Archaea from the gut microbiota of humans: Could be linked to chronic diseases?

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Denise Mafra[1,2,3], Marcia Ribeiro[2], Larissa Fonseca[3], Bruna Regis[4], Ludmila F.M.F. Cardozo[4], Henrique Fragoso dos Santos[5], Hugo Emiliano de Jesus[5], Junia Schultz[6], Paul G. Shiels[7], Peter Stenvinkel[8], Alexandre Rosado[6]

[1]Graduate Program in Biological Sciences – Physiology, Federal University of Rio de Janeiro (UFRJ), Rio de Janeiro (RJ), Brazil
[2]Graduate Program in Nutrition Sciences, Fluminense Federal University (UFF), Niterói, Brazil.
[3]Graduate Program in Medical Sciences, Fluminense Federal University (UFF), Niterói, Brazil.
[4]Graduate Program in Cardiovascular Sciences, Fluminense Federal University (UFF), Niterói, Brazil.
[5]Department of Marine Biology, Fluminense Federal University (UFF), Niterói-RJ, Brazil.
[6]Microbial Ecogenomics and Biotechnology Laboratory, Biological and Environmental Science and Engineering Division, King Abdullah University of Science and Technology (KAUST), Thuwal, Makkah, 23955, Saudi Arabia
[7]Wolfson Wohl Translational Research Centre, University of Glasgow, Garscube Estate, Switchback Road, Bearsden, Glasgow G61 1QH, UK
[8]Division of Renal Medicine and Baxter Novum, Department of Clinical Science, Technology and Intervention, Karolinska Institutet, Stockholm, Sweden.

Corresponding Author

Denise Mafra
Unidade de Pesquisa Clínica. Rua Marquês do Paraná, 303,
Niterói, RJ, Brazil,
Zip code: 24033-900
Phone number: 5521982310313
Email: dmafra30@gmail.com

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Abstract

Archaea comprise a unique domain of organisms with distinct biochemical and genetic differences from bacteria. Methane-forming archaea, methanogens, constitute the predominant group of archaea in the human gut microbiota, with *Methanobrevibacter smithii* being the most prevalent. However, the effect of methanogenic archaea and their methane production on chronic disease remains controversial. As perturbation of the microbiota is a feature of chronic conditions, such as cardiovascular disease, neurodegenerative diseases and chronic kidney disease, assessing the influence of archaea could provide a new clue to mitigating adverse effects associated with dysbiosis. In this review, we will discuss the putative role of archaea in the gut microbiota in humans and the possible link to chronic diseases.

Keywords: Archaea, gut microbiota, methane, chronic kidney disease, cardiovascular disease.

Highlights

- In humans, the predominant Archaea are methanogens in the gastrointestinal system;
- Archaea may reduce ROS and TMAO production and intestinal permeability;
- Methane can indirectly act in a mechanism that regulates the antioxidant response.

Introduction

Archaea (previously termed Archaebacteria) display biochemical and genetic differences from bacteria [1,2]. Some are extremophiles and can survive in volcanic

mud, hot springs, salt lakes, and highly alkaline or acidic waters, as well as in a range of temperate environments, including agricultural soil and plants. A small percentage of archaea are a component of the human gut microbiota, along with viruses, protozoa, bacteria and fungi [3].

In general, the human intestinal microbiome has a range of functions that impact human health, including vitamin synthesis, barrier protection, immune system modulation, digestion of nutrients and protection against pathobionts [4]. In some circumstances, however, opportunistic pathogens can enter the host as a consequence of dysbiosis and or injuries or breaches in host barriers [5]. While these processes and effects are well described for some bacteria, little is known about the diversity of archaea in the vertebrate gut and influencing factors.

In humans, the predominant Archaea are methanogens (hydrogenotrophic), which anaerobically reduce carbon dioxide (CO2) to methane gas (CH4) (**Fig** 1). The most common methanogen in the gut microbiota is *Methanobrevibacter smithii*, with a prevalence of around 95.7% [6]. Compared to healthy individuals, Archaea appear overrepresented in patients with inflammatory bowel disease, human periodontal disease [7], obesity, cancer [8] and diverticulosis [9]. Consequently, interest in the role of methanogenic archaea in human disease processes has increased [3]. However, there is as yet no evidence that they could ever act as pathogens, and there remains a limited study of the role of Archaea in chronic diseases, such as cardiovascular disease (CVD), diabetes and chronic kidney disease (CKD). Evaluating the prevalence and functions of methanogens in the gut microbiota may provide vital information to determine the composition of normative gut microbiota. It may also indicate strategies to mitigate dysbiosis, a common feature in the above diseases. For example, it is noted that methylotrophic methanogens reduce trimethylamine-N-oxide (TMAO) production (a

marker of CVD) by TMA (trimethylamine) depletion in the gut, as some methanogens use TMA to produce CH4 [10].

In this review, we will discuss the role of Archaea in the gut microbiota in humans and whether targeting Archaea may reduce uremic toxins produced by the gut microbiota, such as TMAO in chronic diseases.

Archaea structure and environment

Archaea are unicellular, have no organelles and usually present DNA with a single circular chromosome. In addition to their similar size and shape, all these characteristics are identical to those found in bacteria [11]. However, archaea more closely resemble eukaryotes in DNA replication, transcription, damage repair and translation of genetic information [12]. Nonetheless, Archaea also possess some unique characteristics, such as the absence of peptidoglycans in the cell wall and membrane lipids formed by isoprenoid ether chains joined to sn-glycerol-1-phosphate, unlike bacteria, which have a membrane formed with chains of fatty acids linked to the glycerol-3-phosphate backbone via ester bonds [13].

Archaea are widely distributed in a range of habitats and may be extremophiles, thriving in extreme environments, such as hot springs, polar climates, acidic lakes, volcanoes, deserts, waste and water treatment plants and sites of highly concentrated environmental toxins. Archaeal extremophiles can phenotypically be divided into hyperthermophiles, inhabiting environments with extreme temperature conditions [2] piezophiles, flourishing in environments with high pressure; acidophiles and alkaliphiles, when required at low and high pH, respectively; and halophiles, growing optimally at high salt concentrations [14]. Archaea can also be divided into methanogens, which correspond to the phyla that inhabit anaerobic environments and

produce methane as a byproduct of metabolism [2]. Methanogens play a fundamental role in the carbon cycle, being the only participating domain of methanogenesis. This anaerobic respiration mechanism reduces carbon, oxygen, methyl or acetate with hydrogen (as an electron donor) into methane through methyl-coenzyme M reductase[15,16]. Methanogens can be divided into three main groups based on the substrates used for methanogenesis (**Figure 1)**.

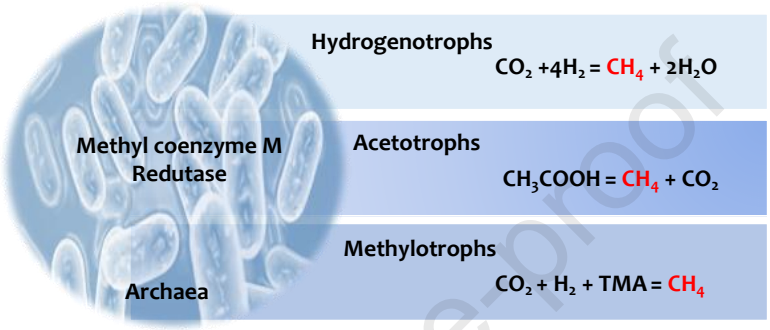


Figure 1. Methanogens are divided into three main physiological groups. Hydrogenotrophs are characterised by the absence of cytochromes and convert carbon dioxide and hydrogen into methane using carbon as the terminal electron acceptor and dihydrogen as the leading electron donor. Acetotrophs have cytochromes and use acetate as the only carbon source for methane production. Methylotrophs also have cytochromes and can produce methane from hydrogen, carbon dioxide, and methyl groups from compounds such as methanol and methylamines (trimethylamine, dimethylamineylamine, monomethyl amine) and methyl-mercapto propionate, among others.

Methanogens use substrates provided by syntrophic interactions (**Figure 2**) with bacteria that carry out the anaerobic degradation of macronutrients, such as carbohydrates, proteins and lipids [3]. For example, dietary carbohydrates undergo hydrolysis by fermentative bacteria in the intestine to form pyruvate (final product of glycolysis), which can be metabolised by secondary fermentative bacteria and produce short-chain fatty acids (acetate, propionate and butyrate), organic acids (lactate, formate, succinate), alcohols (ethanol) and gases (hydrogen and carbon dioxide) [17,18]. Such products are used by hydrogenotrophs and acetotrophs or can later be decomposed and converted by acetogenic bacteria [19].

Hydrogenotrophs can also utilise proteins as the byproduct of protein catabolism that generates hydrogen [3]. The entire process of amino acid metabolism can generate important substrates that fuel the growth of hydrogenotrophs, acetotrophs and methylotrophs [3]. Finally, lipids contribute to methanogenesis through long-chain fatty acids from lipid metabolism, which can be catabolised to short-chain fatty acids by acetogenic bacteria, and glycerol, also from lipids, which can reach the glycolysis pathway and contribute to hydrogenotrophs [3].

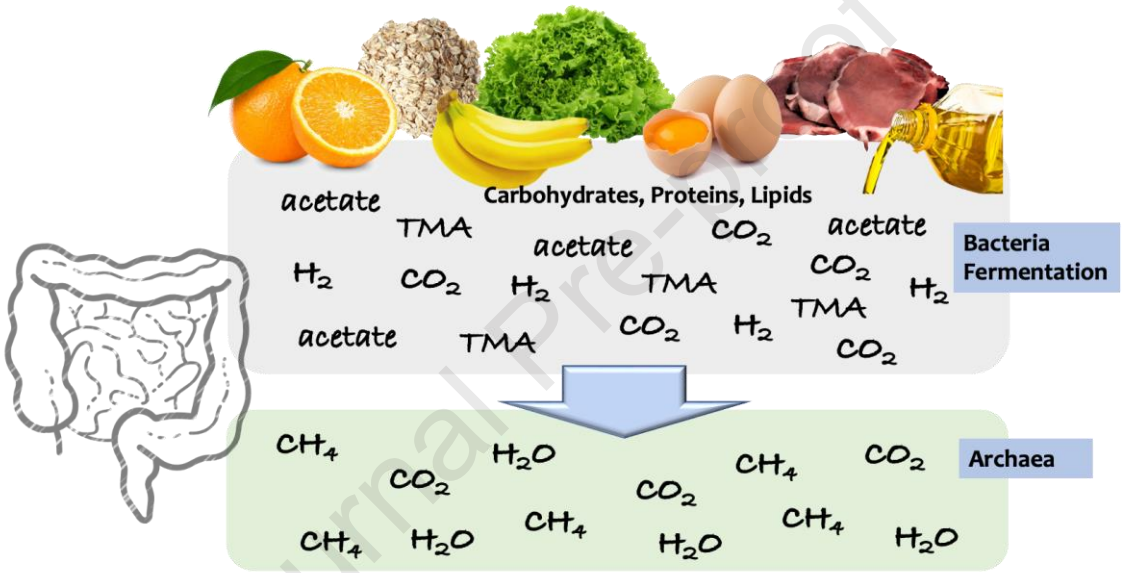


Figure 2. Interactions between methanogens and bacteria in the gut microbiota. Fermentation of carbohydrates, proteins and lipids by bacteria results in the formation of products such as carbon dioxide, hydrogen and acetate, which are metabolized by the archaea-producing water (H_2O), carbon dioxide (CO_2), trimethylamine (TMA) and methane (CH_4).

Archaea are a microorganism group that constitutes a relevant fraction of the biomass present on our planet. They are a significant component of ocean microbiota and are present in pelagic water samples, coastal surface waters[20,21], marine sediment and terrestrial environments [22–24]. Archaea are involved in the biogenic production of methane (CH4) and its oxidation, degradation of the protein [25], carbon fixation [26,27], and sulfur, nitrogen and iron cycling [28] through several different

mechanisms using organic and inorganic compounds under aerobic and anaerobic conditions.

These methanogens are also related to anaerobic methane and short-chain carbon oxidation [29,30], which has already been proposed for bioremediation approaches [31]. It is based on the capability of these anaerobic methane oxidizers (ANME) [30] to use the methane production pathway in a reverse direction [26] and thus degrade hydrocarbons [32–35]. This process is coupled to other processes, such as redox reactions, electron exchange and generation of energy realised by syntrophic bacteria [36]. It is evident that archaea play a vital environmental role and are critical factors in biogeochemical processes.

Archaeal methanogenesis is responsible for an important percentual of greenhouse gas generation since the enteric fermentation in ruminants produces methane [37,38]. Indeed, the livestock sector (beef and dairy production) is responsible for 40% of greenhouse gas emissions [39], contributing significantly to global warming.

The level of released methane is supposed to increase rapidly due to climate warming and, consequently, the thawing of polar permafrost [40].

Methanogens are also directly involved in nitrogen fixation (N2), allowing most life forms to use a more suitable nitrogen compound from the atmosphere. Most archaea assimilate inorganic (NH3 and NO3) or organic compounds [41]. Urea seems to be an essential source of NH3 for ammonia-oxidizing thaumarchaeons in soil [42] and polar waters [43]. Another form of release of nitrogen gas in the atmosphere is from the denitrification process by oxidising inorganic compounds such as NO2−and NO3 [41].

Archaea (sulfidogens) belong to Euryarchaeota, and Crenarchaeota produce hydrogen sulfide (H2S) under anaerobic conditions, mainly in hydrothermal fields and

submarine vents [44]. Bacteria and archaea can reduce elementary sulfur to H2S and are widespread in the environment [45].

It is worth mentioning a hypothesis raised by Hallam et al. (2004), in which methane-producing relatives of Archaea would be able to completely reverse methanogenesis through the oxidation of methane to cellular carbon and energy. The anaerobic methane-oxidizing archaea would be responsible for this reversal [46]. The complete reversal of methane directly impacts the environment, playing an essential role in global warming and the inflow of greenhouse gases. Other researchers have also elucidated this hypothesis [47–49].

Human a*rchaeome: diversity, distribution and* impacts in the gut

Archaea represent approximately 1 to 2% of intestinal microorganisms in the human body and are mainly strictly anaerobic [50]; the most prevalent and abundant phyla are *Methanobacteriales* and *Methanomassiliicoccales* [9], with *Methanobrevibacter smithii* being the most found in the intestine reaching 99-100% among methane producers [51]. Regarding archaeological taxonomy, Rinke et al. (2021) recently proposed a standardised archaeal taxonomy from a phylogeny of 122 proteins following the International Code of Prokaryote Nomenclature. Finally, the authors identified 16 archaeal phyla and reclassified three large monophyletic units from the ancient Euryarchaeota [52].

A recent study by La Cuesta-Zuluaga et al. (2021) has analysed 72 genomes of *Methanomassiliicoccales* and evaluated their presence in metagenomes derived from the human intestine, non-human intestine, and non-host environment. This research observed that archaea belonging to this order are generalists with a general preference for habitat, thus constituting their clade [53]. However, in humans, this group is not

joint, and when it is present, it is not found in high prevalence; in addition, diet can modulate its presence.

The methanogen group seems to be the only group involved in gut dysbiosis in humans, mainly *Methanobrevibacter smithii, Methanobrevibacter stadtmanae* and *Methanobrevibacter luminyensis* [54]. The methane produced by archaea (around 0.35L/day) can be excreted by faeces (≈ 50%) or penetrate the intestinal mucosa and reach circulation. Methane production has been linked with the development of colon cancer [55,56] and diverticulosis [57,58], but this has not been supported by further research. However, strong evidence has indicated a relationship between methane and intestinal motility disorders [59–62].

Studies in dogs have shown that this gas acts directly on intestinal motility, delaying intestinal transit and thus contributing to constipation, probably via the cholinergic pathway (enteric nervous system) [63]. Pimentel et al. (2006) have further elucidated that the methane produced by archaea probably predisposes patients to the development of constipation by inciting segmental contractions (not proppant) [63]. Kunkel et al. (2011) have corroborated these findings, and Rezaie et al. (2017) have found that methane can be used as a constipation marker [64,65].

However, other studies have attributed anti-inflammatory and cytoprotective effects to methane [66]. Boros et al. (2012) were pioneers in reporting the possible anti-inflammatory effect of methane in an ischemia-reperfusion study in inbred beagle dogs [67]. This study observed a significant reduction in reactive oxygen species (ROS) generation and modulation of leukocyte activation after methane administration [67]. Mészáros et al. (2017) also observed similar results when analysing methane inhalation during ischemia and reperfusion in the small intestine of rats. Finally, they observed epithelial barrier preservation, reduction of permeability and improvement of local

microcirculation, leading to lower production of reactive oxygen and nitrogen species [68].

Methane can indirectly act in a mechanism that regulates the Keap1-Nrf2 system, from stimuli to the phosphatidylinositol 3-kinase (PI3K)-Akt pathway in macrophages stimulated by lipopolysaccharides [69]. It is crucial to notice that the Keap1-Nrf2 system is the master endogenous defence mechanism with more than 250 syntheses of antioxidant enzymes. Wang et al. (2017)[70] have also reported that methane could act indirectly or directly in activating the Nrf2 pathway. It seems that byproducts of methane metabolism formed by electrophilic methyl groups can generate alterations and degrade Keap1, a protein in which Nrf2 remains coupled in the cytoplasm. Thus, the authors observed that methane might positively regulate transcriptional Nrf2 expression with a consequent increase in antioxidant enzyme expression [70]. Additionally, methane seems to increase the secretion of glucagon-like peptide 1 (GLP-1), a hormone responsible for increasing glucose-dependent pancreatic insulin secretion [71].

Methanosphaera Stadtmanae seems a potent immunostimulant, as *M. stadtmanae* binds to Toll-like receptor 8 (TLR8), triggers inflammasomes and exerts a more robust inflammatory response [72]. Furthermore, Archaea have been identified by their ability to activate dendritic cells derived from human monocytes, exerting strong inflammatory properties [72,73]. Studies on archaea and their role in inflammation and chronic diseases are still in their infancy, and humans' exact mechanism(s) is still not elucidated.

Could Archaea be a driving force for chronic diseases?

The factors determining the possible relationship between methanogenic archaea and disease have remained undefined. Methanobrevibacter is not associated with diseases, and it is not clear its relationship with flatulence [74]. Evaluating high

methane emitters and low emitters, Kumpitsch et al. (2021) found that high emitters presented an increase in *Methanobrevibacter smithii*, which was associated with a high abundance of *Ruminococcaceae* and *Christensenellaceae,* which are involved with fiber degradation[75]. Supplementation with probiotics reduced the relative abundances of the Methanobrevibacter, which was related to lower production of gases [76].

Since a few years ago, researchers have observed a link between Archaea and neurological diseases, mainly multiple sclerosis (MS) [77–82]. Archaea may act in human genetics due to modulation of HLA gene expression that directly implies the RNA viroidal mRNA interference. Also, archaea may be involved with changes in the length of the non-coding region of genetic material, which performs an important role in the pathogenesis of autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and MS [77]. Another mechanism is related to the production of biofilm from the integration of nanoarchaea, prokaryotes, and viroids resulting in a new tissue phenotype in the neuronal and immune tissues, leading to these diseases[77]. Archaea are also known for chronically activating the immune system and generating superantigens, which leads to the development of autoimmune diseases [77]. Whereas MS is an inflammatory disease mediated by the immune system with similar features to inflammatory bowel disease (IBD), the gut microbiota affects this disease as well as may affect MS and other neurological diseases [81] further. It is known there is an interaction between gut microbiota and the central nervous system through the microbiota-brain axis [79]. Related to this, some studies showed the interrelationship between MS and gut microbiota composition. In the patients with MS, there was a higher abundance of *Methanobrevibacteriaceae* (a genus in the Euryarchaeota) and a high prevalence of methane production from Archaea [78,80,82]. *Methanobrevibacter* is involved in the inflammatory process because of its capacity to recruit immune system

cells related to inflammation and its capacity to activate dendritic cells that are also involved in this process [78]. The same genus was positively correlated with TRAE 5, a regulator of cell T activation, which is overexpressed in MS [78].

Researchers have also considered a link between Archaea and body mass, where *Methanobrevibacter smithii* has been associated with both, obesity and malnutrition [83–85].

Methanogenic archaea are essential to remove excess H_2 from the human gut, reducing the efficiency of microbial fermentation and thereby the yield of energy. This prevents the buildup of H_2 and permits increased polysaccharide fermentation and short-chain fatty acids (SCFAs) production, which are well-known for their anti-inflammatory properties and modulation of the gut barrier[86] also, enhancing the availability of calories to the host, which is one of many mechanisms that link these bacteria with obesity [83,87]. In addition, bacterial NADH dehydrogenases are inhibited by the accumulation of H2, so the imbalance in the concentration of M. Smithii reflects, consequently, in the reduction of ATP production [88]. Studies have shown that obese patients have higher levels of methanogens and archaeal density in their faecal samples and methane breath tests [32,84,87,89–93]. This may be related to the production of SCFAs, improving fermentation efficiency and stimulating the lipogenesis process. Additionally, as the production of methane gas relates to constipation, this could take a long time for the intestine to absorb nutrients, resulting in weight gain[63,84,87,94–96]. However, the results are controversial. Armougom et al. (2009) found higher *M. smithii* in anorexic patients than in obese [83], and Wilder-Smith et al. (2019) found that obese patients had lower breath methane concentrations [97,98].

However, the results are controversial. Currently, studies demonstrate a link between gut microbiota and severe acute malnutrition, pointing to a dramatic depletion

of *M. smithii* [99,100]. Million et al. (2016) [99]demonstrated that *M. smithii* was not detected in children with severe acute malnutrition. This study proposed a theory of association between the oxidation of the intestinal environment and the depletion of anaerobic and methanogenic prokaryotes in malnutrition. Studies show that prokaryotic grow in an aerobic environment as long as the medium has adequate antioxidants [101]. Furthermore, *M. smithii* can produce methane in an aerobic atmosphere using ascorbate, uric acid and glutathione [102]. Thus, these studies provided experimental evidence of a possible causal association between a lack of dietary antioxidants, anaerobic depletion (including *M. smithii*), and a severe reduction in substrate oxidation and energy uptake.

Subsequently, some studies [100,103] were carried out with the aim of clinically investigating the key role of *M. smithii* in severe acute malnutrition. Alou *et al.* (2017) [103] performed culturomics and metagenomics on stool samples from malnourished patients with kwashiorkor and healthy children and detected reduced diversity and depletion of M. *smithii*. The absence of this archaea was associated with the depletion of micronutrients (minerals, prebiotics, antioxidants) and the loss of a favourable environment for its growth.

In order to clarify whether the absence of *M. smithii* is the result of immaturity or a loss of microbiota. Camara, et al. (2021) [100]evaluated the presence of M. smithii in faeces collected from malnourished children at baseline and late to treatment. They observed that *M. smithii* was significantly associated with the absence of malnutrition and that intestinal dysbiosis presented during this comorbidity is not a result of immaturity but rather of a loss of this archaea.

Therefore, these studies provide speculation that the administration of potential probiotics associated with *M. smithii* may be an effective strategy for restoring the

intestinal microbiota in malnourished children [100,103]. Further studies are needed in order to more clearly elucidate this theory.

Archaea may also increase the risk of diabetes mellitus by impaired glucose tolerance and insulin resistance [87]. In a clinical trial, Cesario et al. (2014) found worse glycemic control with increased glycated haemoglobin (Hb1Ac) values in subjects who had methane production in their gut microbiota. Similar results can be observed in another study where methane-producing patients with diabetes mellitus type 1 had poorer glycemic control than nonmethane producers[84].

Several cardiovascular diseases (CVDs) and their risk factors have been identified as examples of interactions between the host and intestinal microbiota [104,105]. Studies suggest that the intestinal microbiome produces numerous metabolites that influence the host-microbiome composition and host health [106–108]. The most prominent molecule in this is trimethylamine N-oxide (TMAO) [109]. TMAO is formed from a bacterial precursor metabolite, trimethylamine (TMA). The latter reaches the bloodstream and undergoes metabolism in the liver, where it will be oxidised by hepatic flavine monooxygenases (more specifically FMO3) to TMAO, which has pro-atherogenic properties [109–111]. Indeed, rats receiving a diet rich in choline have shown high TMAO levels associated with leukocyte activation in endothelial cells, suggesting a role in the atherosclerotic process [112].

Plasma TMAO remains a potential biomarker for CVD development, even after controlling for traditional risk factors [109,113]. The increase in TMAO plasma levels is related to high proinflammatory cytokine levels, causing cardiac inflammation, fibrosis and atherosclerosis [35,114]. Elevated TMAO levels promote the activation of nuclear factor-κB (NF-κB), a transcription factor involved in activating an inflammatory pathway in human aortic endothelial and smooth muscle cells,

contributing to the atherosclerotic process. Additionally, TMAO significantly reduces the expression of Abcg5/8 (which acts to transport cholesterol out of the lumen) [115] and Niemann-Pick c1Like 1 (Npc1L1) (which is involved in cholesterol influx) [116,117]. Furthermore, it has been demonstrated that TMAO contributes to the inhibition of reverse cholesterol transport (RCT) [111] and the formation of foam cells and atherosclerotic plaques by increasing macrophage surface expression of scavenger receptor A (SRA) and the cluster of differentiation 36 (CD36) [106,118]. As broad-spectrum antibiotics suppress the pro-atherogenic effects, this underscores the importance of the intestinal microbiota in the metabolism of this toxin [111]. Strategies can be adopted to reduce TMAO, such as drugs to inhibit the FMO3 enzyme [119]or modulation directed to the bacterial domain.

Candidatus (Ca.) *Methanomethylophilus alvus* Mx1201 can produce methane using H_2 as an electron donor and TMA as an electron acceptor [120]. Another genus belonging to this family is *Methanomassiliicoccus luminyensis*, which has been shown to convert TMA to methane using H_2 *in vitro* [6]. However, although studies indicate that *M. luminyensis* is not a typical representative of the human intestine [121], members of Methanomassiliicoccales can use methylated amines, such as trimethylamine (TMA), as substrates for methanogenesis [122]. The observation that the Archaea domain can transform TMA into methane provides novel opportunities to reach promising strategies in the prevention/treatment of diseases [119], e.g., it has been suggested that methanogens may reduce the production of TMAO in patients with a hereditary defect in flavin-containing monooxygenase 3 [10]. Thus, the concept of Archaebiotics arises, which would be applying specific archaeal intestinal strains capable of transforming TMA into methane and thus consequently reducing TMAO production, generating an inert gas for the host [123,124], being possible biotherapeutic

agents in the prevention and treatment of CVDs [53]. However, literature still includes few studies linking Archaea and CVD, and the presence of *Methanomassiliicoccales* that use TMA for growth is associated with lower faecal TMA concentrations [51].

Ramezani et al. (2018) experimentally tested the concept of archaebiotics. To promote the persistence of archaea, antibiotics were initially administered to mice [125]. Furthermore, mice were fed a diet rich in choline to increase TMAO levels, and after antibiotic therapy, 10^8 mesophilic methanogen cells were administered by single gavage. Surprisingly, *M. smithii* significantly reduced TMAO plasma levels compared to controls. Other methanogenic archaea (*Methanosarcina mazei*, *Methanomicrococcus blatticola*, *Methanohalophilus portucalensis*) reduced TMAO plasma levels. Still, this effect was detectable only in the first days of the experiment after gavage, probably due to low colonisation. After 30 days of the investigation, TMAO plasma levels were reduced, indicating a significant effect of *M. luminyensis* on TMA use. In addition to the direct application of archaea as live biotherapeutics, enzymes involved in methylotrophic metabolism could also be used. A well-known enzyme involved in this metabolism is trimethylamine methyltransferase (MttB), which transfers the methyl group from TMA to other methyltransferases. However, as this enzyme exerts its biological activity with the amino acid pyrrolysine (Pyl) in its active site [126], this would require a need to synthesise the amino acid pyrrolysine (one of the specificities of the genetics of TMA-consuming archaea).

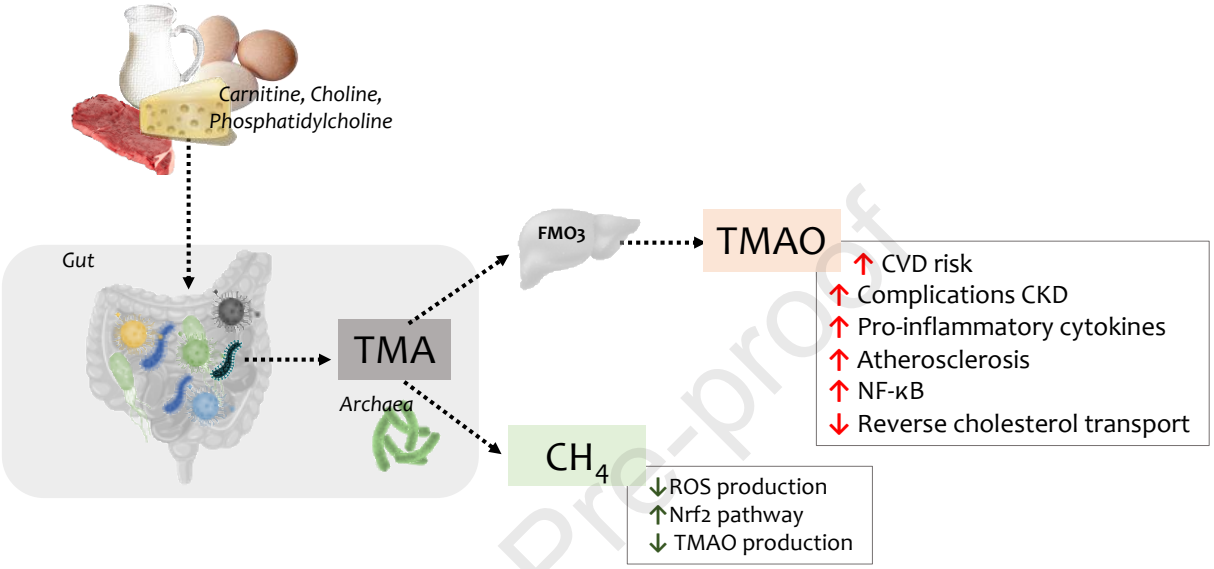
The salutogenic effects of archaea on the microbiome, metabolism, and host physiology need to be further studied *in vitro*, in animal models, and in humans. Specifically, archaea seem to confer beneficial effects in pro-inflammatory disease states (e.g., as observed with an accumulation of TMAO), such as trimethylaminuria

436 (TMAU), CVD and chronic kidney disease (CKD) and thus may have some potential as
437 a therapeutic route to tackle inflammageing.

438 Although it is an important target due to the link with CVD, to the best of our
439 knowledge, no studies have evaluated archaea in the gut of patients with CKD. Sumida
440 et al. (2021) have hypothesised that microorganisms, including archaea, are present in
441 the cell-free blood fraction of these patients. However, in a small study of 32
442 hemodialysis patients, there was no evidence of intact archaeal DNA in the blood [127].
443 Knobbe et al. (2020) evaluated kidney transplant recipients (KTx) to assess possible
444 causes of dysbiosis and diarrhoea often encountered post-transplant [128]. The authors
445 found a lower (28.6%) prevalence of *Methanobrevibacter smithii* in faeces from the
446 KTx group than in faeces from a healthy control group (86.4%) [128]. Another
447 important finding of this study was that the abundance of *Methanobrevibacter smithii*
448 correlated positively with CH4 concentrations in respiration and that CH4
449 concentrations were lower in KTx [128]. A possible explanation for the reduction in
450 *Methanobrevibacter smithii* in the faeces of KTx may be the more significant presence
451 of sulfate-reducing bacteria [128]. These sulfate-reducing bacteria appear to compete
452 for the use of H_2, with *Methanobrevibacter smithii* becoming the predominant organism
453 [129,130].

454 Despite this, it is already known that patients with CKD have dysbiosis with
455 increased production of uremic toxins, including TMAO, which promotes oxidative
456 stress, inflammation and CKD progression [131,132]. Recently, in an experimental
457 model of adenine-induced CKD in rats, supplementation with α-ketoacid for four weeks
458 increased the abundance of Methanobrevibacter, which was negatively correlated with
459 creatinine (Mo et al., 2021). Thus, patients with CKD accumulate TMAO in plasma
460 [133–135], promoting CVD [136]. TMAO can then be absorbed by extrahepatic tissues

461 or excreted through urine, sweat, or breathing [111,137,138]. Indeed, TMAO is an
462 independent predictor of the burden of coronary atherosclerosis and mortality
463 independent of traditional risk factors related to CVD [139]. **Figure 3** shows the
464 possible role of archaea in humans.



465

466 **Figure 3.** Methylotrophic methanogens can produce CH4 from trimethylamine (TMA)
467 formed by fermentation of carnitine, choline, and phosphatidylcholine from the diet. On the other
468 hand, TMA can be absorbed and form trimethylamine-N-oxide (TMAO) in the liver. TMAO is
469 associated with cardiovascular disease (CVD) and chronic kidney disease (CKD) and increases
470 inflammation and atherosclerosis processes. Archaea reduce TMAO production. Methane (CH_4)
471 produced by archaea may be of benefit.
472
473

474 **Conclusions and outlook**

475 In recent decades, an understanding of the environmental role of archaea has increased
476 drastically. Starting with the simple idea that these microorganisms only lived in
477 extreme environments, it has now emerged that archaea are widespread even in
478 temperate habitats and participate in several critical processes and biogeochemical
479 cycles. Indeed, archaeal groups are vital for essential metabolism in nutrient cycles,
480 such as methanogenesis and methane oxidation. Recent studies have implied those
481 archaea may have a beneficial role by reducing ROS production, TMAO production and
482 intestinal permeability while activating the Nrf2 pathway [10,67,68]. It is possible that

targeting intestinal archaeal modulation could be a future strategy for managing dysbiosis and the high cardiovascular risk in patients with CKD. In the future, we believe new approaches in molecular microbial ecology will reveal even new and vital roles attributed to the archaeal domain.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Contribution of authors

All authors contributed significantly to the work's conception, literature collection and interpretation; participated in the writing or critical revision of the article in a manner sufficient to establish ownership of the intellectual content, and read and approved the version of the manuscript being submitted.

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Highlights

- In humans, the predominant Archaea are methanogens in the gastrointestinal system;
- Archaea may reduce ROS and TMAO production and intestinal permeability;
- Methane can indirectly act in a mechanism that regulates the antioxidant response.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: