

Promoter methylation of p16, Runx3, DAPK and CHFR genes is frequent in gastric carcinoma

Shi-Lian Hu¹, Xiang-Yong Kong¹, Zhao-Dong Cheng¹, Yu-Bei Sun², Gan Shen³, Wei-Ping Xu⁴, Lei Wu⁴, Xiu-Cai Xu⁵, Xiao-Dong Jiang¹, and Da-Bing Huang¹

¹Department of Geriatrics, Affiliated Anhui Province Hospital, Anhui Medical University, Hefei;

²Department of Oncology, Anhui Province Hospital, Hefei; ³Cadre's Ward of Anhui PPC Hospital, Hefei;

⁴Anhui Evidence-based Medicine Center, Hefei; ⁵Anhui Provincial Hospital Center Lab, Hefei, China

ABSTRACT

Aims and background. Transcriptional silencing induced by hypermethylation of CpG islands in the promoter regions of genes is believed to be an important mechanism of carcinogenesis in human cancers including gastric cancer. A number of reports on methylation of various genes in gastric cancer have been published, but most of these studies focused on cancer tissues or only a single gene. In this study, we determined the promoter hypermethylation status and mRNA expression of 4 genes: p16, Runx3, DAPK and CHFR.

Methods. Methylation-specific polymerase chain reaction (MSP) was used to determine the methylation status of p16, Runx3, DAPK and CHFR gene promoters in cancer and adjacent normal gastric mucosa specimens from 70 patients with gastric cancer, as well as normal gastric biopsy samples from 30 people without cancer serving as controls. In addition, the mRNA expression of p16, Runx3, DAPK and CHFR was investigated in 34 gastric cancer patients by RT-PCR. Bisulfite DNA sequence analysis was applied to check the positive samples detected by MSP.

Results. When carcinoma specimens were compared with adjacent normal gastric mucosa samples, a significant increase in promoter methylation of p16, Runx3, DAPK and CHFR was observed, while all 30 histologically normal gastric specimens were methylation free for all 4 genes. The methylation rate of the 4 genes increased from normal stomach tissue to tumor-adjacent gastric mucosa to gastric cancer tissue. Concurrent methylation in 2 or more genes was found in 22.9% of tumor-adjacent normal gastric mucosa and 75.7% of cancer tissues. No correlation was found between hypermethylation and other clinicopathological parameters such as sex, age, and tumor location. However, the frequency of DAPK and CHFR methylation in cancer tissues was significantly associated with the extent of differentiation and lymph node metastasis ($P < 0.05$) and the frequency of Runx3 methylation was significantly associated with tumor size ($P < 0.05$). Weak expression and loss of expression of the 4 genes was observed in cancer tissues and was significantly associated with promoter hypermethylation ($P < 0.05$).

Conclusions. Promoter hypermethylation of p16, Runx3, DAPK and CHFR is frequent in gastric cancer. DAPK and CHFR promoter hypermethylation may be an important help in evaluating the differentiation grade and lymph node status of gastric cancer. Weak gene expression and loss of gene expression due to promoter hypermethylation may be a cancer-specific event. Free full text available at www.tumorionline.it

Key words: gastric carcinoma, p16, Runx3, DAPK, CHFR, DNA methylation

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Correspondence to: Professor Shi-lian Hu, Department of Geriatrics, Anhui Province Hospital, Anhui Medical University, Hefei 230001, China.
Tel +86-0551-2283589;
e-mail hushiliansy@yahoo.cn

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