Interactive roles of gut microbiota and gastrointestinal motility in the development of inflammatory disorders

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Gut microbiota play essential roles in host physiology. The gut microbiota both influence and are influenced by gastrointestinal (GI) motility. Disruption of intestinal homeostasis and alterations of the gut microbiota are considered to contribute to the pathogenesis of several disorders. Patients suffering from inflammatory disorders, such as inflammatory bowel disease (IBD) and non-alcoholic steatohepatitis (NASH), reportedly have prolonged orocecal transit times with small intestinal bacterial overgrowth and alterations of gut microbiota. These forms of dysbiosis have been suggested to elicit distinct intestinal immune responses, increased intestinal permeability and bacterial translocation, thereby contributing to the pathogenesis of IBD and/or NASH. In a recent report, we raised the possibility that a drug affecting GI motility might influence gut microbiota and the development of NASH. Thus, we investigated the effects of the gastropokinetic agent mosapride citrate (MC) using a methionine-choline deficient (MCD) diet-induced NASH rodent model. MC treatment exerted a protective effect against MCD diet-induced GI transit time delay, diminished lactic acid bacteria and colonic inflammation, thereby ameliorating NASH with reduced serum endotoxin and increased glucagon-like peptide-1. Recently, the correction of dysbiosis employing probiotics or fecal transplantation has been investigated as a therapeutic strategy for IBD and NASH. Given the interactive functions of gut microbiota and mediators of GI motility, there is possibility that altering GI motility also has potential as a therapeutic strategy.

Keywords: Gut microbiota; gastrointestinal motility; inflammation; inflammatory bowel disease; non-alcoholic steatohepatitis


In the adult intestine, the total number of microorganisms is estimated to exceed about the total number of somatic and germ cells by approximately ten fold. In addition, the microbiome, constituting the collective genomes of all
microbiota, contains at least 100 times as many genes as our own human genome. Thus, gut microbiota are regarded as an essential organ playing an essential role in host physiology [1-4]. These microorganisms participate not only in the digestion and absorption of nutrients, but also in homeostatic maintenance of host immunity [5] and metabolism [6]. Hence, disruption of intestinal homeostasis and alterations of gut microbiota have been suggested to contribute to the pathogenesis of several disorders, including not only gut but also liver diseases [7-9].

Gut microbiota compositions are reportedly influenced by various factors such as genetic background, diet, drug treatment, and gastrointestinal (GI) motility [10-12]. Among these factors, GI motility is among the important control systems impacting gut microbiota, by eliminating excessive bacteria from the intestinal lumen. On the other hand, gut microbiota can also influence GI motility, as was demonstrated in a study employing a germ-free animal model [13]. Thus, gut microbiota and GI motility apparently interact, influencing each other in various ways. Both have recently been suggested to contribute to the pathogenesis of inflammatory disorders such as inflammatory bowel disease (IBD) and non-alcoholic steatohepatitis (NASH).

IBD, encompassing both Crohn’s disease and ulcerative colitis, is considered to result from an inappropriate inflammatory response to gut microbiota in genetically susceptible hosts [14,15]. A growing body of evidence supports the role of gut microbiota in the pathogenesis of IBD. For example, murine IBD models do not develop colitis under germ-free conditions [16], antibiotics are effective for treating IBD [17] and IBD susceptibility genes contain the bacterial sensor associated gene [18]. In fact, IBD patients reportedly had a prolonged orocecal transit time coexistent with small intestinal bacterial overgrowth [19], reduced gut microbiota diversity, and altered gut microbiota composition characterized by decreases in Firmicutes species, especially Faecalibacterium prausnitzii, while Actinobacteria and Proteobacteria were increased [20,21]. In addition, functional changes in response to alterations in gut microbiota might also be involved in the pathogenesis of IBD. A metagenomic analysis of gut microbiota revealed a shift in genes in the oxidative stress pathways in patients with IBD [22]. These observations raised the possibility that oxidative stress from gut microbiota contribute to intestinal inflammation, which involves not only the mucosa and muscular components of the bowel wall, but also the enteric nervous system (ENS) [23]. The ENS affects the motor function of the intestine [24], and abnormalities of the ENS and prolonged orocecal transit time have actually been demonstrated in IBD patients [19,25]. We can thus speculate that these factors contribute to the dysbiosis seen in IBD subjects. Abnormal GI motility might contribute to the development of dysbiosis, due to the aforementioned distinct intestinal immune responses, and thereby to the pathogenesis of IBD.

NASH is a serious disease characterized by hepatocellular lipid accumulation along with inflammation and varying degrees of fibrosis. Some NASH patients eventually develop cirrhosis and/or liver cancer, and at least some of these individuals will ultimately die from liver-related diseases [9,26]. The pathogenesis of NASH has not as yet been fully elucidated, though several lines of evidence have suggested a role of gut microbiota in NASH pathogenesis [27,28]. Patients suffering from NASH reportedly have elevated endotoxin levels [29]. Furthermore, pathogen-associated molecular patterns (PAMPs) or downstream signaling deficiency in mice are known to suppress NASH development [30,31]. Thus, microbial products have been described as playing important roles in the pathogenesis of NASH. Increased intestinal permeability and disruption of the mucosal barrier are necessary for translocation of microbial products from the intestine to the liver via the portal circulation. Patients with non-alcoholic fatty liver disease reportedly show increased intestinal permeability and alterations of intestinal tight junctions, whereas healthy subjects do not [32]. Various causes of intestinal barrier dysfunction have been suggested. First, intestinal inflammation might cause intestinal leakage and translocation of microbial products, because high fat diets promote intestinal inflammation [33] and weight loss reduces intestinal inflammation [34]. Intestinal inflammation also depends on gut microbiota, because germ free mice do not develop intestinal inflammation [33]. Direct evidence of dysbiosis inducing intestinal inflammation and bacterial translocation, factors known to be involved in the pathogenesis of NASH, was obtained in a study using Nlrp3 - and Nlrp6 inflammasome deficient mice [35]. Inflammasomes are sensors of endogenous or exogenous PAMPs or endogenous damage associated molecular patterns that regulate the cleavage of inflammatory cytokine precursors. These mice showed dysbiosis characterized by increased Prevotellaceae species and intestinal inflammation. Subsequently, they showed translocation of bacterial products into the portal circulation which induced an inflammatory response in the liver, thereby promoting NASH progression. Patients with NASH have, in fact, been reported to show altered gut microbiota compositions characterized by increases in Escherichia species belonging to the Proteobacteria and decreases in Bifidobacterium species belonging to the Actinobacteria, as compared with obese subjects [36], and a prolonged orocecal transit time coexistent with small intestinal bacterial overgrowth [37]. Therefore, we hypothesized that a drug affecting GI motility might influence gut microbiota as well as the development and progression of NASH. We recently investigated the effects of
the gastroprotective agent mosapride citrate (MC), an agonist of the 5-hydroxytryptamine (5-HT4) receptor, using a methionine-choline deficient (MCD) diet-induced NASH rodent model [38]. The MCD diet caused GI transit time delay, gut microbiota alteration characterized by decreases in lactic acid bacteria and colonic inflammation, whereas MC treatment exerted a protective effect against these MCD diet-induced changes, thereby diminishing NASH development with reduced serum endotoxin and increased glugagon-like peptide-I levels. Intriguingly, correction of GI transit time by MC treatment reversed the MCD diet-induced decreases in lactic acid bacteria. Interestingly, the level of lactic acid bacteria such as *Bifidobacterium* was actually lower in NASH patients than in obese subjects [36]. Given that previous reports have shown probiotics to enhance intestinal barrier function, exert anti-inflammatory effects and increase GLP-1 secretion [39,40], these changes in gut microbiota in response to MC treatment might protect against NASH development. We found the altered GI transit time in response to MC treatment to partial correct dysbiosis and suppress intestinal inflammation, consequently suppressing the MCD diet-induced NASH progression in association with lower endotoxin levels.

In summary, dysbiosis appears to trigger distinct intestinal immune responses, increased intestinal permeability and bacterial translocation, thereby contributing to the pathogenesis of IBD and/or NASH. The close interactions between gut microbiota and GI motility may explain why disrupting GI motility can lead to the development of dysbiosis. Recently, correcting dysbiosis by administering probiotics and fecal transplantation have been attempted as therapies for diseases involving GI dysbiosis [20,27,41]. Recent evidence, as outlined herein, raises the possibility that altered GI motility may also be an appropriate therapeutic strategy for IBD and NASH.

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Conflicts of interest

The authors have declared that no competing interests exist.

References


