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Decreased miR-200b-3p in cancer cells leads to angiogenesis in HCC by enhancing endothelial ERG expression

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Abstract

Transcription factor ERG (erythroblast transformation-specific (ETS)-related gene) is essential in endothelial differentiation and angiogenesis, in which microRNA (miR)-200b-3p targeting site is expected by miRNA target prediction database. miR-200b is known decreased in hepatocellular carcinoma (HCC), however, the functional relation between ERG and miR-200b-3p, originating from pre-miR-200b, in HCC angiogenesis remains unclear. We investigated whether hepatocyte-derived miR-200b-3p governs angiogenesis in HCC by targeting endothelial ERG. Levels of miR-200b-3p in HCC tissues were significantly lower than those in adjacent non-HCC tissues. Poorly differentiated HCC cell line expressed lower level of miR-200b-3p compared to well-differentiated HCC cell lines. The numbers of ERG-positive endothelial cells were higher in HCC tissues than in adjacent non-HCC tissues. There was a negative correlation between the number of ERG-positive cells and miR-200b-3p expression in HCC tissues. Culture supernatants of HCC cell lines with miR-200b-3p-overexpression reduced cell migration, proliferation and tube forming capacity in endothelial cells relative to the control, while those with miR-200b-3p-inhibition augmented the responses. Exosomes isolated from HCC culture supernatants with miR-200b-3p overexpression suppressed endothelial ERG expression. These results suggest that exosomal miR-200b-3p from hepatocytes suppresses endothelial ERG expression, and decreased miR-200b-3p in cancer cells promotes angiogenesis in HCC tissues by enhancing endothelial ERG expression.