Syndecan-2 Methylation as a New Biomarker for Early Detection of Colorectal Neoplasm

Ji Hyun Kim and Sung Chul Park

Division of Gastroenterology and Hepatology, Department of Internal Medicine, Kangwon National University School of Medicine, Chuncheon, Korea

See "Analysis of Syndecan-2 Methylation in Bowel Lavage Fluid for the Detection of Colorectal Neoplasm" by Young Sook Park, et al. on page 508, Vol. 12, No. 5, 2018

Colorectal cancer (CRC) is the third most common malignancy and the fourth leading cause of cancer deaths globally.¹ Because most CRC progress from adenoma, appropriate screening tests can significantly lower its incidence and mortality.² Despite the high sensitivity and specificity of colonoscopy for CRC screening, it is performed in <50% of CRC patients worldwide due to its high cost, challenges in bowel preparation, invasiveness, and possible complications such as bleeding and perforation. Fecal occult blood test (FOBT) is currently the most common screening test for CRC given that large polyps or CRC have bleeding tendencies. Fecal immunohistochemical test (FIT) has lowered the false positivity of FOBT; however, FIT has low sensitivity for detecting early CRC or precancerous lesions including advanced adenomas >10 mm in size, with >25% villous tissue, or high-grade dysplasia.

The need for less invasive yet effective and safe methods for CRC detection has driven studies on molecular changes related to CRC. Hypermethylation of the CpG island in gene promoter is an epigenetic alteration that occurs frequently in human cancers early in carcinogenesis. Aberrantly methylated DNA is stable in various sample types including stool and blood and has high diagnostic sensitivity. Thus, DNA methylations as biomarkers have been evaluated to improve detection of CRC and precancerous lesion.

Cologuard® (Exact Sciences Corp., Madison, WI, USA) is a multi-target stool DNA test that examines molecular markers including *KRAS* mutation, *NDRG4* and *BMP3* methylations, and β -actin with FIT for CRC screening. The comparison of Cologuard® and FIT showed significantly higher sensitivities of

92.3% and 42.4% for detecting CRC and advanced precancerous lesions, respectively (vs 73.8% and 23.8%, respectively for FIT); however, its specificity (86.6%) was lower than that of FIT (94.9%).³ Although Cologuard® has been approved by the U.S. Food and Drug Administration (FDA) in 2014 as for CRC screening, its high cost and difficult sample pretreatment are considered disadvantageous. A recent study of stool DNA methylation in an Asian population, assessing the methylation of *SFRP2*, *TFPI2*, *NDRG4*, and *BMP3* promoters, showed high sensitivities of 94.3% and 72.2% to detect both CRC and advanced adenoma, respectively, but with a low specificity of 55.0%.⁴ A new blood screening test that examines methylated *SEPT9* (Epi proColon®; Epigenomics AG, Berlin, Germany) was approved by the FDA in 2016. However, a large multicenter prospective study showed low sensitivities of 48.2% and 11.2% for detecting CRC and advanced adenoma, respectively with 91.5% specificity.⁵

Recently, *syndecan-2* (*SDC2*) methylation was highlighted as a potential marker for early CRC detection.⁶ The syndecan-2 protein is an integral membrane protein involved in cell proliferation, cell migration, and interaction between cell and matrix. A DNA microarray analysis of neoplastic samples showed high *SDC2* methylation rate of approximately 95% regardless of the cancer stage.⁶ Further clinical validation using blood from 131 CRC patients and 125 healthy subjects showed sensitivity and specificity of 87.0% and 95.2%, respectively for detecting CRC. Importantly, its high sensitivity of 92.3% for detecting stage I CRC suggests its potential utility for early CRC detection. Another study on methylated *SDC2* showed considerably lower

Correspondence to: Sung Chul Park

Division of Gastroenterology and Hepatology, Department of Internal Medicine, Kangwon National University Hospital, Kangwon National University School of Medicine, 156 Baengnyeong-ro, Chuncheon 24289, Korea

Tel: +82-33-258-2405, Fax: +82-33-258-2146, E-mail: schlp@kangwon.ac.kr

pISSN 1976-2283 eISSN 2005-1212 <https://doi.org/10.5009/gnl18286>

© This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

sensitivity (59.1%) and specificity (84.1%).⁷ Because neoplastic cells exfoliate into the colon before vascular invasion during CRC progression, stool samples may be an appropriate specimen for early CRC detection.

In this issue of *Gut and Liver*, Park *et al.*⁸ reported the feasibility of assessing *SDC2* methylation in bowel lavage fluid (BLF) collected during colonoscopy to detect CRC and precancerous lesions. Using BLF of patients with a colorectal neoplasm (n=136) and healthy subjects (n=54), and fourteen colorectal tumor specimens, *SDC2* methylation was measured with quantitative methylation-specific polymerase chain reaction (PCR). Despite limited tissue samples, *SDC2* methylation was positive in 100% of villous adenoma, high-grade dysplasia, and hyperplastic polyp samples, in 88.9% of tubular adenoma samples, and in 0% of normal mucosal samples, indicating the potential of *SDC2* methylation as a biomarker for early CRC detection. The sensitivities in BLF for detecting CRC (n=10) and villous adenoma (n=17) were 80.0% and 64.7%, respectively with 88.9% specificity. *SDC2* methylation rate was 62.8% for multiple tubular adenoma (n=43), 26.7% for simple tubular adenoma (n=45), and 28.6% for hyperplastic polyp (n=21), indicating a gradual increase in positivity according to lesion severity and number of adenomas. The study demonstrated that *SDC2* methylation is a frequent event in precancerous lesions of the colon and suggested the utility of BLF for CRC detection. However, detection of DNA methylation in BLF may be less sensitive for patients with non-invasive tumor, because few exfoliated cells may be found in BLF. Additionally, BLF requires bowel preparation; thus, its combination with flexible sigmoidoscopy to detect proximal colon tumor, or with computed tomographic colonography to locate flat-type tumor may be useful. A recent study by Oh *et al.*⁹ comparing patients with CRC of various stages (I–IV) (n=50) or precancerous lesions (n=21) and healthy subjects (n=22) showed that stool *SDC2* methylation test by linear target enrichment and quantitative methylation-specific PCR had 90.0% and 33.3% overall sensitivities for detecting CRC and small polyps (<1.0 cm), respectively with 90.9% specificity. Similarly, a study by Niu *et al.*¹⁰ assessing *SDC2* methylation in 497 stool samples showed 81.1% and 58.2% sensitivities for detecting CRC (n=196) and adenoma (≥ 1 cm) (n=122), respectively with 93.3% specificity, which is comparable to that observed by Park *et al.*⁸ and Oh *et al.*⁹ Thus, an *SDC2* methylation test (EarlyTect® Colon Cancer; Genomictree, Inc., Daejeon, South Korea) may be a useful non-invasive screening test for early CRC detection, owing to its high sensitivity and specificity and lower

costs compared to other tests that assess more complex DNA markers. A large population study is needed to demonstrate the utility of such biomarker as a population-based screening tool; an observational cohort study of 634 participants is currently ongoing (NCT03146520). Technical advancements have allowed discoveries of newer biomarkers such as *SDC2* methylation with improved detection sensitivity and specificity at lower costs, which are expected to yield groundbreaking improvement in CRC screening.

CONFLICTS OF INTEREST

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

REFERENCES

1. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. *Gut* 2017;66:683–691.
2. Lee BI, Hong SP, Kim SE, et al. Korean guidelines for colorectal cancer screening and polyp detection. *Intest Res* 2012;10:67–88.
3. Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Multitarget stool DNA testing for colorectal-cancer screening. *N Engl J Med* 2014;370:1287–1297.
4. Park SK, Baek HL, Yu J, et al. Is methylation analysis of SFRP2, TFPI2, NDRG4, and BMP3 promoters suitable for colorectal cancer screening in the Korean population? *Intest Res* 2017;15:495–501.
5. Church TR, Wandell M, Lofton-Day C, et al. Prospective evaluation of methylated SEPT9 in plasma for detection of asymptomatic colorectal cancer. *Gut* 2014;63:317–325.
6. Oh T, Kim N, Moon Y, et al. Genome-wide identification and validation of a novel methylation biomarker, *SDC2*, for blood-based detection of colorectal cancer. *J Mol Diagn* 2013;15:498–507.
7. Mitchell SM, Ho T, Brown GS, et al. Evaluation of methylation biomarkers for detection of circulating tumor DNA and application to colorectal cancer. *Genes (Basel)* 2016;7:E125.
8. Park YS, Kim DS, Cho SW, et al. Analysis of syndecan-2 methylation in bowel lavage fluid for the detection of colorectal neoplasm. *Gut Liver* 2018;12:508–515.
9. Oh TJ, Oh HI, Seo YY, et al. Feasibility of quantifying *SDC2* methylation in stool DNA for early detection of colorectal cancer. *Clin Epigenetics* 2017;9:126.
10. Niu F, Wen J, Fu X, et al. Stool DNA test of methylated syndecan-2 for the early detection of colorectal neoplasia. *Cancer Epidemiol Biomarkers Prev* 2017;26:1411–1419.