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REGULATORY ROLE OF MIR-142-3P ON THE FUNCTIONAL HEPATIC CANCER STEM CELL MARKER CD133

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Tumor relapse after therapy typifies hepatocellular carcinoma (HCC) and is believed to be attributable to residual cancer stem cells (CSCs) that survive initial treatment. We have previously identified a CSC population derived from HCC that is characterized by the expression of the transmembrane glycoprotein, CD133. Despite our growing knowledge of the importance of a functional CD133+ liver CSC subset in driving HCC, the regulatory mechanism of CD133 is not known. Epigenetic changes are believed to be essential in the control of cancer and stem cells. We report here the dynamic epigenetic regulation of the functional liver CSC marker CD133 by promoter methylation and miR-142-3p regulation. Unlike in other tumor types, we found DNA methylation to only play a minor role in the control of CD133 expression in HCC. More importantly, our results revealed that miR-142-3p plays an integral part in the direct targeting of CD133. The interaction between the 3'UTR of CD133 and miR-142-3p was identified by *in silico* prediction and substantiated by luciferase reporter analysis. Expression of CD133 was found to be inversely correlated with miR-142-3p in a panel of liver cell lines and HCC clinical samples. Functional studies with miR-142-3p stably transduced in HCC cells demonstrated a diminished ability to self-renew, initiate tumor growth, invade, migrate, induce capillary tube formation in endothelial cells and resist standard chemotherapy. Rescue experiments whereby CD133 and miR-142-3p is simultaneously overexpressed compensated the deregulated ability of the cells to confer these cancer and stem cell-like features. In summary, our findings suggest promoter methylation to only play a minor role in the regulation of CD133 in HCC; and that miR-142-3p directly targets CD133 to regulate its ability to confer cancer and stem cell-like features in HCC.