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Promoter Methylation Precedes Chromosomal Alterations in Colorectal Cancer Development

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Abstract

Background: Colorectal cancers are characterized by genetic and epigenetic alterations. This study aimed to explore the timing of promoter methylation and relationship with mutations and chromosomal alterations in colorectal carcinogenesis. *Methods*: In a series of 47 nonprogressed adenomas, 41 progressed adenomas (malignant polyps), 38 colorectal carcinomas and 18 paired normal tissues, we evaluated promoter methylation status of *hMLH1, O^6MGMT, APC, $p14^{ARF}$, $p16^{INK4A}$, RASSF1A, GATA-4, GATA-5,* and *CHFR* using methylation-specific PCR. Mutation status of *TP53, APC* and *KRAS* were studied by p53 immunohistochemistry and sequencing of the *APC* and *KRAS* mutation cluster regions. Chromosomal alterations were evaluated by comparative genomic hybridization. *Results*: Our data demonstrate that nonprogressed adenomas, progressed adenomas and carcinomas show similar frequencies of promoter methylation for the majority of the genes. Normal tissues showed significantly lower frequencies of promoter methylation of *APC, $p16^{INK4A}$, GATA-4*, and *GATA-5* (*P*-values: 0.02, 0.02, 1.1×10−5 and 0.008 respectively). P53 immunopositivity and chromosomal abnormalities occur predominantly in carcinomas (*P* values: 1.1×10−5 and 4.1×10−10). *Conclusions*: Since promoter methylation was already present in nonprogressed adenomas without chromosomal alterations, we conclude that promoter methylation can be regarded as an early event preceding *TP53* mutation and chromosomal abnormalities in colorectal cancer development.

Keywords: Colorectal cancer, promoter methylation, genetic alterations, chromosomal instability