

## The role of the PI3K/AKT/mTOR pathway in brain tumor metastasis

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### ABSTRACT

The PI3K/AKT/mTOR (PAM) 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).<sup>[1]</sup> 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.<sup>[2]</sup>

Medulloblastomas are embryonal tumors that originate from fetal tissue due to aberrant developmental signaling.<sup>[3]</sup> 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.<sup>[4]</sup>

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.<sup>[5,6]</sup> These frequently feature aberrant receptor tyrosine kinase (RTK) signaling via the PI3K/AKT/mTOR (PAM) pathway.

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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,<sup>[95]</sup> and its activation by IGF-1 contributes to Snail and Twist expression though PI3K/AKT signaling pathway activation.<sup>[96,97]</sup> Therefore, IGF-1R tyrosine kinase inhibitors or IGF-1 inhibitors, such as osthole, have been used to inhibit GBM proliferation, migration and EMT.<sup>[97,98]</sup> 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.<sup>[99]</sup>

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

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.<sup>[108]</sup>

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.<sup>[109]</sup> 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.<sup>[110]</sup>

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.<sup>[111]</sup> In MB, miR-21 suppression inhibited tumor migration.<sup>[112]</sup> 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.<sup>[113]</sup>

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).<sup>[114]</sup> The most relevant metalloproteases in this invasive process are MMP-2 and MMP-9.<sup>[115]</sup>

One of the upstream pathways controlling MMP production is the PI3K/AKT pathway.<sup>[116]</sup> 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- $\kappa$ B signaling pathway.<sup>[117]</sup> Since Snail induces MMP-9 expression, EMT seems to be necessary for intravasation of lymph vessels in GBM and other cancers.<sup>[119]</sup>

## 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.<sup>[119,120]</sup> 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.<sup>[121,122]</sup>

Members of the class I PI3K family have also been implicated in tumor-associated inflammatory responses. In myeloid cells, p110 $\gamma$  can be activated via tumor-derived chemoattractants, such as IL-6, IL-8, TNF- $\alpha$  and CSF-1. Upon activation, p110 $\gamma$  promotes extravasation into the tumor microenvironment (TME) via integrin  $\alpha$ 4 $\beta$ 1 and promotes inflammation-associated tumor progression.<sup>[26,123]</sup> This is in line with other reports indicating a crucial role of p110 $\gamma$  for immune cell chemotaxis, as well as for chronic inflammation.<sup>[124]</sup>

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.<sup>[125-127]</sup> 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.<sup>[128]</sup> This result was supported by a report showing that mTOR inhibition with rapamycin polarizes microglia cells to express a tumor suppressive M1 phenotype.<sup>[129]</sup> 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.<sup>[130]</sup> It has been shown that PI3K binding

to CSF1R stimulates spreading and motility in macrophages and their enhancement of tumor cell invasion.<sup>[131]</sup> Inhibition of p110 $\delta$  impairs CSF-1 induced macrophage spreading and their invasive capacity.<sup>[132]</sup> 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.<sup>[133,134]</sup> Unfortunately, the overall response rate of GBMs to kinase inhibitors in clinical trials has been poor so far.<sup>[135]</sup> 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.<sup>[135]</sup> 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.<sup>[136]</sup> In addition, the importance of monitoring target inhibition and negative feedback has been shown in a phase I trial in PTEN-deficient glioblastomas.<sup>[137]</sup> 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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## Conflicts of interest

There are no conflicts of interest.

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