Aberrant DNA methylation as sensitive and promising biomarkers in diagnosing of cancers

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A recent study by Yu et al. and co-workers have provided potential usefulness of methylation of CDH1 promoter in preoperative peritoneal washes (PPW) as a marker for prognostic indicator in gastric cancer patients (1). Epigenetic gene silencing by promoter CpG islands hypermethylation and subsequent transcriptional gene silencing are important mechanisms in the inactivation of tumor suppressor genes (2). DNA methylation has been deeply involved in the development and progression of many types of cancer and extensive researches in this field have suggested strong potentiality for the DNA methylation signatures to prognostically differentiate cancers beyond current clinical classifications (3-6). DNA methylation can also occur at the early stage of tumorigenesis in precursor lesions and aged or inflamed tissues (7-12) suggesting that epigenetic changes constitute the earliest steps toward neoplastic transformation by creating molecular diversity, which may be useful for identifying populations being at risk of developing carcinomas. Moreover, it is possible to detect very tiny amounts of methylated molecules among samples (13). Therefore, aberrant methylation can be considered as sensitive and very promising biomarkers in early diagnosing of tumors. For example, there have been studies showing the usefulness of DNA methylation analysis of mucosal wash as a tumor marker in the stomach and colon (14,15). It has been also proposed tumor cells can release DNA to peripheral blood and enriched circulating DNA level can be found in the serum of cancer patients, several times higher than cancer free subjects. Previous studies showed that methylation of multiple genes, derived from cancer tissues, were detected in blood plasma, urine, sputum and peritoneal washes in several cancers (16-21). The results suggest that examination of DNA methylaton in any source of samples could be utilized as a molecular diagnostic marker of cancer.

Yu *et al*. and co-workers evaluated this concept in gastric cancer. They collected preoperative peritoneal washes (PPW) from 92 gastric patients undergoing surgery. They chose CDH1 promoter as a candidate marker, which has been frequently methylated in gastric cancer and used real-time methylation specific-PCR, a sensitive method for measurement of methylated DNA. The result demonstrated good correlation of CDH1methylation with more aggressive clinicpathological subtypes of gastric cancer including larger sizes of tumors, infiltration type, lymphatic and venal invasion, higher T stage, lymph node and distant metastasis. There was a significant worse disease-free survival (DFS) among the patients with CDH1 methylation in their PPW. Cox regression analysis confirmed CDH1 methylation in PPW was an independent risk factor for gastric cancer patients, with a remarkable decrease in DFS after postoperative 30 months (1).

The current result supports the strong potentiality of DNA methylation as molecular diagnostic marker in universal types of samples, and opened the avenue for further researches of this field for the application of DNA methylation as a clinical test in diagnostic test in cancer treatment.

In recent years, several methods have been developed to provide a genome-wide landscape of the DNA.methylation status, highlighting the importance of unbiased approaches for DNA methylation mapping in cancer (3,4,6). Moreover, recent comprehensive genome-scale understanding of the DNA methylation loss and gain in cancer revealed

that most methylation alterations in cancer occur not in promoters, and also not in CpG islands, but in sequences up to 2 kb distant, termed 'CpG island shores', which shows tight link to gene expression (22). Advances in this field may further enable the clinical application of DNA methylation status as a diagnostic marker for cancer, and the discovery of specific methylation changes raises the possibility that specific epigenetic therapy may be useful for cancer treatment as shown in several neoplasms such as MDS and lymphoma (23).

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