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Perspective

Molecular Pathways Involved in Angiogenesis in Glioblastoma

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DESCRIPTION

Glioblastoma (GBM) represents the most aggressive and lethal primary brain tumor in adults, characterized by rapid proliferation, diffuse infiltration and pronounced vascularization. Angiogenesis, the process of new blood vessel formation from pre-existing vasculature, is a hallmark of GBM that supports tumor growth, invasion and resistance to therapy. Understanding the molecular pathways that govern angiogenesis in glioblastoma is crucial for developing targeted therapies and improving patient outcomes. GBM tumors are highly vascularized, often demonstrating abnormal, tortuous and leaky blood vessels that contribute to hypoxia and treatment resistance. Several key molecular pathways orchestrate angiogenesis in GBM, integrating signals from tumor cells, stromal components and the tumor microenvironment.

One of the most extensively studied angiogenic pathways in GBM involves the Vascular Endothelial Growth Factor (VEGF) family and its receptors. Hypoxia-inducible factor-1 alpha (HIF-1α), stabilized under the hypoxic conditions prevalent in GBM, transcriptionally upregulates VEGF-A. VEGF-A binds to VEGFR-2 on endothelial cells, triggering signaling cascades such as the PI3K/Akt and MAPK pathways that promote endothelial proliferation, migration and new vessel formation. This pathway is central to GBM angiogenesis and has been the primary target of anti-angiogenic therapies like bevacizumab, a monoclonal antibody against VEGF-A. However, GBM angiogenesis is multifaceted and involves other molecular players beyond VEGF. The angiopoietin-Tie signaling axis is another critical regulator. Angiopoietin-1 (Ang1) and Angiopoietin-2 (Ang2) bind to the Tie2 receptor on endothelial cells, with Ang1 generally promoting vessel maturation and stability, whereas Ang2 acts context-dependently, destabilizing vessels and facilitating angiogenic sprouting. Elevated levels of Ang2 in GBM have been linked to increased vascular permeability and poor prognosis, underscoring the complexity of vessel regulation.

Integrins, transmembrane receptors mediating cell-ECM interactions, also contribute to angiogenesis by modulating endothelial cell adhesion and migration. Specifically, integrins αvβ3 and αvβ5 are upregulated in GBM-associated vasculature and interact with ECM components such as fibronectin and vitronectin to facilitate angiogenic remodeling. These integrins activate downstream signaling pathways, including Focal Adhesion Kinase (FAK) and Src, promoting endothelial survival and angiogenesis. The Platelet-Derived Growth Factor (PDGF) pathway further exemplifies the crosstalk between tumor cells and vasculature. PDGF-BB, secreted by GBM cells, recruits pericytes and smooth muscle cells to stabilize new blood vessels, which is critical for maintaining the aberrant but functional tumor vasculature. Dysregulation of PDGF signaling contributes to the abnormal vessel morphology characteristic of GBM.

Notably, emerging evidence highlights the role of Notch signaling in regulating angiogenesis and vascular maturation in glioblastoma. The Notch pathway influences endothelial tip and stalk cell differentiation, essential for proper vessel sprouting. Aberrant Notch signaling can disrupt vascular architecture and has been implicated in therapeutic resistance. Moreover, recent studies have illuminated the importance of Glioma Stem-Like Cells (GSCs) in promoting angiogenesis. GSCs secrete pro-angiogenic factors including VEGF and intriguingly, some can transdifferentiate into endothelial-like cells, directly contributing to neovascularization. This plasticity represents an additional layer of complexity in GBM vascular biology.

The tumor microenvironment also influences angiogenesis through inflammatory cytokines and extracellular matrix remodeling enzymes such as Matrix MetalloProteinases (MMPs). MMPs degrade ECM barriers, facilitating endothelial cell migration and release of sequestered growth factors, thereby amplifying angiogenic signaling. Collectively, these interconnected molecular pathways create a robust and adaptive angiogenic network that sustains GBM progression. However, the redundancy and plasticity inherent in these pathways pose significant challenges for therapeutic targeting. Anti-VEGF therapies, while initially effective at normalizing vasculature and reducing edema, often lead to evasive resistance mechanisms *via* upregulation of alternative angiogenic factors like Ang2, PDGF and fibroblast growth factors (FGFs).

CONCLUSION

Angiogenesis in glioblastoma is governed by a complex interplay of molecular pathways involving VEGF, angiopoietins, integrins,

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PDGF, Notch signaling and contributions from glioma stem-like cells and the tumor microenvironment. This multifaceted network underpins the aggressive vascular phenotype of GBM, driving tumor growth, invasion and therapeutic resistance. Future therapeutic strategies must move beyond single-pathway inhibition to combinatorial approaches targeting multiple angiogenic signals simultaneously. Targeting not only endothelial cells but also tumor-derived factors and glioma stem-like cell plasticity holds promise for disrupting the supportive vascular niche in GBM.

Advances in molecular profiling and innovative models such as patient-derived xenografts and 3D organoids will deepen our understanding of angiogenic mechanisms and therapy resistance. Precision medicine approaches integrating anti-angiogenic agents with immunotherapy and molecularly targeted treatments may offer new hope for patients battling this devastating disease. Continued research into the molecular underpinnings of GBM angiogenesis is vital for designing more effective, durable interventions to combat tumor vascularization and improve survival outcomes in glioblastoma patients worldwide.