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Editorial

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Glioblastoma Multiforme (GBM) Therapy: Targeting Angiogenesis and Inflammation Pathways

Andrew M. Albrecht[1], Jingxuan Yang[1] and Min Li[1]*

Glioblastoma multiforme (GBM) is the most common and deadly primary brain tumor due to its high rate of metastasis and aggressive infiltration into surrounding tissues. Because of the high resistance to standard therapy [1], the median survival time of GBM is only 15 months for a patient undergoing reductive surgical resection followed by chemotherapeutics such as temozolomide (TMZ) as well as adjuvant radiotherapy [2]. The current therapies are ineffective largely due to the poor drug delivery and the incomplete knowledge of the signaling pathways controlling the malignant behavior, leading to an extremely high occurrence of relapse. As we learn more about the epigenetic factors and genetic mutations that drive GBM's progression, we are left with the question: is it possible to develop a novel treatment which can effectively inhibit GBM cell growth and metastasis? Although the mechanisms of GBM pathogenesis and progression are not completely understood, recent advances in the understanding of the signaling pathways that underlie GBM progression and the interaction of the tumor cells with the microenvironment have led to new insights in development of novel therapeutic approaches targeting multiple oncogenic pathways associated with GBM. The aberrant signaling transduction pathways which utilize vascular endothelial growth factor receptors (VEGFR) and platelet derived growth factor receptors (PDGFR) are a major hallmark of GBM pathogenesis and vascular invasion. Likewise, inflammatory cytokines such as IL-6 and IL-8 have been implicated in the establishment of the tumor microenvironment, and thus in the resistance of GBM to traditional treatment. Due to the highly complex and genetically mutated nature of this disease, neither of these pathways has been shown to be a completely effective target for molecular intervention. However, there is a strong possibility that if used in combination, there might be a synergistic therapeutic potential. This article describes two major deregulated signaling pathways in GBM, the angiogenesis and inflammation pathways, and discusses some of the promising therapeutics attempting to target these pathways.

The leading implication behind the cause of GBM is the accumulation of random genetic defects in genes controlling multiple key pathways [3]. Traditional chemotherapeutic drugs such as TMZ induce apoptosis by non-specifically alkylating guanidine residues in the target cell's DNA. However, these drugs are ineffective due to the ubiquity of these numerous genetic mutations which allow over-expression and apoptotic resistance by conferring survival benefit by an alternate pathway. Further complicating the issue is the fact that these signaling pathways allow for bidirectional chemical communication to the microenvironment [4]. Recent evidence as to which signaling proteins are most often over-expressed indicates an aberrant increase in the endothelial-derived growth factor receptor (EDGFR) family [5]. This receptor is pivotal in providing mediation between extracellular and intracellular environments, and is directly correlated with a poor prognosis. By activating multiple pathways within the tumor, such as the NOTCH and STAT3 pathway, there is an increase in expression of various transcription factors allowing unchecked cell growth and invasive vascular invasion. By selectively targeting the anomalous expression of these receptors where a multitude of signaling pathways converges, there is a strong possibility of reducing tumorigenic potential. EGFRvIII, the most commonly over-expressed EGFR, has shown potential benefit as a therapeutic target controlling many pathways involved in tumorigenesis of GBM [6]. Similarly, current phase II clinical trials with drugs such as bevacizuma, a monoclonal targeted antibody which blocks VEGF from binding to its receptor, show promising results. However, the monotherapeutic effects of such molecular targeting agents are unclear, and evidence suggests this new line of treatment is most effective when used in combination with standard treatment protocols. A study by Clark et al. demonstrated that patients who received bevacizuma without surgical resection showed worse outcome than patients receiving treatment post-operatively [7]. While further studies into the mechanisms at play needed, molecular targeting therapies against the angiogenesis pathways are a promising area of future treatment.

Beyond the scope of immediate intracellular signaling is a more complex bi-directional signaling system between the tumor and its microenvironment. Such interactions are most often mediated by cytokines secreted by the immune system and by the tumor cells themselves. Aside from VEGF, the most predominant over-expressed cytokines are IL-6 and IL-8. These molecules aid in establishing the surrounding hypoxic tumor microenvironment and thus direct the cell proliferation, metastatic potential, and resistance to chemotherapy and radiation. IL-6 and IL-8 are inversely correlated to patient survival, and have been shown to up-regulate expression of key oncogenic transcription factors. Based on their ubiquity and importance in the tumorigenic process, these two cytokines make an attractive target for chemical intervention. Research performed by Furnari et al. demonstrated the potential therapeutic benefit of cytokine molecular targeting by strongly reducing the metastatic behavior of GBM tumor growth in IL-6 knockout mice [8]. However, although both IL-6 and IL-8 promote cancerous angiogenesis and neo-vascularization by enabling communication between tumor cells and their microenvironment, they are secreted by different cell populations and act through different intracellular signaling mechanisms. Further complexity lies in the inherent heterogeneity of glioma cell lines, as small sub-populations of the cancer has been shown to secrete a unique cytokine profile in comparison to another

***Corresponding author:** Min Li, Ph.D, The Vivian L. Smith Department of Neurosurgery, The University of Texas Medical School at Houston, 6431 Fannin Street, MSE R266, Houston, TX 77030, Tel: (713) 500-6491; Fax: (713) 500-6493; E-mail: Min.Li@uth.tmc.edu

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sub-population [9]. Thus, while targeted therapy aimed at cytokines is a promising avenue of research, it is likely necessary to utilize this treatment option in combination with more traditional therapeutic measures.

While still in early phases of research, studies into combined therapies targeting over-expressed intracellular signals alongside aberrant cytokines have shown greater potential benefit than the individual monotherapies. The current benefit of dual targeted molecular therapy seems to lie in the ability of one of these drugs to potentiate the effects of the adjuvant treatment, leading to a synergistic benefit. A study by Twitty et al. demonstrated this efficacy by targeting both IL-6 via shRNA as well as STAT3 activation via interruption of a common molecular signaling pathway, severely reducing tumor growth *in vitro* [9]. A similar studied performed by Wang and colleagues used shRNAs to target IL-6 receptors in glioma stem cells, showing moderate attenuation of tumor growth in the in vivo mouse population. However, when combined with a small-molecule inhibitor of STAT3, this therapy proved significantly more effective [8].

Although a potential benefit of utilizing these therapies is on the horizon, more information is needed before a clear picture is able to be drawn around the inherent cause of GBM. While a promising start, further study into the complex web of inter-cellular crosstalk is necessary before real progress in the area of combination therapy can be made. **The Journal of Spine and Neurosurgery (JSNS)** endows researchers with the most pertinent and up-to-date findings in the areas of neurosurgical research, clinical evaluation, and diagnosis. SciTechnol provides this journal with an international team of expert editors and reviewers at the top of their fields, and ensures the most timely and reliable peer-reviewed information on all topics relating to spine and neuroscience. This journal is available in a wide variety of formats, and includes audio conversion software and digital distribution to ensure reliability in publication and ease of information access.

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Author Affiliation

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[1]*The Vivian L. Smith Department of Neurosurgery, The University of Texas Medical School at Houston, Houston, Texas 77030, USA*

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