

## **Glioma-derived miRNA-containing extracellular vesicles induce angiogenesis by reprogramming brain endothelial cells**

### **ABSTRACT**

Glioblastoma (GBM) is characterized by aberrant vascularization and a complex tumor microenvironment. The failure of anti-angiogenic therapies suggests pathways of GBM neovascularization, possibly attributable to glioblastoma stem cells (GSCs) and their interplay with the tumor microenvironment. It has been established that GSC-derived extracellular vesicles (GSC-EVs) and their cargoes are proangiogenic in vitro. To further elucidate EV-mediated mechanisms of neovascularization in vitro, we perform RNA-seq and DNA methylation profiling of human brain endothelial cells exposed to GSC-EVs. To correlate these results to tumors in vivo, we perform histoeypigenetic analysis of GBM molecular profiles in the TCGA collection. Remarkably, GSC-EVs and normal vascular growth factors stimulate highly distinct gene regulatory responses that converge on angiogenesis. The response to GSC-EVs shows a footprint of post-transcriptional gene silencing by EV-derived miRNAs. Our results provide insights into targetable angiogenesis pathways in GBM and miRNA candidates for liquid biopsy biomarkers.

**Keyword:** Angiogenesis; Biomarker; Cancer stem cell; Deconvolution; exRNA; Extracellular vesicle; Glioblastoma; miRNA; Reprogramming; Tumor microenvironment