AI-11c-MET-MEDIATED ENDOTHELIAL-MESENCHYMAL TRANSITION DRIVES GLIOBLASTOMA PROGRESSION AND THERAPEUTIC RESISTANCE

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AI-11. **c-MET-MEDIATED ENDOTHELIAL-MESENCHYMAL TRANSITION DRIVES GLIOBLASTOMA PROGRESSION AND THERAPEUTIC RESISTANCE**

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Excessive and abnormal vasculature characterizes the microenvironment that fuels the progression of malignant tumors including glioblastoma multiforme (GBM), the grade IV glioma. GBM is among the most lethal human malignancies, distinguished by extensive microvascular hyperplasia due to intravessel endothelial cell (EC) proliferation with unknown etiology. Here, we show that c-Met phosphorylation induces endothelial-mesenchymal transition (Endo-MT), contributing significantly to vascular abnormality, GBM progression, and therapeutic resistance. Utilizing murine orthotropic GBM models induced by transplantation of GL26 glioma cells and RCAS/tv-a-mediated somatic gene transfer of platelet-derived growth factor (PDGF) in Ink-4a/Arf−/− PTEN−/− mice, we reveal robust Endo-MT in tumor vasculature, characterized by expression of the fibroblast-specific marker FSP-1 in 60% of CD31+ or CD105+ ECs, and the co-expression level correlates with the aggressiveness of glioma in humans. Cell fate analysis by lineage tracing Tie2+ ECs shows over half of FSP-1+ fibroblasts are of EC origin in the mouse GBM models. Tumor-conditioned medium induces in vitro EC acquisition of mesenchymal gene signature including FSP-1 and N-cadherin expression, confirming the microenvironment-dependent Endo-MT. Furthermore, proteomic analysis identifies a critical role of c-Met in Endo-MT, which is required for the increased EC proliferation and migration and vessel hyperpermeability in the GBM microenvironment. EC-specific c-Met phosphorylation induces MMP-14 expression, leading to Endo-MT and vascular abnormality. Finally, pharmacological inhibition of c-Met phosphorylation normalizes blood vessels, reduces vascular density and Endo-MT, blocks tumor progression, and sensitizes tumor to temozolomide treatment; all of which improves overall survival in the GBM-bearing mice. These findings reveal a novel mechanism controlling aberrant vascularization and GBM progression, and suggest that targeting c-Met phosphorylation and Endo-MT may offer selective and efficient therapeutic strategies for the treatment-resistant GBM, and possibly other malignant tumors.