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MicroRNA-26a is a key regulon that inhibits progression and metastasis of c-Myc/EZH2 double high advanced hepatocellular carcinoma

Xiang Zhang, Xiao Zhang, Ting Wang, Lei Wang, Zhijun Tan, Wei Wei, Bo Yan, Jing Zhao, Kaichun Wu, Angang Yang, Rui Zhang, Lintao Jia

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Overexpressed c-Myc and EZH2 usually mean high malignancy in cancers. Most of mortality from cancer is attributable to metastasis. MicroRNAs(miRNAs), like transcription factors, can regulate hundreds of genes. Here, we identify microRNA-26a(miR-26a) suppresses EZH2 and c-Myc by targeting EZH2 and CDK8 in Wnt pathway. MiR-26a is a well-known tumor-suppressive miRNA in multiple cancers, but how it is downregulated in hepatocellular carcinoma(HCC) is still unclear. Here, we disclose miR-26a is epigenetic silenced by a c-Myc-mediated PRC2-depandent way in HCC. Besides, we reveal that miR-26a suppress migration of HCC by targeting p21-activated kinase 2(PAK2), which is a critical effector linking Rho GTPases to cytoskeleton reorganization. In diethylnitrosamine(DEN)-induced liver cancer model, which most accurately recapitulates gene pattern of advanced HCC in human, the miR-26a-mediated circuit emerges gradually, even in lung metastasis. This circuit is then validated in clinical data. Furthermore，the results obtained in DEN-induced mouse HCC model shows, after treatment with miR-26a in an AAV-delivery system, a significant reduction both in situ and metastatic neoplastic foci. Collectively, our finding demonstrated miR-26a could be a regulon that suppress progression and metastasis of c-Myc/EZH2 double high advanced HCC.