Chapter 2

The Pathology of Methanogenic Archaea in Human Gastrointestinal Tract Disease

Suzanne L. Ishaq, Peter L. Moses and
André-Denis G. Wright

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/64637

Abstract

Methane-producing archaea have recently been associated with disorders of the gastrointestinal tract and dysbiosis of the resident microbiota. Some of these conditions include inflammatory bowel disease (Crohn's disease (CD) and ulcerative colitis (UC)), chronic constipation, small intestinal bacterial overgrowth, gastrointestinal cancer, anorexia, and obesity. The causal relationship and the putative mechanism by which archaea may be associated with human disease are poorly understood, as are the strategies to alter methanogen populations in humans. It is estimated that 30–62% of humans produce methane detectable in exhaled breath and in the gastrointestinal tract. However, it is not yet known what portion of the human population have detectable methanogenic archaea. Hydrogen and methane are often measured in the breath as clinical indicators of intolerance to lactose and other carbohydrates. Breath gas analysis is also employed to diagnose suspected small intestinal bacterial overgrowth and irritable bowel syndrome, although standards are lacking. The diagnostic value for breath gas measurement in human disease is evolving; therefore, standardized breath gas measurements combined with ever-improving molecular methodologies could provide novel strategies to prevent, diagnose, or manage numerous colonic disorders. In cases where methanogens are potentially pathogenic, more data are required to develop therapeutic antimicrobials or other mitigation strategies.

Keywords: methanogens, colorectal cancer, irritable bowel syndrome, methane

1. Introduction

1.1. Methanogen diversity in the gastrointestinal tract

Archaea represent the third domain of life, in addition to Prokaryota, which they more or less physically resemble, and Eukaryota, with which they have more genetic similarities. Many archaea are classified as extremophiles, but those which live in the digestive tract of animals are known as methanogens. Archaeal diversity in the gastrointestinal tract (GIT) is far less than that of bacteria, and more specifically monogastrics have a much lower diversity as compared to herbivorous ruminant animals. In both host types, species belonging to the genus *Methanobrevibacter* have been cited as the dominant methanogens in the GIT. In fact, *Mbr. smithii* is the dominant species found in the human GIT, followed by *Methanosphaera stadtmanae* [1–5]. This lack of relative diversity is largely a function of diet, the presence or absence of other microorganisms, or digestive tract physiology, but it may play a role in human intestinal dysbiosis. A general increase in microbial diversity has been correlated with a healthy gut microbiome that is resistant to physical or biotic disruptions, as there is redundancy in metabolic pathways and the increased competition precludes dominance by one particular taxon. Higher methanogen diversity was correlated with lower breath methane production in humans [1].

Methanogens use hydrogen, in the form of free protons, H_2 gas, NADH and NADPH cofactors, acetate, or formate, to reduce carbon dioxide and produce methane gas. Thus, methanogens rely on the by-products of bacterial fermentation of carbohydrates (i.e., carbon, hydrogen, acetate, formate, or methanol) as precursor materials required for methanogenesis and their own energy production. Dietary carbohydrates which are not broken down or absorbed by the host are available to bacteria for fermentation [6], and a large amount of unused carbohydrates may consequently increase bacterial fermentation and archaeal methanogenesis. A diet high in fiber and structural carbohydrates, which are largely indigestible to animal and human enzymes (i.e., cellulose, hemicellulose, and lignin), is associated with populations of *Methanobrevibacter ruminantium* [7], while a diet high in starch and other easily digestible carbohydrates is associated with *Mbr. smithii* [8, 9]. *Mbr. smithii* has been shown to improve polysaccharide digestion by GIT bacteria and fungi, and even influence the production of acetate or formate for its own use [10, 11]. *Msp. stadtmanae* requires methanol, a compound that is the by-product of pectin fermentation, for its methanogenesis pathway, which accounts for its presence in omnivores [1, 2, 5, 12].

Methanogens also have a slower growth rate than bacteria, which is sensitive to concentrations of hydrogen required as an electron donor during methanogenesis, as well as other nutrients. Few methanogenic taxa are motile, and these are limited to the order Methanococcales, and the genera *Methanospirillum, Methanolobus, Methanogenium*, and *Methanomicrobium* (order: Methanomicrobiales) [13, 14]. This difficulty of remaining situated in the intestines is a limiting factor in methanogen density. In humans, methanogens tend to be denser in the left colon, where fecal matter becomes more solid and transit time slows down [15], but they have also been found in the small intestine [16]. In addition, passing through the gastric stomach is challenging, which may explain why oral and intestinal populations of archaea and bacteria

http://dx.doi.org/10.5772/64637

do not share an overlapping diversity [17, 18]. To overcome challenges to intestinal retention, some species of methanogens have adapted to the human colon and are able to thrive. *Mbr. smithii* produces surface glycans and adhesion-like proteins which improves their interaction with host epithelia and allows for persistence in the gut, as well as wider range of fermentation by-products, which can be used for methanogenesis, allowing for the flexibility of the human diet [3].

1.2. Intestinal methane and the effect on the host

Colonic gases are among the most tangible features of digestion, yet physicians are typically unable to offer long-term relief from clinical complaints related to excessive gas and associated discomfort. Studies characterizing colonic gases have linked changes in volume or composition to individuals with gastrointestinal disorders (see below). These studies have suggested that hydrogen gas, methane, hydrogen sulfide, and carbon dioxide are by-products related to the interplay between hydrogen-producing fermentative bacteria and hydrogen consumers (reductive acetogenic bacteria, sulfate-reducing bacteria, and methanogenic archaea). The primary benefit of methanogenesis in the GIT is to decrease hydrogen (hydrogen gas, NADH, NADPH) resulting from carbohydrate fermentation by bacteria, protozoa, and fungi [19]. Hydrogen gas in the intestines can shorten intestinal transit times of feces by 10–47% [20]. Moreover, hydrogen has been shown to have antioxidant properties as an oxygen scavenger [21, 22]. It is possible that in the healthy colon, physiological hydrogen concentrations might protect the mucosa from oxidative insults, whereas an impaired hydrogen economy might facilitate inflammation or carcinogenesis.

However, excessive hydrogen in the GIT can be detrimental to commensal microorganisms. The decrease in hydrogen through the generation of inert methane gas helps to prevent hydrogen damage to host or symbiotic microbial cells [23]. In ruminant animals, which have a four-chambered stomach, methanogens associated with ciliate protozoa act as a hydrogen sink [24], especially in the first two stomach chambers, the rumen and reticulum. There are a few commensal protozoan species that can be found in the human intestinal tract [25], but it is not yet known if they symbiotically interact with methanogens. Generally, this interaction only occurs with protozoa that have a hydrogenosome organelle, which metabolizes pyruvate and uses hydrogen ions as electron acceptors. In humans, the only protozoa that have a hydrogenosome are trichomonads, such as *Trichomonas hominis* and *Trichomonas tenax*, both of which are nonpathogenic [25, 26].

Alternative hydrogen sinks in humans include sulfate-reducing bacteria (SRB), which produce hydrogen sulfide gas that is absorbed and detoxified by the liver, or acetogenic bacteria, which produce the short-chain fatty acid acetate that can be metabolized by the host or other microorganisms. Some of these pathways are mutually exclusive in humans, and either SRB or methanogens will be present in large numbers [27]. Although higher hydrogen sulfide and SRB levels have been detected in patients with irritable bowel disease (IBD), and to a lesser extent in colorectal cancer (CRC), this colonic gas might have beneficial effects as a gaso-transmitter [28]. Acetogens, on the other hand, have up to a 100 times higher hydrogen concentration threshold, and thus cannot out-compete methanogens for precursors [29, 30].

Consequently, acetogenesis is rare in the human GIT, and if present is usually restricted to the right colon [31].

Unlike hydrogen, there are as yet no known biological sinks for methane in the intestines [32], although methanotrophic bacteria exist in a variety of water and soil environments. Instead, some methane is excreted from the colon, and most is absorbed into the blood stream and expelled from the lungs via exhalation. This allows methane production to be indirectly and noninvasively measured, since breath methane concentration is correlated with methanogen cell density in the intestines [1]. An undetectable concentration of breath methane does not equate to the absence of archaea, and therefore false-negative interpretations of breath gas analysis may result when breath methane is at undetectably low levels [33, 34]. Reported estimations suggest that between 30 and 62% of healthy humans produce detectable methane [31, 35]. The presence of methane gas in the intestines may influence or reduce intestinal transit time, and the correlation between breath methane production and transit time has been observed even in healthy individuals [19]. This was further examined using animal models, in which the overabundance of methane gas caused a reduction in transit time while increasing intestinal contractions [20, 36], thus increasing pressure inside the intestine by an average of 137% [20]. Alteration of intestinal motility may benefit slow-growing methanogen populations, which are limited by their ability to attach to host mucosal epithelia and maintain themselves in the intestines.

This increased gas production and resulting pressure cause bloating, discomfort, flatulence, or belching. In addition to detrimental physical effects, it has been speculated that methane potentially causes chemical and biological effects as a "gaso-transmitter" [37], in the same way that hydrogen sulfide affects smooth muscle activity [37] or nitrous oxide (N_2O) is used in biological systems to control vascular tone [38]. Studies using isolated gastrointestinal tissue suggest that this interaction is between methane and enteric nervous tissue, rather than the central nervous system [20]. Clinically, hydrogen and methane measured in breath can indicate lactose and glucose intolerance, small-intestine bacterial overgrowth (SIBO), irritable bowel syndrome (IBS), or other gastrointestinal diseases [35, 36, 39–42]. Therefore, standardized breath gas measurements combined with ever-improving molecular methodologies could provide novel strategies to prevent, diagnose, or manage numerous colonic disorders as defined by the Rome III diagnostic criteria [43].

2. The role of archaea in metabolic disorders

Obesity in adults is most commonly defined using body mass index (BMI) (kg body weight/height in meters squared), and for Caucasian adults, is defined as a BMI of ≥30 kg/m^2. For over a decade, shifts in intestinal bacteria diversity have been associated with weight gain or obesity in humans, generally following an increase in the proportion of Firmicutes [44], a decrease in Bacteroidetes, which has shown some anti-obesity influences [44–46], and with a shift in more minor phyla. Generally, this shift in intestinal bacteria leads to an increase in host energy harvest by improving polysaccharide digestion and host epithelial absorption which, in turn,

http://dx.doi.org/10.5772/64637

causes weight gain [47–49]. Alternatively, a change in host genetics or immune system function can also cause a shift in bacterial diversity. The lack of host immune-modulating factors, such as Toll-like receptor 5 (TLR5) and fasting-induced adipocyte factor (Fiaf), produced insulin resistance, increased adiposity (especially visceral), and shifted GIT bacterial diversity and functionality in mice [49, 50]. Additionally, endotoxinemia, or the presence of microbial endotoxins (e.g., lipopolysaccharide-A (LPS)) in intestines or blood, has been shown to induce obesity, glucose intolerance, weight gain, and adiposity in response to a high-fat diet [51–53].

It would seem that bacterial diversity and density may have a specific role in metabolic dysbiosis, as treatment with oral antibiotics has been shown effective at improving fasting and oral glucose tolerance test (OGTT) levels in obese or insulin-resistant mice [54], or mitigating endotoxinemia and reducing cecal LPS concentrations in mice on a high-fat diet [51, 55]. Both obesity and diabetes are also correlated with low-grade chronic intestinal inflammation, likely caused by bacterial LPS. The presence of LPS, among other systemic immune responses, causes host macrophages to express pro-inflammatory cytokines, and in adipose-associated macrophages this only increases local insulin resistance and lipid storage [51, 53].

More recent studies have focused on the shifts in archaea associated with high-fat/high-calorie diets or weight gain, especially as *Mbr. smithii* has been shown to increase polysaccharide digestion by bacteria and fungi [10, 11] and may play a specific role in increasing energy harvest. *Mbr. smithii* has been shown to increase in density in rats when switching to a high-fat diet, and was associated with higher weight gain when given as a supplement regardless of the diet [16]. In humans, BMI was higher in breath methane-positive subjects (45.2 ± 2.3 kg/m^2) than in breath methane-negative subjects (38.5 ± 0.8 kg/m^2, $P = 0.001$) [56]. In a separate study, methane- and hydrogen-positive subjects again had higher BMI than other groups (M+/H+ 26.5 ± 7.1 kg/m^2, $P < 0.02$), and also had significantly higher percent body fat (M+/H+ $34.1 \pm 10.9\%$, $P < 0.001$) [41]. Interestingly, *Mbr. smithii* density was found to be highly elevated in anorexic patients (5.26×10^8 rRNA copies/g feces), even more so than in obese patients (1.68×10^8 rRNA copies/g feces), as compared to healthy bodyweight subjects (9.78×10^7 rRNA copies/g feces) [57].

Obesity is strongly associated with an increased risk for diabetes mellitus, or type-2 diabetes, which is an inducible metabolic disease characterized by a lack of pancreatic production of insulin, or a resistance to insulin at the cellular level. Type-1 diabetes is an autoimmune disease characterized by the destruction of pancreatic beta cells which normally produce insulin. Diabetes can lead to a host of other health problems, most especially cardiovascular disease, renal failure, increased glaucoma and potential blindness, and reduced circulation, which increases the risk for ulcers and infection in the peripheral limbs. Few studies investigate the potential link between methanogens and diabetes. Type-1 diabetic patients with no complications showed a significant increase in intestinal transit time, although it was not associated with other gastric symptoms [58]. Type-1 diabetes with an autonomic diabetic neuropathy complication affects heart rate, blood pressure, perspiration, or digestion. Some patients with this neuropathy have also been positive for SIBO [59, 60], which was associated with an increased daily insulin requirement [60], or detectable methane production, which was associated with a worse glycemic index [59]. Breath methane producers, which had compara-

ble BMI and baseline insulin resistance to non-methane producers, had higher serum glucose levels and a longer return to normal resting glucose after OGTT [61]. The mechanistic relationship between methanogens, methane, and diabetes has yet to be explained.

3. The role of archaea in colon cancer

Colorectal cancer is the most commonly diagnosed malignancy in the Western World, being the fourth most common cancer diagnosis in the United States but the second leading cause of cancer-related deaths [62]. In nonsmokers, it is the leading cause of cancer-related death in men and the second leading cause of cancer-related death in women (after breast cancer). The 5-year survival rate varies by stage and type, ranging from 53 to 92% [62]. All colorectal cancers originate from adenomas or flat dysplasia, and are often asymptomatic, though occult bleeding may result and ultimately may be associated with an unexplained iron deficiency anemia. Large tumors in the distal or left colon may result in a compromised bowel lumen and potentially lead to symptoms including constipation, diarrhea, or bowel obstruction. The histopathology of CRC is complicated and involves a number of differently defined molecular pathways. There is evidence of microbial dysbiosis in CRC patients, as well as higher levels of breath methane in patients with CRC and premalignant polyps, as presented below.

Viral causative agents have been identified in a variety of cancers, but it is only recently that prokaryotic- or eukaryotic-causative or protective agents have been investigated. Cancer has been associated with a reduced bacterial diversity in the digestive tract [63], as well as in the mammary glands [64]. Specific agents have been identified, which cause localized cancers through their molecular interactions with host cells [65], such as *Helicobacter pylori* in stomach cancers or a link between the diplomonad protozoan *Giardia* in pancreatic and gallbladder cancer, but no archaea have yet been cited as a possible agent [66]. A recent review by Gill and Brinkman [67] discusses the role of bacterial phages (viruses that exclusively infect bacteria) in bringing mobility and virulence factors to bacteria, while archaea are infected by archaeon-specific phages which are unlikely to have independently evolved similar virulence factors to bacterial phages. Additionally, while archaea and bacteria are both prokaryotic, though in different phylogenetic domains, there is little evidence of horizontal gene transfer between them [67].

There is some discussion about the change in the density of methanogens in individuals with colorectal cancer [33, 68, 69]. Methanogen density was shown to be inversely related to the fecal concentration of butyrate, a short-chain fatty acid produced by bacterial fermentation [70]. Butyrate has been shown to provide energy for digestive tract epithelia cells, upregulate host immune system and mucin production, alter toxic or mutagenic compounds, and reduce the size and number of crypt foci, which are abnormal glands in intestinal epithelia that lead to colorectal polyps [71–73]. An altered gut microbiome in colorectal patients could shift bacterial fermentation away from butyrate production to something more favorable to methanogenesis.

http://dx.doi.org/10.5772/64637

Methane production was increased in patients with precancerous symptoms and colorectal cancer [39, 74], and was directly proportional to constipation but inversely proportional to diarrhea in chemotherapy patients [75]. In the same study, pH was also directly proportional to constipation but inversely proportional to diarrhea in chemotherapy patients [75]. Methane itself has not been shown to be carcinogenic. However, the oxidation of methane forms formaldehyde, which is carcinogenic [76]. On the other hand, hydrogen sulfide gas produced by SRB has shown to promote angiogenesis (which tumors rely on), and has been shown to be genotoxic when DNA repair is inhibited [77]. Colon cancer biopsies have shown an increase in the enzyme cystathionine-β-synthase (CBS), which allows host cancer cells to produce their own hydrogen sulfide, and a silencing of this gene was able to reduce tumor cell growth, proliferation, and migration [78].

4. The role of archaea in irritable bowel syndrome

The symptoms of IBS vary between patients, and may include diarrhea, constipation, excess flatus secondary to hydrogen or methane production, bloating, abdominal pain, and visceral hypersensitivity [79]. Hydrogen sulfide gas from SRB was shown to increase luminal hypersensitivity [80]. In addition, IBS is associated with changes in the diversity and density of intestinal bacteria [42, 81–83], as well as with an increase in hydrogen production [84]. In some patients with IBS, the change in bacterial populations is amplified, leading to SIBO. SIBO is also seen in non-IBS patients, but it is much more prevalent in IBS patients, especially those with constipation as opposed to diarrhea [85, 86]. A common technique for the management of symptoms includes switching patients to a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) [87]. Two-thirds of patients report symptoms linked to diet [88], especially gas production and bloating following ingestion of lactose [89], other carbohydrates, or fats [40, 88].

While the specific cause of IBS still remains unclear, the altered bacterial diversity causes a shift in carbohydrate fermentation and altered gas production. If this shift favors methanogenesis, the result is a decrease in transit time and an increase in constipation. The presence of methanogens in the digestive tract, and the production of methane, has been associated with patients with IBS, and especially with chronic constipation and reduced passage rate in the intestines (slow transit) [42, 85, 90]. Methanogen density was found to be lower in IBS patients as compared to controls [69, 91], although density and methane production were increased in IBS patients with constipation as compared to IBS patients without constipation [90]. *Methanobrevibacter* spp. are increased with diets high in easily digestible carbohydrates, but decreased in diets high in amino acids/proteins and fatty acids [8], specifically *Mbr. smithii* [9]. More specifically, *Mbr. smithii* was higher in IBS patients with constipation and higher methane production [90], and they have previously been shown as the dominant species in healthy individuals who have high methane production [1].

5. The role of archaea in inflammatory bowel disease

Contrary to recent findings in patients with IBS, low methane production [35, 42] and lower methanogen density [69] were seen in patients with IBD, which includes the specific entities Crohn's and ulcerative colitis. In contrast to IBS, IBD patients demonstrate chronic inflammatory changes in the colon (UC) or in the small bowel, or a combination of small bowel and colon involvement (CD).

Recently, it was demonstrated that two archaeal species normally found in the digestive system, *Mbr. smithii* and *Msp. stadtmanae*, can have differential immunogenic properties in the lungs of mice when aerosolized and inhaled [92]. Furthermore, *Msp. stadtmanae* was found to be a strong inducer of the inflammatory response [92], and it is likely that this may occur even in the GIT where it is normally found. Blais Lecours et al. [93] investigated the immunogenic potential of archaea in humans relating to patients with IBD. Mononuclear cells stimulated with *Msp. stadtmanae* produced higher concentrations of tumor necrosis factor (TNF) (39.5 ng/ml) compared to *Mbr. smithii* stimulation (9.1 ng/ml) [93]. Bacterial concentrations and frequency of *Mbr. smithii*-containing stools were similar in both healthy controls and patients with IBD; however, the number of stool samples positive for the inflammatory archaea *Msp. stadtmanae* was higher in patients than in controls (47 vs 20%) [93]. Importantly, only IBD patients developed a significant anti-*Msp. stadtmanae* immunoglobulin G (IgG) response [93], indicating that the composition of the microbiome appears to be an important determinate of the presence or absence of autoimmunity. Recent advances in mucosal immunology and culture-independent sequencing of the microbiome support the hypothesis that alterations in the microbiota can alter the host immune response as is observed in IBD [94]. A specific role for archaeal species has yet to be clearly defined.

6. The role of archaea in other intestinal dysbiosis

There are many rare gastrointestinal diseases and general conditions of dysbiosis which are not well understood, but which may have a link to methane production in the intestines. Pneumatosis cystoides intestinalis (PCI) is a condition in which gas-filled cysts occur in the smooth muscle wall of the intestines, where it cannot be relieved by flatulence. It is believed to be caused by bacteria in the intestinal wall. Interestingly, patients with PCI have lower prevalence of breath methane production than patients with IBS, CD, UC, and even healthy control subjects [35].

Non-IBS constipated patients with slow transit were more likely to have detectable levels of breath methane (75 vs 44%) than constipated patients with normal transit, and both were more likely to have detectable breath methane than nonconstipated controls (28%) [95]. This trend was also reported in other studies [56, 85].

Diverticulitis, a condition involving the herniation of the intestinal mucosal and submucosal layers back through the intestinal smooth muscle and creates pockets that harbor infections, has only been noted since the early 1800s [96]. Interestingly, it is most common in the left colon

http://dx.doi.org/10.5772/64637

in subjects from Western countries and the right colon in subjects from Asian countries [96], which is likely a function of the "Western diet." Diverticulitis was associated with a high prevalence of methanogens in stool and high methane output [33], as well as fiber intake, age-associated changes in the colon wall, low colonic motility, and high intraluminal pressure; however, methane output was not associated with right colon diverticulitis [97]. As methanogen density is higher in the left colon [15], an increase in methane production that reduced transit time and increased intraluminal pressure would seem to be a contributing factor to the development of left colon diverticulitis.

7. Mitigation strategies

IBS is the most common functional gastrointestinal disorder and affects up to 12–15% of adults in the United States. Roughly 1.6 million Americans currently suffer with CD or UC, collectively known as IBD. IBS adversely impacts quality of life and medical expenditures, with significant costs arising from health-care visits and reduced workplace productivity, while IBD is a chronic, relapsing, debilitating disease associated with both environmental and genetic factors. IBD affects one in 200 Americans (80,000 children) at an estimated direct cost of $1.84 billion dollars. Conventional therapy attempts to modulate the immune response in the gut as it relates to IBD, yet many individuals continue to require surgery to control their disease or address its complications. There is a longstanding belief that dysbiosis (altered microbial environment) in the GIT plays an important etiologic role in the pathogenesis of IBS and IBD. There is significant scientific and public interest in compositional understanding of the intestinal microbiome (the specific constellation of microorganisms populating the gut) to better understand the role of the microbiome in health and disease. The contribution of individual organisms, including archaea, in the pathogenesis of GI disease is complex because of the rudimentary understanding of the compositional components of the microbiome.

The control of methanogen populations has long been a strategy in livestock to improve animal dietary efficiency, as methane production is an energy sink, as well as to reduce greenhouse gas emissions. In ruminant livestock, as discussed in a review by Hook et al. [24], this is largely done by manipulating the diet to improve the digestibility of feed and increase passage rate through the digestive tract to both deprive methanogens of potential precursors and to manually flush them out of the system. A change in diet is a potential avenue for reducing methanogen populations in humans, as methanogenesis is associated with sugar-/starch-based diets in monogastrics [27]. Environmental effects may also play a role, as children living near landfills, which had higher atmospheric methane than areas away from landfills, had a higher breath methane output and higher *Mbr. smithii* cell density than control children, regardless of their socioeconomic level [34]. Previous to that study, it was shown that the bacterial and fungal counts dispersed from landfills into air were up to 20 times higher than microbial counts from other areas [98].

Antibiotics have commonly been used to treat gastrointestinal disease or symptoms such as fasting and OGTT (glucose) levels [54], endotoxinemia and cecal LPS concentrations [51, 55],

or global IBS symptoms [99]. Archaea are largely resistant to antimicrobial agents, which target bacteria, as they have different cell wall components and structure, and the few antimicrobials which they are susceptible to have been summarized in a recent review [100]. Notably, *Methanobrevibacter* species have only been shown to be susceptible to mevastatin and levastatin, both hydroxymethylglutaryl (HMG)-SCoA reductase inhibitors [101].

Our increasing knowledge of the potential long-term effects on gut microbial diversity has led to a trend of alternative treatments or mitigating methods over antibiotics. A recent review of probiotics showed them to be effective in relieving digestive dysbiosis symptoms or treating gastrointestinal conditions [79, 81, 102, 103]. The use of prebiotics directly infused into the colon, such as short-chain fatty acids, however, did not increase colonic motility [104]. While probiotics and other dietary additives have been used to reduce methanogenesis in ruminant livestock [24], the effect of probiotics on methanogen populations in humans has not yet been investigated. While current research suggests that methanogens and methane production may exacerbate symptoms, causative relations have only been shown in bacteria, and thus it is bacteria which should be the ultimate target for mitigation strategies in unhealthy populations.

Direct microbial remediation and mitigation have only been recently considered in human medicine with the advent of fecal transfer treatments from healthy donors. While this has mainly been aimed at remediating pathogenic bacterial populations, the implications for this technology to reduce methanogenesis and improve gastrointestinal conditions are clear. It may be possible to use fecal transfer treatments to increase the diversity of GIT archaea and thus promote competition to reduce methane production, to colonize with less-efficient methanogens, or to potentially increase competition by increasing SRB populations, which may have its own health implications for detoxifying hydrogen sulfate gas. Most interestingly, the transfer of fecal microbiota or cultures of specific methanogens has shown to also induce metabolic states in the recipients; fecal transfers, or colonization from parent to child, from overweight or pregnant individuals has been shown to increase weight gain in recipients [10, 16, 48, 105, 106]. While the possibility of this transfer to improve weight gain in severely malnourished individuals remains possible but not yet clinically applied, the more commercially appealing treatment of obesity using fecal transfers from lean individuals has yet to be explored.

8. Summary

Methane has been implicated in a number of gastrointestinal diseases, but methanogens have not yet been identified as causative agents. More work is needed in order to understand the interactions between archaea and host epithelia, as well as whether the root dysbiosis is caused by bacteria, archaea, or host epithelia. In addition, more sensitive, quick, and minimally invasive assessment techniques are needed to assess methane production, methanogen diversity, and methanogen density. In cases where methanogens are potentially pathogenic, more data are required to develop therapeutic antimicrobials or other mitigation strategies.

http://dx.doi.org/10.5772/64637

Author details

Suzanne L. Ishaq[1*], Peter L. Moses[2] and André-Denis G. Wright[3]

*Address all correspondence to: suzanne.pellegrini@montana.edu

1 Department of Animal and Range Sciences, Montana State University, Bozeman, USA

2 University of Vermont, College of Medicine, Burlington, USA

3 Department of Animal and Comparative Biomedical Sciences, University of Arizona, Tucson, USA

References

[1] Moses PL, Ishaq SL, Gupta K, Mauer SM, Wright A-DG: Biodiversity of human gut methanogens varies with concentration of exhaled breath methane. In Am Coll Gastroenterol 80th Annu Meet. Honolulu: American College of Gastroenterology; 2015: P776.

[2] Dridi B, Henry M, El Khéchine A, Raoult D, Drancourt M: High prevalence of Methanobrevibacter smithii and Methanosphaera stadtmanae detected in the human gut using an improved DNA detection protocol. PLoS One 2009, 4:e7063.

[3] Samuel BS, Hansen EE, Manchester JK, Coutinho PM, Henrissat B, Fulton R, Latreille P, Kim K, Wilson RK, Gordon JI: Genomic and metabolic adaptations of Methanobrevibacter smithii to the human gut. Proc Natl Acad Sci USA 2007, 104:10643–10648.

[4] Dridi B, Henry M, Richet H, Raoult D, Drancourt M: Age-related prevalence of Methanomassiliicoccus luminyensis in the human gut microbiome. APMIS 2012, 120:773–777.

[5] Fricke WF, Seedorf H, Henne A, Krüer M, Liesegang H, Hedderich R, Gottschalk G, Thauer RK: The genome sequence of Methanosphaera stadtmanae reveals why this human intestinal archaeon is restricted to methanol and H2 for methane formation and ATP synthesis. J Bacteriol 2006, 188:642–658.

[6] Levitt MD, Bond JH: Volume, composition, and source of intestinal gas. Gastroenterology 1970, 59:921–929.

[7] Zhou M, Hernandez-Sanabria E, Guan LL: Characterization of variation in rumen methanogenic communities under different dietary and host feed efficiency conditions, as determined by PCR-denaturing gradient gel electrophoresis analysis. Appl Environ Microbiol 2010, 76:3776–3786.

[8] Hoffmann C, Dollive S, Grunberg S, Chen J, Li H, Wu GD, Lewis JD, Bushman FD: Archaea and fungi of the human gut microbiome: correlations with diet and bacterial residents. PLoS One 2013, 8:e66019.

[9] Carberry CA, Waters SM, Kenny DA, Creevey CJ: Rumen methanogenic genotypes differ in abundance according to host residual feed intake phenotype and diet type. Appl Envir Microbiol 2014, 80:586–594.

[10] Samuel BS, Gordon JI: A humanized gnotobiotic mouse model of host-archaeal-bacterial mutualism. Proc Natl Acad Sci USA 2006, 103:10011–10016.

[11] Joblin KN, Naylor GE, Williams AG: Effect of Methanobrevibacter smithii on xylanolytic activity of anaerobic ruminal fungi. Appl Envir Microbiol 1990, 56:2287–2295.

[12] Facey H V, Northwood KS, Wright A-DG: Molecular diversity of methanogens in fecal samples from captive Sumatran orangutans (Pongo abelii). Amer J Primatol 2012, 74:408–413.

[13] Jones WJ, Nagle DP, Whitman WB: Methanogens and the diversity of archaebacteria. Microbiol Rev 1987, 51:135–177.

[14] Thomas NA, Jarrell KF: Characterization of flagellum gene families of methanogenic archaea and localization of novel flagellum accessory proteins. J Bacteriol 2001, 183:7154–7164.

[15] Flourie B, Etanchaud F, Florent C, Pellier P, Bouhnik Y, Rambaud JC: Comparative study of hydrogen and methane production in the human colon using caecal and faecal homogenates. Gut 1990, 31:684–685.

[16] Mathur R, Kim G, Morales W, Sung J, Rooks E, Pokkunuri V, Weitsman S, Barlow GM, Chang C, Pimentel M: Intestinal Methanobrevibacter smithii but not total bacteria is related to diet-induced weight gain in rats. Obesity (Silver Spring) 2013, 21:748–754.

[17] Horz H-P, Conrads G: Methanogenic archaea and oral infections—ways to unravel the black box. J Oral Microbiol 2011, 3:1–11.

[18] Maukonen J, Mättö J, Suihko M-L, Saarela M: Intra-individual diversity and similarity of salivary and faecal microbiota. J Med Microbiol 2008, 57(Pt 12):1560–1568.

[19] Cloarec D, Bornet F, Gouilloud S, Barry JL, Salim B, Galmiche JP: Breath hydrogen response to lactulose in healthy subjects: relationship to methane producing status. Gut 1990, 31:300–304.

[20] Jahng J, Jung IS, Choi EJ, Conklin JL, Park H: The effects of methane and hydrogen gases produced by enteric bacteria on ileal motility and colonic transit time. Neurogastroenterol Motil 2012, 24:185–190, e92.

[21] Ohsawa I, Ishikawa M, Takahashi K, Watanabe M, Nishimaki K, Yamagata K, Katsura K-I, Katayama Y, Asoh S, Ohta S: Hydrogen acts as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals. Nat Med 2007, 13:688–694.

http://dx.doi.org/10.5772/64637

[22] Ohta S: Recent progress toward hydrogen medicine: potential of molecular hydrogen for preventive and therapeutic applications. Curr Pharm Des 2011, 17:2241–2252.

[23] Janssen PH: Influence of hydrogen on rumen methane formation and fermentation balances through microbial growth kinetics and fermentation thermodynamics. Anim Feed Sci Technol 2010, 160:1–22.

[24] Hook SE, Wright A-DG, McBride BW: Methanogens: methane producers of the rumen and mitigation strategies. Archaea 2010, 2010:945785.

[25] Issa R: Non-pathogenic protozoa. Int J Pharma Pharm Sci 2014, 6:30–40.

[26] Molecular Detection of Human Parasitic Pathogens. Dongyou Liu, editor. New York: CRC Press; 2012, 895 p. ISBN: 978-1-4398-1242-6

[27] Christl SU, Murgatroyd PR, Gibson GR, Cummings JH: Production, metabolism, and excretion of hydrogen in the large intestine. Gastroenterology 1992, 102(4 Pt 1):1269–1277.

[28] Zhang Y, Tang Z-H, Ren Z, Qu S-L, Liu M-H, Liu L-S, Jiang Z-S: Hydrogen sulfide, the next potent preventive and therapeutic agent in aging and age-associated diseases. Mol Cell Biol 2013, 33:1104–1113.

[29] Cord-Ruwisch R, Seitz H-J, Conrad R: The capacity of hydrogentrophic anaerobic bacteria to compete for traces of hydrogen depends on the redox potential of the electron acceptor. Arch Microbiol 1988, 149:350–357.

[30] Lopez S, McIntosh FM, Wallace RJ, Newbold CJ: Effect of adding acetogenic bacteria on methane production by mixed rumen microorganisms. Anim Feed Sci Technol 1999, 78:1–9.

[31] Sahakian AB, Jee S-R, Pimentel M: Methane and the gastrointestinal tract. Dig Dis Sci 2010, 55:2135–2143.

[32] Kormas KA, Meziti A, Mente E, Frentzos A: Dietary differences are reflected on the gut prokaryotic community structure of wild and commercially reared sea bream (Sparus aurata). Microbiologyopen 2014, 3:718–728.

[33] Weaver GA, Krause JA, Miller TL, Wolin MJ: Incidence of methanogenic bacteria in a sigmoidoscopy population: an association of methanogenic bacteria and diverticulosis. Gut 1986, 27:698–704.

[34] de Araujo Filho HB, Carmo-Rodrigues MS, Mello CS, Melli LCFL, Tahan S, Pignatari ACC, de Morais MB: Children living near a sanitary landfill have increased breath methane and Methanobrevibacter smithii in their intestinal microbiota. Archaea 2014, 2014:576249.

[35] McKay LF, Eastwood MA, Brydon WG: Methane excretion in man—a study of breath, flatus, and faeces. Gut 1985, 26:69–74.

[36] Pimentel M, Lin HC, Enayati P, van den Burg B, Lee H-R, Chen JH, Park S, Kong Y, Conklin J: Methane, a gas produced by enteric bacteria, slows intestinal transit and augments small intestinal contractile activity. Am J Physiol Gastrointest Liver Physiol 2006, 290:G1089–G1095.

[37] Wang R: Two's company, three's a crowd: can H2S be the third endogenous gaseous transmitter? FASEB J 2002, 16:1792–1798.

[38] Ignarro LJ, Buga GM, Wood KS, Byrns RE, Chaudhuri G: Endothelium-derived relaxing factor produced and released from artery and vein is nitric oxide. Proc Natl Acad Sci 1987, 84:9265–9269.

[39] Haines A, Metz G, Dilawari J, Blendis L, Wiggins H: Breath-methane in patients with cancer of the large bowel. Lancet (London, England) 1977, 2:481–483.

[40] Rana SV, Malik A: Breath tests and irritable bowel syndrome. World J Gastroenterol 2014, 20:7587–7601.

[41] Mathur R, Amichai M, Chua KS, Mirocha J, Barlow GM, Pimentel M: Methane and hydrogen positivity on breath test is associated with greater body mass index and body fat. J Clin Endocrinol Metab 2013, 98:E698–E702.

[42] Pimentel M, Mayer AG, Park S, Chow EJ, Hasan A, Kong Y: Methane production during lactulose breath test is associated with gastrointestinal disease presentation. Dig Dis Sci 2003, 48:86–92.

[43] Drossman DA: The functional gastrointestinal disorders and the Rome III process. Gastroenterol 2006, 130:1377–1390.

[44] Ley RE, Bäckhed F, Turnbaugh PJ, Lozupone CA, Knight RD, Gordon JI: Obesity alters gut microbial ecology. Proc Natl Acad Sci USA 2005, 102:11070–11075.

[45] Tsai Y-T, Cheng P-C, Pan T-M: Anti-obesity effects of gut microbiota are associated with lactic acid bacteria. Appl Microbiol Biotech 2013, 1:1–10.

[46] Turnbaugh PJ, Hamady M, Yatsunenko T, Cantarel BL, Duncan AE, Ley RE, Sogin ML, Jones WJ, Roe BA, Affourtit JP, Egholm M, Henrissat B, Heath AC, Knight R, Gordon JI: A core gut microbiome in obese and lean twins. Nature 2009, 457:480–484.

[47] Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI: An obesity-associated gut microbiome with increased capacity for energy harvest. Nature 2006, 444:424–438.

[48] Koren O, Goodrich JK, Cullender TC, Spor A, Laitinen K, Bäckhed HK, Gonzalez A, Werner JJ, Angenent LT, Knight R, Bäckhed F, Isolauri E, Salminen S, Ley RE: Host remodeling of the gut microbiome and metabolic changes during pregnancy. Cell 2012, 150:470–480.

[49] Bäckhed F, Ding H, Wang T, Hooper L V, Koh GY, Nagy A, Semenkovich CF, Gordon JI: The gut microbiota as an environmental factor that regulates fat storage. Proc Natl Acad Sci USA 2004, 101:15718–15723.

[50] Vijay-Kumar M, Aitken JD, Carvalho FA, Cullender TC, Mwangi S, Srinivasan S, Sitaraman S V, Knight R, Ley RE, Gewirtz AT: Metabolic syndrome and altered gut microbiota in mice lacking Toll-like receptor 5. Science 2010, 328:228–231.

[51] Cani PD, Bibiloni R, Knauf C, Waget A, Neyrinck AM, Delzenne NM, Burcelin R: Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. Diabetes 2008, 57:1470–1481.

[52] Creely SJ, McTernan PG, Kusminski CM, Fisher fM, Da Silva NF, Khanolkar M, Evans M, Harte AL, Kumar S: Lipopolysaccharide activates an innate immune system response in human adipose tissue in obesity and type 2 diabetes. Am J Physiol Endocrinol Metab 2007, 292:E740–E747.

[53] Cani PD, Amar J, Iglesias MA, Poggi M, Knauf C, Bastelica D, Neyrinck AM, Fava F, Tuohy KM, Chabo C, Waget A, Delmée E, Cousin B, Sulpice T, Chamontin B, Ferrières J, Tanti J-F, Gibson GR, Casteilla L, Delzenne NM, Alessi MC, Burcelin R: Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes 2007, 56:1761–1772.

[54] Musso G, Gambino R, Cassader M: Obesity, diabetes, and gut microbiota: the hygiene hypothesis expanded? Diabetes Care 2010, 33:2277–2284.

[55] Chou CJ, Membrez M, Blancher F: Gut decontamination with norfloxacin and ampicillin enhances insulin sensitivity in mice. Nestlé Nutr Work Ser Paediatr Program 2008, 62:127–140.

[56] Basseri RJ, Basseri B, Pimentel M, Chong K, Youdim A, Low K, Hwang L, Soffer E, Chang C, Mathur R: Intestinal methane production in obese individuals is associated with a higher body mass index. Gastroenterol Hepatol (N Y) 2012, 8:22–28.

[57] Armougom F, Henry M, Vialettes B, Raccah D, Raoult D: Monitoring bacterial community of human gut microbiota reveals an increase in Lactobacillus in obese patients and methanogens in anorexic patients. PLoS One 2009, 4:e7125.

[58] Faria M, Pavin EJ, Parisi MCR, Lorena SLS, Brunetto SQ, Ramos CD, Pavan CR, Mesquita MA: Delayed small intestinal transit in patients with long-standing type 1 diabetes mellitus: investigation of the relationships with clinical features, gastric emptying, psychological distress, and nutritional parameters. Diabetes Technol Ther 2013, 15:32–38.

[59] Cesario V, Di Rienzo TA, Campanale M, D'angelo G, Barbaro F, Gigante G, Vitale G, Scavone G, Pitocco D, Gasbarrini A, Ojetti V: Methane intestinal production and poor metabolic control in type I diabetes complicated by autonomic neuropathy. Minerva Endocrinol 2014, 39:201–207.

[60] Ojetti V, Pitocco D, Scarpellini E, Zaccardi F, Scaldaferri F, Gigante G, Gasbarrini G, Ghirlanda G, Gasbarrini A: Small bowel bacterial overgrowth and type 1 diabetes. Eur Rev Med Pharmacol Sci 2009, 13:419–423.

[61] Mathur R, Goyal D, Kim G, Barlow GM, Chua KS, Pimentel M: Methane-producing human subjects have higher serum glucose levels during oral glucose challenge than non-methane producers: a pilot study of the effects of enteric methanogens on glycemic regulation. Res J Endocrinol Metab 2014, 2.

[62] American Cancer Society. 2016. Accessed March 10, 2016. Available from: www.cancer.org

[63] Mazmanian SK, Liu CH, Tzianabos AO, Kasper DL: An immunomodulatory molecule of symbiotic bacteria directs maturation of the host immune system. Cell 2005, 122:107–118.

[64] Xuan C, Shamonki JM, Chung A, Dinome ML, Chung M, Sieling PA, Lee DJ: Microbial dysbiosis is associated with human breast cancer. PLoS One 2014, 9:e83744.

[65] Blaser MJ: Understanding microbe-induced cancers. Cancer Prev Res (Phila) 2008, 1:15–20.

[66] Eckburg PB, Lepp PW, Relman DA: Archaea and their potential role in human disease. Infect Immun 2003, 71:591–596.

[67] Gill EE, Brinkman FSL: The proportional lack of archaeal pathogens: do viruses/phages hold the key? Bioessays 2011, 33:248–254.

[68] Roccarina D, Lauritano EC, Gabrielli M, Franceschi F, Ojetti V, Gasbarrini A: The role of methane in intestinal diseases. Am J Gastroenterol 2010, 105:1250–1256.

[69] Scanlan PD, Shanahan F, Marchesi JR: Human methanogen diversity and incidence in healthy and diseased colonic groups using mcrA gene analysis. BMC Microbiol 2008, 8:79.

[70] Abell GCJ, Conlon Ma, McOrist AL: Methanogenic archaea in adult human faecal samples are inversely related to butyrate concentration. Microb Ecol Health Dis 2006, 18(September):154–160.

[71] Kim YS, Milner JA: Dietary modulation of colon cancer risk. J Nutr 2007, 137(11 Suppl): 2576S–2579S.

[72] Smith CJ, Rocha ER, Pastor BJ: The medically important Bacteroides spp. in health and disease. Prokaryotes 2006, 7:381–427.

[73] Scheppach W: Effects of short chain fatty acids on gut morphology and function. Gut 1994, 35(1 Suppl):S35–S38.

[74] Piqué JM, Pallarés M, Cusó E, Vilar-Bonet J, Gassull MA: Methane production and colon cancer. Gastroenterology 1984, 87:601–605.

[75] Holma R, Korpela R, Sairanen U, Blom M, Rautio M, Poussa T, Saxelin M, Osterlund P: Colonic methane production modifies gastrointestinal toxicity associated with adjuvant 5-fluorouracil chemotherapy for colorectal cancer. J Clin Gastroenterol 2013, 47:45–51.

[76] Liebling T, Rosenman KD, Pastides H, Griffith RG, Lemeshow S: Cancer mortality among workers exposed to formaldehyde. Am J Ind Med 1984, 5:423–428.

[77] Attene-Ramos MS, Wagner ED, Plewa MJ, Gaskins HR: Evidence that hydrogen sulfide is a genotoxic agent. Mol Cancer Res 2006, 4:9–14.

[78] Szabo C, Coletta C, Chao C, Módis K, Szczesny B, Papapetropoulos A, Hellmich MR: Tumor-derived hydrogen sulfide, produced by cystathionine-β-synthase, stimulates bioenergetics, cell proliferation, and angiogenesis in colon cancer. Proc Natl Acad Sci USA 2013, 110:12474–12479.

[79] Aragon G, Graham DB, Borum M, Doman DB: Probiotic therapy for irritable bowel syndrome. Gastroenterol Hepatol (N Y) 2010, 6:39–44.

[80] Xu G-Y, Winston JH, Shenoy M, Zhou S, Chen JDZ, Pasricha PJ: The endogenous hydrogen sulfide producing enzyme cystathionine-beta synthase contributes to visceral hypersensitivity in a rat model of irritable bowel syndrome. Mol Pain 2009, 5:44.

[81] Maccaferri S, Candela M, Turroni S, Centanni M, Severgnini M, Consolandi C, Cavina P, Brigidi P: IBS-associated phylogenetic unbalances of the intestinal microbiota are not reverted by probiotic supplementation. Gut Microbes 2012, 3:406–413.

[82] Saulnier DM, Riehle K, Mistretta T-A, Diaz M-A, Mandal D, Raza S, Weidler EM, Qin X, Coarfa C, Milosavljevic A, Petrosino JF, Highlander S, Gibbs R, Lynch S V, Shulman RJ, Versalovic J: Gastrointestinal microbiome signatures of pediatric patients with irritable bowel syndrome. Gastroenterology 2011, 141:1782–1791.

[83] Nelson TA, Holmes S, Alekseyenko A V, Shenoy M, DeSantis TZ, Wu CH, Andersen GL, Winston J, Sonnenburg J, Pasricha PJ, Spormann A: PhyloChip microarray analysis reveals altered gastrointestinal microbial communities in a rat model of colonic hypersensitivity. Neurogastroenterol and Motil 2011, 23:169–177, e41–2.

[84] Kumar S, Misra A, Ghoshal UC: Patients with irritable bowel syndrome exhale more hydrogen than healthy subjects in fasting state. J Neurogastroenterol Motil 2010, 16:299–305.

[85] Furnari M, Savarino E, Bruzzone L, Moscatelli A, Gemignani L, Giannini EG, Zentilin P, Dulbecco P, Savarino V: Reassessment of the role of methane production between irritable bowel syndrome and functional constipation. J Gastroenterol Liver Dis 2012, 21:157–163.

[86] Mann NS, Limoges-Gonzales M: The prevalence of small intestinal bacterial overgrowth in irritable bowel syndrome. Hepatogastroenterology 2009, 56:718–721.

[87] Magge S, Lembo A: Low-FODMAP diet for treatment of irritable bowel syndrome. Gastroenterol Hepatol (N Y) 2012, 8:739–745.

[88] Simrén M, Månsson A, Langkilde AM, Svedlund J, Abrahamsson H, Bengtsson U, Björnsson ES: Food-related gastrointestinal symptoms in the irritable bowel syndrome. Digestion 2001, 63:108–115.

[89] Zhu Y, Zheng X, Cong Y, Chu H, Fried M, Dai N, Fox M: Bloating and distention in irritable bowel syndrome: the role of gas production and visceral sensation after lactose ingestion in a population with lactase deficiency. Am J Gastroenterol 2013, 108:1516–1525.

[90] Kim G, Deepinder F, Morales W, Hwang L, Weitsman S, Chang C, Gunsalus R, Pimentel M: Methanobrevibacter smithii is the predominant methanogen in patients with constipation-predominant IBS and methane on breath. Dig Dis Sci 2012, 57:3213–3218.

[91] Rajilić-Stojanović M, Heilig HGHJ, Molenaar D, Kajander K, Surakka A, Smidt H, de Vos WM: Development and application of the human intestinal tract chip, a phylogenetic microarray: analysis of universally conserved phylotypes in the abundant microbiota of young and elderly adults. Env Microbiol 2009, 11:1736–1751.

[92] Blais Lecours P, Duchaine C, Taillefer M, Tremblay C, Veillette M, Cormier Y, Marsolais D: Immunogenic properties of archaeal species found in bioaerosols. PLoS One 2011, 6:e23326.

[93] Blais Lecours P, Marsolais D, Cormier Y, Berberi M, Haché C, Bourdages R, Duchaine C: Increased prevalence of Methanosphaera stadtmanae in inflammatory bowel diseases. PLoS One 2014, 9:e87734.

[94] Paun A, Danska JS: Immuno-ecology: how the microbiome regulates tolerance and autoimmunity. Curr Opin Immunol 2015, 37:34–39.

[95] Attaluri A, Jackson M, Valestin J, Rao SSC: Methanogenic flora is associated with altered colonic transit but not stool characteristics in constipation without IBS. Amer J Gastroenterol 2010, 105:1407–1411.

[96] Painter NS, Burkitt DP: Diverticular disease of the colon: a deficiency disease of Western civilization. Br Med J 1971, 2:450–454.

[97] Jang S-I, Kim J-H, Youn YH, Park H, Lee SI, Conklin JL: Relationship between intestinal gas and the development of right colonic diverticula. J Neurogastroenterol Motil 2010, 16:418–423.

[98] Rahkonen P, Ettala M, Laukkanen M, Salkinoja-Salonen M: Airborne microbes and endotoxins in the work environment of two sanitary landfills in Finland. Aerosol Sci Technol 1990, 13:505–513.

[99] Pimentel M, Lembo A, Chey WD, Zakko S, Ringel Y, Yu J, Mareya SM, Shaw AL, Bortey E, Forbes WP: Rifaximin therapy for patients with irritable bowel syndrome without constipation. New Eng J Med 2011, 364:22–32.

[100] Pimentel M, Gunsalus RP, Rao SSC, Zhang H: Methanogens in human health and disease. Amer J Gastroenterol 2012, 1:28–33.

[101] Miller TL, Wolin MJ: Methanogens in human and animal intestinal tracts. Syst Appl Microbiol 1986, 7:223–229.

[102] Choi CH, Chang SK: Alteration of gut microbiota and efficacy of probiotics in functional constipation. J Neurogastroenterol Motil 2015, 21:4–7.

[103] Ringel Y, Quigley EM, Lin HC: Using probiotics in gastrointestinal disorders. Amer J Gastroenterol Suppl 2012, 1:34–40.

[104] Jouët P, Moussata D, Duboc H, Boschetti G, Attar A, Gorbatchef C, Sabaté J-M, Coffin B, Flourié B: Effect of short-chain fatty acids and acidification on the phasic and tonic motor activity of the human colon. Neurogastroenterol Motil 2013, 25:943–949.

[105] Alang N, Kelly CR: Weight gain after fecal microbiota transplantation. Open Forum Infect Dis 2015, 2:ofv004.

[106] Ridaura VK, Faith JJ, Rey FE, Cheng J, Duncan AE, Kau AL, Griffin NW, Lombard V, Henrissat B, Bain JR, Muehlbauer MJ, Ilkayeva O, Semenkovich CF, Funai K, Hayashi DK, Lyle BJ, Martini MC, Ursell LK, Clemente JC, Van Treuren W, Walters WA, Knight R, Newgard CB, Heath AC, Gordon JI: Gut microbiota from twins discordant for obesity modulate metabolism in mice. Science 2013, 341:1241214.