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Discovery and validation of *Syndecan2* methylation for serum DNA-based test for early detection of patients with colorectal cancer and precancerous lesions

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proper screening for colorectal cancer (CRC) can reduce morbidity and mortality by this disease. However, the current Ascreening modalities are inadequate due to high cost and poor compliance leading to a low participation rate. Therefore, it would be urgently necessary to develop an alternative screening tool such as biomarker-based blood test. We have attempted identify DNA methylation sites which can be utilized as a biomarker for the non-invasive diagnostics of CRC patient at earliest stage.For this, we utilized methylation microarray analysis coupled with enriched methylated DNA bymethylated DNA isolation assay (MeDIA) and discovered differentially methylated genes between tumor and non-tumor tissues. Through step-wise filteringprocedures we then selected an aberrant SDC2 methylation as a potential biomarker for discriminating CRC patients from healthy individuals. When we analyzed methylation status of SDC2 in tumor and non-tumor samples by pyro-sequencing we found that abnormal SDC2 methylation is somatically acquired in the majority of patients with CRC (98%, n=133).We then revealed that the quantitative SDC2 methylation (qMSP) test by real-time PCR in serum DNA can successfully detect of various stage of CRC patients (n=131) with overall high sensitivity (87%, n=131) and specificity (95% n=125). Notably, the sensitivity was 92% for stage I. Currently we extended this to investigate whether aberrant presence of SDC2 methylation in blood can also distinguish patients with adenoma from normal subjects. For quantitative SDC2 methylation assay in heterogeneous and minute amount of serum DNA from precancerous patientswe have optimized detection method of qMSP (meSDC2 IP-qMSP) by degenerated inosine-primer design. The limit of detection for methylated SDC2 test was 100 pg/mL of serum corresponding to ~30 genome copies.A meSDC2 IP-qMSP in serum DNA from independent group of CRC patients(n=146) with various stages (I-IV), 100 adenoma patients and 51 colonoscopy-verified normal subjects showed the overall sensitivities of 91.1% (95% CI, 85.3% to 95.2%) and 71.0% (95% CI, 61.1% to 79.6%) for CRC and adenomatous polyps, respectively with a specificity of 86.3% (95% CI, 73.7% to 94.3%). The sensitivity was 93.5% (29/31) for stage I of CRC.SDC2 methylation level in serum from preoperative patients dramatically disappeared or dropped to lower after curative surgery (P=0.002) indicating this phenomenon is a CRC-specific. We demonstrated that a simple blood DNA test that measures an abnormal presence of SDC2 methylation in serum DNA can successfully distinguish not only CRC patients but also those with adenoma from healthy subjects.

Biography

Sungwhan An is the Founder and Chief Executive Officer of Genomictree, Inc.; molecular diagnostic company based in South Korea since 2000. He is an Adjunctive Professor in Cancer Center of Yonsei University, College of Medicine, South Korea and also had been worked as a Research Assistant Professor from 2003 to 2009. After that he earned PhD degree in the field of molecular virology at the University of Texas at Austin in U.S.A. He then went through a Postdoctoral training course involved in translational research work investigating transcriptomics in HCV infection using DNA microarray at Dr. Harry Greenberg's lab in the Stanford University School of Medicine from early 1999 to late 2000. Currently his interest is to discover and develop new DNA methylation biomarkers for the detection of cancers in non-invasive way. In addition, he has been focusing to develop multiplex assay technique for the multiple markers including multiple cancer mutations and infectious agents.

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