ABSTRACT

The PI3K/AKT/mTOR pathway is involved in a variety of cellular functions and often contributes to oncogenesis and cancer progression. It has been recognized that this pathway is frequently activated in the most common central nervous system cancers of adults and children, malignant gliomas and medulloblastomas (MB). In these tumors, the PAM network controls key functions necessary for cell invasion and metastasis, such as cell motility. This review summarizes the current knowledge about the role of PAM signaling in cell invasion and metastasis in gliomas and MB. Current approaches to inhibit cell invasion and metastasis by targeting the PAM pathway will also be discussed.

Key words: PI3K/AKT/mTOR pathway; glioblastoma; medulloblastoma; metastasis

INTRODUCTION

Tumors of the central nervous system include a broad range of neoplasms that arise from different cell lineages. The most common variants in adult and pediatric populations are malignant gliomas and MB, respectively.

Glioblastoma (GBM) is a highly aggressive tumor that arises from different glial cell types. Based on WHO classification, GBM is a grade IV astrocytoma that either develops de novo (primary GBM) or gradually from lower grade astrocytomas (secondary GBM).[1] Due to limited therapy options, the median survival is a dismal 15 months with standard of care, which includes surgical resection, temozolomide chemotherapy and radiation.[2] Medulloblastomas are embryonal tumors that originate from fetal tissue due to aberrant developmental signaling.[3] By using treatment protocols that combine chemotherapy, surgery and cranio-spinal radiotherapy, 70-80% of patients can be cured, albeit with debilitating long term side effects.[4] Advances in molecular biology have led to remarkable insights into the understanding of the underlying molecular pathogenesis of malignant gliomas and MB and have revealed specific pathways and signaling networks that promote tumorigenesis in these malignancies.[5,6] These frequently feature aberrant receptor tyrosine kinase (RTK) signaling via the PI3K/AKT/mTOR (PAM) pathway.

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The PAM signaling axis integrates extracellular signals via RTK and G protein-coupled receptors and regulates a host of intracellular functions, such as cell cycle, metabolism, migration and apoptosis.[7-9] Phosphatidylinositol 3-kinase (PI3K) phosphorylates the 3'-hydroxyl group of phosphatidylinositol, producing second messengers that recruit cytoplasmic proteins to the membrane. These include various modulators of small GTPase activity, TEC family tyrosine kinases and members of the AGC protein kinase family like AKT (also known as Protein Kinase B, PKB).[10] The serine-threonine kinase mTOR, a regulator of translation and protein synthesis, is activated by AKT signaling.

Since many hallmarks of malignancy are controlled by PAM signaling, genetic and epigenetic alterations in various components of this pathway are frequent events in central nervous system (CNS) cancers. These include gain-of-function mutations and amplifications in genes encoding RTKs such as epidermal growth factor receptor (EGFR), loss-of-function mutations of the phosphatase and tensin homolog deleted on chromosome 10 (PTEN), phosphatidylinositol-3-kinases; MEK: mitogen-activated ERK kinase; EGFR: epidermal growth factor receptor; ERK: extracellular-signal regulated kinase

**Table 1**: Stage of clinical development of PAM pathway inhibitors for brain tumors[138]

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Target</th>
<th>Stage of clinical development for brain tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-1126 (RGDS-conjugated LY294002 prodrug)</td>
<td>Pan-PI3K</td>
<td>Phase I</td>
</tr>
<tr>
<td>PX-866</td>
<td>Pan-PI3K</td>
<td>Phase II</td>
</tr>
<tr>
<td>Pictilisib (GDC-0941)</td>
<td>Pan-PI3K</td>
<td>Phase II</td>
</tr>
<tr>
<td>Wortmannin</td>
<td>Dual PI3K/mTOR</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Dactolisib (NVP-BEZ235)</td>
<td>Dual PI3K/mTOR</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Perifosine (KRX-0401)</td>
<td>Akt</td>
<td>Phase II</td>
</tr>
<tr>
<td>KP-372-1</td>
<td>Akt</td>
<td>Preclinical</td>
</tr>
<tr>
<td>KP-372-2</td>
<td>Akt</td>
<td>Preclinical</td>
</tr>
<tr>
<td>A-44654</td>
<td>Akt</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Bevacizumab (Avastin)</td>
<td>VEGF-A</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Affibercept</td>
<td>VEGF and placental growth factor</td>
<td>Phase III</td>
</tr>
<tr>
<td>Cediranib (AZD2171)</td>
<td>VEGFR, Flt1/4, PDGFR, FGFR1, c-KIT</td>
<td>Phase I</td>
</tr>
<tr>
<td>Cabozantinib (XL-184)</td>
<td>c-MET and VEGFR2</td>
<td>Phase I</td>
</tr>
<tr>
<td>SGX-523</td>
<td>c-MET</td>
<td>Phase I</td>
</tr>
<tr>
<td>Osthole</td>
<td>IGF-1/IGF-1R and calcium channel blocker</td>
<td>Preclinical</td>
</tr>
</tbody>
</table>

PAM: PI3K/AKT/mTOR; VEGF: vascular endothelial growth factor; PDGFR: platelet derived growth factor receptor; IGF-1: insulin-like growth factor-1
tumor suppressor gene, and oncogenic mutations in various PI3K isoforms that lead to a constitutively activated pathway.[11,12] Aberrant PAM signaling also favors essential steps for cell invasion and metastasis in CNS malignancies [Figure 1]. The implications of aberrant PAM signaling in angiogenesis, epithelial to mesenchymal transition (EMT) and immune response modulation is currently under intense investigation.[13-15] Components of the PAM pathway are therefore being considered as potential drug targets [Table 1] to inhibit the often fatal events of metastasis and cell invasion.[16-18]

**ANGIOGENESIS**

Angiogenesis is a process consisting of the generation of blood vessels and is essential for the growth of tumor mass beyond 1mm in diameter.[19] This process allows tumors to become invasive by supporting them with nutrients and oxygen. Tumor and host cells synthesize and secrete pro-angiogenic factors, such as vascular endothelial growth factor (VEGF), that activate quiescent endothelial cells and induce the formation of new blood vessels from pre-existing vascular structures.[20]

The PAM pathway plays a critical role in this neovascularization process by controlling the hypoxia-inducible factor 1-alpha (HIF-1α) mediated expression and secretion of VEGF.[21,22] In cancer cells, VEGF stimulation can be mediated by chronic stimulation by growth factors, such as insulin-like growth factor-1 (IGF-1); constitutive activation of PI3K; or constitutive activation of AKT due to chronic stimulation by growth factors, which can be mediated by chronic stimulation by growth factors, such as insulin-like growth factor-1 (IGF-1); constitutive activation of PI3K; or constitutive activation of AKT due to chronic stimulation by growth factors. The important role of the PAM pathway in angiogenesis has been confirmed in various malignancies where inhibition of pan-PI3K by LY294002 and downregulation of p110α (or recently, PI3KC2α) were shown to block tumor vascularization.[15,22,25] In myeloid cells, PI3KY was reported to be involved in the activation of integrin αvβ1, leading to myeloid cell invasion into tumors and, in turn, to tumor angiogenesis.[26]

In GBM, the most aggressive glioma subtype, the PAM pathway also plays a crucial role in the induction of invasion, angiogenesis and the expression of VEGF in cells.[24,27] Therefore, new small molecule inhibitors targeting PI3K enzymes are being tested in this CNS malignancy. These include the PI3K inhibitors SF1126 (a RGDS-conjugated LY294002 prodrug) and PX-866, and the dual PI3K/mTOR inhibitor NVP-BEZ235.[26,29] These compounds were shown to induce a substantial inhibition of the expression of VEGF, thus reducing the invasive and angiogenic capabilities of GBM cells. In fact, PX-866 has recently entered phase II studies in patients with recurrent GBM. Unfortunately, preliminary results of this trial have shown a low overall response rate.[31]

The combined inhibition of VEGF and vascular endothelial growth factor receptor (VEGF/VEGFR) is currently thought to be an effective way to control GBM growth.[32-34] Examples of VEGF/VEGFR inhibitors are bevacizumab, already in phase III trial,[35] and afibbercept, a VEGF/VEGFR inhibitor that also targets placental growth factor.[36] Unfortunately, long-term treatment with afibbercept was reported to induce an invasive phenotype of GBM.[37,38]

In addition, RTK inhibitors such as cediranib (an inhibitor of VEGFR, platelet-derived growth factor receptor, fibroblast growth factor receptor 1, and v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog), have also been used with promising results.[39,40] Inhibitors of c-MET such as cabozantinib are also being considered, and have been reported to induce a significant increase in overall survival of mice bearing GBM xenografts.[41] However, anti-angiogenic therapies targeting VEGF/VEGFR have had less of an effect than expected.[42] This could be because, in highly vascularized tissues like the lung and brain, tumors can often proliferate around existing vessels and hijack them, a process called vessel co-option.[43,44] These pre-existing blood vessels circumvent the need to generate new tumor vasculature, and may explain the inefficacy of anti-proliferative therapies in GBM, the most vascularized tumor in humans.[38]

Autophagy is an evolutionarily conserved, catabolic process that maintains cellular biosynthesis through the degradation and recycling of proteins and organelles to support metabolism and survival during starvation. This process has been shown to have a complex relationship with angiogenesis induction in various malignancies. While some studies have reported that autophagy inhibits angiogenesis,[45,46] other studies have found that induction of autophagy promoted cancer and its inhibition prevented angiogenesis.[47,48] This illustrates the dual role that autophagy plays in cancer, acting as a pro-survival or pro-death mechanism depending on the tumor type and stage.[49]

Autophagy is induced by different cellular stress-mediated signaling pathways, the inputs of which are integrated by the protein kinase mammalian target of rapamycin (mTOR). The mTOR complex 1 (mTORC1) is a negative regulator of autophagy and a downstream target of the PI3K/AKT pathway.[50] Anti-cancer agents that target this pathway are able to induce autophagy, which has a cytoprotective role as well as an anti-angiogenic potential similar to the action of the dual PI3K-mTOR inhibitor NVP-BEZ235.[51,52]

High-grade gliomas have been reported to have lower expression of autophagy-related proteins than low-grade gliomas.[44] The amplification of EGFR, which is often found in these tumors, is known to suppress autophagy.[53] The progression of astrocytic tumors is associated with a decrease in autophagic capacity.[54] In most of these CNS malignancies, the modulation of autophagy sensitizes tumor cells to standard chemotherapy and radiotherapy.
induced cell death.

**EMT, CELL INVASION AND MOTILITY**

EMT is a biological process that allows immobile epithelial cells to acquire a mobile mesenchymal phenotype, becoming detached and invasive. It was initially described in the context of embryonic differentiation. In tumor cells, this process, together with the induction of neo-angiogenesis, initiates cancer metastasis, inducing enhanced migratory properties, invasiveness and resistance to apoptosis.\(^{[66]}\)

During EMT, a variety of transcription factors are upregulated in metastatic cells, such as Snail, Slug, Twist and Zeb.\(^{[60]}\) Snail can be activated by a number of pathways, including hypoxia, HIF-1, HIF-2, Notch, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), and transforming growth factor beta (TGF-β), a pro-apoptotic factor. Snail up-regulates AKT phosphorylation and Bcl-X\(_l\) countering the induction of apoptosis,\(^{[61]}\) and down-regulates cyclin D2, inhibiting cell cycle progression.\(^{[62]}\)

Twist, which promotes loss of E-cadherin mediated cell-cell adhesion and cell motility,\(^{[63]}\) has been linked to the PI3K/AKT pathway in various malignancies. This link is established by the AKT2 isoform, a Twist-mediated transcriptional regulator that activates Twist, constituting a positive feedback loop that promotes EMT.\(^{[64,65]}\) Twist also maintains hyper-activation of the PI3K/AKT pathway in breast cancer cells, through its transcriptional target TGF-β2.\(^{[66]}\)

AKT hyper-activation and PIK3CA knock-in can promote EMT in various human cancers.\(^{[61-66]}\) The association between EMT and PI3K activation has also been reported in ERα-negative endometrial carcinomas.\(^{[67]}\)

Twist overexpression has also been correlated with the induction of tumor cell invasion in GBM.\(^{[68]}\) However, these malignancies usually do not metastasize out of the CNS, mainly due to their rapid relapse rate and poor prognosis.\(^{[69]}\) Even so, there are reports describing GBM metastasis,\(^{[70]}\) involving the spread of GBM cells out the CNS through cerebrospinal fluid, blood or lymphatic vessels.\(^{[71,72]}\)

Medulloblastoma, on the other hand, has a high tendency to disseminate to the spinal cord and leptomeninges of the cerebellum and forebrain. These tumors are classified into 4 molecular subgroups: wingless (WNT), sonic hedgehog (SHH), group 3 and group 4.\(^{[73]}\) Group 3, characterized by cMYC amplification, is associated with metastatic disease.\(^{[74]}\)

The PI3K/AKT pathway is activated in 50% of GBMs. In the case of MB, there are a number of studies concerning alterations in this pathway.\(^{[65,75,76]}\) This pathway appears to facilitate an invasive phenotype of GBM and MB, especially in terms of motility and resistance to stress.\(^{[77]}\)

The class IA PI3K isoform p110α is the most relevant PI3K isoform affecting cell growth and survival. The gene encoding this isoform, PIK3CA, is usually mutated in GBM (27%).\(^{[78]}\) In this malignancy, PIK3CA mutated form plays a main role in cell growth under anchorage-independent conditions. In MB, however, this PI3K isoform is typically overexpressed,\(^{[79]}\) promoting cell proliferation, for example, through the regulation of the leukemia inhibitory factor receptor α (LIFR α).\(^{[80]}\) The inhibition of p110α impairs cancer cell growth, migration, and survival in these CNS malignancies.\(^{[16,79]}\)

Other class IA PI3K isoforms are also overexpressed in brain tumors, such as p110δ, which has been reported to be overexpressed at the mRNA level in primary GBM, controlling migration in these cells.\(^{[81,82]}\) The isoform p110γ, which is overexpressed in primary MB, contributes to cisplatin resistance and has emerged as a novel target for combinatorial treatments.\(^{[83]}\) The class II PI3K isoform PI3KC2δ, which is overexpressed in a variety of cancers, acts as a modulator of cell migration, survival and proliferation in leukemia and brain tumors.\(^{[84]}\) The highly specific pan-PI3K inhibitor GDC-0941 has recently been shown to have anti-migratory, anti-proliferative and pro-apoptotic effects in MB cell lines, showing synergy with the standard chemotherapeutic drug etoposide and good clinical tolerability.\(^{[85]}\)

Other elements of the PI3K/AKT pathway are also being considered as potential targets to inhibit cell proliferation and migration in GBM and MB. One example is AKT, which usually shows high levels of phosphorylation in these brain tumors.\(^{[86]}\) Its inhibition by KP-372-1, KP-372-2, A-443654, or perifosine, was reported to inhibit cell growth and induce radio-sensitizing effects in GBM and MB.\(^{[87-89]}\) Clinical trials of perifosine in GBM patients are ongoing.\(^{[90]}\)

PTEN is a tumor suppressor usually mutated and inactivated in GBM, with an inverse correlation between its expression and glioma grade.\(^{[91]}\) In MB, PTEN is rarely mutated but frequently downregulated, by promoter hypermethylation and/or allelic losses, inducing AKT activation.\(^{[84]}\)

PTEN, together with the MAPK signaling pathway, has a primary role in the regulation of G1/S cell cycle checkpoint-defective astrocytoma invasion, and its deletion increases migration, invasion and resistance to apoptosis in GBM cell lines.\(^{[92]}\) PTEN controls integrin-dependent migration through the regulation of Src family kinase activation, in a PI3K/AKT-independent manner.\(^{[93]}\) The re-expression of PTEN in GBM cell lines increases the cellular content and activity of the p53 tumor suppressor protein inducing cell cycle arrest and increasing the sensitivity of the tumor cells to various chemotherapeutic agents such as etoposide.\(^{[94]}\)

Upstream regulators of EMT induction, such as insulin-like
growth Factor-1 receptor (IGF-1R), c-MET and the CXCR4 receptor, have been proposed as potential targets to inhibit GBM or MB invasion.

IGF-1R is typically overexpressed in malignant GBM,[95] and its activation by IGF-1 contributes to Snail and Twist expression though PI3K/AKT signaling pathway activation.[96,97] Therefore, IGF-1R tyrosine kinase inhibitors or IGF-1 inhibitors, such as osthole, have been used to inhibit GBM proliferation, migration and EMT.[97,98] In a recent study of 218 cases of human GBM, IGF-1R overexpression was reported as an independent prognostic factor associated with shorter survival time and a less favorable response to temozolomide.[99]

C-MET expression levels correlate with tumor grade in CNS malignancies,[100] and its activation also mediates EMT-promoting signals in cancer cells via class I, PI3K.[101,102] In MB, c-MET signaling is deregulated, thus inducing tumor growth and an anaplastic histology.[103] The use of c-MET kinase inhibitors, such as SGX523, suppressed tumor growth in GBM cell lines.[104] This inhibition blocked the EMT induced by VEGF ablation in a GBM mouse model[105] and induced an effective decrease in MB cell migration and invasion.[106,107]

Stromal cell derived factor (SDF-1) or CXCL2 and its chemokine receptor CXCR4 can induce EMT in GBM via activation of PI3K/AKT and extracellular-signal-regulated kinases (ERK) pathways, and its inhibition suppressed EMT in glioma cell lines by upregulating E-cadherin.[108]

However, single agents targeting the PAM pathway have been reported to be an inefficient approach in MB and to increase invasion in the surviving fraction of GBM.[109] Therefore, new therapeutic approaches should be based on increasing the therapeutic window by targeting two different routes, namely the PAM and ERK pathways, or on combining PAM inhibitors with chemotherapeutic agents.[110]

MicroRNAs have also been shown to play an important role in various CNS malignancies, and miR-142-5p and miR-25 are upregulated in all of them.[111] In MB, miR-21 suppression inhibited tumor migration.[112] MiR-183 has a pro-tumorigenic effect in the MYC-driven MB subgroup through the inhibition of apoptosis, deregulation of the mTOR pathway and modulation of cell motility and migration.[113]

During the EMT process, malignant cells start to intravasate into the surrounding blood vessels in order to migrate to other parts of the body. To accomplish this, the extracellular matrix and basement membrane of blood vessels have to be degraded by matrix metalloproteases (MMP).[114] The most relevant metalloproteases in this invasive process are MMP-2 and MMP-9.[115]

One of the upstream pathways controlling MMP production is the PI3K/AKT pathway.[116] As a consequence, drugs like wortmannin, a drug that inhibits the secretion of MMP-2, blocks GBM invasion through the down-regulation of the PI3K/AKT/NF-κB signaling pathway.[117] Since Snail induces MMP-9 expression, EMT seems to be necessary for intravasation of lymph vessels in GBM and other cancers.[118]

**PI3KS IN INFLAMMATION/ MICROENVIRONMENT**

The process of inflammation has been extensively linked to tumor progression, as it can stimulate immune suppression, angiogenesis and tumor metastasis.[119,120] In response to tumor-derived growth factors and chemokines, inflammatory cells of the immune system are recruited to the tumor microenvironment. There, cells normally involved in chronic inflammation, such as mast cells, granulocytes and monocytes, provide the tumor with angiogenic factors, enzymes for extracellular matrix (EM) remodeling and growth factors to create a favorable milieu for expansion and dissemination.[121,122]

Members of the class I PI3K family have also been implicated in tumor-associated inflammatory responses. In myeloid cells, p110γ can be activated via tumor-derived chemoattractants, such as IL-6, IL-8, TNF-α and CSF-1. Upon activation, p110γ promotes extravasation into the tumor microenvironment (TME) via integrin α4β1 and promotes inflammation-associated tumor progression.[26,123]

This is in line with other reports indicating a crucial role of p110γ for immune cell chemotaxis, as well as for chronic inflammation.[124]

Microglial cells are resident macrophages of the CNS. Depending on the signaling context, these cells possess a dual role in tumor biology. By secreting cytokines like IL-6, IL-10 and immune suppressive molecules, gliomas can polarize microglia into tumor supporting M2 phenotypes that participate in matrix remodeling and cell invasion.[125-127] In a recent study, PAM signaling was upregulated in microglial cells that were exposed to glioma derived factors, indicating that PAM signaling is needed to force microglial cells into a tumor supportive M2 state.[128] This result was supported by a report showing that mTOR inhibition with rapamycin polarizes microglia cells to express a tumor suppressive M1 phenotype.[129] To date, the exact molecular mechanism by which PI3K signaling contributes to M2-polarization of microglia is still unknown and should be the subject of further investigation.

The tumor microenvironment of MB is also being investigated. A recent study associated the SHH-MB subtype with high infiltration of tumor associated macrophages (TAM) and strong expression of the inflammatory genes CSF1R and CD163.[130] It has been shown that PI3K binding
to CSF1R stimulates spreading and motility in macrophages and their enhancement of tumor cell invasion.\textsuperscript{103} Inhibition of p110δ impairs CSF-1 induced macrophage spreading and their invasive capacity.\textsuperscript{102} Hence, it may be worth investigating whether selective inhibition of PI3Ks in the SHH-MB subtype impairs TAM-driven tumor invasiveness. The CD163 gene is a surface marker that is strongly expressed by tumor promoting M2 macrophages, but it is not clear whether or not MB cells polarize surrounding TAM via PI3K to enhance tumor invasion.

**CLINICAL TRIALS OF KINASE INHIBITORS IN GliOBLASTOMA**

Oncogenic kinase signaling (e.g. via the PAM pathway) is crucial in GBM and hence attractive for targeted therapy.\textsuperscript{113,114} Unfortunately, the overall response rate of GBMs to kinase inhibitors in clinical trials has been poor so far.\textsuperscript{115} One reason for these disappointing results may be inadequate trial design. Systematic flaws such as small sample sizes, absent control groups and unverified drug activity have been reported in the past.\textsuperscript{135} Therefore, various changes in study design have been proposed to improve the reliability of the results. Clinical trials enriched for patients with an aberrant kinase target are likely to give a better picture of the overall performance of a particular inhibitor.\textsuperscript{116} In addition, the importance of monitoring target inhibition and negative feedback has been shown in a phase I trial in PTEN-deficient glioblastomas.\textsuperscript{117} To improve the results of clinical trials using kinase inhibitors, it appears necessary to set higher requirements for preclinical models and to verify efficacy in a broader spectrum of GBM models in order to address each model’s shortcomings. Given the fact that kinase signaling pathways are often dysregulated in parallel, it may also prove worthwhile to evaluate combinations of different kinase inhibitors.

**CONCLUSION**

Aberrant PAM signaling can promote crucial metastatic events such as angiogenesis, EMT, and modulation of immune cells in both MB and GBM. Targeting the PAM network may be a useful way to inhibit these often fatal events. Understanding the molecular mechanisms and the context by which different components of the PAM pathway contribute to tumor progression is a prerequisite for the design of novel treatment strategies. Some of these mechanisms, such as the interaction between malignant CNS cells and TME, have only recently become the focus of investigation and are still incompletely understood. Further studies are necessary to elucidate these mechanisms and to determine which components of the PAM pathway should be targeted to inhibit the metastasis of CNS malignancies.

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