IDENTIFICATION OF INTRAGENIC METHYLATION IN THE TUSC1 GENE AS A NOVEL PROGNOSTIC MARKER OF HEPATOCELLULAR CARCINOMA

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Aim: Patients with hepatocellular carcinoma (HCC) have a poor prognosis, and novel molecular targets for treating recurrence and progression of the disease along with associated biomarkers are urgently required. In the present study, expression and the regulatory mechanism of TUSC1 (tumor suppressor candidate 1) were investigated to determine if it is a candidate tumor suppressor gene for HCC, which shows repressed transcription that involves aberrant DNA methylation.

Methods: TUSC1 mRNA expression levels in HCC cell lines and 94 pairs of surgical specimens were determined using quantitative real-time reverse transcription polymerase chain reaction assay. Methylation status of HCC cell lines and clinical samples were analyzed to investigate the regulatory mechanism of TUSC1 transcription and the relationship between the methylation status of the TUSC1 gene and clinicopathological factors. The expression and distribution of the TUSC1 protein in liver tissues were determined using immunohistochemistry.

Results: A majority of HCC cell lines (89%) and surgical specimens (84%) demonstrated reduced expression levels of TUSC1 mRNA compared with paired non-cancerous liver tissues. The mean mRNA expression level in HCC was significantly lower than in corresponding non-cancerous liver. In contrast, no significant difference was found in TUSC1 mRNA expression level between adjacent normal and cirrhotic liver tissue from HCC patients. The TUSC1 protein expression pattern in HCC and liver tissues was consistent with TUSC1 mRNA expression. Twenty-nine (31%) of 94 patients showed intragenic hypermethylation of the TUSC1 gene in HCC, and hypermethylation was significantly associated with advanced pathological stage. Subsequently, patients with hypermethylation of TUSC1 gene had a significantly poorer prognosis than patients without hypermethylation.

Conclusions: Our results suggest that TUSC1 is a candidate tumor suppressor gene and intragenic hypermethylation is one of the suppressive mechanisms that regulate TUSC1 transcription in HCC. Intragenic methylation of the TUSC1 gene may serve as a novel prognostic marker of HCC.

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