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Integration of microbiome and epigenome to decipher the pathogenesis of autoimmune diseases

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ABSTRACT

The interaction between genetic predisposition and environmental factors are of great significance in the pathogenesis and development of autoimmune diseases (AIDs). The human mucosa is the most frequent site that interacts with the exterior environment, and commensal microbiota at the gut and other human mucosal cavities play a crucial role in the regulation of immune system. Growing evidence has shown that the compositional and functional changes of mucosal microbiota are closely related to AIDs. Gut dysbiosis not only influence the expression level of Toll-like receptors (TLRs) of antigen presenting cells, but also contribute to Th17/Treg imbalance. Epigenetic modifications triggered by environmental factors is an important mechanism that leads to altered gene expression. Researches addressing the role of DNA methylation, histone modification and non-coding RNA in AIDs have been increasing in recent years. Furthermore, studies showed that human microbiota and their metabolites can regulate immune cells and cytokines via epigenomic modifications. For example, short-chain fatty acids (SCFAs) produced by gut microbiota promote the differentiation of naïve T cell into Treg by suppressing histone deacetylases (HDACs). Therefore, we propose that dysbiosis and resulting metabolites may cause aberrant immune responses via epigenetic modifications, and lead to AIDs.

With the development of high-throughput sequencing, metagenome analysis has been applied to investigate the dysbiosis in AIDs patients. We have tested the fecal, dental and salivary samples from treatment-naïve rheumatoid arthritis (RA) individuals by metagenomic shotgun sequencing and a metagenome-wide association study. Dysbiosis was detected in the gut and oral microbiomes of RA patients, but it was partially restored after treatment. We also found functional changes of microbiota and molecular mimicry of human antigens in RA individuals.

By integrating the analysis of multi-omics of microbiome and epigenome, we could explore the interaction between human immune system and microbiota, and thereby unmasking specific and more sensitive biomarkers as well as potential therapeutic targets. Future studies aiming at the crosstalk between human dysbiosis and epigenetic modifications and their influences on AIDs will facilitate our understanding and better managing of these debilitating AIDs.

Contents

Abbreviation: AIDs, autoimmune diseases.

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1. Introduction

Autoimmune diseases (AIDs) such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), are characterized by breaking of immune tolerance which leads to the accumulation of autoreactive lymphocytes and excessive production of autoantibodies. The pathogenesis of AIDs is still not clear, though a few studies have revealed some related genetic susceptibility loci. According to epidemiological studies, the concordance rate of monozygotic twins with SLE or RA is 10%–40% [1], which suggests the involvement of non-genetic factors such as environmental triggers are also important in the pathogenesis and development of AIDs.

There is a latent phase in RA patients with only serum elevation of RA-related autoantibodies but without clinically evident synovitis, which indicates that RA may originate from an extra-articular location, for example, a mucosal site [2,3]. Mucosal surfaces of human closely interact with the exterior environment, and commensal microbiota at the gut and other human mucosal cavities play a crucial role in the development and regulation of immune system [3]. Microbiome is the collective of microbial genomes that reside in an environmental niche. The gene number of human microbiome, especially gut microbiome, is much bigger than the human genome [4,5]. With the development of high throughput sequencing (HTS) and the establishment of metagenomics, metagenome-wide association study (MGWAS) has been widely used in studies of human diseases. Recent works indicates that human microbiome are closely related to many diseases, including AIDs such as SLE [6–8], RA [9–13], inflammatory bowel disease (IBD) [14], type 1 diabetes mellitus (T1D) [15]. Epigenetics are stable heritable traits regulating gene expression which cannot be explained by changes in DNA sequences. Epigenetic modifications are implicated in the pathogenesis of many complicated diseases, including AIDs [16–18]. Furthermore, as an environment cue inside human body, human microbiome is also possible to influence gene expression by epigenetic modifications, which turns out to be a way of crosstalk between microbiome and host cells.

Techniques of microbiome and epigenome have already been applied in AIDs research, but studies combining them together in exploring AIDs pathogenesis have not really started yet. Epigenetic modifications could lead to transcriptional respond of human genes to environmental cues. Therefore, human microbiome, as an important environmental factor closely related to human body, may play a crucial role in AIDs induction and aggravation via epigenetic modifications (Fig. 1). In this review, we will focus on the crosstalk between human microbiome and immune system, the microbiome changes in AIDs and their possible pathogenic immunological mechanisms. Further, the possible mechanism of how human microbiome mediate the pathogenesis of AIDs through epigenetic machinery will be discussed.

2. Human microbiome and immune system

The gut of fetus is almost sterile. Colonization of microbes in human gut starts at birth from maternal microbiota of genital tract, colon and the overall environment [19]. Important determinants of the gut microbiotic composition for infants include delivery mode, feeding type, gestational age, infant hospitalization stay, and antibiotic use [20]. The population and species of gut microbiota are small in neonates, but they will be well established in the next 2 years and remains relatively constant throughout life [21]. Although the gut microbiome can alter along with environmental triggers such as diet changes, the gut microbiome changes resulted from transient antibiotic use showed a considerable indigenous recovery potential, and were genetically regulated [22]. Local mucosal cells, related microbiota and their metabolites should be treated as a whole. The metabolic enzymes produced by gut microbiota are crucial in human metabolites digestion and utilization [23]. Gut microbiota help further digest exogenous undigested food by anaerobic glycolysis in colon, and degrade endogenous chemical compounds secreted by host cells and microbial cells. Intestinal epithelial cells (IECs) are the main channels for the crosstalk between host cells and microbiome, as well as the impact of microbiome on host immune function.

Studies using germ-free (GF) mice and specific pathogen-free (SPF) mice unmasked the influence of commensal bacteria on the structure and function of immune system. Compared with SPF mice, GF mice have smaller independent lymphoid follicles [24] and Peyer's patches [25], and decreased intestinal secretory IgA and plasma cells [26], while the invariant natural killer T cells (iNKT) were significantly increased at the gut and lung of GF mice [27]. Besides, in GF mice, the helper T cells 17 (Th17) of intestinal lamina propria and the regulatory T cells (Treg) of colon lamina propria were both downregulated to a lower level [28,29]. Normal gut microbiota can promote the differentiation of regulatory B cells(Breg) in spleen as well as mesenteric lymph nodes by IL-1β and IL-6 production, while Breg restrained excessive inflammation via IL-10 secretion [30]. Not only can gut microbiome regulates local mucosal immunity, it also influences systemic immunity and the formation of peripheral lymphoid organs. For example, the serum IgA level decreased in GF mice [31]. In another study, commensal fungi drove migration of $CD103^{+}RALDH^{+}$ dendritic cells (DC) to the peripheral lymph nodes after birth in mice. By producing large amount of retinoic acid, these cells directed the homing of lymphocytes to both gut-associated lymphoid tissues (GALT) and peripheral lymph nodes. Moreover, some of these DCs