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Mir141 and Mir200c Regulate Progenitor Cell Features in Hepatocellular carcinomas.

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The heterogeneous nature of hepatocellular carcinomas (HCCs) is reflected by a variable clinical outcome. Keratin(K) 19 positivity in HCC has been correlated with a higher recurrence and shorter overall survival. Nevertheless the underlying mechanisms that regulate progenitor cell features in HCCs still remain unclear. In this study we want to unravel those mechanisms on an epigenetic level. Genome wide RT² miRNA PCR Arrays were performed on K19 positive and negative HCC liver biopsies(n=10). Synthetic miRNAs were transfected into PLC/PRF/5 cell line for transient overexpression and knockdown. The biological effect was objectivised by means of qPCR and correlated with human HCC samples(n=14). Localization of miRNAs and target proteins was obtained by means of in situ hybridization and immunohistochemistry(n=20). MicroRNA profiling of K19 positive HCCs reveals a signature involving metastasis pathways and cholangiocyte/hepatoblastoma characteristics. In addition there is a strong decline in the expression of mir-122, known to be enriched in healthy liver tissue. Mir-141, mir-200c and mir-429 are strongly up-regulated in K19 positive HCCs, whereas mir-885-5p was significantly reduced. Overexpression of mir-141 as well as mir-200c in a PLC/PRF/5 cell line induced the expression of several known progenitor cell markers (i.e. KRT19, KRT7, EPCAM) and reduced typical hepatocytic markers (i.e. ALB, HNF4A). In situ hybridization revealed that mir-141 and 200c are located in cholangiocytes and hepatic progenitor cells, which supports the idea of progenitor-derived origin of K19 positive HCCs. The microRNA profile of K19 positive HCCs poses new insights into the pathogenesis of this aggressive subtype of HCCs. Several microRNAs regulate the progenitor features in HCCs and are also found in the non-neoplastic progenitor cells, indicating that the same mechanisms are active in human progenitor cells and K19 positive HCCs.