

## **Methylation of CpG islands in the promoter regions of P16, hMLH1 and CDH1 genes in patients with gastric cancer**

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**PURPOSE:** Aberrant methylation of CpG islands in the promoter regions of tumor suppressor genes has been demonstrated to be one of the mechanisms for epigenetic loss of gene function and tumor development. In this study, we analyzed promoter methylation of the following genes in 120 cases of primary gastric carcinoma: P16, hMLH1, and CDH1, in order to explore their effects in the development of gastric cancer and their relationship to clinical parameters.

**METHODS:** We examined the promoter methylation in primary tumor and the matched adjacent tissue from 120 patients with pathologically diagnosed primary gastric cancer by methylation-specific PCR (MSP). All of them did not receive preoperative radiotherapy or chemotherapy.

**RESULTS:** Promoter methylation was detected in 36.7% (44/120) cases for P16; 24.2% (29/120) cases for hMLH1; and 25% (30/120) cases for CDH1 of samples from primary tumors. In comparison, methylation was also detected in P16 (25.8%), hMLH1 (8.3%), and CDH1 (14.2%) of matched normal mucosa from adjacent tissue. Promoter methylation of hMLH1 and CDH1 was statistically significant ( $p < 0.05$ ) in primary tumor and adjacent normal tissue. Moreover, methylation of hMLH1 and CDH1 in primary tumor and adjacent normal tissue occurred concordantly ( $\text{Kappa}_{\text{hMLH1}} = 0.403$ ,  $\text{Kappa}_{\text{CDH1}} = 0.268$ ,  $P < 0.001$ ). Promoter methylation of P16 and CDH1 did not appear to be statistically correlated with multiple clinical pathological characteristics, such as patients' gender, age, tumor location, tumor size, differentiation, TNM staging, lymph node metastasis, Borrmann type, distant metastasis, peritoneal metastasis, smoking, drinking history and whether the tumor recurrence. Borrmann type ( $p = 0.030$ ) and alcohol history ( $p = 0.019$ ) showed statistical significance for promoter methylation of hMLH1 in primary tumor. Methylation of hMLH1 was 66.7% (4/6) in Borrmann type I and II, and 21.9% (25/114) in type III and IV. Methylation of hMLH1 was 40% (12/30) and 18.9% (17/90) in patients with or without alcohol history. In addition, there was no statistical significance between promoter methylation of p16 and CDH1 in primary tumor and overall survival.

**CONCLUSIONS:** Aberrant methylation of CpG islands in the promoter regions of P16, hMLH1 and CDH1 genes is a frequent event. Promoter methylation of CDH1 and hMLH1 might be an important molecular event in the development of gastric cancer and a molecular marker of early diagnosis. Promoter methylation of hMLH1 might be an independent prognostic factor for gastric cancer.