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INTEGRATED ANALYSES IDENTIFY A POOR-PROGNOSIS SUBTYPE OF HEPATOCELLULAR CARCINOMA REGULATED BY A CORE microRNA REGULATORY CIRCUITRY

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Cancer stem cells (CSCs) cause tumor heterogeneity, relapse, and resistance to therapy. The underpinnings of CSCs remain to be elucidated, especially the underlying gene regulatory network. We here conducted integrated analyses and identified a miRNA-regulatory network defining a stemness subtype with poor-prognosis from TCGA hepatocellular carcinoma (HCC) cohort with independent validations. The poor-prognosis subtype was characterized by the signature expression pattern of CSCs orchestrated by two miRNAs and their mRNA targets that formed a core regulatory circuitry (CRC). Within the CRC, miR483-3p bound a complementary sequence on *SOX9* promoter, facilitating the recruitment of RNA polymerase II and STAT3, which was essential for *SOX9* transcription activation. SOX9 can further activate *SOX4* expression. Both *SOX4* and its associated activator lncSOX4 were the direct targets of miR204-5p. *SOX4* and miR204-5p formed double-negative feedback loop through mutual inhibition. The expression level of miR204-5p was tightly modulated by miR483-3p, whose promoter was significantly demethylated in the stemness subtype. Activation of the CRC essential for the self-renewal and maintenance of liver CSCs culminated in downregulation of miR204-5p and upregulation of miR483-3p, *SOX9*, and *SOX4*. Functional significance of the CRC for HCC metastasis and drug resistance was further demonstrated with various *in vitro* and *in vivo* assays.

BIOGRAPHY

Jiangwen Zhang graduated from Johns Hopkins University with PhD He has worked at Harvard University Genome Center as Senior System Biologist for years before joining University of Hong Kong in 2013. His lab has broad interest in genetic and epigenetic regulation in development and diseases. Currently, his lab is focusing on epigenetic regulation of tumorigenesis. His lab employs high through-put 'omics' assays and large scale computation to dissect the gene regulatory network and signaling pathways involved in oncogenesis.

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