MiRNA199a-3p controls liver Tumor Microenvironment (TME)

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Increasing significance of tumor– stromal interaction in development and progression of cancer implies that signaling molecules in the tumor microenvironment (TME) might be the effective therapeutic targets for hepatocellular carcinoma (HCC). Here, the role of microRNA miR-199a-3p in the regulation of TME and development of HCC has been investigated by several *in vitro* and *in vivo* assays. Expression of miR-199a-3p was observed significantly low in HCC tissues and its overexpression remarkably inhibited *in vivo* tumor growth and metastasis to lung in NOD-SCID mice. *In vitro* restoration of miR-199a-3p expression either in endothelial cells (ECs) or in cancer cells (CACs) significantly diminished migration of ECs in co-culture assay. Again incubation of miR-199a-3p transfected ECs with either conditioned media (CM) of CACs or recombinant VEGF has reduced tube formation, in ECs and it was also dropped upon growth in CM of either anti-VEGF antibody-treated or miR-199a-3p-transfected CACs. In addition, bioinformatics and luciferase-reporter assays revealed that miR-199a-3p inhibited VEGF secretion from CACs and VEGFR1 and VEGFR2 expression on ECs and thus restricted cross talk between CACs and ECs. Again, restoration of miR-199a-3p in hepatic stellate cells (HSCs) reduced migration and invasion of CACs in co-culture assay, while it was enhanced by the overexpression of HGF suggesting miR-199a-3p has hindered HSC-CACs cross talk probably by inhibiting HGF and regulating matrix metalloproteinase MMP2, which were found as targets of miR-199a-3p subsequently by luciferase-reporter assay and gelatin zymography, respectively. Thus, these findings collectively highlight that miR-199a-3p restricts metastasis, invasion and angiogenesis in HCC and hence it may be considered as one of the powerful effective therapeutics for management of HCC patients.