Delays in CpG islands methylation are related to gastric cancer and subsequent gastric dysplasia

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Aim/Background: Helicobacter pylori (HP) infection promotes phenotype-stabilizing overmethylation and gastric mucosal atrophy. The early stage of HP-associated methylation is unstable and amenable to cancer evolution. This stage may be prolonged by gastric atrophy having a methylation-inhibiting effect. The influence of mucosal atrophy on the timing of overmethylation was analyzed to delineate the epigenetic risk period for developing gastric cancer and dysplasia.

Methods: Normal-appearing biopsy specimens were obtained from 110 HP-positive controls, 95 HP-negative controls, 99 cancer patients, and 118 dysplasia patients. Gastric mucosal atrophy was assessed with the endoscopic-atrophic-border score. The methylation-variable sites of stomach-specific TFF3 and eight CpG-island genes adjacent to Alu (CDH1, ABRDCA, PPARG, TRAPPC2L) or LTR (MMP2, CDKN2A, RUNX2, RUNX3) retroelements were analyzed using radioisotope-labeled methylation-specific PCR.

Results: Of the two CpG-island gene types, the Alu-type genes were frequently and promptly overmethylated in HP positive controls with mild and moderate atrophy at similar ages (mean age, 51 and 49 years), and the timing of TFF3 overmethylation was significantly delayed in those with moderate atrophy (58 years, \( P = 0.005 \)). Alu-type overmethylation (58 years) occurred later than TFF3 overmethylation (56 years) in moderate atrophic cases of cancer patients, but not in those of dysplasia patients, suggesting that the early unstable methylation was prolonged for nine years (49 to 58 years) in cancer patients. The delayed timing of Alu-type overmethylation was observed in severe atrophic cases of both cancer and dysplasia patients.

Conclusions: HP-associated CpG-island methylation was delayed in gastric cancer patients with moderate atrophy and was related to gastric dysplasia as a late stabilization step.

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