SCREENING

Aberrant methylation—early biomarker for CRC

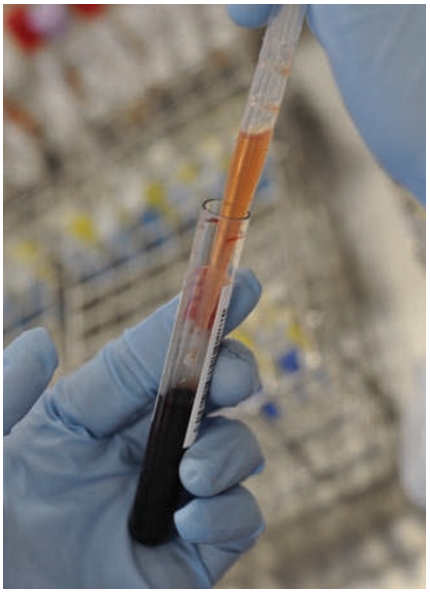
Colorectal cancer is one of the most commonly diagnosed malignancies worldwide. Early detection of the disease could, therefore, have significant clinical benefits for patients. Colorectal cancer develops as part of a multistep process that involves the progressive accumulation of genetic and epigenetic alterations. Aberrant methylation of CpG islands in the promoter region of tumor suppressor genes has been reported in colorectal cancer and several other malignancies. Moreover, the presence of circulating DNA with aberrant methylation of tumor suppressor genes in the plasma of patients with colorectal cancer has been recently reported. Scientists from Korea investigated epigenetic molecular markers in the plasma of patients with colorectal cancer for early detection of the disease.

In a retrospective study, Lee and colleagues investigated the methylation status of 10 genes in fresh-frozen tumor tissue and corresponding plasma samples of 243 patients with stage I and stage II sporadic colorectal cancer, and 64 patients with colorectal adenoma. The researchers used methylation-specific PCR and assessed genes involved in cell cycle regulation (*p14* and *p16*), DNA repair and protection (*hMLH1* and *MGMT*), signal transduction (*APC, RARβ2, RASSF2A* and *Wif-1*), apoptosis (*DAPK*) and chromatin remodeling (*HLTF*). Inactivating mutations and silencing by hypermethylation of these genes have already been implicated in the pathogenesis of colorectal cancer.

It is imperative to differentiate age-related methylation and tumor-specific methylation for the early detection of colorectal cancer; therefore, the researchers also analyzed the methylation status in normal colorectal mucosa from the 276 healthy individuals who had undergone colonoscopy ($n = 148$). Lee and colleagues did not detect aberrant methylation of *DAPK, RARβ2* and *RASSF2A*. In 2–4% of normal colonic mucosal tissue, however, *p14, p16, APC, HLTF, MGMT* and *Wif-1* were found to be methylated. The methylation status of the genes investigated was not correlated with patients' age, but was found to be tumor-specific. The researchers detected 18–74% of methylation of these genes in tumor tissues; more specifically, 18% for *p14*, 34% for *p16*, 27% for *APC*, 34% for *DAPK*, 32% for *HLTF*, 21% for *hMLH1*, 39% for *MGMT*, 24% for *RARβ2*, 58% for *RASSF2A* and 74% for *Wif-1*.

Moreover, the methylation status of all the genes, except *HLTF* was found to be an independent predictive factor of colorectal cancer although the sensitivity of detection in plasma was low. In order to increase the sensitivity of detection of DNA methylation in plasma, multigene analysis was performed. The methylation of *APC, MGMT, RASSF2A* and *Wif-1* showed the best sensitivity and specificity as a diagnostic biomarker. Methylation of one or more of these genes was detected in 91% of tumor tissues and in 86% of plasma samples.

The researchers conclude that tumor-specific methylation of *APC, MGMT, RASSF2A* and *Wif-1* might be a valuable biomarker in plasma for the early detection of colorectal cancer.



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Original article Lee, B. *et al.* Aberrant methylation of *APC, MGMT, RASSF2A*, and *Wif-1* genes in plasma as biomarker for early detection of colorectal cancer. *Clin. Cancer Res.* **15**, 6185–6191 (2009).