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Epigenetic Alterations in Inflammatory Bowel Disease and Cancer

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Overwhelming evidences supports the idea that inflammatory bowel disease (IBD) is caused by a complex interplay between genetic alterations of multiple genes and an aberrant interaction with environmental factors. There is growing evidence that epigenetic factors can play a significant part in the pathogenesis of IBD. Significant effort has been invested in uncovering genetic and epigenetic factors, which may increase the risk of IBD, but progress has been slow, and few IBD-specific factors have been detected so far. It has been known for decades that DNA methylation is the most well studied epigenetic modification, and analysis of DNA methylation is leading to a new generation of cancer biomarkers. Therefore, in this review, we summarize the role of DNA methylation alteration in IBD pathogenesis, and discuss specific genes or genetic loci using recent molecular technology advances. Here, we suggest that DNA methylation should be studied in depth to understand the molecular pathways of IBD pathogenesis, and discuss epigenetic studies of IBD that may have a significant impact on the field of IBD research. **(Intest Res 2015;13:112-121)**

Key Words: Inflammatory bowel diseases; Neoplasms; Epigenomics; DNA methylation

INTRODUCTION

Tumorigenesis is a multistep process, including initiation, promotion, and progression, and a multifactorial pathology characterized by the accumulation of a multitude of alterations, including genetic, cytogenetic, and epigenetic changes.[1] To completely construct an organism, classical genetic processes are not sufficient. For proper development and cell functioning, epigenetic phenomena, controlling gene expression, are absolutely required. The term "epigenetic" refers to a heritable change in the pattern of gene expression that is mediated by mechanisms other than alterations in the primary nucleotide sequence of a gene.[2,3] As evidence for genetic changes in cancer cells has increased since the 1980s, interest in the contribution of epigenetic changes to neoplasia has waned. The situation has changed dramatically in more recent years, however, because of convincing evidence for the abnormal silencing of genes in cancer cells.[4,5] It has been known that epigenetic alteration is one of the most important gene regulatory mechanisms. Unlike genetic alterations, epigenetic events are not changes in gene function that occur in conjunction with DNA sequence changes.

Epigenetic regulation of gene expression is mediated by mechanisms such as DNA methylation, histone modification, and positioning of nucleosome along DNA. The interplay between epigenetic components guarantees a proper balance between transcriptional activity and repression by changing chromatin architecture. Thus, regulation of the packaging of DNA ensures maintenance of correct chromosome replication, gene expression, and stable gene silencing.[6] DNA methylation is one of the most intensely studied

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epigenetic modifications in mammals and has an important impact on normal cell physiology. As this DNA modification seems to be a critical player in transcriptional regulation, it is not surprising that defects in this mechanism may lead to various diseases, including cancer.[7] Recently, epigenetic studies have been conducted in many different fields of biology, and particularly in the cancer field.

THE MOLECULAR BASIS OF DNA METHYLATION

Although only four bases -adenine, guanine, cytosine, and thymidine- compose the primary sequence of DNA, covalent modification of postreplicative DNA, that is DNA that has replicated itself in a dividing cell, that produces a "fifth base". A reaction using S-adenosyl-methionine as a methyl donor and catalyzed by enzymes called DNA methyltransferases (DNMTs) adds a methyl group to the cytosine ring to form methyl cytosine (Fig. 1A).

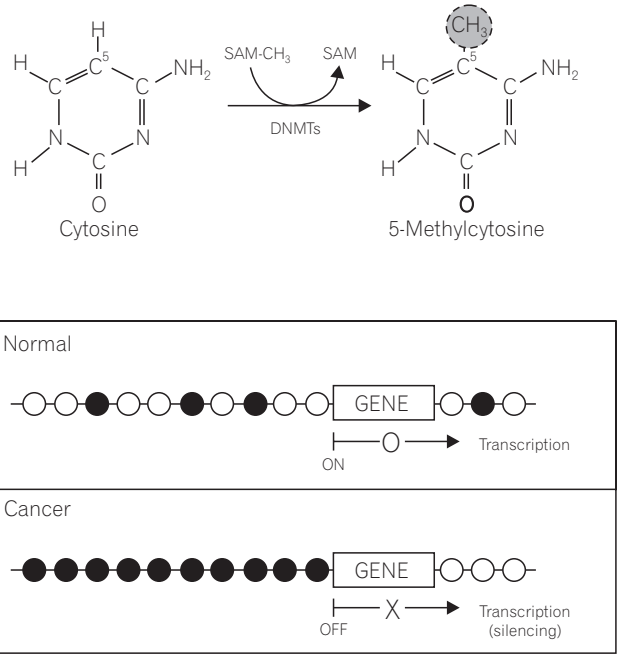

Fig. 1. Methylation patterns between normal cells and tumor cells. (A) Conversion of cytosine to 5-methylcytosine by DNA methyltransferase (DNMT). DNMT catalyzes the transfer of a methyl group (CH3) from S-adenosylmethionine (SAM) to the 5-carbon position of cytosine. (B) Methylation patterns between normal cells and tumor cells. In normal cells, cytosine-phospho-guanine (CpG) sites are globally methylated which means most CpG sites outside CpG islands are methylated (black circles), whereas most CpG island sites in gene expression promoters are unmethylated (white circles). Therefore, unmethylation status of CpG islands in gene promoters permits active gene expression. In cancer cells, CpG islands in gene promoter regions become abnormally methylated and this causes transcriptional silencing of genes. Circles indicate CpG dinucleotides.

In humans and other mammals, this modification is imposed only on cytosines that precede a guanosine in the DNA sequence (the cytosine-phospho-guanine [CpG] dinucleotide). The overall frequency of CpGs in the genome is substantially less than what would be mathematically predicted. The distribution in the genome of CpG dinucleotides on which DNA methylation occurs is unusually asymmetric. In contrast to the relative small portion of CpGs in the genome as a whole, these dinucleotides can be clustered in small stretches of DNA termed "CpG islands".[2] These regions are often associated with sites where the transcription of DNA into RNA begins, which can be the promoter region of genes.

The methylation reaction of cytosines is mediated by a class of enzymes called DNMTs that catalyze the transfer of the methyl group from s-adenosyl-methionine onto cytosine. Five members of the DNMT family have been identified in mammals: DNMT1, DNMT2, DNMT3a, DNMT3b, and DNMT3L. However, as far as we know, only DNMT1, DNMT3a, and DNMT3b interplay to produce the global cytosine methylation pattern. These independently encoded proteins are classified as *de novo* enzymes (DNMT3a and DNM3b) or as a maintenance enzyme (DNMT1). DNMT2 and DNMT3L are not thought to function as cytosine methyltransferases. However, DNMT3L was shown to stimulate *de novo* DNA methylation by DNMT3a and to mediate transcriptional repression through interaction with histone deacetylases 1.[8,9]

Abnormal patterns of DNA methylation in cancer cells have been recognized for over 30 years. In particular, an abnormal gain of DNA methylation, hypermethylation, is now established as a very common event in cancer cells which often involves normally unmethylated gene promoter CpG islands[5] (Fig. 1B). This promoter change can be associated with transcriptional silencing, and thus loss of function, of tumor suppressor genes and may be a key event contributing to the oncogenic process.[10,11] The tumor suppressors that are inactivated by hypermethylation can affect DNA repair, programmed cell death, angiogenesis, cell cycle regulation, and tumor cell invasion. For example, the mismatch repair gene *hMLH1* is frequently silenced by methylation and results in mismatch repair deficiency in cancers of the colon, stomach, and endometrium.[12,13] Other well-known examples of genes silenced by hypermethylation include the *VHL* tumor suppressor in renal cell carcinoma,[14] the *BRCA1* tumor suppressor,[15] the cyclin-dependent kinase inhibitor *CDKN2A* (*p16*),[16] and the retinoblastoma susceptibility gene *RB1*.[17] Recently, several hundred genes silenced by DNA

hypermethylation in various cancers have been identified using genome-wide approaches.[18,19]

DNA METHYLATION AND CANCER

Aberrant DNA methylation was the first epigenetic hallmark to be associated with cancer as a consequence of the alteration it causes in normal gene regulation.[20] These alterations are of three types: hypermethylation, hypomethylation, and loss of imprinting. DNA hypermethylation refers principally to the gain of methylation at specific sites that are unmethylated under normal conditions. This aberrant methylation occurs mainly in promoter CpG islands, which are considered to be DNA sequences (>200-bp window) with a GC content greater than 50%.[21] This phenomenon of aberrant promoter CpG island hypermethylation has been associated with the stabilization of transcriptional repression and loss of gene function, and occurs fundamentally in tumor suppressor genes (Table 1).[7,22]

DNA hypomethylation is associated mainly with the loss of DNA methylation in genome-wide regions, although it can also occur locally. Feinberg and Vogelstein were the first to report that substantially more hypomethylation was found in the genes of cancer cells compared with their normal counterparts in two distinct histological types of cancer.[20] DNA hypomethylation occurs in many gene-poor genomic areas, including repetitive elements, retrotransposons, and introns, where it leads to genomic instability.[7] In repeat sequences, this is achieved by a higher rate of chromosomal rearrangements and, in retrotransposons, by a higher probability of translocation to other genomic regions.[23,24] During tumor progression, the degree of hypomethylation of genomic DNA increases as the lesion derives from a benign proliferation of cells to an invasive cancer.[25] Example of these exceptions are the fully methylated CpG islands associated with many transcriptionally silent genes on the X chromosome of females and the silenced alleles of some "imprinted genes", which through parental determination are programmed such that only one allele of the gene is expressed in normal tissues.[2,26] Loss of imprinting is defined as the loss of the parental allele specific monoallelic expression of genes due to aberrant hypomethylation profiles at one of the two parental alleles. For example, loss of imprinting of *IGF2* has been associated with an increased risk of cancer, including colorectal cancer. This event has been observed in different types of neoplasia.[27] A number of studies have described DNA hypomethylation in several tumor types, such as colorectal and gastric cancers, melanomas, and others.[28]

Table 1. Representative Tumor Suppressor Genes Silenced by Cytosine-Phospho-Guanine (CpG) Island Promoter Hypermethylation in Various Cancer Types

Gene	Cancer types				
	Colon	Leukemia	Lung	Breast	Prostate
APC	■		■	■	■
BMAL1		■			
BRCA1				■	
CDH1	■	■	■	■	■
CDH13	■	■	■	■	
CDKN2A (p16^{INK4a})	■	■	■	■	■
CDKN2B (p15^{INK4b})		■			
p14^{ARF}	■				
COX2	■				
CRBP1	■	■			
DAPK1	■	■	■		
ESR1		■	■	■	■
GATA4	■				
GATA5	■				
GSTP1			■		■
HIC1	■	■	■	■	
IGFBP3			■		
MGMT	■	■	■		
MLH1	■				
NORE1A			■		
PYCARD			■	■	
RARB2	■	■	■		
RASSF1A	■	■	■	■	■
TLE1		■			
TP73		■			

APC, adenomatous polyposis coli; *BMAL1*, brain and muscle arntlike protein 1; *BRCA1*, breast cancer 1, early onset; *CDH1*, cadherin 1; *CDH13*, cadherin 13; *CDKN2A (p16^{INK4a})*, cyclin-dependent kinase inhibitor 2A; *CDKN2B (p15^{INK4b})*, cyclin-dependent kinase inhibitor 2B; *p14^{ARF}*, cyclin-dependent kinase inhibitor 2A; *COX2*, cytochrome c oxidase subunit 2; *CRBP1*, cellular retinol binding protein 1; *DAPK1*, death-associated protein kinase 1; *ESR1*, estrogen receptor 1; *GATA4*, GATA binding protein 4; *GATA5*, GATA binding protein 5; *GSTP1*, glutathione S-transferase pi 1; *HIC1*, hypermethylated in cancer 1; *IGFBP3*, insulin-like growth factor binding protein 3; *MGMT*, O^6-methylguanine-DNA methyltransferase; *MLH1*, MutL homolog 1; *NORE1A*, Ras association (RalGDS/AF-6) domain family member 5; *PYCARD*, PYD and CARD domain containing; *RARB2*, retinoic acid receptor b2; *RASSF1A*, ras association (RalGDS/AF-6) domain family 1A; *TLE1*, transducin-like enhancer of split 1, homolog of drosophila E (sp1); *TP73*, tumor protein p73.

Table 2. DNA Methylation Studies in IBD

Subjects	Study design	Samples	Techniques	Highlighted differentially methylated loci	Number of loci showing differential DNA methylation	Reference
Discordant monozygotic twins (4 CD, 7 UC), childhood IBD control (14 CD, 8 UC)	Training set discordant monozygotic twins, testing set childhood IBD control	Peripheral leukocytes PBMCs	Methylation-specific amplification array 450K Illumina BeadChip Bisulfite pyrosequencing	*TEPP*	1	58
18 patients with IBD (9 CD, 9 UC)	Case control	Epstein-Barr virus-transformed B cells	Illumina GoldenGate Restriction length polymorphisms	*Bcl3, PPARG, STAT3, OSM, STAT5, IL12RB, SOX1, COL18A1, LMTK2, CASP2, TJP2, SMAD2, HCK, IL12B, LMO1*	49	59
21 ileal CD 19 controls	Case control, testing set on childhood IBD	Whole blood	Illumina 27K BeadChip	*MAPK13, FASLG, PRF1, S100A13, RIPK3, IL-21R*	50	60
25 patients with IBD (9 CD, 9 UC, 7 BD), 22 controls	Case control	PBMCs	Pyrosequencing	*STAT4*	4	61
8 with active UC, 8 with quiescent UC, 8 with active CD, 8 with quiescent CD, 8 without IBD	Case control Active versus quiescent Pyrosequencing validation Quantitative reversetranscriptase polymerase chain reaction mRNA quantification	Rectal biopsy specimens (whole tissue and separated epithelial cells)	Illumina 27K BeadChip	*THRAP2, FANCC, TNFSF4, TNFSF12, FUT7, CARD9, ICAM3, IL8RB*	>500	45
20 UC discordant monozygotic twins 135 unrelated subjects	3-layer EWAS: 1. Training set 2. Methylation variable positions 3. Differentially methylated regions	Intestinal biopsy specimens (whole tissue)	1. Affymetrix array 2. Illumina 27K BeadChip 3. MeDip 385K	*CFI, SPINK4, THY1/CD90*	61	62
9 CD, 17 UC and 26 non-disease	Case control Training set (14 vs 14) and testing set (12 vs 12)	Intestinal tissue from surgery (whole tissue)	Illumina GoldenGate Restriction length polymorphisms	*BGN, SERPINA5, TNFSF1A, AATK, GABRA5, MAPK10, STAT5A*	7	44

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Table 2. Continued

Subjects	Study design	Samples	Techniques	Highlighted differentially methylated loci	Number of loci showing differential DNA methylation	Reference
25 patients with IBD (9 CD, 9 UC, 7 BD), 22 controls	Case control	Colonic mucosal tissue during colonoscopy	Pyrosequencing	*STAT4*	4	61

PBMCs, peripheral blood mononuclear cells; *TEPP*, testis, prostate and placenta expressed; *Bcl3*, B-cell CLL/lymphoma 3; *PPARG*, peroxisome proliferator-activated receptor gamma; *STAT3*, signal transducer and activator of transcription 3 (acute-phase response factor); *OSM*, oncostatin M; *STAT5*, signal transducer and activator of transcription 5A; *IL12RB*, interleukin 12 receptor, beta 1; *SOX1*, SRY (sex determining region Y)-box 1; *COL18A1*, collagen, type XVIII, alpha 1; *LMTK2*, lemur tyrosine kinase 2; *CASP2*, caspase 2, apoptosis-related cysteine peptidase; *TJP2*, tight junction protein 2; *SMAD2*, SMAD family member 2; *HCK*, HCK proto-oncogene, Src family tyrosine kinase; *IL12B*, interleukin 12B; *LMO1*, LIM domain only 1 (rhombotin 1); *MAPK13*, mitogen-activated protein kinase 13; *FASLG*, Fas ligand (TNF superfamily, member 6); *PRF1*, perforin 1 (pore forming protein); *S100A13*, S100 calcium binding protein A13; *RIPK3*, receptor-interacting serine-threonine kinase 3; *IL-21R*, interleukin 21 receptor; BD, Behçet's disease; STAT4, signal transducer and activator of transcription 4; *THRAP2*, thyroid hormone receptor associated protein 2; *FANCC*, Fanconi anemia, complementation group C; *TNFSF4*, tumor necrosis factor (ligand) superfamily, member 4; *TNFSF12*, tumor necrosis factor (ligand) superfamily, member 12; *FUT7*, fucosyltransferase 7 (alpha (1,3) fucosyltransferase); *CARD9*, caspase recruitment domain family, member 9; *ICAM3*, intercellular adhesion molecule 3; *IL8RB*, interleukin 8 receptor, beta; EWAS, epigenome-wide methylation association studies; *CFI*, complement factor I, *SPINK4*, serine peptidase inhibitor, Kazal type 4; *THY1/CD90*, Thy-1 cell surface antigen; *BGN*, biglycan; *SERPINA5*, serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 5; *TNFSF1A*, Tnf tumor necrosis factor; *AATK*, apoptosis-associated tyrosine kinase; *GABRA5*, gamma-aminobutyric acid (GABA) A receptor, alpha 5; *MAPK10*, mitogen-activated protein kinase 10; *STAT5A*, signal transducer and activator of transcription 5A.

DNA METHYLATION IN UC

IBD, encompassing CD and UC, are chronic, relapsing, remitting, or continuously active diseases of the gastrointestinal tract and are occasionally associated with extra-intestinal manifestations.[29] Unlike in Europe and the US, during the last two decades, IBD has been very rare in Asia.[30] Although recent population-based and referral center cohorts have shown a rising incidence and prevalence of IBD in Asia.[31]

Although the exact etiology of IBD remains unknown, current research focuses on dysregulation of the immune response against the intestinal flora in genetically susceptible individuals.[29,32] The pathogenesis of IBD is believed to involve an aberrant immune response to intestinal microbiota in genetically susceptible individuals.[33,34] Genetic studies have provided many candidate loci in the past decade, and the innate and acquired immune responses have been implicated in pathogenesis.[33] However, identified genetic factors account for only a modest proportion of the disease variance: 13.6% for CD and 7.5% for UC.[35] Overall, all known genetic risk factors can only account for approximately 20% of the genetic risk.[36,37]

More specifically, IBD could be caused by interactions between the host and the environment, which encompass the intestinal microbiota, the immune system, the genetic composition of the host, and specific environmental factors such as the effects of smoking, breastfeeding, drugs, dietary products, and so on.[29,34,35] Regarding the interaction between environment and genome, epigenetic mechanisms and more specifically DNA methylation seem to be of great importance.[38]

UC represents one major sub-phenotype of human IBD. In past decades, UC has displayed a remarkably steep rise in incidence, which cannot be explained by genetic variants alone. Beyond germ line DNA variants, epigenetic variants, e.g., DNA methylation and histone modifications, could modulate disease-relevant gene function.[39] Methylation studies extend to different kinds of genes and genetic loci, trying to detect the possible correlation of their methylation to IBD. Indeed, epigenetic modifications represent promising candidates for elucidating processes of disease manifestation beyond the identified risk loci based on recent literature (Table 2).

There are several reports that the hypermethylation of many gene promoters is associated with UC patients. Firstly, Gloria et al.[40] has reported that DNA methylation relates to UC pathogenesis, which found that incorporation of the 3^{H}-methyl group into DNA was 10-fold higher in UC patients

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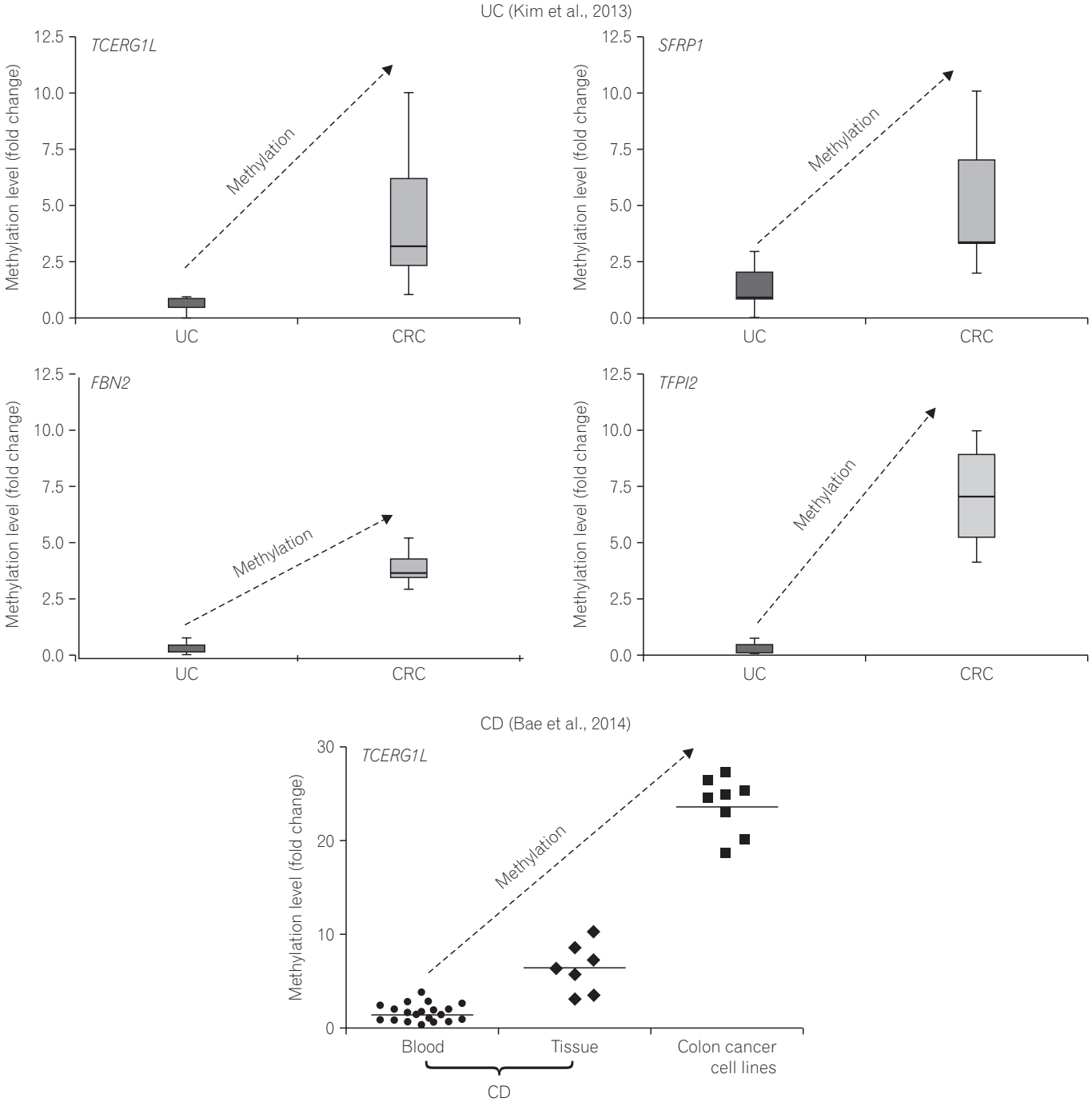

Fig. 2. Methylation level of candidate genes in IBD patients. DNA methylation of several candidate genes has been detected in UC tissues, CD tissues, and CD patient blood samples. The graph was quoted and modified from our previous publications (UC data from Kim et al.,[43] 2013 and CD data from Bae et al.,[47] 2014). CRC, colorectal cancer; *TCERG1L*, transcription elongation regulator 1-like; *SFRP1*, secreted frizzled-related protein 1; *FBN2*, fibrillin 2; *TFPI2*, tissue factor pathway inhibitor 2.

than in controls, and significantly higher in histologically active than in inactive disease. Other studies on many kinds of genes, such as *E-cadherin* (cell-cell adhesion molecule), *p16* (P16INK4a), *CDH1*, *GDNF*, and *MDR1*, proved that their promoter methylation was detected in high frequencies in UC patients. The most interesting gene here is *CDH1* encoding E-cadherin, which plays a central role in epithelial cell-cell adhesion. Since *CDH1* has been reported to be

down-regulated in areas of UC inflammation, there is growing evidence of DNA methylation of *CDH1* in IBD disease. Therefore, promoter hypermethylation of this gene has confirmed that it is associated with long standing inflammation, and that fact that the DNA methylation of this gene may be implicated in UC may make it a useful biomarker for detecting patients at high risk for developing colorectal cancer.[41,42] Very recently, we reported that we had newly identified a number of genes (*SFRP1*, *TFPI2*, *TCERG1L*, and *FBN2*) that are highly methylated in colon cancer patients using a genome-wide approach in Korean UC patients[43] (Fig. 2). Taken together, DNA methylation appears to be emerging as a common phenomenon in UC, especially in mucosal biopsies from inflamed tissue. Moreover, DNA methylation has been related to many different clinical aspects, such as disease severity, disease duration, disease phenotype, disease extent, and active inflammation and dysplasia.

DNA METHYLATION IN CD

Several reports have suggested that there are significant differential DNA methylation statuses between normal and inflamed tissues from CD and UC patients.[44-46] One of the most comprehensive genome wide studies attempted to elucidate the molecular basis of CD disease, and identified a number of distinct susceptibility loci conclusively associated with CD pathogenesis.[37] Although, unlike in UC, limited data have been reported regarding the contribution of DNA methylation status to CD pathogenesis, very recently we reported that we could detect DNA promoter hypermethylation in CD patients' serum using the cancer specific and highly frequency methylated gene *TCERG1L*[47] (Fig. 2). Our data strongly suggest that DNA methylation could be a valuable molecular tool for screen CD or UC patients. However, more specific genes or loci should be identified, and comprehensive DNA methylation genome-wide studies should be conducted to further the understanding the contribution of DNA methylation in CD.

DNA METHYLATION BIOMARKERS FOR CLINICAL USE

Despite our constantly growing understanding of carcinogenesis, there is still an urgent need to design novel, powerful tools that can be applied in clinical practice. Cancer biomarkers are indispensable not only for early diagnosis, but also for improving prognoses, the prediction of therapeutic response, monitoring therapy, or assessing the risk of recurrence after curative surgery. Cancer-specific hypermethylation of CpG islands represents one of the most prevalent molecular changes in cancer cells, and detection of abnormal methylation has proven to be of great use in clinical practice.

The use of DNA markers has various advantages over proteins. Unlike proteins, DNA is stable, easy to isolate from different kinds of material, and relatively small amounts of material are needed to perform assays. This is due to several inherent advantages in strategies for the detection of hypermethylation. DNA is a relatively stable substance and can be obtained from a wide range of sources. It can be stored for long periods after collection from patients. DNA methylation is a widespread alteration throughout the cancer genome. This allows for the possibility of using assays to query many points in the genome and for combining their use in highly predictive models. Highly sensitive and specific technologies now exist that can query the methylation state of specific DNA locations using minimal amounts of nucleic acid that can be obtained from a wide array of clinical specimens. These techniques include methylation-specific PCR, high-performance liquid chromatography, mass spectrometry-based methylation detection (EpiTYPER), Methy-Light, pyrosequencing, and next generation sequencing.[14,48,49] Assays like methylation-specific PCR and EpiTYPER are able to detect DNA methylation from even minute amounts of material such as urine and saliva, and are capable of utilizing DNA from both frozen and paraffin-embedded archived tissue. These advantages have enabled investigators to evaluate the diagnostic and prognostic utility of methylation of a large number of genes in a many tumor types.[6] Some genetic alterations have already been proposed as being valuable in diagnosis,[50] but it has also been suggested that changes in DNA methylation patterns may also aid in following cancer progression.[51]

DNA methylation markers have been developed using targeted candidate gene approaches, as well as by systematic screening for markers using genome-scanning techniques.[52] Therefore, DNA-methylation-based technologies have a promising future in both clinical diagnostics and therapeutics. DNA methylation markers have obvious applications in diagnostics, but can also contribute indirectly to therapeutics as predictors of therapeutic response. According to the review by Laird,[52] DNA methylation patterns have proven to be most useful in the sensitive detection of disease, whereas profiling methods are useful for stratification approaches.

With these genome-wide techniques for their identification and subsequent functional analyses, the number of

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potential DNA methylation biomarker genes available and the knowledge of their roles in cancer are rapidly increasing. One of the most important criteria for clinically useful biomarkers is whether they are applicable to surrogate tissues such as blood or other fluids that can be obtained through minimally invasive procedures. The sensitive and specific detection of tumor-specific DNA methylation patterns at distal sites makes DNA methylation a great candidate biomarker for early the detection of cancer and the clinical management of cancer patients.[53,54] DNA methylation can be used as a molecular prognosis biomarker of potentially curable, stage I non-small-cell lung cancer,[55] for which several methylated genes allow the identification of high risk patients who require special adjuvant therapies. In colon cancer, methylation of *IGFBP3* and *EVL* genes, which are identified from genome-wide techniques, predicted poor outcomes in colon cancer patients.[56]

DNA methylation biomarkers can also predict responses to chemotherapy. The best example is promoter hypermethylation of O^6-methylguanine-DNA methyltrasferase (*MGMT*), a DNA repair enzyme, in glioma. *MGMT* hypermethylation was detected in 40% of glioma and colorectal cancers in a study of a huge primary tumor cohort.[57]

CONCLUSIONS

Epigenetic studies carry significant discovery potential and may provide new insights into our understanding of the pathogenesis of IBD. Several examples of DNA methylation of specific genes or loci could be key factors in the translational study of IBD. Recent advances in our knowledge of IBD-associated DNA methylation underlie many promising clinical applications such as molecular biomarkers for diagnosis and prognosis as well as prediction of treatment outcomes. Even if the results from different studies are encouraging, limitations have thus far prevented widespread clinical application. One possible reason could be that DNA methylation frequency of many candidate genes is not high enough to achieve the sensitivity needed for clinical use. Various experiments new to the field of IBD research can be applied to the detection of IBD. Discovery of epigenetic changes in CD and UC patients may lead to the development of new therapies for IBD. In addition, technical advances in the near future are expected to reduce these problems, and DNA methylation is expected to play a key role in the development of personalized medicine.

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