MicroRNA-6084 Orchestrates Angiogenesis and Liver Metastasis in Colorectal Cancer via Extracellular Vesicles

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Abstract

The prognosis for colorectal cancer (CRC) patients with liver metastasis remains poor, and the molecular mechanisms driving CRC liver metastasis are still not fully understood. Extracellular vesicles (EVs) derived from hypoxic tumors have emerged as key player in inducing angiogenesis by transferring non-coding RNAs. However, the specific role of CRC-derived hypoxic EVs (H-EVs) in regulating the formation of the pre-metastatic microenvironment (PMN) by inducing angiogenesis remains unclear. CCK8, transwell migration, wound healing, tube formation assays were used to evaluate the effect of H-EVs on endothelial cells in vitro. Immunofluorescence (IF), dual luciferase reporter assays, chromatin immunoprecipitation (CHIP), Co- immunoprecipitation (Co-IP) were used investigate miR-6084-related regulatory mechanisms. Liver metastasis mouse models and matrigel plug in assays were utilized to validated findings in vivo. Real-time quantitative polymerase chain reaction (RT-qPCR) assays of patient-derived plasma EVs, RNA-fluorescence in situ hybridization (RNA-FISH) and immunohistochemistry (IHC) assays of patient-derived CRC tissue were utilized to assess the potential of miR-6084 as diagnostic and prognostic biomarker. Our study demonstrates that H-EVs induce both angiogenesis and liver metastasis, both in vitro and in vivo. Through microRNA microarray analysis, we identified a reduction in miR-6084 levels within H-EVs. We found that miR-6084 inhibits angiogenesis by transferring to endothelial cells via EVs. In endothelial cells, miR-6084 directly targets ANGPTL4 mRNA, thus inhibiting angiogenesis through the ANGPTL4-mediated JAK2/STAT3 pathway. Furthermore, we uncovered that SP1 acts as a transcription factor regulating miR-6084 transcription, while HIF-1α modulates miR-6084 expression by promoting SP1 protein dephosphorylation and facilitating ubiquitin–proteasome degradation in SW620 cells. In clinical samples, we observed low expression of miR-6084 in plasma-derived EVs from CRC patients with liver metastasis. Our findings suggest that CRC-derived hypoxic EVs promote angiogenesis and liver metastasis through the HIF-1α/SP1/miR-6084/ANGPTL4 axis. Additionally, miR-6084 holds promise as a potential diagnostic and prognostic biomarker for CRC liver metastasis.

Keywords

Colorectal Cancer, Extracellular Vesicles, Angiogenesis, Metastasis, Hypoxia