EDITORIAL

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Prognostic Significance of CpG Island Methylator Phenotype in Colorectal Cancer

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See "The Role of the CpG Island Methylator Phenotype on Survival Outcome in Colon Cancer" by Ki Joo Kang, et al. on page 202, Vol. 9. No. 2, 2015

Colorectal cancer (CRC) is one of the major causes of cancer-related morbidity and mortality worldwide. Despite of recent advances of variable therapeutic techniques in CRC, cancer progression and metastasis remain the major contributors to cancer-related morbidity and mortality.[1] Cancer progression and metastasis are complex processes and arise through the accumulation of multiple genetic and epigenetic alterations.[2] Therefore, advances in our understanding of these molecular alterations of CRC enable us to predict outcomes, personalize medicine and improve the care of CRC patients.

Over the past years, meticulous morphologic and molecular features of CRC have led to the development of three major pathways including chromosomal instability (CIN), microsatellite instability (MSI), and cytosine-phospho-guanine (CpG) island methylator phenotype (CIMP).[3,4] Most CRCs develop from conventional adenoma through the traditional adenoma-carcinoma pathway characterized by CIN involving *KRAS*, *C-MYC*, *APC*, and *p53* mutations.[3,4] About 15% to 20% of CRCs develop through the MSI arising from defects in the DNA mismatch repair (MMR) system to correct errors that often occur during DNA replication, and associated with Lynch syndrome. MSI is controlled by MMR genes including *MLH1*, *MSH2*, *MSH6*, and *PMS2*.[3,4] CIMP, characterized by the hypermethylation of CpG islands has been identified as an important third major pathway, which accounts for almost 40% of CRCs. Especially, hypermethylation of CpG islands located in the promoter region leads to transcriptional silencing of tumor suppressor genes and other tumor-related genes.[4-6] Therefore, CIMP status can influence the prognosis of CRC patients.

Previous studies investigated clinicopathological and molecular features of CRC according to the CIMP status, and focused on the association between CIMP status and CRC prognosis. CIMP-high CRCs present with distinct clinicopathological and molecular features such as older age, female gender, proximal tumor location, poor differentiation, and high rate of MSI, *KRAS* and *BRAF* mutation, compared to CIMP-low/negative CRCs.[5-7] However, the association between CIMP status and CRC prognosis are inconsistent in previous published reports.[5-7]

In this issue of *Gut and Liver*, Kang *et al*.[8], investigated the MSI and CIMP status in Korean colon cancer patients except many rectal cancer patients, and examined their correlation with clinicopathological features including survival. The authors showed that regardless of the MSI status, CIMP-high colon cancer was associated with a poor survival outcome, and colon cancer with CIMP-high/MSI-negative in subgroup analysis showed a poor survival outcome compared to CIMP-low and negative/MSI-negative colon cancers. However, as the authors described, this study population was relatively small and had low incidence of MSI-high or CIMP-high cancers, which might influence some results, especially the association of CIMP status for CRC prognosis.[8]

Other Korean studies also showed that CIMP-high CRCs were significantly associated with female gender, proximal tumor location, poor differentiation, nodal metastasis, more advanced cancer, *BRAF* mutations, MSI, and poor prognosis.[9,10] According to the combination of CIMP and MSI status, the CIMP-high/MSI-negative subtype showed the worst clinical outcome due to *BRAF* mutation.[9,10] The clinicopathological and molecular features of CIMP-high CRCs in Korean studies[8-10] were similar with those of previous published reports.[5-7] However, although

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CIMP-high CRC patients were related to poor prognosis in many studies including Korean studies, other studies reported no association between CIMP-high CRC patient and prognosis or even noted a better survival benefit from adjuvant chemotherapy.[5-7]

There are several explanations for this discrepancy. First, results are inconsistent, perhaps due to variable factors including MSI, *KRAS* and *BRAF* mutations, variations in use of adjuvant chemotherapy, the ambiguous pathophysiolgy of CIMP, methodologic differences such as differences in the selected methylation markers and definitions of CIMP.[5,6] Actually, specific methylated loci using for definition of CIMP and prevalence of CIMP status are different among studies. It is the major concern in studying CIMP status in variable cancers. Second, CIMP is an event that predominantly occurs in early stage of carcinogenesis and may less involve to cancer progression. Therefore, although much effort has been made to identify the impact of CIMP status as prognostic biomarkers in clinical practice, it still cannot be concluded whether association between CIMP status and CRC prognosis exist.

In future, large-scale well-designed studies should be considered in order to clarify the impact of CIMP on the prognostic significance in CRC patients.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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