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Dysbiosis of Gut Microbiome and Its Impact on Epigenetic Regulation

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Abstract

High throughput methods have increased knowledge about the epigenome and microbiome, and allowed determination of the plausible link between the gut microbiome and epigenetic modification of the host. This has shed light on the development of various diseases such as immune-mediated, metabolic, and cardiovascular diseases, and even cancer. Dysbiosis, imbalanced gut microbiome which is frequently observed in such diseases, may be involved in regulating the epigenome of the host via direct changes in the gut microbiota or indirect changes of their metabolites, which are a variety of bioactive substances such as short chain fatty acids (SCFAs), biotin, folic acid, and other bioactive molecules. Indeed, correlation between host epigenetic regulation and alteration of gut microbiota or metabolites produced by intestinal microorganisms has been reported for various diseases. Therefore, the gut microbiome could be a diagnostic marker for certain diseases, and re-balancing dysbiosis through transplantation of the healthy gut microbiome could constitute an effective therapeutic strategy. Here, we discuss the relationship between dysbiosis of gut microbiota and the host epigenome, and suggest that the microbiome and epigenome are possible targets for disease diagnostics and therapeutics.

Keywords: Gut microbiota; Dysbiosis; Epigenome; Regulation

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Introduction

Gene expression is regulated by epigenetic modifications such as DNA methylation, histone modifications, and binding of non-coding RNAs [1,2]. Gut microbiota can affect epigenetic processes of the host, consequently causing diseases such as allergy, Inflammatory Bowel Disease (IBD), autoimmune disease, metabolic syndrome, colorectal cancer, stress-related disorders, and neurodevelopmental disorders [3-9]. This possibly results from dysbiosis, a negative alteration of the gut microbiota, as well as changes in microbial metabolites, which are triggered by environmental factors such as diet, age, toxic chemicals, and pharmacological factors [10,11]. In fact, a pilot study reported a significant relationship between the predominant bacterial phyla and methylation patterns of the host in the human gut [12]. In addition, studies showed a strong influence of microbial metabolites such as Short-Chain Fatty Acids (SCFAs), in regulation of epigenetic programming in various tissues, including proximal colon, liver, and White Adipose Tissue (WAT) [13].

Few years ago, epigenome analysis, including analysis of DNA methylation and histone modifications, involved the use of global or locus-specific methods such as High-Performance Capillary Electrophoresis (HPLC), Mass Spectrometry (MS), and western blot (11). However, recent developments in genome-wide high throughput methods such as Whole-Genome Bisulfite Sequencing (WGBS), reduced representation bisulfite sequencing (RRBS), methylated DNA immunoprecipitation sequencing (MeDIP-seq) for DNA methylation analysis, and Chromatin Immunoprecipitation (ChIP)-seq for histone modifications [11,14] has revolutionized epigenetic research. These methods have enabled determination of the relationship between the epigenome and the gut microbiome. Here, we will review the role of intestinal microorganisms in epigenetic regulation in terms of dysbiosis, the causative association of the gut microbiome with epigenetic modification of the host in diseases, and their potential for use in diagnostic and therapeutic strategies.

Dysbiosis and Diseases

Dysbiosis of gut microbiota

The diversity of the human gut microbiota has been extensively studied by high throughput analysis, revealing that the gut

microbiota varies between individuals but mainly consists of members of the Bacteroidetes and *Firmicutes phyla* [15,16]. Approximately one thousand different microorganisms co-inhabit the gut and they have crucial roles in maintaining homeostasis and health of the gastrointestinal tract [17,18]. Metchnikoff first coined the term "dysbiosis" [19] and the definition was extended to include a state in which changes in the diversity and abundance of gut microbiota, their metabolic activities, and local distribution produced harmful effects [20]. Actually, dysbiosis indicates an increase in the population of gut bacteria with pathogenic traits, which occasionally causes diseases [21,22]. For instance, an increase in the number of *Fusobacterium*, the pathogenic bacterium which was first detected in colon cancer, has been frequently observed in IBD [23]. Dysbiosis can be induced by various environmental factors such as diet, stress, and exposure to antibiotics, stress, toxins, drugs, and pathogens [22,24-26]. Accumulated evidence regarding clinical implications of dysbiosis via direct or indirect influences on related diseases, including immune disease and others, are reviewed below.

Dysbiosis and diseases

Dysbiosis is closely related to systemic immune diseases including IBD, multiple sclerosis (MS) and autoimmune diseases [27-31]. Certain reports show that the change of symbiosis to dysbiosis in the intestinal tract is related to the development of systemic immune diseases through multiple routes such as changes in gut permeability and secretion of microbial enzymes [31,32]. The decrease in SCFAs during dysbiosis has significant implications in the regulation of the immune system, including intestinal barrier malfunction and reduction in anti-inflammatory effects [33,34]. In dysbiosis, the accumulated pathogenic bacteria increases intestinal barrier permeability and pathogens can be readily transferred to the host, causing diseases such as IBD [35,36]. In addition, protein-glutamine γ-glutamyltransferases (transglutaminases, Tgs) secreted by the gut microbiota under dysbiotic condition leads to altered posttranslational modification of the gut lumen, activating cascades of immune response that initiates pathological autoimmune processes [31].

In addition, some researchers have also examined the effects of dysbiosis on various other diseases. Jiang et al. recently reported that the dysbiosis of gut microbiota increased the permeability of the gut and the blood-brain barrier and mediated or activated pathogenesis of Alzheimer's disease [37]. Tang et al. reviewed the possible molecular pathways that connect gut microbiota to cardiovascular or cardio metabolic diseases, such as the trimethylamine/trimethylamine N-oxide pathway, SCFA pathway, and the primary and secondary bile acids pathways [38]. Other studies showed that dysbiosis was related to obstructive sleep apnea-induced hypertension [39] and metabolic diseases such as obesity and impaired liver function [40,41].

Dysbiosis and Epigenetic Regulation

Direct relation between gut microbiota and epigenetic regulation

A study has demonstrated that gut microbiota can affect epigenetic regulation in immune homeostasis by direct interaction with invariant natural killer cells (iNKTs) [42]. iNKT cells play important roles in ulcerative colitis (UC), IBD, and asthma by recognizing lipid antigens presented by CD1d molecules and secreting proinflammatory cytokines such as interleukin-4 (IL-4) and IL-13 [43,44]. Olszak et al. reported that microbial exposure to iNKT cells in germ-free mice decreased DNA methylation of the gene encoding the C-X-C motif chemokine ligand 16 (*Cxcl16*) and reduced its expression [42]. Cxcl16 acts as a chemo-attractant of activated CD8 T cells, NKT cells, and Th1-polarized T cells [45], and therefore, reduced levels of Cxcl16 leads to less accumulation of iNKT and improves barrier function. Therefore, the authors indicated the importance of contact with commensal microbes in early life for protection from immune-mediated disease such as IBD and asthma via restriction of the long-lasting activation of the iNKT pathway.

Indirect relation between gut microbiota and epigenetic regulation through metabolites

Owing to the direct contact of diet-derived nutrients with the gut microbiome, nutritional modification can induce rapid shifts in the gut microbiome and probably cause diseases related to microbial dysbiosis [46]. Alterations in the gut microbiome may induce changes in microbial metabolites, which can be important but indirect regulators of the host epigenome. The intestinal microorganisms produce various low molecular weight bioactive substances including SCFAs, biotin, and other microbial metabolites such as folate and vitamin $B_{2,}$ which exert beneficial effects on physiological and epigenetic regulation [47,48].

B-group vitamins produced by the gut microbiota

Most of the B vitamins such as riboflavin (vitamin B_2), niacin (vitamin B_3), pantothenic acid (vitamin B_5), and biotin (vitamin B_7) are synthesized by the gut microbiota [49]. Mammalian cells cannot synthesize B vitamins and thus, microbial production is partially required to meet the nutritional requirements of the host. In addition, the B vitamins produced by the gut microbiota contribute significantly to epigenomic processes [50]. For example, B vitamins act as cofactors of enzymes involved in epigenetic processes [51]. Nicotinamide adenine dinucleotide (NAD), the active form of niacin, is a cofactor of NAD-dependent histone deacetylases (HDACs), which catalyze the deacetylation of histones [52]. Pantothenate is the main acetyl group donor in the conversion of coenzyme A (Co-A) to acetyl-CoA [53]. Adequate supplies of acetyl-CoA support acetyl-CoA-dependent histone acetylation [54]. Biotinylation of histones [55] affects chromatin instability and thus cell proliferation, gene silencing, and the cellular response to DNA repair [56]. Folate acts as a key methyl group donor during the synthesis of precursors of nucleic acids and DNA methylation [57]. Folate is mainly supplied by the diet; however, it can also be synthesized by the colonic microbiota such as *Bifidobacterium bifidum* and *Bifidobacterium longum* [58,59]. Riboflavin (vitamin B_2) serves as a cofactor of methylenetetrahydrofolate reductase (MTHFR), which is a folate-dependent enzyme involved in one-carbon metabolism, including DNA methylation [60]. Owing to its direct involvement

as a coenzyme in DNA methylation, the role of folate in epigenetic regulation is well-established. However, its role as a microbial metabolite in epigenetic regulation remains unknown [57]. According to Nagy-Szakal et al. supplementing pregnant mice with methyl donors such as folate, betaine, choline, and vitamin B_{12} significantly changed microbiota composition in the offspring [61], indicating the putative role of microbiota-metabolized folate in epigenetic regulation.

SCFAs

The most popular and well-studied microbial metabolites are SCFAs produced from indigestible carbohydrates as substrates of microbial fermentation. Indigestible carbohydrates include dietary fiber, resistant starch, oligosaccharides, and plant cell-wall polysaccharides [62]. The predominant SCFAs are acetate, butyrate, and propionate, which are produced mainly in the cecum and proximal colon in the molar ratio of 3:1:1 [63,64]. Theoretically, it is assumed that 10 g of indigestible carbohydrate fermentation yield around 100 mmol SCFAs [65]. Major groups of SCFA-producing gut microorganisms are listed in a review by Macfarlane et al. [62] SCFAs are absorbed in the cecum and proximal colon, from where they subsequently enter the mesenteric vein and drain into specific tissues; for instance, butyrate uptake is greater in the colonic epithelium, whereas propionate is preferentially utilized by the liver [66,67]. Thereafter, SCFAs contribute significantly to the daily energy requirement of the tissues and exert their physiological and epigenome-regulatory effects in various tissues [62].

Among SCFAs, butyrate and its source bacteria have been paid particular attention due to its multiple benefits, such as being the preferred energy source of colonic epithelial cells [68]. The most important butyrate-producing bacteria are *Faecalibacterium prausnitzii (clostridial cluster IV), Eubacterium rectale, Eubacterium hallii, and Roseburia* species *(clostridial cluster XIVa)* [68,69]. Its epigenetic function as a natural histone deacetylase inhibitor (HDACi) is well-established [70]. HDAC and histone acetyltransferases (HAT) are key enzymes that regulate gene expression by modulation of histone acetylation. Butyrate is a more potent natural HDACi that inhibits HDAC1/2 activity compared to acetate and propionate, which selectively inhibit HDAC2 and HDAC3, respectively [71-73]. This feature is utilized as a therapeutic strategy for treating diseases such as type 2 diabetes [74], cancer, and IBD [75,76].

Dysbiosis and Epigenetic Regulation of Disease

Several studies regarding the putative effect of aberrant gut microbiome in epigenetic modulation of diseases exist. A recent pilot study showed a correlation between the predominant gut microbiota and differential DNA methylation of genes associated with the development of obesity and cardiovascular disease (12). Furthermore, in their pilot birth cohort study, Tachibana et al. investigated whether the maternal gut microbiome influences the fetal risk of developing type 2 diabetes in the future by determining DNA methylation status using a high throughput method, Infinium HumanMethylaion450 BeadChip (Illumina), in 10 pregnant participants [77]. They identified an association between the proportion of Firmicutes in the maternal gut and the differential methylation rates in *UBE2E2* and *KCNQ1* in the umbilical cord samples, both of which are involved in insulin secretion. This study provided a possible connection between gut microbiota and epigenetic processes, particularly the methylation of type 2 diabetes-associated genes; however, further studies with a larger sample sizes are required. Dysbiosis of gut microbiota, characterized by higher numbers of the members of the genus *Bacteroides* and low butyrate production, is presumably induced by diet and can increase intestinal permeability followed by autoimmunity for type 1 diabetes [78]. This connection was explained by the differences in methylation of genes related to the pathogenesis of type 1 diabetes that were reported in their study.

Accumulated evidence demonstrated that SCFAs may act as intermediates in the interaction between the commensal microbiota and epigenetic modification of the host genome, resulting in diseases such as obesity, diabetes, and intestinal diseases such as ulcerative colitis (UC), Crohn's disease (CD), and colon cancer [79-83]. Schwiertz et al. reported differences in gut microbiota between lean and obese subjects and increased fecal SCFAs concentration in overweight individuals [82]. Furthermore, Remely et al. suggested that SCFA-producing bacteria and their products mediate the epigenetic regulation of gene expression [84]. In their study, lower diversity of the microbiota and scarcity of *Faecalibacterium prausnitzii* were observed in patients with obesity and type 2 diabetes compared to those in the lean control. The altered gut microbiota was concurrent with significantly lower methylation on the promoter region of SCFAs receptor *GPR41/FFAR3* in obese subjects.

Under microbial dysbiosis, a reduction or absence of butyrate-producing bacteria is a frequently observed feature in patients with UC and CD [85,86]. Nugent et al.'s metabolomic analysis in rectal biopsies of patients with colorectal adenomas showed a decreased butyrate level possibly due to the altered metabolome caused by microbial dysbiosis [87]. They suggested that these impairments are likely to contribute to the development of adenomas and colorectal cancer.

Diagnostic and Therapeutic Application of the Role of Gut Microbiome on Epigenetic Regulation

Interest in the diagnostic and therapeutic application of the altered microbiome and epigenetic regulation in clinical practice is emerging. Determination of epigenomic modifications could be an effective approach for diagnosing and treating certain diseases [55]. Impaired DNA methylation, a predominant oncological feature, has been considered as a potential therapy target. Particularly, aberrant hypermethylation of specific CpG islands of tumor-suppressor genes, for instance, that of a BRCA1 carrier mutation, has been considered as good biomarkers for detecting the development of breast cancer [88]. Similarly,

assessment of microbial alteration also could be an effective diagnostic marker for certain diseases, including colon cancer and IBD [89-91]. Alterations in microbial community was identified at different states of colorectal carcinogenesis, with enrichment of microorganisms of the genus *Fusobacterium, Parvimonas*, *Gemella,* and *Leptotrichia,* and reduction in the numbers of *Bacteroides*, *Blautia*, *Sutterella*, *Collinsella aerofaciens,* and *Alistipes putredinis* in only the early stage of carcinogenesis. This implies that the identified bacteria could be candidates of a colorectal cancer-associated microbial marker [92]. Additionally, several reports regarding microbial dysbiosis frequently observed in early stage of IBD, suggesting a possible role of the gut microbiome as a diagnostic marker of IBD [93,94]. In addition, Maslowski et al. suggested the possibility of using SCFAs as a therapeutic agent as it can control inflammatory responses in immune disease such as colitis, arthritis, and asthma through the interaction with SCFA receptor, GPR43/FFAR2. Furthermore, Vrieze et al. investigated the effects of transferring gut microbiota from lean donors to patients with metabolic syndrome and found an increase in insulin sensitivity and butyrate-producing microbiota in the feces, suggesting that gut microbiota can be used as therapeutic agents [95]. However, studies on the diagnosis and treatment of diseases using microbiome-epigenome correlation data are still in their infancy. This approach requires further research considering its cost-effectiveness and accuracy in application **(Table 1)**.

Conclusion

The human epigenome can be affected by various environmental factors, particularly those that affect the gut microbiota and their metabolites. The effects of the gut microbiome on host epigenetic regulation with respect to various diseases have been reviewed. Moreover, the link between the gut microbiome and the epigenome can be used as effective targets for the diagnosis and treatment of diseases. The recent developments in high-throughput technologies have broadened our understanding of gut microbiota and epigenomes, and it would serve as a key tool in identifying targets for diagnosis and treatment.

Table 1: Possible diagnosis and therapy using the interaction with gut microbiome and epigenetic.

Disease	Links to gut microbiome	Links to epigenetics	Diagnosis and therapy
Colorectal Cancer (CRC)	Increased abundance of *Fusobacterium nucleatum* and *Providencia* but decreased abundance *Lactobacillus* and butyrate-producing bacteria such as *Roseburia* and *Fecalibacterium* in CRC [96,97].	Butyrate, one of the most abundant SCFAs, is well known as HDACi which have antiangiogenic and antimetastatic effects in cancer [98,99], by epigenetically activating tumor-suppressor genes such as *p21* and *bax* [100] or suppressing carcinogenetic genes including Cox-2 [101].	• Oral administration of *Bifidobacterium* and *Bacteroides* which were suggested as therapeutic probiotics for cancer immunotherapy [102,103]. • Butyrate [104] or the prebiotic sources such as acemannan in Aloe vera gel [105] with their chemopreventive effect.
Diabetes	High ratio of Firmicutes/Bacteroidetes in type 2 diabetes with high abundance of lactic acid bacteria but low of *Faecalibacterium prausnitzii*	Changes in cell wall components such as LPS and peptidoglycan resulting from dysbiosis are involved in the epigenetic regulation of the inflammatory response [106-109].	• Improved diets targeting to recover dysbiosis and epigenetic changes of pro-inflammatory genes in metabolic syndrome [106]. • Transplantation of gut microbiota from lean and healthy donors to patients with metabolic syndrome (95).
Obesity	Decreased production of butyrate by gut microbiota and lower diversity of the microbiota with low abundance of *F. prausnitzii* [84].	Hypomethylation at the promoter regions of SCFAs receptor GPR41/FFAR3 in obese patients.	• GLP-1 agonist who contributed to the moderate increase of *F. prausnitzii* and the reverse of a hypomethylation of the promoter regions of GPR41/FFAR3 in patients with obesity and type 2 diabetes [84].
IBD	Lower abundance of *Streptococcus* and the increased abundance of *Bacteroides*, *Parabacteroides*, and *Roseburia* [107]. Lower abundance of *Akkermansia muciniphila* in UC patients [108].	Hypomethylation at the differentially methylated regions (DMR) of KHDC3L (C6orf221) in UC patients, which were highly correlated with the dysbiosis [107]. Modulation of Fiaf, GPR43, HDACs, and PPARγ expression by *A. muciniphila* and propionate [83,109].	• Identification of colonic mucosal DMRs can provide epigenetical and metagenomical targets for therapeutic measures [107]. • Assessment of the gut microbial dysbiosis at the early stage of CD.

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