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Review

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Gut Archaea in the context of human diseases*

Archeony jelitowe w kontekście chorób człowieka

Agnieszka Krawczyk[1], Dominika Salamon[1], Kinga Kowalska-Duplaga[2], Tomasz Gosiewski[1]

[1]Department of Molecular Medical Microbiology, Chair of Microbiology, Faculty of Medicine, Jagiellonian University Medical College, Krakow, Poland
[2]Department of Pediatrics, Gastroenterology and Nutrition, Faculty of Medicine, Jagiellonian University Medical College, Krakow, Poland

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Summary: Recently, thanks to the revolution of molecular biology techniques, there has been a rapid development of research on human intestinal microbiome. The use of modern molecular methods has confirmed that the human gastrointestinal tract is the habitat of a huge number of microorganisms forming a complex ecosystem. This ecosystem contains microorganisms belonging to three main domains: Bacteria, Archaea and Eukaryota, which play an important role in human health and disease. Recently, more and more evidence has emerged indicating the role of microorganisms in pathogenesis of multiple diseases. As a result of this, intestinal microorganisms have been recognized on the one hand as a factor that may be involved in inducing metabolic, inflammatory or neuropsychiatric diseases, and on the other hand as a potential therapeutic target. When considering the pathogenesis of specific diseases, most researchers focus primarily on the role of bacteria and fungi, while there are only few studies that include archaeons. These microorganisms, even though relatively small in number, may prove to be a key element in research on the role of the microbiome in the etiology of various diseases. The aim of this work is a systematic review of knowledge on the participation of intestinal archaeons in the course of selected diseases.

Keywords: **archaea, gut microbiota, chronic diseases, methanogens**

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Author's address: dr hab. Tomasz Gosiewski, prof. UJ, Department of Molecular Medical Microbiology, Chair of Microbiology, Faculty of Medicine, Jagiellonian University Medical College, ul. Czysta 18, 31-121 Kraków, Poland, Kraków; e-mail: tomasz.gosiewski@uj.edu.pl

Abbreviations: **BMI** – body mass index, **CRC** – colorectal cancer, **GALT** – gut-associated lymphoid tissue, **IBD** – inflammatory bowel disease, **IBS** – irritable bowel syndrome, **IBS-C** – constipation-predominant irritable bowel syndrome, **IBS-D** – diarrhea-predominant irritable bowel syndrome, **IBS-M** – mixed irritable bowel syndrome, **IB-U** – unclassified irritable bowel syndrome, **IL-1β** – interleukin 1β, **MALT** – mucosa-associated lymphoid tissue, **moDCs** – monocyte-derived dendritic cells, **MSS** – Methanosphaer-stadtmanae, **PBMCs** – peripheral blood mononuclear cells, **qPCR** – quantitative polymerase chain reaction, **SCFA** – short-chain fatty acids, **TMA** – trimethylamine, **TMAO** – trimethylamine N-oxide, **TNF-α** – tumor necrosis factor.

INTRODUCTION

Recently, thanks to the revolution of molecular biology techniques, there has been a rapid development of research on human intestinal microbiome. The use of modern molecular methods has confirmed that the human gastrointestinal tract is the habitat of a huge number of microorganisms forming a complex ecosystem. This ecosystem contains microorganisms belonging to three main domains: Bacteria, Archaea and Eukaryota, which play an important role in human health and disease [6]. Their common genome (microbiome) contains 100 times more genes than the human genome (which has about 30 thousand genes) [50]. The main task of the digestive system is to participate in the digestion and absorption of nutrients; however, its role is not limited to these two functions only. The gut-associated lymphoid tissue (GALT) as a part of mucosa-associated lymphoid tissue (MALT) plays an important role in immunological processes. Moreover, microorganisms present in the gastrointestinal tract are responsible for the production of some vitamins, take part in protection against pathogenic microorganisms, contribute to sealing the intestinal barrier, show anti-carcinogenic effects, stimulate the process of angiogenesis and also play a key role in the functioning of the host immune system [31]. A properly balanced intestinal microbiota is an essential component of the human body, necessary to maintain homeostasis and good health.

Recently, more and more evidence has emerged indicating the role of microorganisms in the pathogenesis of multiple diseases. As a result of this, intestinal microorganisms have been recognized, on the one hand, as a factor that may be involved in inducing metabolic, inflammatory or neuropsychiatric diseases and, on the other hand, as a potential therapeutic target [24, 26, 30, 44, 51]. When considering the pathogenesis of specific diseases, most researchers focus primarily on the role of bacteria and fungi [17, 27, 35], which dominate quantitatively in the gastrointestinal tract, while there are still few studies that include archaeons. These microorganisms, even though relatively small in number, may prove to be a key element in research on the role of the microbiome in the etiology of various diseases.

Archaea is divided into three main groups: methanogenic (methanogens), halophilic and thermophilic archaeons. Among archaeons colonizing the human gastrointestinal tract, methanogens are the most numerous group. The most common species is *Methanobrevibacter smithii,* whose presence is found in almost 96% of individuals. Moreover, 30% of the population is colonized by *Methanosphaera stadtmanae* [9]. Few studies also indicate the presence of methanogenes of the genus *Methanosarcina* [46], halophiles of the *Halobacteriaceae* family and thermophilic archaeons of the genus *Sulfolobus* [43] and *Nitrososphaera*,which are capable of ammonia oxidation [21].

Archaeons are characterized by a unique structure of the cell wall, which contains pseudomureaine (consisting of N-acetylglucosamine and a polymer of N-acetylotalosaminouronic acid), methanechondroitin or sulphate heteropoly-saccharide composed of uronic acids, N-acetylamino sugars, monosaccharides and glycine [12].

The Archaea cell membrane contains L-glycerol-1-phosphate and branched isoprenoid chains are attached to glycerol molecules. Ether bonds between isoprenoid molecules and glycerol are an important element, as other living organisms have ester bonds here. A large group of archaeons is also characterized by the presence of specific external structures, such as cannulae, hooks ("hami"), archaella or pili. They enable e.g. movement, adhesion to different surfaces and cells, creation of biofilms, exchange of nutrients between cells or creation of a dense cell network [12]. Some of the archaeons are also capable of producing archaeocytes and signal molecules – acyl-homoserine lactones, which are primarily responsible for communication between the cells. The genetic material of archaeons is packed in the nucleosome thread, whose core is formed by histone proteins, which makes them resemble more eukaryotic organisms than bacteria [12].

Although Archaea is known to be part of the commensal microbiota of humans, the answer to the question of whether these microorganisms can play a role in the pathogenesis of certain diseases in humans and how they affect the host organism and other gastrointestinal colonizing microorganisms is still unknown.

The aim of this work is a systematic review of knowledge on the participation of intestinal archaeons in the course of selected diseases.

THE ROLE OF ARCHAEONS IN INFLAMMATORY BOWEL DISEASE

Patients with inflammatory bowel disease (IBD), which includes Crohn's disease and ulcerative colitis, have qualitative and quantitative disorders in the composition of intestinal microbiota. The studies to date have focused primarily on the participation of bacteria in the pathogenesis of IBD [13, 20, 35]; however, it has rarely been noted that archaeons may also play an important role in the disease development.

Conway de Macario et al. were the first to demonstrate broad immunogenic properties of glycan structures of Archaea pseudopeptidoglycans [7], which may be of fundamental importance in the stimulation of hyperactive immune response leading to the development of autoimmune diseases, including IBD. In turn, Blais-Lecours et al. demonstrated that *M. stadtmanae* (MSS) is significantly more common in patients with IBD than in healthy individuals. What is more, in plasma of the examined patients, in whom previously the presence of MSS was found in the faeces, the increased

concentration of MSS-specific IgG antibodies was demonstrated, as opposed to those in whom this species was not detected in the gastrointestinal tract [3]. It is worth adding that peripheral blood mononuclear cells (PBMCs) collected from healthy volunteers, which were stimulated during culture with *M. stadtmanae*, showed more than a 4-fold higher tumor necrosis factor (TNF-α) synthesis compared to PBMCs stimulated by the most common species of methanogenic archaea in the gastrointestinal tract – *M. smithii* [3].

Other independent studies have also documented the contribution of MSS to the excessive activation of pro-inflammatory proteins. Bang et al. demonstrated that human monocyte-derived dendritic cells (moDCs) stimulated by MSS activated the release of TNF-α at the level oscillating between 45–62 ng/ml and interleukin 1β (IL-1β) in the amount of 1.2–2.8 ng/ml, whereas moDC stimulated by *M. smithii* cells induced the secretion of these cytokines to a lesser extent, 2–5 ng/ml TNF-α and 0.2 IL-1β, respectively [1]. These results confirm the huge immunogenic potential of MSS and may indicate the role of these microorganisms in the pathogenesis of IBD.

THE LINK BETWEEN ARCHAEONS AND OBESITY

The research on obesity in animal models concerning the participation of archaeons in the development of this disease, focuses primarily on the role of methanogenes. Samuel and Gordon demonstrated that the inoculation of mice bred under germ-free conditions with *Bacteroides thetaiotaomicron* and methanogenic archaea species – *M. smithii*, resulted in significantly higher body weight gain in these rodents compared to individuals colonized exclusively by *B. thetaiotaomicron* or a combination of *B. thetaiotaomicron* and *Desulfovibrio piger* (sulfate – reducing bacteria) [45]. As shown in further analysis, *M. smithii* influenced energy metabolism as a "metabolic intermediary" through a series of interrelated fermentation mechanisms with other bacteria, which had significantly influenced the amount of calories absorbed and their storage in the form of fats [45]. Subsequent studies, combining whole genome transcriptional profiling, mass spectrometry and biochemical assays (using RNA isolated from mouse feces), were conducted to determine the effect of *M. smithii* on the utilization of glycans by *B. thetaiotaomicronin in vivo*. As it turned out, *M. smithii* drastically altered *B. thetaiotaomicron's* transcriptome; 638 genes were described as significantly up-regulated and 462 genes were defined as significantly down-regulated in relation to their levels of expression in monoassociated mice with *B. thetaiotaomicron* ($p<0.05$). The presence of *M. smithii* has reduced the expression of *B. thetaiotaomicron* genes involved in carbohydrate metabolism, including 57 glycosidic hydrolyses, while it induced three fructofuranosidases [45]. The above relations "redirected" the metabolism of *B. thetaiotaomicron* to the fermentation of fructates to acetates; increased ability to obtain calories from this class of polysaccharides had a significant effect on the storage of calories in the form of fats. Mutualism of bacteria with archaeons resulted in increased production and absorption of short-chain fatty acids (SCFA) and stimulation of lipogenesis. It also led to an increase in total triglyceride levels in the liver. After *B. thetaiotaomicron*/*M. smithii* biassociation, the total body fat stores increased by 47%, in particular the increase in obesity was not accompanied by statistically significant differences in food consumption [45]. Similar relationships were observed in the co-culture of archaeons and fungi [23]. Methanogens indirectly altered the fungal fermentation processes, which resulted in increased digestion of some polysaccharides and consequently increased body fat storage [23]. The above results clearly indicate that the growth of adipose tissue is not only dependent on the quantity and quality of supplied food but also largely depends on the fermentation capacity of intestinal microbiota, including archaeons [45]. Similar conclusions were reached by Mathur et al. The researchers demonstrated that the change of rat diet from normal to high-fat correlates with the increase of *M. smithii* in faeces and bioptates taken from the small intestine [34]. Importantly, rats with the highest weight gain were characterized by a significantly higher abundance of *M. smithii* than rats whose weight remained unchanged or increased slightly ($p < 0.01$). After the feeding period with high-fat feed, some of the rodents were put on normal diet and, after following 253 days, the body weight of all animals was compared. As it turned out, the rats with the highest weight showed the highest degree of colonization by *M. smithii*, regardless of whether they were on a normal diet or a high-fat diet in the final stage of the study. These individuals were characterized not only by an increased number of methanogens, but they also had all the examined bowel segments colonized by *M. smithii* [34]. The results of these studies seem to confirm the hypothesis that the extent of intestinal colonization by methanogens in animal models is related to body weight changes. The metabolic processes carried out by these archaeon species contribute to more efficient energy generation from carbohydrates, which may lead to the accumulation of additional calories and body weight gain.

It seems that the relationships described above can be confirmed in human studies. One of the methods used to assess the occurrence of methanogenic archaeons in the human gastrointestinal tract is the measurement of methane in the exhaled breath. It is assumed that the amount of exhaled methane is correlated with the number of these microorganisms in the gastrointestinal tract, which was confirmed by quantitative polymerase chain reaction (qPCR) [2, 13]. Methane measurements in the end-expiratory breath sample taken from overweight patients and normal body weight individuals showed that the presence of this gas was associated with a higher average body mass index (BMI), both in the population with normal weight and in obese individuals. The mean BMI of methane-positive obese patients was 45.2 kg/m^2 compared to 38.5kg/m^2 in methane-negative subjects [2].

Due to the fact that archaeons use hydrogen in methanogenesis, the measurement of the concentration of this gas in the exhaled breath is also used to assess the occurrence of methanogens. The simultaneous presence of methane and hydrogen showed a higher degree of positive correlation with the BMI value. In patients with confirmed presence of both gases, BMI was higher on average by 4.5 kg/m^2 compared to those who had only methane presence in the exhaled breath [33].

M. smithii using hydrogen atoms accelerates the fermentation of carbohydrates (especially polysaccharides). The production of short-chain fatty acids is increased, which are subsequently absorbed in the gastrointestinal tract and stored as an additional source of energy for the host. This, in turn, contributes to weight gain, which has been confirmed in numerous animal studies [34, 45]. For this reason, the measurement of both hydrogen and methane in the exhaled breath can become a simple test to detect the risk of obesity. More detailed studies using molecular methods have shown that obese individuals were characterized by a much higher number of methanogenic Archaea using hydrogen as compared to individuals with normal body weight [54]. In obese patients, the average number of archaeons was 5.5×10^6 copies of the gene/gram of faeces, compared to undetectable levels in a healthy control group. It is noteworthy that the number of archaeons has decreased significantly among obese individuals after gastric bypass surgery [54]. The relation between increased body weight and methanogenes was also described by Mbakwa et al. In a cohort study involving 472 children, they demonstrated that the presence and higher numbers of *M. smithii* in the gastrointestinal tract were positively correlated with higher body weight, higher BMI and overweight [36].

So far, it has not been clearly established whether the increased number of methanogens among obese people is the primary cause of weight gain or whether it is only a secondary effect related to, among others, diet or co-occurring intestinal dysbiosis. Nevertheless, research on the significance of archaeons in obesity seems promising and may contribute to a better understanding of metabolic processes taking place in the intestine. Moreover, they may provide in the future a basis for the implementation of targeted antibiotic or probiotic therapy as a therapeutic option supporting other methods of the treatment of obesity.

THE ROLE OF ARCHAEONS IN COLORECTAL CANCER

Numerous studies show a link between gastrointestinal cancers and environmental factors such as diet or lifestyle [47, 48, 53]. It has been suggested that the risk of disease also depends on the interaction between diet and gastrointestinal microorganisms, including archaeons. One of the first studies, shedding light on the possible contribution of methanogens in the pathogenesis of colorectal cancer (CRC), was presented by Haines et al. The researchers showed that the presence of methane in the exhaled breath was found in almost 80% of patients with colorectal cancer, while among a healthy population, a positive result was found in less than 40% of subjects [19]. Similar results were obtained by Pique et al., who found that in exhaled breath samples taken from patients, methane was present in 91.4% of oncological patients, whereas among healthy population the presence of this gas was found in 40% of people. Interestingly, among 36 patients in whom the cancer was resected, the percentage of those with positive methane results in exhaled air, dropped to 47.2% [41]. These results contributed in the following years to the increase of interest in methane archaeons in the etiology of gastrointestinal cancers. Following this lead, Mira-Pascual et al. have attempted to determine the incidence of archaeons in patients with colorectal cancer using pyrosequencing and qPCR. They observed that both faeces and tissue bioptats taken from patients with CRC presented with increased colonization by archaeons compared to healthy individuals [37]. Moreover, the researchers found out a positive correlation between CRC process development and the level of *Methanobacteriales* (R = 0.537) and *Methanobrevibacterium* (R = 0.574) in faecal samples ($p<0.05$). Two subgroups of CRC patients were identified: patients with malignant form – adenocarcinoma and patients with benign type – tubular adenoma. The number of *Methanobacteriales* among patients with malignant form of cancer was higher compared to patients with tubular adenoma (6.28 gene/mg copies vs. 4.24 in faecal samples and 4.87 vs. 4.27 in tissue biopsy, respectively). Increased colonization by *M. smithii* was also observed in patients with adenocarcinoma vs. tubular adenoma – 4.98 vs. 3.54, respectively [37].

PARTICIPATION OF ARCHAEA IN THE IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome (IBS) is a frequently diagnosed functional gastrointestinal disorder. According to the Rome IV criteria, the group of these diseases is currently called disorders of intestinal-brain interaction. Depending on the dominant symptoms, there are four subtypes of IBS: diarrhea-predominant (IBS-D), constipation-predominant (IBS-C), mixed (IBS-M) and unclassified (IBS-U) [28]. Numerous studies have shown that patients with IBS suffer from intestinal dysbiosis, including an abnormal population of archaeons [52]. The main focus of Archaea domain in this disease entity is *M. smithii*, which is the dominant producer of methane in the intestines [10]. It has been proven that methane slows down the gut transit time and its concentration negatively correlates with the frequency of bowel movements [5, 39]. Numerous studies have shown that in the vast majority of patients with IBS-C, high concentration of methane in the exhaled breath was found [5, 18, 22, 40]. Moreover, the detection of methane in lactulose breath test in patients with IBS-C positively correlated with the severity of constipation [5], as well as with the presence and abundance of *M. smithii* [25]. Interestingly, in patients with IBS-D,

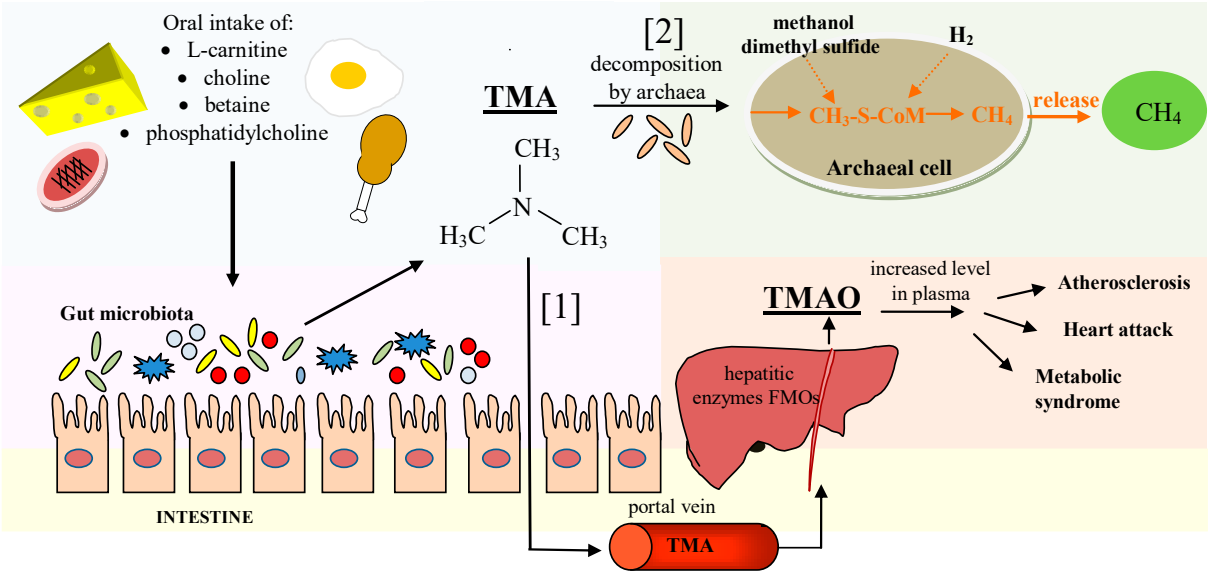

Fig. 1. Schematic diagram showing the metabolic pathway of TMA in the intestines. Dietary substances (L-carnitine, choline, betaine, phosphatidylocholine) introduced into the intestine by the oral route are converted by the gut microbiota into TMA; [1] – TMA is transported to the liver, where it is transformed by liver enzymes into TMAO. Further, TMAO concentration in blood increases, which contributes, among others, to atherosclerosis. [2] – an alternative pathway of TMA decomposition to CH4 by Archaea

hydrogen was found to be more frequent in the glucose breath test compared to patients with IBS-C (71% vs. 42%, respectively) [32].

Confirmation of the participation of methanogens in the pathogenesis of IBS may be provided by the results of studies, evaluating targeted antibiotic therapy for methanogenic archaeons. The use of rifaximine or neomycin in patients with IBS-C, to which methanogenic archaeons are susceptible [11], improved the intestinal passage. Moreover, the improvement of intestinal peristalsis and increase in the number of bowel movements correlated with a decrease in the level of methane in the exhaled breath and reduction of abdominal pain, as well as an overall improvement in patients' condition [15, 16, 29, 38]. Accurate quantitative molecular analyses based on qPCR showed that *M. smithii* was present in 95% of patients with IBS-C, 75% of patients with IBS-D and 100% of patients with IBS-U. The number of *M. smitii* was significantly higher in all IBS patients compared to the of healthy control group (log10 5.4 vs. log10 1.9 of *M. smithii* gene copies) [14]. The analysis in subgroups showed that IBS-C patients were characterized by more numerous Archaea in relation to IBS-D patients (log10 6.1 vs. log10 3.4 respectively). The excess of *M. smithii* was negatively correlated with the frequency of bowel movements in patients with IBS. Significantly, the presence of methane in the exhaled breath positively correlated with the occurrence of abdominal bloating. This symptom was present in 83% of methane-positive subjects compared to 36% of methane-negative persons [14].

The above-mentioned results allow us to believe that the increase in *M. smithii* can be considered a factor predisposing to the development of constipation and related discomfort caused by flatulence or abdominal pain. It is believed that methane produced by the archaeons acts as a neuromuscular transmitter, slowing down the intestinal peristaltic movement. This thesis may be supported by clinical studies, which demonstrate the relation between the presence of methane in breath tests or number of methanogens and diseases associated with delayed intestinal transit, such as IBS-C [49].

Important evidence confirming this hypothesis is the efficacy of antibiotic therapy targeted at methanogenic archaeons. Nevertheless, any speculations about Archaea's involvement in the pathogenesis of IBS needs to be confirmed by a larger number of studies in order to explain the exact mechanisms underlying the disease and to verify whether the increased number of methanogens among patients is the cause of IBS or only a secondary effect of the disease.

THE ROLE OF ARCHAEONS IN ATHEROSCLEROSIS

Recent studies have shown that intestinal archaeons can play a key role in atherosclerosis. In this condition, the possibilities of therapeutic use of archaeons are primarily studied [4, 42].

High concentrations of trimethylamine N-oxide (TMAO) play an important role in atherosclerosis pathogenesis. It has been demonstrated that TMAO may promote vasculitis, induce the production of reactive oxygen species, modulate the metabolism of cholesterol and sterols and impair the transport of cholesterol to the liver, resulting in increased cholesterol transport to blood vessels, which in turn significantly contributes to atherosclerosis [8].

TMAO is formed from trimethylamine (TMA), which is produced from carnitine, phosphatidylcholine, choline, betaine or trimethylisine by intestinal micro-organisms. The resulting TMA is captured by hepatocytes and metabolized to toxic TMAO [42]. It is known that methanogenic archaeons may use methylated amines, such as TMA, as growth substrates, which gives hope for their use in the form of "archaebiotics" (Fig. 1).

Brugere et al. were among the first to propose the use of methanogenes in the form of probiotics, given the antiatherosclerotic potential of *Methanomassiliicoccus luminyensis*, which proved effective in reducing TMAO concentration [4]. More extensive studies involving five different strains of archaeons were carried out by Ramezani et al. The researchers investigated the efficacy of intestinal colonization with methanogenic archaeonson lowering plasma TMAO concentrations. Universal model of laboratory mouse (C57BL6J) and Apoe-/- mice (which are an animal model for cardiovascular diseases, including atherosclerosis) were inoculated by five archaeon species [42]. Mice remained on a diet with high choline and TMA content and during the 30-day experiment, the number of intestinal archaeons in animal faeces and TMAO concentration in rodent plasma were evaluated. All archaeons administered to mice (i.e. *Methanomicrococcus blatticola, Methanosarcina mazei, Methanohalophilus portucalensis, Methanomassiliicoccus luminyensis* and *Methanobrevibacter smithii*) were found to be capable of intestinal colonization. Importantly, all of them reduced plasma TMAO levels. *M. smithii*, *M. mazei* and *M. blatticola* showed the greatest ability to reduce trimethylamine N-oxide. TMAO concentration in C57BL6J mice inoculated with these strains was equal to TMAO concentration respectively: 14.8 µM, 6.9 µM, 5.9 µM, while in the control group not colonized by archaeons, the level of this chemical compound oscillated at 98.5 µM. Similar relationships were observed for Apoe mice-/-. The TMAO concentration in *M. smithii* inoculated mice was 18.2 µM compared to 120.8 µM in the control group. It is interesting that Apoe-/- mice, inoculated by *M. smithii*, were characterized by a 44% decrease in aortic plaque area and 52.2% reduction in the fat content in the atherosclerotic plaques compared to those not colonized by archaeons [42].

The therapeutic use of specific intestinal microorganisms, such as archaeons capable of breaking down toxins and converting them into an inert molecule, is a new concept, which has yet to be verified and confirmed by further studies. However, the above-mentioned research gives great hope for the future implementation of this type of therapeutic approach in the treatment of certain diseases, such as atherosclerosis.

CONCLUSION

Archaeons are still very poorly known organisms, but thanks to the development of molecular biology techniques and the ever-growing knowledge of the human intestinal microbiome, they are described more and more precisely in numerous studies. Their role as a natural component of intestinal microbiota is still not fully understood, but there is growing evidence that some of them may be involved in the aetiology of certain diseases, even if not directly, by "enforcing" changes of metabolic pathways on other intestinal microorganisms. Also interesting are the studies on the potential possibilities of using archaeons in the form of probiotics in certain diseases. Any speculation on the participation of archaeons in the determination and prevention of diseases remains in the circle of interest, and in view of the studies cited in this paper, it seems extremely important and advisable to conduct further, more detailed analyses in this area.

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