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A CIRC RNA SIGNATURE PREDICTS POSTOPERATIVE RECURRENCE IN STAGE II/III COLON CANCER

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Background Current staging methods seem to have only a limited role in predicting the risk of disease recurrence and benefit of adjuvant chemotherapy for patients with stage II/III colon cancer. Circular RNA is a novel type of noncoding RNA with a potential use as biomarkers; however, whether circRNA-based signatures could serve as novel prognostic biomarkers for stage II/III colon cancer is unknown.

Methods 20 paired of frozen tumor tissues and adjacent normal tissues of stage II/III colon cancer were collected and conducted an RNA-sequencing study and profiled circRNAs by a series of bioinformatics analyses to identify the significant circRNA markers. QPCR assay was used to test those markers on the samples from the training and validation cohorts. LASSO-bagging procedure was used to select the top four markers to build the regression model. The cell migration assay in vitro and metastasis study in vivo were performed to detect the function of the top four markers.

Results Dysregulated circRNAs showed strong classification properties in distinguishing the recurrent and nonrecurrent colon cancer patients. A novel prognostic tool (cirScore) based on four circRNAs (i.e., hsa_circ_0122319, hsa_circ_0087391, hsa_circ_0079480 and hsa_circ_0008039) is developed and validated to improve the prognostic stratification for patients with radically resected stage II/III colon cancer. The proposed cirScore can effectively classify patients with stage II/III colon cancer into groups with low and high risks of disease recurrence. Loss-of-function assays indicated that the representative circRNAs plays functional roles in the sophisticated regulation of colon cancer progression.

Conclusions Our current study addresses an important gap, which is the refinement of our prognostic tools for stage II/III colon cancer, by using a novel approach that takes into consideration the circular RNA. The proposed cirScore might be used in the future to guide better and more personalized treatment decisions for patients with stage II/III colon cancer.

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IGF2BP2 FACILITATES TUMOR PROGRESSION VIA AN M6A-DEPENDENT MECHANISM IN COLORECTAL CARCINOMA

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Background RNA N6-methyladenosine (m6A) is an emerging regulatory mechanism for gene expression and participates in tumor progression in several cancer types. M6A 'readers' were reported to be involved in controlling the fate of mRNA, and insulin-like growth factor 2 mRNA binding protein 2 (IGF2BP2) was reported to be associated with methylated mRNA stability and promote tumor progress. However, its

role in colorectal carcinoma (CRC) and its target m6A-specific target genes remains unexplored.

Methods Western blot, real-time quantitative PCR and immunohistochemical (IHC) analysis were used to detect IGF2BP2 expression in cell lines and patient's tissues. The MTS assay, migration assay, sphere formation assay was performed to detect the function of IGF2BP2. Cell-based xenograft model and PDX model revealed the clinical benefits of target IGF2BP2 *in vivo*. RNA immunoprecipitation (RIP) sequence was used to screen the target genes of IGF2BP2 and RNA pull-down assay was used to verify the direct binding of IGF2BP2 and targets genes.

Results IGF2BP2 was significantly upregulated in human CRC tumor tissues and CRC cell lines and high expression of IGF2BP2 was associated with poor prognosis of CRC patients. Knockdown of IGF2BP2 in CRC cell lines drastically suppressed cellular proliferation and stemness phenotype *in vitro*. IGF2BP2 inhibition suppresses CRC tumorigenesis and metastasis in both cell models and PDX models *in vivo*. RIP-seq analysis and RIP-qPCR revealed that SOX2 mRNA was the potential target gene of IGF2BP2. RNA pull-down assay showed the direct binding of IGF2BP2 and SOX2 transcripts which could be impaired by mutating m6a site of SOX2 transcripts. After IGF2BP2 inhibition, the RNA and protein level of SOX2 were downregulated due to the half-life of SOX2 mRNA decreased. Moreover, the downstream genes of SOX2 showed a positive correlation with IGF2BP2 expression in CRC patients.

Conclusions In summary, we demonstrated that IGF2BP2 was frequently upregulated in human CRC and contributing to CRC malignancy. IGF2BP2 maintained methylated SOX2 mRNA stability to facilitate cellular stemness features through the m6A-dependent mechanism. Thus, our findings reveal an important role of IGF2BP2 and provide a potential target of treatment in colorectal carcinoma.

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NUCLEUS-TRANSLOCATED GCLM FACILITATES TUMOR PROGRESSION THROUGH INCREASING TRANSCRIPTION OF OCT4 IN COLORECTAL CARCINOMA

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Background Glutamate-cysteine ligase modifier (GCLM) subunits, combined with catalytic (GCLC) subunits, has been known for the first rate-limiting enzyme for glutathione (GSH) synthesis. Increasing studies have shown that the non-metabolic functions of many metabolic enzymes also play a crucial role in tumor progress. However, the non-metabolic functions of GCLM remain unexplored. Hence, we wonder if there are unorthodox functions of GCLM under redox stress participating colorectal Carcinoma(CRC) tumorigenesis.

Methods Western blot, real-time quantitative PCR and immunohistochemical analysis were used to detect the relative expression of GCLM in cell lines and patients' specimens. The MTS assay, migration and invasion assay, sphere formation assay were performed to detect the functions of GCLM *in vitro*, and the xenograft models and PDX models in nude mice *in vivo*. Cytosolic and nuclear extraction, immunofluorescent analysis were used to show the location of GCLM.