranib, or with anti-VEGF antibody – bevacizumab being the most studied\(^{19,23}\). The exact mechanism by which the blockade of VEGF and VEGFR inhibits functions on the tumor is not completely understood, although decreases in proliferation and angiogenesis, as well as infiltration of myeloid cells, have been reported\(^{23,24}\).

Other studies have indicated that even though some improvements were observed in patients with disease recurrence\(^{19}\), no significant recovery was noted when the antibodies were used in newly diagnosed glioblastoma\(^{25}\). There is a case report in which bevacizumab treatment was found effective in decreasing the tumor size but the patient presented tumor recurrence afterwards; moreover, the data showed that the treatment induced a down-regulation of VEGFR and the activation of anti-apoptotic protein B-cell lymphoma 2 (Bcl-2). Interestingly, the expression and activation of matrix metalloproteinases (MMP) also increased\(^{26}\). To determine the importance of VEGFR activation, a study analyzed the progression of patients treated with tyrosine kinase inhibitors (TKI), which are known to act in VEGFR pathway’s downstream. The treatment improved prognosis; however, the authors indicated that it is important to consider individual circumstances owing to the inherent heterogeneity in GBM\(^{27}\). Together, these results indicate that blocking growth factors with antibodies is inadequate in patients. Moreover, they may not be the best-suited molecules to be used in such therapy. Several other techniques have been used in many models, such as miRNA, siRNA, and oligodeoxynucleotides, and have provided promising results\(^{28-31}\). These techniques are commonly used for understanding the molecular mechanisms of disease pathology and could be used as treatment options. However, more research in delivery systems and more evidence in patients are needed.
It is commonly reported that GBM recurrence is caused by the persistence of cancer stem cells (CSCs), which reside in specialized niches. Angiogenesis is important for the formation of new niches[33], which may correlate with GBM being highly angiogenic. CSCs have the ability to differentiate, form neovascularization, and express VEGFR, which is needed for the maintenance of vessels[33]. Moreover, VEGF/VEGFR in GBM growth may not be achieved solely through an angiogenic function; previous reports have indicated that in both hypoxic and normoxic conditions, VEGF induces CSC proliferation[34], involving the interaction with, among other possible proteins, neuropilin 1 (NRP1) which is a determinant factor in the activation of VEGFR proliferation, tumorigenesis, and even therapy evasion[35]. A xenograft study reported that the combined use of CXCR4 protein antagonist (POL5551) and VEGFR inhibitor (mcr84) increased survival rates and reduced the population of cells that expressed stemness markers[32]. In contrast, it has been shown that the blocking of VEGFR using VEGF antagonists induces the expression of CXCR4, thus indicating a crosstalk between these two pathways. Interestingly, this interaction also involved another important growth factor and its receptor – the transforming growth factor (TGF) – which exemplifies how complicated signaling pathways can be in GBM[20].

**Transforming growth factor β (TGFβ)**

The TGFβ family is a group of homodimeric polypeptides that are activated after they bind to three different types of receptors (TGFβR). Type I and type II receptors are serine/threonine kinases, and type III receptors are proteoglycans without kinase activity. Once TGFβ binds to the type III receptor, the type II receptor recognizes the ligand and forms a complex with the type I receptor that entails autophosphorylation[36]. After the receptors’ activation, the type I receptor activates Smads, which work as transcription factors that, in turn, induce a variety of functions including cell growth and differentiation, immunosuppression, angiogenesis and interaction with the extracellular matrix[36]. Activation by other mechanisms has also been described. For example, through MAPK, nucleolin protein promotes migration, proliferation, and possible epithelial-mesenchymal transition[37]. However, as TGFβ functions both as a tumor suppressor and promoter, the results are controversial and a particular role has not been defined[38,39].

Interactions with other growth factors and molecules have also been reported for TGFβ, particularly through PDGF, whereby increases in tumor proliferation, invasion, metastasis, and angiogenesis have been described[38]. These effects may affect or be closely related to stemness since the inhibition of TGFβ induces cell differentiation[40]. This possible role in CSCs also affects the tumor’s response to radiation since the blockage of TGFβ decreases survival, invasion, and angiogenesis[31]. In addition, it was also reported that TGFβ induces VEGF[42], and the signaling of these two may induce changes in gene expression[43]. Different intracellular pathways may be activated, including MAPK, JNK, and PI3K[38,42,44,45]. It has been reported that MAPK stimulation induces MMP9 activation, which increases motility and invasiveness[44]. However, as mentioned, other studies have reported opposite effects, indicating that no correlation was found between TGFβ, vasculature, and the inhibition of U87 cell growth in vitro and in vivo[39].

More studies are required to clarify the mechanisms by which the TGFβ pathway may affect tumor growth, including a probable role as a suppressor of immune response[46]. In this regard, a clinical study showed that the blocking of TGFβ improved long-term survival, although the sample may have been too small to be strongly conclusive[47]. An alternative that has given good results is the targeting of TGF using antisense oligodeoxynucleotides (ODN), which are sequences that regulate content-specific targets[47-49]. A particular ODN, trabedersen (AP-12009) has been tested in both tumor cells and clinical trials with promising results: an increased survival rate was achieved with a relatively safe intratumoral administration. Clinical trials indicated that patients treated with trabedersen have better prognosis, although most authors emphasize on the importance of continuous evaluation in patients[47,50-53].

As mentioned, one of the therapeutic approaches for glioma involves the use of antibodies, particularly towards VEGFR and EGFR. However, immunotherapy has been considered and proved to be inefficient for these growth factors as the blood-brain barrier presents a problem for the delivery of this type of molecules. Inhibitors have also been tested for the proteins mentioned, as well as for platelet-derived growth factor receptors (PDGFR) and TGF. While inhibitors present advantages in terms of delivery, their effectiveness continues to be challenging and further research is required to obtain a better molecule. TGF is a promising candidate for targeting molecules particularly using ODNs, which regulate protein content directly.

**Fibroblastic growth factor (FGF) and Hedgehog (Hh) pathways**

FGF is a polypeptide mitogen and differentiation factor that includes the highly studied acidic (FGF1) and basic
(FGF2) members. These molecules act through their specific receptors (FGFR) to activate MAPK and PI3K, and have effects on proliferation, angiogenesis, invasiveness, and survival in GBM. As previously mentioned, evidence of the participation of growth factors in these processes has recently attracted attention based on their possible connection to CSCs. Even though it is not clear how FGF could be connected to a stem phenotype, there are reports indicating that the factor promotes stemness and its absence induces differentiation. The knockout of EGFR and FGFR has been found to down-regulate U251 cells expressing the stem marker CD133.

Additionally, another important pathway in GBM is the Hh pathway, which includes Sonic, Indian, and Desert proteins. These soluble proteins bind to the Patched (PTCH) receptor and stop its inhibitory function over the Smoothened (Smo) receptor, activating a cascade that comprises PKA, Fused (Fu), and Fused Suppressor (Su-Fu), all of which activate the Gli family of transcription factors (Gli1, 2, and 3). This pathway affects proliferation, cell survival, and migration; as for the other factors discussed, its probable role in stemness has also been studied, particularly in differentiation and migration.

**Platelet-derived growth factor (PDGF)**

The PDGF family consists of dimers of peptides PDGF A, B, C, and D that bind to heterodimeric dimers and function as tyrosine kinase receptors (PDGFRα and β). After dimerization and trans-autophosphorylation, several intracellular signals can follow, including Ras, MAPK, PI3K, PLC, and STAT. PDGF/PDGFR interaction activates cell cycle, DNA synthesis, migration, and chemotaxis. The structures of PDGF A and B are very similar with a highly conserved core domain and an N-terminal peptide that is cleaved. An alternative long terminal peptide that is cleaved. An alternative long.

**Insulin-like growth factor-I (IGF-I)**

IGF-I is a hormone that plays a key role in the regulation of cellular proliferation and apoptosis in relation to nutrient availability, and it also modulates adhesion and cell motility. It acts through the IGF-I receptor (IGF-IR), which is a tyrosine kinase protein that has 70% homology with the insulin receptor. IGF-IR can be activated by IGF-I, IGF-II, and insulin at supraphysiological levels. Several studies have suggested that IGF-I is involved in the control of proliferation in cancerous cells and that it may participate in the process of transformation itself. An elevated expression of IGF-I and IGF-II in gliomas, meningiomas, and other tumors has been reported.

Both types of IGF-Rs are overexpressed in glioblastomas compared to normal brain tissue, and in particular, IGF-IR expression is suggested to act as a prognostic factor associated with shorter survival and a less satisfactory response to temozolomide. Additionally, the IGF-IR pathway appears to be involved in glioma stem cells’ ability to adapt to repeated radiation, leading to radio-resistant cells. However, radio-resistant tumors treated with IGF-IR inhibitors have resulted in a significant increase in radiosensitivity.

It has been reported that in an in vivo model, the invasion and proliferation of glioblastomas are significantly reduced by blocking IGF-IR, while showing an increase in apoptosis and a reduction in intratumoral vascularization at the same time. In the plasma, however, the majority of IGFs are attached to a family of binding proteins, which control the availability of free IGFs to the...
tissues\(^{87}\).

It has been shown that the IGF-binding protein 2 (IGFBP2) is overexpressed in high-grade glioma, whereby it has been recognized as an impulse to glioma progression and associated with poor prognosis\(^{88}\). However, its inhibition leads to a decrease in tumor progression and an increase in patient’s survival\(^{89}\), suggesting that it could also be a therapeutic target.

Several clinical trials have been carried out where cell cultures were established from human glioblastomas and transfected with antisense or triple helix IGF-I vectors in order to silence the expression of IGF-I. Subsequently, the cultures were irradiated and injected into the patient (animals or humans) as a “vaccine”. Significant changes have been observed through this treatment, such as an increase in apoptosis and a decrease in the tumor growth, as well as an increased percentage of immune cells. Moreover, prolongation in survival time was observed and no unusual side effects were noted after the treatment\(^{90}-96\). These results are promising and may encourage further research using IGF-I as a therapeutic target for glioblastoma.

As a final note, it is important to remark that the activation of IGF-IR also triggers the activation of the PI3K/Akt pathway in the brain\(^{84}\).

**Kinases and signaling**

Many processes occurring in cancer have been linked to the action of different growth factors and their receptors. Despite long-standing studies, there is a new focus on the role of these receptors, in particular the populations of cells such as CSCs. However, the pathways and mechanisms involved are not always clearly understood. It is important to take into consideration that the manner in which these receptors will respond is highly dependent upon the intramolecular signals that are activated, several of which have been mentioned but we will focus on the three most studied kinases in glioma: MAPK, PKC, and PI3K.

**Mitogen-activated protein kinases (MAPKs)**

The MAPKs or extracellular regulated kinases (ERKs) pathway is a canonical mechanism in which different receptor tyrosine kinases (RTKs) can affect gene transcription inside the cell; it is, therefore, a link between membrane signals and genetic expression. In this mechanism, RTKs activate Ras, which in turn activates Raf, followed by MEK and MAPK. Other pathways, however, may activate this kinase, including protein kinase C (PKC)\(^{60,69}\) and even CD133 – the latter by unknown mechanisms\(^{98}\). This interaction with CD133 may feature MAPK as a protein associated with stemness, although more studies are required to fully understand MAPK’s importance in this cell population\(^{99}\).

It has also been reported that MAPK interacts with the PI3K pathway; this interaction affects the nuclear localization of MAPK\(^{100}\) probably through the regulation of mTOR-inducing transcription and cell cycle progression\(^{101}\). Another regulator of this pathway is casein kinase 2 (CK2), which decreases MAPK phosphorylation and regulates autophagy\(^{102}\), indicating that it is related to cell death, although other pathways are likely to participate in the process.

The MAPK cascade is known to be crucial for proliferation and migration, and it probably plays a part in GBM’s resistance to therapy\(^{97,101,103}\). The inhibition of this pathway blocks MMP expression induced by EGF, resulting in a decrease in migration\(^{104}\). It has been reported that MAPK, and not PI3K, is responsible for EGF-induced invasion through the urokinase plasminogen activator (uPA). As such, combining different therapies is important to block alternative pathways and improve overall patient survival rates\(^{103}\).

In view of all the different actions and interactions related to MAPK, its activation by phosphorylation has been proposed to be a prognostic marker\(^{105,106}\), particularly owing to the strong correlation between phosphorylated MAPK (pMAPK), proliferation, and resistance. Interestingly, the role of MAPK may be important not only because of its relationship with GBM cells but also because of its niched role in producing an inflammatory environment. A previous study indicated that p38 MAPK blockage suppresses inflammatory response of GBM cells as well as IL-6 and IL-8 production, and this inflammatory condition promotes invasiveness, probably through MMP activation\(^{107}\). VEGFR has also been linked to invasiveness and migration, and a study on the combined inhibition of MAPK and VEGFR indicated that the blockage of both pathways increases survival\(^{105}\) once again emphasizing the importance of multiple targeting to inhibit several GBM processes.

**Protein Kinase C (PKC)**

PKC is a family of isoenzymes with serine/threonine kinase activity. It can be classified according to its regulatory regions: classical (activated by calcium, diacylglycerol [DAG], and phorbol esters like phorbol 12-myristate-13-acetate [PMA]), novel (not activated by calcium), and atypical (not activated by calcium, DAG,
or phorbol esters). Once triggered, these proteins can activate and interact with other cascades such as MAPK and PI3K, and regulate processes such as proliferation, differentiation, apoptosis, and angiogenesis. These events make PKC an important target in cancer, particularly in glioma where its importance has been thoroughly discussed as PKC shows increased expression and activity in this kind of tumors. There are reports indicating that PKC is important for progesterone-receptor-mediated proliferation in glioma cells, adding to the possible mechanisms of PKC function. Other reports also indicated that PKC induces proliferation, invasion, and metastasis through PI3K, Bad or Cdk7/Cdk2, mTOR, and Akt activation.

Its interactions with other pathways include MAPK since PKC may activate the cascade through a direct interaction with EGFR and may also increase cell proliferation. PKC has also been targeted and proposed as a marker for GBM therapy and prognosis. It has been reported that the combined use of temozolomide and tamoxifen significantly reduces PKC phosphorylation; however, the biological effects are cell-dependent and include increased apoptosis or necrosis, and decreased proliferation or motility. The importance of PKC in therapy resistance has been highlighted, particularly PKC’s implication in cell cycle regulation. PKCα activates MAPK and MMP, thus increasing infiltration ability; PKCδ has been linked to radiation-induced apoptosis as well as MMP activation, and PKCε induces proliferation and apoptosis evasion. Moreover, our group has reported that PKCα and PKCδ, through progesterone receptor phosphorylation, induce proliferation and migration. However, further investigation is necessary to completely understand the role of different PKC isoforms in GBM growth as the effects of these kinases tend to be cell-specific and vary according to very particular cell conditions, hence complicating the use of PKC inhibitors in therapy.

**PI3K/Akt/mTOR**

PI3K signaling pathway plays an important role in metabolism, apoptosis, cell growth, survival, and proliferation. The activation of PI3K (through cell surface receptors) induces the conversion of plasma membrane lipid phosphatidylinositol-4,5-biphosphate (PIP2) to phosphatidylinositol-3,4,5-triphosphate (PIP3). Next, signaling proteins such as Akt and phosphoinositide-dependent kinase 1 (PDK1) would accumulate at the sites of PI3K activation by directly binding with PIP3. Its association with PIP3 at the membrane causes these proteins to approach each other, which then facilitates the phosphorylation of Akt by PDK1. This phosphorylation activates Akt, resulting in the phosphorylation of other proteins that affect cell growth, cell cycle, and cell survival. PI3K also indirectly activates mTOR, a protein kinase critical to cell growth.

PI3K/Akt/mTOR are downstream components of several growth factor pathways such as EGFR and insulin growth factor receptors (IGFRs), which have been described to be up-regulated in glioblastomas. Additionally, several PI3K-activating mutations have been found in a majority of glioblastoma patients, thus suggesting the importance of this pro-survival pathway in the development and progression of glioblastomas. It has been reported that the activation of the PI3K pathway is more common in glioblastomas than lower-grade astrocytomas and it is directly related to the reduction of patients’ survival time. mTOR is one of the main downstream targets of Akt and it can act as a link between growth factor signals and the production of proteins related to cell survival, growth, and proliferation. However, mTOR is also a negative regulator of PI3K, making it a hard target to reach. In this regard, various molecules with dual PI3K/mTOR inhibition activity have been developed and tested in glioma cells both in vivo and in vitro with favorable results, causing proliferative arrest, autophagy, and down-regulation of VEGF with no observable toxicity, which opens the door to the development of new therapeutic strategies.

Another downstream target of PI3K/Akt is the glycogen synthase kinase 3β (GSK3β), which is a serine-threonine protein kinase that phosphorylates the glycogen synthase (GS), inhibiting the conversion of glucose to glycogen. Additionally, the GSK3β is also involved in different cellular functions such as metabolism, homeostasis, development, and apoptosis. Interestingly, it can act as a tumor suppressor in some types of cancer while potentiating growth in others. In glioblastomas, higher expression levels of GSK3β are frequently detected in comparison with non-neoplastic brain tissues and importantly, they show a constitutive activation. There are reports that indicated that the inhibition of GSK3β induces apoptosis and diminishes the survival, proliferation, clonogenicity, and migration of glioblastoma cells. Furthermore, the inhibition of GSK3β sensitized glioblastoma cells to chemotherapeutic agents and ionizing radiation, and a significant growth delay was observed in vivo in glioblastomas treated with siRNA or inhibitors vs. GSK3β. Currently, there are several drugs such as lithium chloride, valproic acid, olanzapine, and cimetidine, among others, which are used to treat other diseases but have shown an inhibitory effect on GSK3β.
It has been reported that glioblastomas have defects in apoptotic pathways including Bcl-2\(^{[140,141]}\), which is also a downstream target of the PI3K/Akt pathway\(^{[142]}\). Cancer cells are protected from apoptosis by the up-regulation of various anti-apoptotic molecules such as Bcl-2, which has been reported to be overexpressed in glioblastoma\(^{[143,144]}\). The inhibition of Bcl-2 significantly diminishes cell viability and induces apoptotic cell death \textit{in vitro}. Interestingly, when Bcl-2 and PI3K inhibitors are combined, a greater response is observed with a further decrease in cellular viability and increase in apoptosis by various mechanisms such as the loss of mitochondrial membrane potential, activation of caspases, and release of cytochrome c\(^{[145-147]}\). An abolishment in the capacity of stem-like glioma cells to form neurospheres was also observed\(^{[145]}\). The use of a Bcl-2 inhibitor also prolongs survival in an intracranial glioma xenograft model.

**Conclusion**

Glioblastoma has proven to be a challenging disease in terms of treatment, in part because much is still unknown or uncertain regarding its intracellular signaling. This is particularly evident after discussing the diversity of pathways, receptors, and kinases that participate in processes such as proliferation, angiogenesis, migration, and infiltration (some of these proteins are represented in Figure 1). Another feature that characterizes GBM is the great heterogeneity shown in biopsies and cell lines, which adds to the complexity of studying both the pathogenesis and treatment of this type of cancer. In this review, we aim to show some of the most studied tyrosine kinase receptors and kinases. We discussed some of the treatments that target these receptors and commented on how ineffective these sorts of treatments have been. We also highlighted that the use of antibodies has been shown to be ineffective. Therefore, the \textit{in situ} down-regulation of growth factors or their receptors appears to be a growing approach, as inhibitors have also been proven to be not as effective as shown in several models. More studies are still required to understand how GBM cells have acquired such resistance, why inhibitors and antibodies are not as effective as expected, what other ways can be used to regulate signaling pathways in specific cell types inside the tumor, and most importantly how this disease can eventually be successfully treated, besides delaying or stopping its recurrence, and prolonging the patient’s survival.

**Conflict of interest**

The authors declare no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

**References**

13. Furgason JM, Koncar RF, Michelhaugh SK, Sarkar FH, doi: 10.18282/amor.v2.i5.100


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64. Ehtesham M, Sarangi A, Valadez JG, Chanthaphaychith S,


111. Aziz MH, Hafeez BB, Sand JM, Pierce DB, Aziz SW, et


117. Aeder SE, Martin PM, Soh JW, Hussaini IM. PKC-η mediates glioblastoma cell proliferation through the Akt and mTOR signaling pathways. Oncogene 2004; 23(56): 9062–9069. doi: 10.1038/sj.onc.1208093.


