



Epigenetic Regulation of Gut Microbial Dysbiosis

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Abstract Microbiota inside the gut plays a vital role in maintaining human health. Microbial dysbiosis is associated with various complications leading to a range of diseases. Epigenetic changes enforced by various environmental and lifestyle factors lead to heritable modifications. These epigenetic modifications include DNA methylation, histone modifications, chromatin remodelling, and ribonucleic acid-based mechanisms. This review summarizes the impacts of environmental factors on the gut microbiome, epigenetic modifications, and their role in cardiovascular diseases.

Keywords Epigenetics · Dysbiosis · Human · Health · Disease · Microbiome · Microorganism

Introduction

Microbes including viruses, archaea, and bacteria live symbiotically on mucosal surfaces, mouth, gut, and skin of human beings. Around 1,000 unique species of microbes have been identified to survive in the human gut. The microbial colonization initiates from birth and maintains throughout the life span [1, 2]. Various studies have demonstrated important roles of microorganisms in diverse fields, such as fermentation [3, 4], biomolecules [5, 6], bioremediation [7–10], anti-toxicity [11, 12], and diseases and health [13–18]. Pathogenesis, including the recent outbreak of coronavirus, can be effectively treated through the application of these bioactive molecules, vaccines, and nanomaterials [11, 14, 19–24]. Microbiota coevolution with mammalian host results in the plethora of vital functions, such as metabolic signaling, energy metabolism, regulation of integrity, mobility of the gut barrier, and formation of the immune system. Gut microbiota plays a significant role in the manifestation of metabolic disorders and infections [1, 12, 25, 26].

International Human Epigenome Consortium and the Human Epigenome Projects have been initiated to understand the overall epigenetic mechanisms involved in human diseases and health. The changes in non-coding RNA were believed to cause obesity, diabetes, and neurodegenerative diseases and those affecting lung and liver [27, 28] (Fig. 1). The epigenetic DNA imprinting is usually the most active during the early 1,000 days period from conception. During this journey, early nutrition plays a major role in regulating developmental programming. This phase of development possibly decides the individual susceptibility to diseases like obesity, diabetes, cardiovascular diseases (CVDs), and other chronic non-communicable conditions that may occur later in life [29]. In this

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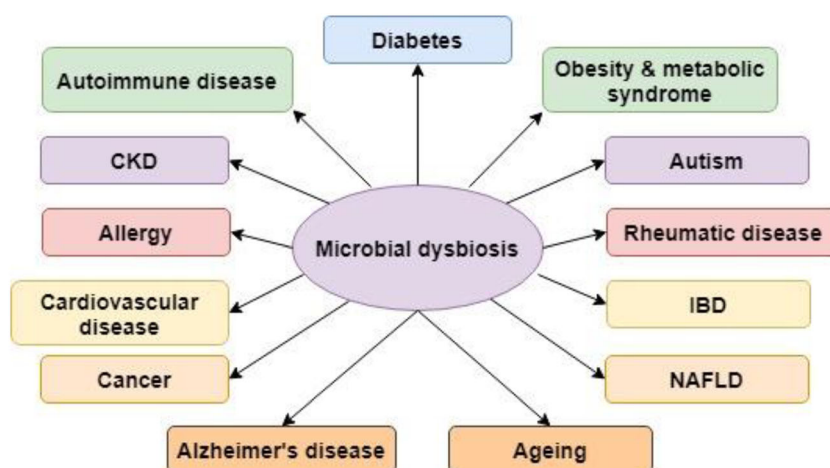
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Fig. 1 Microbial dysbiosis and diseases. CKD-Chronic kidney diseases, IBD-Inflammatory bowel diseases, NAFLD-Non-alcoholic fatty liver diseases



review, we describe the interactive roles of the microbiome and epigenetic regulation on human health.

Gut Microbiome and Health

Glycaemia is controlled through the gut-brain axis. Insulin resistance and hyperglycaemia are associated with disturbed communication between the enteric nervous system, and hypothalamus to the nutritional state [30]. Bacterial strains belonging to *Clostridium*, *Bifidobacterium*, *Lactobacillus*, *Faecalibacterium*, *Roseburia*, and *Escherichia coli* are involved in patients with Diabetes. *Faecalibacterium* and *Roseburia* produce short-chain fatty acids (SCFAs) such as butyrate, which play a significant role in differentiating T_{reg} cells and exhibit anti-inflammatory properties [30, 31]. The altered intestinal flora during Chronic kidney diseases (CKDs) exhibit an abundance of *Proteobacteria*, *Verrucomicrobia*, and *Fusobacteria*, leading to the elevated levels of lipopolysaccharide (LPS) and inflammation associated with the increased levels of C-reactive protein, interleukin-6, and tumor necrosis factor- α in serum [32]. In neurodevelopment disorders (autism which affects one out of 59 children in the USA), many functions get impaired due to microbiome dysbiosis such as maintenance of intestinal epithelial cell's tight junctions, elimination of waste and toxins, absorption of nutrition, food metabolism, production of neurotransmitters, and regulation of the immune system, and prevention of the gut colonization by pathogenic bacteria [33]. Epigenetic dysregulation is an important factor in the autism etiology, representing the effect of drugs, environment, and food on the intestinal microbiome [34]. Alzheimer's disease (neurodegenerative) is mediated by the enhanced permeability of the blood–brain barrier and the gut due to microbiota dysbiosis through signalling pathways and cytokines [35].

Epigenetic is defined as the heritable sequence-independent DNA changes and operates through histone modification (methylation, phosphorylation, and acetylation), DNA methylation, and micro-RNA-based mechanisms [36]. It plays a prominent role in the pathogenesis of CVDs, including cardiomyopathy, cardiac fibrosis, congenital heart disease, atherosclerosis, hypertension, and heart failure. The imbalance of gut microbiota leads to obesity (metabolic diseases) involving the enhanced activity of the endocannabinoid system, increased levels of LPS, and the abundance of carbohydrate fermenting bacteria [37]. Alterations in gut microbiome led to Inflammatory Bowel diseases (IBD, affects 3.5 million people) due to a reduction in SCFA producing obligate anaerobes and a rise in facultative anaerobes (*E. coli*) [38]. The microbiome interactions with the host play an important role in the pathogenesis of non-alcoholic fatty liver diseases (NAFLD) [39].

Epigenetic Alterations and Microbiome

DNA methylation is one of the most ubiquitous and fundamental mechanisms of epigenetics alteration that occurs on CpG island (5'-C-p-G-3') by DNA methyltransferases (DNMTs). DNMTs are highly susceptible to nutrient availability and are influenced by gut microbial metabolism [40]. The silencing of the estrogen receptors (ER α , and ER β) due to DNA methylation, results in atherosclerosis. 5-aza-2-deoxycytidine (demethylating agent) up regulated the expression of COL15A1, ER α , and ER β . Resveratrol up regulated the expression of sirtuins (SIRT1- silent mating type information regulation type 2 homolog 1), and Acetylsalicylic acid targets ABCA1 via gene-specific DNA methylation. Through global DNA methylation, Cocoa down regulates DNMTs and methylenetetrahydrofolate reductase, and folic acid regulates multiple gene

expression. These compounds are associated with the therapy of atherosclerosis and coronary heart disease [41].

Around 28,000 genes have been mapped for long non-coding RNAs (lncRNAs, > 200nucleotides). Like master transcription factors most of the lncRNAs show tissue-specific expression patterns, also controls diverse operations involving metabolism, nuclear organization, embryogenesis and development, differentiation, X-inactivation, proliferation/cell cycle progression, epigenetic and transcriptional regulation [42]. Out of 2000 miRNAs recognized in humans, 150–200 are associated with CVDs. The presence of miRNAs in feces of humans and mice could be considered as an indicator of intestinal malignancies. The bacterial genes usually get influenced by miRNA (an inverse correlation between the concentration of microRNA and microbial density). Microbiota imbalance—miR-181 axis has a key role in the development of insulin resistance and obesity [42].

Ageing related CVDs involve telomere attrition, dysregulated nutrient sensing, stem cell exhaustion, genomic instability, mitochondrial dysfunction, epigenetic alterations, altered intercellular communication, loss of proteostasis, and cellular senescence [43]. Gut microbes metabolize choline and L-carnitine into trimethylamine-*N*-oxide (TMAO) via TMA by liver flavinmonooxygenase 3. The evidence of links between CVD to gut microbiota via TMAO is considered as a novel opportunity for therapeutic intervention for hypertension, heart failure, stroke, CKDs, Alzheimer's, platelet aggregation, obesity, Type-1 and Type-2 diabetes, and atherosclerosis through the uses of TMAO inhibitor [43, 44]. The sirtuins 1 and 6 (SIRT1 and 6) have a strong influence on DNA methylation and play a vital role in chromatin structure modulation through histone deacetylation. SIRT1 enhances endothelium-dependent vasorelaxation through deacetylation of endothelial nitric oxide synthase and plays a beneficial role against cardiovascular ageing by promoting autophagy and by suppressing oxidative stress and inflammation [45]. Senescence-accelerated mouse prone 8 is one of the most suitable models to study non-chronological and natural vascular ageing. Ceramides get accumulated/enhanced during ageing and age-related stress conditions, thus involved in cell cycle arrest/apoptotic signalling. During ageing, chronic cellular damage results in over cargo accumulation or due to diminished autophagic flux making autophagy insufficient causing the interacting signals between gut microbiota, ageing, and sphingolipids [46].

Microbiota Based Health Interventions

Protein sources (casein, soy, cod, beef, chicken, and pork) modulate energy efficiency, and obesity progression by affecting gut microbiota. The terrestrial animal-based proteins have been found to be more obesogenic than those of seafood or vegetables [26, 47]. Human and animal-based studies have suggested that the level of *Lactobacilli* and *Bifidobacterium* can be increased after consuming soy foods and is beneficial for reducing the risk of diseases. Metabolites (betaine, folate, choline, and vitamin B₁₂) are potentially implicated in the synthesis of 6-methyltetrahydrofolate (methyl donor) to generate S-adenosylmethionine, which participates in DNA methylation [47]. The gut metabolites like folate, acetate, and butyrate are responsible for epigenetic modifications through the regulation of various enzyme activities. The SCFA, butyrate is known to be a potent histone deacetylase (HDAC) inhibitor which promotes histone hyper acetylation and enhances the accessibility for gene transcription. Butyrate-based HDAC inhibition triggered its anti-inflammatory property by repressing nuclear factor κB and interferon γ production, and by enhancing peroxisome proliferator-activated receptor γ (PPARγ) expression in colon cancer. PPARγ is protective against cardiac diseases, therefore butyrate and its sub-products like sodium butyrate acts as an anti-inflammatory agent against CVDs. Butyrate has another protective potential which operates by histone H₃ modification which alters G1-specific cell cycle proteins leading to the arrest of the proliferation of smooth muscle cells and induces the production of regulatory T cells in the colon to boost the immune system [47].

Probiotics (living microorganisms), which when given out in sufficient amounts confer health benefits on the host. *Lactobacilli* containing fermented milk products have been reported for the longevity of Bulgarians. The mechanism of probiosis comprises stimulation of epithelial cell proliferation, immunomodulation, manipulation of intestinal microbial communities, differentiation, and fortification of the intestinal barrier, and the suppression of pathogens [48]. Faecal microbiota transplantation carries therapeutic potential against functional gastrointestinal disorders, obesity, metabolic syndromes, and inflammatory bowel disease through the administration of faecal microbiota into the recipient's intestinal tract from a healthy donor. This transplantation changes the microbial composition of the gut of the recipient and makes them healthier [49]. Many drugs are playing the bidirectional communication with the microbiome. Known drugs in case of diabetes that interact with the microbiome include anti-diabetic drugs like metformin, a thiazolidinedione, inulin-type fructans, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor,

andalpha-glucosidase inhibitor. Gut microbiota composition studies suggested that increased frequency of moderate exercise from never to daily enhances diversity among the phylum firmicutes (including *Faecalibacteriumprausnitzii*, and species from the genus *Coproccoccus*, *Lachnospira*, and *Oscillospira*) that promotes a healthier environment in the gut. Regular physical exercise associates strongly with cardiovascular health benefits during ageing through the mechanism of epigenetic modifications [50].

Conclusion

Gut microbiome and host bidirectional communications play an important role in the prevention and treatment of many diseases like diabetes, autism, Alzheimer's, CVDs, CKD, IBD, obesity, fatty liver, and lung diseases. The detailed works on microbes and their metabolic products are expected to modulate the associations of microbes.

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Compliance with Ethical Standards

Conflict of interest The authors declare no conflict of interest.

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