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Intestinal microbiome as a novel therapeutic target for local and systemic inflammation

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ABSTRACT

Recently, the pathogenesis of systemic inflammatory disease such as inflammatory bowel disease (IBD), multiple sclerosis (MS), systemic inflammatory arthritis, asthma, and non-alcoholic fatty liver disease has been reported to be related to the dysbiosis of gut microbiota. The contribution of special bacteria for the development of those diseases has been elucidated by disease animal models such as germ-free mice. Besides, the contribution by several bacteria for the pathogenesis of those diseases has been suggested by detailed analysis of the 16 small ribosomal subunit RNA (16S rRNA) from stool samples of the patients. Gut microbiota-targeted treatment for systemic inflammatory diseases such as fecal microbiota transplant (FMT), and probiotics has been now reported. Though there are several issues to be understood, these treatments have been highlighted as an innovative approach to intractable systemic inflammatory disease. In the present review, recent reports regarding the relation between gut microbiota and systemic inflammatory diseases are discussed with treatments to target gut microbiota.

Contents

1. Introduction

The gut microbiota has a strong relationship with its host and aids in maintaining health and protecting against diseases. In the human body, the intestinal tract is the largest reservoir of the microbiota (Sender, Fuchs, & Milo, 2016). More than 1000 bacterial species are found in the intestinal microbiota whose composition remains relatively stable in each individual but greatly diverse between individuals (Kamada & Nunez, 2014). The composition and diversity of gut microbiota can alter with several devastating conditions such as age, sex, stool consistency, use of antibiotics, infection, pregnancy and long-term changes of lifestyles and medication such as proton pump inhibitors (Naito, Kashiwagi, Takagi, Andoh, & Inoue, 2018; Rodriguez et al., 2015; Takagi et al., 2019; Takagi et al., 2018b). Metformin, which is one of anti-hyperglycemic drug to diabetes, has been also reported to alter gut microbiota community. Especially, the decrease of *Bacteroides fragilis* with increase of bile acid glycoursodeoxycholic acid has been reported to induce the inhibition of intestinal famesoid X receptor (FXR) leading to improve metabolic disease (Sun et al., 2018). Recently, it has been reported that maternal gestational weight gain is one of the important factor to predict infant metabolic maturation of gut microbiomes (Baumann-Dudenhoeffer, D'Souza, Tarr, Warner, & Dantas, 2018).

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The composition of gut microbiota in infants of obese mothers has been also reported to relate with childhood obesity and non-alcoholic fatty liver disease (NAFLD) (Soderborg et al., 2018).

With the establishment of high throughput DNA sequencing, gut microbiota is now identified on the basis of the 16 small ribosomal subunit RNA (16S rRNA), a gene that is distinctive of prokaryotic cells. Though the 16S rRNA subunit has highly conserved regions common to most bacteria and 16S sequencing technology can be used to identify a particular microbial community, it has a limitation in defining bacterial species and differentiating with commensal and pathogenic strains (Poretsky, Rodriguez, Luo, Tsementzi, & Konstantinidis, 2014). Accordingly, whole genome shotgun sequencing is now used to identify the functional and enzymatic capabilities of gut microbiota (Tyson et al., 2004). Not only the direct effect of microbiota, but also the microbial metabolites has been reported to relate with the pathogenesis of various disease. Recently, imidazole propionate produced by gut microbiota has been reported to contribute to the pathogenesis of type 2 diabetes impairing cellular insulin signaling (Koh et al., 2018).

This review summarizes the recent understanding of the relation between gut microbiota and chronic inflammatory disease which has been reported to be associated with gut microbiota. We also propose the potential of microbiota-targeted treatment against these diseases.

2. Intestinal microbiota-related systemic inflammatory diseases

2.1. Inflammatory bowel disease

Two common forms of IBD consist of ulcerative colitis (UC) and Crohn's disease (CD), which are multifactorial, idiopathic, persistent and recurring gastrointestinal inflammations (Lennard-Jones, 1989). The inflammatory lesion of CD occurs anywhere along the whole gastrointestinal tract, whereas the disease location of UC is restricted to the large intestine. Both diseases are associated with relapsing diarrhea, fever, and abdominal pain; affecting patients' quality of life. Though the detailed pathogenesis of IBD are still unknown, from decades ago, the pathogenesis involving host factors combined with environmental factors of IBD has been reported (Franceschi et al., 1987; Gent, Hellier, Grace, Swarbrick, & Coggon, 1994; Hugot et al., 2001). Experimental colitis is significantly attenuated or absent in germ-free animals and those treated with antibiotics (Gkouskou, Deligianni, Tsatsanis, & Eliopoulos, 2014; Hudcovic, Stepankova, Cebra, & Tlaskalova-Hogenova, 2001; Sellon et al., 1998). Besides, germ-free animals have not developed an intestinal immune system compared to conventionally raised animals, showing smaller and fewer Peyer's patches, mesenteric lymph nodes, and isolated lymphoid follicles (Round & Mazmanian, 2009; Turnbaugh et al., 2007). The certain helper T cell subtypes in the intestinal tract are also missed in germ-free mice (Ivanov et al., 2009). Certain pathobionts can induce experimental colitis in genetically IBD-prone animals. The occurrence of colitis in IL-10- or IL-12-deficient mice promoted by *E.coli*, or *Enterococcus faecalis* was reversed by the colonization of *Bacteroides vulgatus* (Mazmanian, Liu, Tzianabos, & Kasper, 2005; Qiu, Zhang, Yang, Hong, & Yu, 2013; Sokol et al., 2008). In addition, spontaneous development of colitis in *T-bet*−/−, *Rag2*−/− mice were correlated with Enterobacteriaceae species, such as *Klebsiella pneumoniae* and *Proteus mirabilis* because of their abilities to induce TNFα in innate immune cells (Garrett et al., 2010). These data strongly suggest a crosstalk between gut microbiota and host factors for development of IBD.

Several metagenomic analyses revealed a reduced diversity of fecal microbiota in patients with UC and CD compared to that in healthy controls (Manichanh et al., 2006; Nishikawa, Kudo, Sakata, Benno, & Sugiyama, 2009). The transplantation of gut microbiota isolated from IBD patients to germ-free mice demonstrated the elevation of pro-inflammatory cytokines in mice colonic mucosa. Besides, severe colitis occurred in colitis-prone genetically-predisposed germ-free mice with transplantation of IBD-associated microbiota compared to those colonized by healthy human microbiota (Nagao-Kitamoto et al., 2016). These results indicate that gut dysbiosis is related to the disease onset and progression of IBD. In general, the patients with CD or UC have reduced members of the phyla Bacteroidetes and Firmicutes, whereas species that belong to the phyla Actinobacteria and Proteobacteria are increased in mucosa-associated microbiota (Frank et al., 2007; Mondot et al., 2011; Qin et al., 2010; Willing et al., 2010). The reduction of Firmicutes such as *Faecalibacterium prausnitzii* and *Roseburia hominis* has been reported as an example of dysbiotic features (Machiels et al., 2014; Sokol et al., 2008; Willing et al., 2010). *F. prausnitzii* and *R. hominis* demonstrate an anti-inflammatory by reducing pro-inflammatory cytokines (IL-12, IFN-γ) and increasing anti-inflammatory cytokines (IL-10) (Sokol et al., 2008). In addition to the anti-inflammatory effect, *F. prausnitzii* and *R. hominis* produce butyrate, which is a primary energy substrate, and induce a cellular protective effect (Morgan et al., 2012). *F. prausnitzii* and *R. hominis* are also known to induce the differentiation of Treg via GPR43 receptor (Abdollahi-Roodsaz, Abramson, & Scher, 2016; Machiels et al., 2014), and inversely correlate with disease activity of UC (Machiels et al., 2014). *Phascolarctobacterium*, a member of Firmicutes, produces propionate in the presence of *Paraprevotella* and also induces Treg (Watanabe, Nagai, & Morotomi, 2012). Furthermore, reduction of *F. prausnitzii* has been related to postoperative recurrence of Crohn's disease, and its administration in mouse models reduces gut inflammation (Sokol et al., 2008). The elevation of virulent microbes such as *Enterobacteriaceae* species and *Bacteroides fragilis* producing high endotoxic LPS has demonstrated gut inflammation and colitis in mice. This mechanism is speculated to suppress regulatory T-lymphocytes and activation of effector helper-T cells through host TLR5 signaling pathway (Gronbach et al., 2014).

Recent therapeutic approaches for IBD target the aberrant pro-inflammatory immune response in the intestinal mucosa because of an upregulated host inflammatory response. The therapeutic target of IBD is several proinflammatory cytokines such as TNF-alpha, IL-12, and IL-23 and α4β7-integrin, which traffic T-lymphocytes to gut tissue (Christensen et al., 2015; Feagan et al., 2013). However, a large population of IBD patients tends to recur despite intensive treatment using those agents (Croft et al., 2013). Administration of genetically modified probiotics such as *Lactococcus lactis* to CD patients leads to remission via increasing mucosal IL-10 expression which induces anti-inflammatory effects (Braat et al., 2006). Besides, the treatment of prebiotics to stimulate the growth of beneficial gut microbes such as butyrate-synthesizing bacteria is expected to be a concept to treat IBD (De Preter et al., 2013; Joossens et al., 2012). Prebiotic OF-IN administration induced a significant reduction in mucolytic *Ruminococcus gnavus* and significant increase of beneficial *Bifidobacterium longum*, which was strongly correlated with the clinical improvement in CD (Joossens et al., 2012). This effect is demonstrated through the anti-oxidant and anti-inflammatory effects of *B. longum* which reduce intestinal tissue injury. With these novel approaches in treating or managing IBD, it may be possible to resolve the individual variation in therapeutic response by previous treatments and promote a challenge to curative treatment of IBD.

2.2. Multiple sclerosis

The intestinal microbiota is involved in many functions of the central nervous system (CNS) such as regulating the permeability of the blood-brain barrier, reducing astrocyte pathogenesis, activating microglia, and expressing genes for myelination (Mirza & Mao-Draayer, 2017). Multiple sclerosis (MS) is a chronic autoimmune inflammatory, and neurodegenerative disorder of the central nervous system causing progressive irreversible neurologic disability (Brownlee, Hardy, Fazekas, & Miller, 2017). Though it is not clear whether bacterial pathogens act as initiators of MS, various metabolic by-products produced by intestinal microbiota can affect the CNS, thereby suppressing autoimmunity which is

involved in the pathogenesis of MS. Diets which can influence the composition of commensal intestinal microbiota impact the severity of MS in both relapsing-remitting MS and primary progressive MS (Riccio & Rossano, 2015).

The analysis of animal models of MS such as experimental autoimmune encephalomyelitis (EAE) models suggests the importance of intestinal microbiota in the occurrence of MS. The EAE model is induced with the injection of myelin proteins with bacterial adjuvants showing self-antigen and promoting Th1 and Th17 responses. This response results in neuron demyelination (Mirza & Mao-Draayer, 2017). The development of spontaneous and inducible EAE attributed to impaired generation of Th17 cells fails in germ-free mice (Berer et al., 2011; Lee, Menezes, Umesaki, & Mazmanian, 2011). Besides, antibiotic treatments inducing Treg cells and IL-10-producing B cells suppressed the clinical severity in EAE models (Ochoa-Reparaz et al., 2010). Segmented filamentous bacteria (SFB) is known to induce Th17 population in the intestine, and mono-colonization of SFB can induce EAE in germ-free mice. However, the colonization of *Bacteroides fragilis* to germ-free mice showed resistance to EAE via the induction of Treg cells (Lee et al., 2011; Ochoa-Reparaz, Mielcarz, Haque-Begum, & Kasper, 2010). These results indicate the potential roles of certain gut microbiota in the pathogenesis of MS via their ability to modulate immune responses.

Recently, based on the development of metagenomics, the clinical correlation between MS and gut microbiota has been investigated. These reports demonstrate the significant alteration of microbial profiles, not of bacterial richness and diversity, in the intestine of MS patients compared to that in healthy controls. It has been reported that a decrease in *Fecalibacterium* (Cantarel et al., 2015), *Prevotella*, and *Anaerostipes* (Miyake et al., 2015) is observed in MS patients. Butyrate produced by *Fecalibacterium* is associated with anti-inflammatory effects via the increase of Treg cells. Miyake et al. also demonstrated a decrease in several *Bacteroides* such as *Bacteroides stercoris*, *Bacteroides coprocola*, and *Bacteroides coprophilus* in the intestinal microflora in patients with MS (Miyake et al., 2015). Recently, *Parabacteroides* and *Prevotella* (under Phylum Bacteroidetes), and *Adlercreutzia* (under Phylum Actinobacteria) were reduced in the feces from patients with relapsing-remitting MS, whereas the *Pseudomonas*, *Mycoplana*, *Haemophilus* (under Phylum Proteobacteria) were more abundant in MS patients compared to that in healthy controls (Chen et al., 2016). The relapse in MS is associated with intestinal colonization of *Clostridium perfringens* type B. It is suggested that the toxins produced by *Clostridium perfringens* type B lead to microvascular complications and damages of oligodendrocytes (Dorca-Arevalo et al., 2008; Finnie, Blumbergs, & Manavis, 1999; Lonchamp et al., 2010; Mete et al., 2013). Based on these results, a decrease in Bacteroidetes and Firmicutes phyla which have been suggested to indicate that intestinal dysbiosis correlates with the development of MS.

2.3. Systemic inflammatory arthritis (Rheumatoid arthritis)

Rheumatoid arthritis (RA) is a chronic autoimmune disorder with inflammation in large and small joints causing to joint deformity (McInnes & Schett, 2011). Genetic factors are suggested to be associated with the pathogenesis of RA because of relatively higher concordance of 12-15% in monozygotic twins than 2-4% of dizygotic twins (Silman et al., 1993). However, environmental factors are thought to contribute the pathogenesis of RA with low concordance even in monozygotic twins. Several studies have suggested the involvement of intestinal microbial factors in the pathogenesis and development of RA.

There are several spontaneous animal arthritis models such as SKG, K/BxN and IL-1 receptor antagonist knockout mice and HLA-B27 transgenic rats, and these animals fail to induce arthritis under germ-free conditions (Abdollahi-Roodsaz et al., 2008; Rehaume et al., 2014; Taurog et al., 1994; Wu et al., 2010). Recently, DBA1 mice in which arthritis was induced with high-quality collagen were used to analyze the relation between intestinal microbiota and development of arthritis. The DBA1 mice were maintained in germ-free conditions and were subsequently colonized with microbiota from collagen induced arthritis (CIA). However, susceptible mice developed more severe inflammatory arthritis than the mice colonized with microbiota from CIA resistant mice (Liu et al., 2016). These results indicate that microbiota may modulate the sensitivity of arthritis models via the modulation of the immune response.

In patients with RA, *Lactobacillus salivarius* (Zhang et al., 2015) and *Prevotella copri* (Scher et al., 2013) are increased in their intestinal and oral cavity compared to healthy controls, which correlates with clinical severity. Several studies have also supported these results which showed the early development of RA with *Prevotella copri* (Maeda et al., 2016; Scher et al., 2013), and early RA patients with *Lactobacillus* species (Liu, Zou, Zeng, Fang, & Wei, 2013). In addition to reduced populations of the microbiota, reduced intestinal microbial diversity compared with healthy controls was also demonstrated (Chen et al., 2016). Though the increase of pathogenic microbes such as *Eggerthella* and *Collinsella* and decrease of beneficial bacteria such as *Faecalibacterium* are pathognomonic (Chen, Chia, et al., 2016), treatment with disease modifying anti-rheumatic drugs (DMARDs) can reverse the intestinal microbial disproportion in RA patients close to that of healthy controls (Zhang et al., 2015).

2.4. Systemic inflammatory arthritis (Spondyloarthritis)

Spondyloarthritis is a group of inflammatory conditions with features of axial skeleton arthritis, enthesitis, uveitis, colitis, dermatologic involvement, and association with HLA-B27 allele. The mice model of spondyloarthritis is ankylosing enthesopathy (ANKENT) mice which spontaneously develop progressive ankylosis and enthesitis resembling human spondyloarthritis (Weinreich et al., 1995). Under germ-free conditions, these mice fail to induce enthesitis and ankylosis (Rehakova et al., 2000) However, following subsequent colonization with commensal intestinal bacteria, these mice develop enthesitis and ankylosis (Sinkorova, Capkova, Niederlova, Stepankova, & Sinkora, 2008). HLA-B27 transgenic rats do not develop spondyloarthritis when they are grown under germ-free conditions, but develop peripheral arthritis and intestinal inflammation when colonized with commensal intestinal bacteria (Taurog et al., 1994). Intestinal dysbiosis is observed in these transgenic animals showing higher abundance of *Paraprevotella* and lower abundance of *Rikenellaceae* (Lin et al., 2014).

Patients with spondyloarthritis have characteristic gut microbial features compared to healthy controls demonstrating a higher abundance of *Lachnospiraceae*, *Ruminococcaceae*, *Rikenellaceae*, *Porphyromonadaceae*, and *Bacteroidaceae*, and lower abundance of *Veillonellaceae* and *Prevotellaceae* (Costello et al., 2015).

2.5. Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a heterogeneous chronic inflammatory disease characterized by persistent inflammation affecting multiple organs of the body. The production of autoantibodies leading to the formation of antigen-antibody immune complexes is driven in this disease. New Zealand black (NZB) mouse is one of the disease models of SLE. Under germ-free conditions, this mouse had lower rates and reduced severity of renal disease (Unni, Holley, McDuffie, & Titus, 1975). MRL/lpr mice, which are lupus-prone, showed an increase of *Lachnospiraceae*, *Ruminococcaceae*, and *Rikenellaceae*, with the reduction of *Lactobacillaceae* compared with control mice. The clinical phenotype was improved with the correlation of the abundance of *Lactobacillaceae* which is decreased with retinoic acid exposure (Zhang, Liao, Sparks, & Luo, 2014).

Human studies of intestinal microbiota of SLE patients in Spanish and Chinese cohorts were conducted and it is demonstrated that Firmicutes/Bacteroidetes ratio was decreased compared to healthy

controls (He, Shao, Li, Xie, & Wen, 2016; Hevia et al., 2014). Recently, the analysis of gut microbiota of NZB/W F1 mice, which is a model mouse of SLE, was demonstrated (Luo et al., 2018). The composition of gut microbiota showed a significant difference before and after the onset of lupus disease in NZB/W F1 mice. As the disease progressed, greater diversity and increased representation of several bacterial genera such as *Clostridium*, *Dehalobacterium*, *Lactobacillus*, and *Oscillospia* were observed. In this report, though Firmicutes/Bacteroidetes ratio did not differ between SLE patients and healthy controls, the genera of *Odoribacter* and *Blautia* decreased in SLE patients.

2.6. Asthma

Asthma is an inflammatory disorder related to Th2-derived inflammatory responses by inhaling allergens and resulting hyperresponsiveness of airway and bronchial obstruction. Microbial stimulation in early childhood, such as multiple siblings, contacting farm animals, and pets prevents the onset of asthma (Guaraldi & Salvatori, 2012; Ownby, Johnson, & Peterson, 2002; Riedler et al., 2001; Strachan, 1989). Exposure of conventional microbiota to germ-free mice which are sensitized and challenged with ovalbumin (OVA) suffer from a higher allergic airway inflammation compared to SPF mice. However, this inflammation can be reversed by colonization with conventional microbiota in neonatal germ-free mice; but not in adult germ-free mice (Olszak et al., 2012). Not only the exposure to microbes in early life, but also the microbial composition has been reported to be important factor to prevent the development of asthma.

Distinct patterns of intestinal microbiota which can predict the development of asthma has been reported. The intestinal microbiota of the infants with allergic inflammation consists of the increase of *Clostridia* and *Enterococci* and decrease of *Lactobacilli*, and *Bifidobacteria* compared to healthy controls (Bjorksten, Sepp, Julge, Voor, & Mikelsaar, 2001; Kalliomaki et al., 2001; Penders et al., 2007). *Staphylococcus* and *Streptococcus*, which are similar to maternal skin microbiota, are enriched in the intestinal microbiota of babies born via Cesarian section. This composition of intestinal microbiota shows significantly higher risks for allergic disease (Renz-Polster et al., 2005). The use of antibiotics during pregnancy has also been reported to affect the intestinal and pulmonary microbiota of infants leading to an increase the incidence of asthma and other allergic diseases (Russell et al., 2012; Stensballe, Simonsen, Jensen, Bonnelykke, & Bisgaard, 2013). Recently, the difference of intestinal microbiota at the phylum level, particular *Bacteroidetes* and *Firmicutes*, has been demonstrated to differentiate adult asthma patients and healthy controls (Begley et al., 2018). A metagenome-wide association study of gut microbiota revealed that the lack of diversity of gut microbiota is shown in asthma patients. In that report, intestinal SCFA metabolism is important in the pathogenesis of asthma and certain bacteria related to SCFA metabolism such as *Faecalibacterium prausnitzii*, *Sutteralla wadsworthensis*, and *Bacteroides stercoris* were significantly decreased in the intestinal microbiota of asthma patients (Wang et al., 2018).

2.7. Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is liver damage ranging from simple steatosis to non-alcoholic steatohepatitis (NASH) with the development of fibrosis and cirrhosis and even hepatocellular carcinoma (Burt, Lackner, & Tiniakos, 2015). Approximately 6-35% of general population suffers from NAFLD with a median incidence of 20% (Bellentani, 2017; Vernon, Baranova, & Younossi, 2011). Decades ago, gut microbiota has been reported to interact with liver, mentioned as "gut-liver axis" (Volta et al., 1987) because of high blood supply from portal vein, which drains blood from mesenteric veins of the intestinal tract. Seventy percent of food supply through the portal vein reaches to the liver where first-pass metabolism for the gastrointestinal luminal contents occurs (Szabo, 2015). Though the pathogenesis of NAFLD includes environmental, genetic, and metabolic factors, changes of intestinal microbiota are also related to its development (Gkolfakis, Dimitriadis, & Triantafyllou, 2015; Le Roy et al., 2013). The increased abundance of *Lactobacillus acidophilus* has been reported to associate with hepatic lipid accumulation and inflammatory cell infiltration in high-fat diet (HFD)-treated mice (Zeng et al., 2013). It has been reported that germ-free mice showed less weight gain than conventional mice with sugar-rich and lipid-rich diet (Backhed et al., 2004; Backhed, Manchester, Semenkovich, & Gordon, 2007), and after microbial colonization of germ-free mice, total body fat and liver triglyceride content were increased (Backhed et al., 2004). Colonized feces from the patients of NASH with high-fat diet significantly increased epididymal fat weight, hepatic steatosis, multifocal necrosis and infiltration of liver with inflammatory cells (Chiu et al., 2017). In the patients of NAFLD, increased levels of *Lactobacillaceae*, *Lachnospiraceae*, and *Veillonellaceae*, but decreased level of *Ruminococcaceae* was shown (Raman et al., 2013).

The physical intestinal barrier is composed of a mucus layer, microbes and a single layer of epithelial cells supported by tight junction proteins. On the other hand, a biochemical barrier is supported and mediated by the molecules of antimicrobial properties such as bile acid and antimicrobial proteins (Dupont, Heinbockel, Brandenburg, & Hornef, 2014). Another intestinal barrier is the immune system, including secretory immunoglobulin A and lymphoid follicles containing a variety of immune cells such as B cells, T cells, dendritic cells, and neutrophils (Mu, Kirby, Reilly, & Luo, 2017). Dysfunction of these intestinal barriers results in the translocation of microbes, metabolites, and other microbial products from intestinal lumen to liver. Patients with alcoholic liver disease or cirrhosis have been reported to increase intestinal permeability contributing to disease progression (Rainer et al., 2018). Although the intestinal barrier of the patients with NAFLD is thought to be compromised, the results of animal models increasing intestinal permeability with fatty liver has not been confirmed in all studies (Bluemel et al., 2018). Besides, only 39.1% of NAFLD patients had demonstrated the increase of intestinal permeability based on a meta-analysis (Luther et al., 2015). One of the mechanisms to reduce intestinal permeability is binding of microbial products to Toll-like receptor (TLR)-4, and this pathway contributed to the development of fatty liver in a rodent model (Seki & Schnabl, 2012). However, the inhibition of TLR-4 with JKB-121 did not improve hepatic fatty content or fibrosis with the patients of NASH in recent clinical trials (Diehl, Harrison, & Caldwell, 2018). Based on these results, intestinal barrier dysfunction with subsequent translocation of microbial products has only partially contributed to the development and progression of fatty liver disease.

Several metabolites in serum have been thought to associate with the severity of fibrosis in NAFLD. Among these metabolites, choline and choline-related metabolites, bile acids, SCFAs, and ethanol are thought to be microbiota-derived metabolites. Decreased level of choline can lead to fatty liver disease through reducing the efflux of very-low-density lipoproteins from hepatocytes (Mehedint & Zeisel, 2013). Trimethylamine (TMA) is a product of choline metabolism by intestinal microbiota (Zeisel, daCosta, Youssef, & Hensey, 1989). Once TMA reaches the liver vial the portal vein, it is oxidized by hepatic flavin-containing monooxygenases to TMAO. Though no direct evidence has associated TMA with the induction of NAFLD, TMAO might contribute to the development of NAFLD. TMAO increases insulin resistance in mice with high fat diet and promotes inflammation in adipose tissue (Gao et al., 2014). A clinical study revealed that the serum levels of TMAO have been significantly higher in patients with NAFLD than in healthy controls, and correlates with the severity of steatosis (Chen et al., 2016). In a preclinical study, it was reported that bile acid can contribute to the development of NAFLD by changing nuclear bile acid receptor farnesoid X receptor (FXR) signaling (Fuchs, Claudel, & Trauner, 2013; Jiao et al., 2018) which regulates glucose and lipid metabolism. Bile acid also binds to G-protein-coupled receptor TGR5, regulating inflammation in liver and glucose homeostasis. Administration of TGF5

or FXR to mice reduced NAFLD by inhibiting lipogenesis, improving hypercholesterolemia, and decreasing hepatic inflammation (Jadhav et al., 2018; McMahan et al., 2013). In the clinical studies, dysregulation of bile acid homeostasis is associated with the occurrence of NAFLD. The concentration of chenodeoxycholic acid (CDCA), deoxycholic acid (DCA), and ursodeoxycholic acid are increased in serum and urine samples of patients with NAFLD compared to healthy controls (Ferslew et al., 2015). The plasma level of glycocholate, taurocholate, glycochenodeoxycholate, taurochenodeoxycholate and ursodeoxycholic acid were increased in patients with NASH compared with patients with NAFLD. Besides, it has been reported that taurolithocholic acid, glycocholate and taurocholate are correlated with the severity of portal inflammation, steatosis and hepatocyte ballooning (Puri et al., 2017). Taken together, alteration of bile acid metabolism affects the development of NAFL and NASH through FXR and TGR5 signaling. The major SCFAs in the intestines include acetate, propionate and butyrate which are generated by gut microbe fermentation of non-digestible carbohydrates. G-protein-coupled receptors (GPRs) such as GPR41 and GPR43 are activated by SCFAs. It has been reported that the activation of GPR43 in adipocytes inhibits lipolysis and decreases plasma fatty acid (Ge et al., 2008). Apart from the binding to GPRs, butyrate directly modulates the development of NAFLD and NASH by activating AMP-activated protein kinase (AMPK) which stimulates glucose and lipid metabolism (Long & Zierath, 2006). However, increased level of acetate in the liver can cause triglyceride accumulation (Alves-Bezerra & Cohen, 2017) and increased level of propionate promotes gluconeogenesis (Weidemann, Hems, Williams, Spray, & Krebs, 1970). Triglyceride accumulation and gluconeogenesis have each been associated with the development of NAFLD. Clinical studies demonstrate that the concentration of formate and acetate are higher in fecal samples from adult patients with severe fibrosis, whereas the concentration of butyrate and propionate are higher in fecal samples from mild to moderate NAFLD (Loomba et al., 2017). However, the amount of SCFA such as formate, acetate, and valerate were lower in the samples from children with MAFLD (Michail et al., 2015). SCFAs therefore promotes and prevents the development of NAFLD and NASH. These contrasting results could be explained by differences in patients' age, diet, environmental factors or experimental differences. In summary, the role of SCFAs in the pathogenesis of NAFLD or NASH requires further investigation. Large-scale clinical studies are necessary to reveal whether systemic and fecal levels of SCFAs are related to the pathogenesis of NAFLD.

3. Microbiota-target treatment

3.1. Fecal microbiota transplant (FMT)

FMT is the transfer of intestinal microbiota from a healthy donor to a patient and has been proposed as a potential treatment for *Clostridium difficile* infection (CDI) (van Nood et al., 2013). FMT can be administered by filtered fecal material or pills containing frozen biosamples (Kelly et al., 2016; Weingarden, Hamilton, Sadowsky, & Khoruts, 2013; Youngster et al., 2014). Though some conditions such as metabolic syndrome are successful targets of FMT, the efficacy to IBD has shown contrasting results. A non-randomized study of colonoscopic FMT in 6 patients with chronic active UC who were resistant for multiple treatment showed the change of microbial composition in the intestines, but these patients did not achieve clinical remission (Kump et al., 2013). In the RCT with 50 UC patients who were mild to moderate in clinical stage, demonstrated that naso-duodenal FMT from a healthy donor led to 30% of achievement of clinical remission compared to 20% of controlled (autologous FMT) (Rossen et al., 2015). The recipients' intestinal microbiota also showed a high similarity in that study. Following a randomized trial of 75 UC patients with mild to moderate clinical stage with FMT via enema demonstrated the negative results defined the endpoints as Mayo score of 2 with Mayo endoscopic score 0 at week 7. However positive results were shown in the subsequent 22 patients with 24% of responders versus 5% in placebo group from a single donor (Moayyedi et al., 2015). A FOCUS trial of 81 patients with mild to moderate UC patients reported strong positive results for UC patients, inducing clinical remission and endoscopic response at 8 weeks (Moayyedi et al., 2015). In this trial, FMT was performed with initial colonoscopic infusion followed by enema and 27% of FMT treated patients achieved steroid-free clinical remissions compared to 8% of control. The trial for the patients with steroid dependent UC has been reported. In this study, 41 patents of steroid dependent UC underwent FMT. Steroid-free clinical remission was achieved in 19 out of 41 (46.3%) patients at week 24, whereas clinical response and endoscopic remission were achieved in 31 out of 41 (75.6%) and 26 out of 41 (63.4%) patients, respectively. All patients with clinical response were able to withdraw steroids (Sood et al., 2019). Recent meta-analysis of FMT to IBD patients has been reported including 31 reports. It has been reported that donors in Asia were younger than the West and final remission rate for UC and CD were 39.6% and 47.5%, respectively (Lai et al., 2019). Another study showed no impact of fresh or frozen donor stool, delivery route, and antibiotic pretreatment on the efficacy of FMT in IBD (Fang, Fu, & Wang, 2018). Though most studies of FMT have used whole microbial conditions from single or pooled donors, use of defined bacterial communities has several benefits such as simpler logics, better manufacturing/quality control processes, and more clearly defined regulatory aspects. Moreover, most FMT studies have set a limited period with post-FMT. Further study is necessary to demonstrate the efficacy and safety of treatment in IBD patients for prolonged periods of FMT to maintain the remission.

NAFLD is also thought to be a target of FMT. Though the clinical study of NAFLD patients to elucidate the effect of FMT has not been conducted, its effect in HFD diet-induced steatohepatitis mouse models has been demonstrated (Zhou et al., 2017). After FMT, the gut microbiota disturbance was improved in HFD-fed mice with increase of *Christensenellaceae* and *Lactobacillus*. Butyrate concentration of cecal content and the intestinal tight junction protein ZO-1 were increased by FMT in HFD-fed mice. Consequently, HFD-induced steatohepatitis in mice was significantly improved by FMT. These results suggest a potential therapeutic strategy of FMT for the patients of NAFLD.

3.2. Probiotics

Probiotics are live microorganisms providing health benefits to the host (Rijkers et al., 2011) and have demonstrated therapeutic effects in various disease models associated with intestinal dysbiosis. Probiotics have demonstrated effects against local and systemic animal inflammatory models. The severity of DSS-induced mouse colitis was attenuated by a cocktail of four *Lactobacillus* and *Bifidobacterium* strains (Toumi et al., 2014). OVA-induced airway inflammation was attenuated by oral administrations of *Lactobacillus rhamnosus* (Wu, Chen, Lee, Ko, & Lue, 2016). A collagen-induced arthritis model was diminished by *L. casei*, and *L. acidophilus* inhibiting the expression of proinflammatory cytokines and inducing anti-inflammatory cytokines (Amdekar, Singh, Kumar, Sharma, & Singh, 2013). Clinical trials demonstrating the efficacy of probiotics are restricting compared to preclinical data. The risk of antibiotic-associated diarrhea and *Clostridium difficile* infection (CDI) over the age of 50 was reduced bya probiotic drink containing *L. casei*, *L. bulgaricus* and *Streptococcus thermophilus* (Hickson et al., 2007). The allergy symptoms induced by birch pollen were shown to reduce probiotic combination of *L. acidophilus* and *Bifidobacterium lactis* (Ouwehand et al., 2009). In obese children with NAFLD, consistent effects were also observed by administering probiotics such as the *L. rhamnosus* strain GG (Vajro et al., 2011) and mixed bacteria of *L. bulgaricus* and *S. thermophiles* (Aller et al., 2011). Though the efficacy of probiotics was supported in those clinical trials, the administration of probiotics is not strongly recommended due to insufficient data to support its efficacy (Lemon, Armitage, Relman, & Fischbach, 2012). VSL#3 is a mixture of *L. casei*, *L. plantarum*, *L. acidophilus*, *L. delbrueckii* subsp.

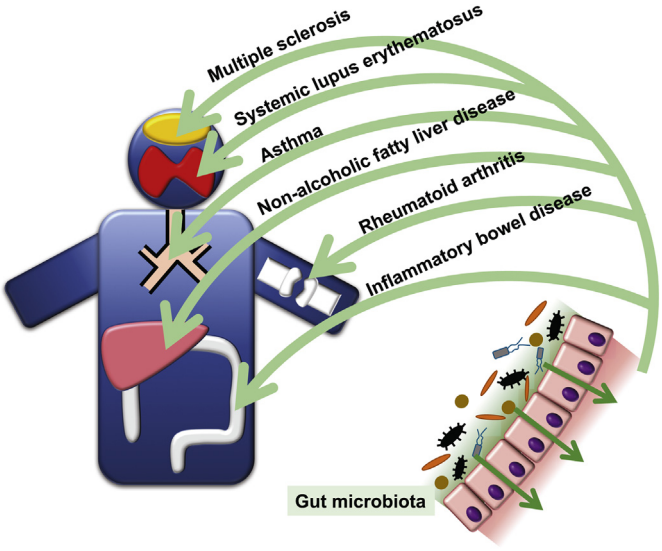

Fig. 1. The pathogenesis of systemic inflammatory diseases such as multiple sclerosis, systemic lupus erythematosus, asthma, non-alcoholic fatty liver disease, rheumatoid arthritis, and inflammatory bowel disease are connected with gut microbiota.

bulgaricus, *B. longum*, *B. breve*, *B. infantis*, and *S. salivarius*. Recent meta-analysis has demonstrated a significant increase of remission rate for UC patients with VSL#3 treatment compared to control (Shen, Zuo, & Mao, 2014). VSL#3 has also been reported to show effectiveness in obese children with NAFLD (Alisi et al., 2014). Supplements of VSL#3 for 4 months significantly improved hepatic function and increased glucagon-like peptide (GLP-1)/active glucagon-like peptide (aGLP1) levels suggesting that the effects of VSL#3 might be GLP-1-dependent. In another study, the effect of probiotics treatment to obese children with NAFLD by administering probiotics such as *L. rhamnosus* strain GG (Vajro et al., 2011) and mixed bacteria of *L. bulgaricus* and *S. thermophiles* (Aller et al., 2011). The application of exogenous commensal and probiotic strains to gut, which the composition of microbiota has already established, is greatly influenced by the background microbiota. Recent study showed that exclusive metabolic niche induced by administration of marine polysaccharide, porphyran, enables new strain to engraft in mice colon (Shepherd, DeLoache, Pruss, Whitaker, & Sonnenburg, 2018).

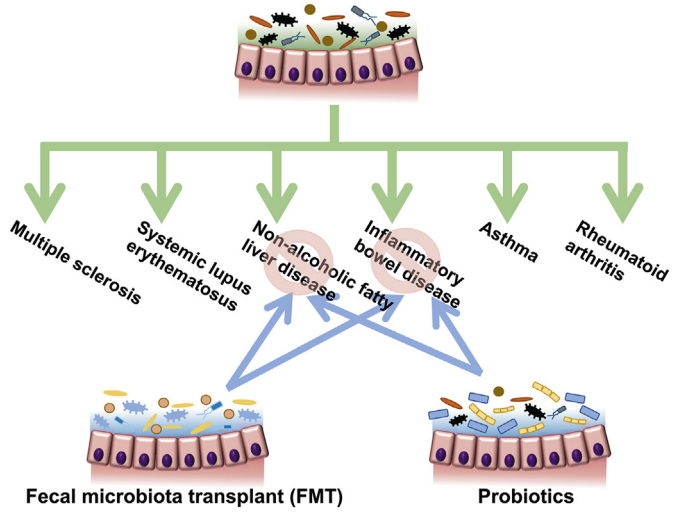

Fig. 2. The possibility to treat non-alcoholic fatty liver disease and inflammatory bowel disease has been reported by fecal microbiota transplant (FMT) and administration of probiotics.

4. Conclusions

Recently, abundant data characterizing the complex interaction between foods, microbes, and derived metabolites have been explored in relation to local intestinal and systemic immune responses. As mentioned in this review, the intestinal microbiota is largely involved in the pathogenesis of various chronic inflammatory diseases, such as IBD, MS, SLE, asthma, RA, and NAFLD (Fig. 1). For the onset or development of these diseases, several bacterial species in the gut are identified as important players. Therefore, the precise detection technique of intestinal dysbiosis and pathogenic microbiota is necessary to diagnose the disease. This may lead to potential therapeutic targets (Fig. 2). Further study about the intestinal microbiota will precede the new approach for refractory chronic inflammatory disease.

Conflict of interest

Yuji Naito received scholarship fund from EA Pharma. Co. Ltd. and collaboration research fund from Fujifilm Medical Co., Ltd., and has been paid lecture fees by Mylan EPD Co., Takeda Pharma. Co. Ltd., Mochida Pharma. Co. Ltd., EA Pharma. Co. Ltd., Otsuka Pharma. Co. Ltd., Nippon Kayaku Co. Ltd., and Miyarisan Pharma. Co. Ltd.. The research was partly funded by these funds. Neither the funding agency nor any outside organization has participated in study design or have any competing of interest. These companies had final approval of the manuscript.

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