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Angiogenesis and Resistance Mechanisms in Glioblastoma: Targeting Alternative Vascularization Pathways to Overcome Therapy Resistance

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Abstract

Introduction: Glioblastoma (GBM), the most aggressive form of primary brain tumor in adults, remains a significant clinical challenge due to its high recurrence and poor prognosis. Characterized by rapid growth, invasiveness, and resistance to therapy, GBM relies on a sophisticated vascular network to sustain its progression. Angiogenesis, the process of forming new blood vessels, is central to meeting the metabolic demands of the tumor. To address this issue, there is a growing consensus on the need for multi-pronged therapeutic strategies that not only inhibit angiogenesis but also disrupt alternative neovascular mechanisms. Promising approaches include combining anti-angiogenic drugs with agents targeting pathways like neurogenic locus notch homolog protein (NOTCH), Wnt, and C-X-C motif chemokine receptor 4 (CXCR4)/stromal cellderived factor 1 alpha (SDF-1α) to impede vessel co-option, VM, and GSC trans-differentiation.

Methods: The search strategy consisted of using material from the PubMed data, focusing on key terms such as: "angiogenesis", "glioblastoma", "glioma", "oncogenesis", "anti-VEGF treatment", "signaling pathways", "hypoxia", "vessels", "resistance", and "neurosurgery.

Results: As a result of the analysis of existing recent studies, GBM exhibits an adaptive capacity to utilize various neovascular mechanisms, including vessel co-option, vasculogenic mimicry (VM), and the transdifferentiation of glioma stem cells (GSCs) into vascular-like structures, to circumvent traditional antiangiogenic therapies. Initial successes with anti-angiogenic treatments targeting vascular endothelial growth factor (VEGF) showed improvements in progression-free survival. Still, they failed to significantly impact the overall survival due to the tumor's activation of compensatory pathways. Hypoxia, a critical driver of angiogenesis, stabilizes hypoxia-inducible factors (HIF-1α and HIF-2α), which upregulate pro-angiogenic gene expression and facilitate adaptive neovascular responses. These adaptations include vessel co-option, where tumor cells utilize pre-existing vasculature, and VM, where tumor cells form endothelial-like channels independent of typical angiogenesis. Moreover, the role of GSCs in forming new vascular structures through transdifferentiation further complicates treatment, enabling the tumor to maintain its blood supply even when VEGF pathways are blocked.

Discussion: This review highlights the necessity for comprehensive and targeted treatment strategies that encompass the full spectrum of neovascular mechanisms in GBM. Such strategies are crucial for

developing more effective therapies that can extend patient survival and improve overall treatment outcomes.

Conclusion: To address the challenge of understanding tumor angiogenesis and ways to inhibit it, there is a growing consensus on the need for multifaceted therapeutic strategies that not only suppress angiogenesis but also disrupt alternative neovascular mechanisms. The most successfull approaches include the use of antiangiogenic drugs in combination with agents targeting pathways such as the neurogenic locus of the notch homolog protein (NOTCH), Wnt, and C-X-C receptor chemokine motif 4 (CXCR4)/stromal cell-derived factor 1 alpha (SDF-1α) aiming to inhibit vessel co-option, VM, and GSC transdifferentiation.

Keywords: Glioblastoma; angiogenesis; glioma stem cells; hypoxia.; neovascularization; therapy resistance; vasculogenic mimicry; vessel co-option.