Clinical Reviews in Allergy & Immunology (2019) 57:456–466
https://doi.org/10.1007/s12016-019-08766-5

Methanogenic Archaea: Emerging Partners in the Field of Allergic Diseases

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Published online: 14 September 2019

Abstract
Archaea, which form one of four domains of life alongside Eukarya, Bacteria, and giant viruses, have long been neglected as components of the human microbiota and potential opportunistic infectious pathogens. In this review, we focus on methanogenic Archaea, which rely on hydrogen for their metabolism and growth. On one hand, methanogenic Archaea in the gut are functional associates of the fermentative digestion of dietary fibers, favoring the production of beneficial short-chain fatty acids and likely contributing to the weaning reaction during the neonatal window of opportunity. On the other hand, methanogenic Archaea trigger the activation of innate and adaptive responses and the generation of specific T and B cells in animals and humans. In mouse models, lung hypersensitivity reactions can be induced by inhaled methanogenic Archaea mimicking human professional exposure to organic dust. Changes in methanogenic Archaea of the microbiota are detected in an array of dysimmune conditions comprising inflammatory bowel disease, obesity, malnutrition, anorexia, colorectal cancer, and diverticulosis. At the subcellular level, methanogenic Archaea are activators of the TLR8-dependent NLRP3 inflammasome, modulate the release of antimicrobial peptides and drive the production of proinflammatory, Th-1, Th-2, and Th-17 cytokines. Our objective was to introduce the most recent and major pieces of evidence supporting the involvement of Archaea in the balance between health and dysimmune diseases, with a particular focus on atopic and allergic conditions.

Keywords Archaea · Methanogenic Archaea · Microbiota · Allergy · Atopy · Hypersensitivity

Introduction

The human microbiota has attracted increasing attention over the last 15 years, resulting in an ever-growing body of knowledge and the premices of purposeful therapeutic harnessing. In the complex network of microbial communities thriving in association with the human host [1], bacteria [2, 3], viruses [4], fungi [5, 6], and helminths [7] are widely recognized as microbiota contributors. However, a distinct life domain, the Archaea [8], has long been overlooked by researchers.

Archaea were first discovered and studied as unicellular "extremophiles" [9]. We and others established Archaea as members of human microbiota [10–12]. Archaea have developed original metabolic pathways to thrive, and methanogenic Archaea (MA) are strict anaerobes able to use hydrogen as a reducing agent [13, 14]. So far, MA have been detected in the intestinal, oral, nasal, sinusal, pulmonary, vaginal, and cutaneous microbiota in humans [9–12, 15–22], and might represent the most significant part of the archaeal microbiota. Alterations in the MA component of microbiota have been associated with diseases, mainly of the gastrointestinal tract [23, 24]. MA have also been described as emerging opportunistic pathogens [9]. Such findings suggest MA may also interfere with host immunity during atopic/allergic responses. We therefore set out for a review of current pieces of evidence on MA as a relevant component of human microbiota, with special focus on atopic/allergic conditions.

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Archaea in the Context of Human Microbiota

Alongside with Eukarya and Bacteria, Archaea are single-celled, prokaryotic microorganisms. Some archaeal attributes are unique, e.g. membranes are built with L-glycerol ether/isoprenoid chains instead of D-glycerol fatty acid esters and cell walls lack peptidoglycan [9], while others are shared with eukaryotes or bacteria [9, 25] (Table 1).

Archaea exhibit a higher level of morphological diversity compared with bacteria. Spherical, spiral, flat, square- or rod-shaped, and Gram-negative or Gram-positive Archaea live as isolated cells, aggregates, or filaments and multiply by binary fusion, budding, or fragmentation. Archaea can be aerobic, optionally anaerobic, or strictly anaerobic and nutritionally extend from chemolithoautotrophic to organotrophic. Finally, some Archaea are mesophilic while others thrive in hyperthermophilic environments [26].

Among strict anaerobic Archaea, MA utilize hydrogen as an electron donor for oxioreduction reactions transforming carbon, oxygen, acetate, and various methyl-containing species into methane [13, 14, 23]. MA belong to five orders: Methanobacteriales, Methanococcales, Methanomicrobiales, Methanosarcinales, and Methanopyrales, currently divided into ten families and twenty-eight species. They have been detected in different habitats spanning an array of sediments (salt and fresh water, hypersaline, marine, and geothermal marine sediments), together with hot springs, oil fields, rice paddies, anaerobic digesters, free unicellular eukaryota, gastrointestinal tract of animals, and rumen digesters [27, 28].

The human body harbors many species of MA (Table 2). Currently, the best-described commensal habitat is the gastrointestinal tract, where MA are found as early as the neonatal period [9, 29–31, 59] (Fig. 1). From a metabolic viewpoint, hydrogen consumption by gut MA increases the efficiency of bacterial fermentation and improves energy delivery to the host [13, 32]. Fermentative saccharolytic bacteria produce short-chain fatty acids (SCFA) and hydrogen, with the former accounting for up to 10% of the host's energy intake [14] and the latter being scavenged by MA. A fiber-rich diet resulting in SCFA maintains a virtuous circle beneficial (i) for the host through energy substrates, healthy epithelial barriers, and protection from intestinal pathogens [60, 61]; (ii) for fermentative bacteria; and (iii) for MA.

The diversity of MA strains within the same species of microbiota-associated *Methanobrevibacter* (*M.*) *smithii* has been demonstrated [62].

Table 1 Comparison of structural and metabolic features in bacteria, eukaryotes, and Archaea

Features	Bacteria	Eukaryote	Archaea
DNA separated from the cytoplasm by a membrane	No (except in Planctomycetes)	Yes (nuclear membrane)	No
Presence of intracellular organelles	No	Yes (mitochondria, chloroplasts)	Yes
Presence of a wall around the cells	Yes (with few exceptions), composed of peptidoglycans containing muramic acid	In some eukaryotes (plants, fungi, etc.), but never contains muramic acid	Yes (with a few exceptions), the composition varies according to the groups, but there is never muramic acid
Types of lipids present in the cytoplasmic membrane	Fatty acid chains linked to a glycerol-3-phosphate by ester bonds	Fatty acid chains linked to a glycerol-3-phosphate by ester bonds	Connected aliphatic chains connected to a glycerol-1-phosphate by ether bonds
Formation of gas vesicles	Yes	No	Yes
RNAt initiator of the translation	N-Formylmethionine	Methionine	Methionine
Polycistronic mRNAs	Yes	No	Yes
Maturation of mRNAs (de-stoning of introns, placement of a cap and a poly-A tail)	No	Yes	No
Ribosome type	70S	80S	70S
Reaction of elongation factor 2 with diphtheria toxin	No	Yes	Yes
Number of types of RNA polymerases	1	3	1
Type II promoters for RNA polymerase	Absent	Present	Present
Type of ATPase	A	B	B
Ability to produce methane	No	No	Yes, in some lineages
Ability to fix nitrogen	Yes	No	Yes
Photosynthesis based on chlorophyll	Yes	Yes	No
Ability to perform chemolithotrophy	Yes	No	Yes

Table 2 Localization of methanogenic Archaea in microbiota. Asterisks denote species that have been associated with infectious pathogenicity

Anatomical site	Species	References
Gut	*Methanobrevibacter smithii*	[10, 12, 14, 15, 18–20, 24, 29–46]
	Methanosphaera stadtmanae	
	Methanobrevibacter oralis	
	Methanomassiliicoccus luminyensis	
	Methanobrevibacter arboriphilus	
	Ca. Methanomethylophilus alvus	
	Methanobrevibacter millerae	
	Ca. Methanomassiliicoccus intestinalis	
	Methanoculleus chikugoensis	
Oral	*Methanobrevibacter oralis**	[16, 17, 47–53]
	Methanosarcina mazei	
	Methanobacterium congolense	
	Methanobrevibacter massiliense	
	Methanoculleus bourgensis	
	Candidatus Nitrososphaera evergladensis	
Nasal	*Methanobrevibacter*	[21]
Cutaneous	*Methanosarcina* spp.	[10, 21]
	Methanosaeta concilii	
Vaginal	*Methanobrevibacter smithii*	[10, 22, 30]
Urinary	*Methanobrevibacter smithii**	[54]
Sinusal	*Methanobrevibacter oralis**	[55]
	*Methanobrevibacter massiliense**	
Abscess	*Methanobrevibacter oralis**	[56–58]
	*Methanobrevibacter smithii**	

MA have been traditionally considered non-pathogenic, however, the identification of an increasing number of MA species in association with infections strongly suggests a genuine infective potential [47, 55–57, 62] (Table 2).

Tools for MA Investigation

High concentrations of MA in the gastrointestinal tract give rise to a detectable excretion of methane in the exhaled air. The measure of exhaled methane is a simple and noninvasive means for evaluating an individual's intestinal MA load [13]. The prevalence of detectable methane producers in the general population is estimated at 33–36% [63].

MA detection in samples can be performed with various methods, such as microscopy with fluorescence in situ hybridization (FISH), extraction of MA-specific DNA with further polymerase chain reaction amplification of 16S rRNA and *mcr*A gene fragments, isolation and culture [18, 21, 29, 30, 64, 65]. They can also be identified by desorption time-of-flight mass spectrometry/matrix-assisted laser ionization (MALDI-TOF MS), and genotyped by multi-spacer or whole genome sequencing [11, 29].

Recent progress in electron microscopy, metagenomics, and advanced bioinformatics allowed investigating the role of MA in human diseases. These tools first allowed to establish MA as opportunistic and emerging pathogens [9].

From a functional viewpoint, MA living in the context of microbiota fulfill a major function through the reduction of hydrogen, the accumulation whereof is a limiting factor for fermentative bacteria in the gut [23]. However, scarce data on host-MA and microbiota-MA crosstalk are available.

MA in Human Diseases

The most consistent range of evidence for an association between MA and disease comes from studies on gastrointestinal conditions.

Diverticulosis

The association of gut MA with the occurrence of diverticulosis is well accepted [23], but experimental evidence is scarce.

An early study [33] included 130 subjects divided into five groups according to the presence and type of colonic diseases: normal colon (36 subjects), diverticulosis (57), inflammatory bowel disease (11), polyposis (34), and malignancy (11). Isolation of MA from stool samples was performed through

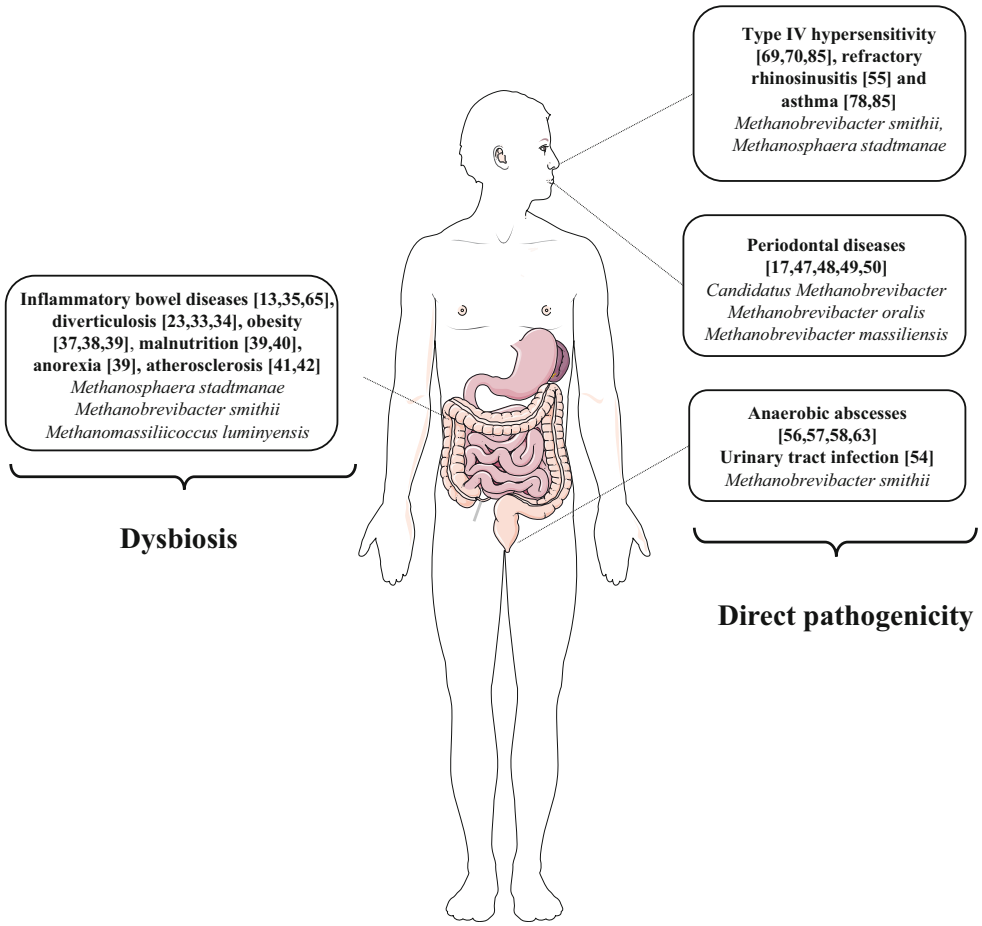

Fig. 1 Methanogenic Archaea associated with human diseases and their locations. MA found in the oral and intestinal microbiota are associated with obesity, anorexia, malnutrition, inflammatory bowel diseases, with periodontal diseases and with type IV hypersensitivity, respectively. References are indicated in square brackets

cultivation on a plating medium containing cephalotin and clindamycin, followed by epifluorescence microscopy assessment of the natural fluorescence of MA. Ninety-four (72%) of the subjects had MA with concentrations ranging from 6 to 30×10^{10} per gram of dry fecal samples. *M. smithii* was the predominant species irrespective of the normal or diseased colonic status. However, MA concentrations equal to or greater than 10^7 per gram of dry feces were found in 58% of patients with diverticulosis compared with 25% in those without diverticulosis ($p = 0.01$).

Yazici et al. conducted a retrospective study in 264 subjects aged 51 to 92 years (69.3% white, 30.5% obese with a BMI > 30) [34]. All subjects underwent a measurement of the methane level in the exhaled air and a colonoscopy. Methane producers were defined as having 5 ppm or more of exhaled methane. Diverticulosis was associated with an increased probability of being a methane producer (50.9% vs 34%, $p = 0.0025$) and with higher average levels of methane in exhaled air (7.89 ppm vs 4.94 ppm, $p = 0.04$). After adjusting for confounding factors, the methane level in exhaled air was an independent predictor of diverticulosis as a colonoscopy finding.

Overall, the association of intestinal MA with the development of diverticulosis is still awaiting further characterization with respect to the exact location of MA in the digestive tract, to a potential causality link, and to the mechanisms of MA involvement in the pathophysiology of diverticulosis.

Inflammatory Bowel Diseasess

Inflammatory bowel diseases (IBD) mainly comprise Crohn's disease and ulcerative colitis. A significant decrease in *M. smithii* was reported in British IBD patients compared with healthy subjects as early as 2008 [64] and was confirmed recently in an Iranian cohort [35], while in a Canadian population, an increase in *M. stadtmanae* was found [36]. The *mcr*A gene and quantitative PCR were used for stool analysis. These results may indicate opposite effects for the two main MA of human gut microbiota, a finding possibly related to metabolic differences between *M. smithii* and *M. stadtmanae* [13], with *M. smithii* as a rather beneficial gut commensal. This hypothesis is in line with its proposed potential use as a biomarker of IBD [35].

Obesity

Differences in the distal intestinal microbiota of obese compared with lean mice were reported as early as 2006, as DNA samples from the cecal microbial communities comprised more MA in obese than in lean mice [37].

These findings were later confirmed in humans. Zhang et al. used real-time PCR targeting the 16S rRNA gene with detection by SYBR-green (for bacteria) or TaqMan (for MA) to analyze gut microbiota composition in 9 unrelated individuals living in separate households [38]. Three categories were defined: normal weight "nw" ($n = 3$, mean BMI 23 kg/m^2), morbid obesity "ob" ($n = 3$, mean BMI 48 kg/m^2), and post-gastric bypass "gb" having undergone Roux-en-Y gastric bypass 8–15 months before ($n = 3$, mean BMI at the time of the study 28 kg/m^2, mean preoperative BMI 41 kg/m^2). None of the subjects had received antibiotics, probiotics, or prebiotics for at least 3 months prior to fecal sampling. Significantly higher numbers of MA were found in the "ob" individuals compared with "nw" and "gb". On average per gram of stool, "ob" subjects had 5.5×10^6 copies of 16S rRNA genes, compared with non-detectable levels in the "nw" group and to 7.5×10^3 copies in 1 of 3 "gb" subjects. In this study, the increase in hydrogen-consuming MA paralleled an increase in hydrogen-producing bacteria, suggesting higher energy uptake at the intestinal level in the "ob" group and its reversibility after the gastric bypass procedure [38].

Malnutrition and Anorexia

Interestingly, *M. smithii* has also been reported in anorexia nervosa patients with a higher load than in obese or lean subjects [39]. In anorexia patients, fermentative bacteria are less represented, and this increase in *M. smithii* might represent an adaptive change in order to increase the energy uptake under conditions of insufficient food intake. This adaptive change may be insufficient in cases of prolonged food deprivation, resulting in virtual depletion of MA [40].

Periodontal Disease

We and others detected and isolated MA in samples from patients suffering of periodontitis and peri-implantitis by various techniques including real-time PCR and sequencing, specific culture, metagenomics and in situ hybridization [17, 48].

Patients with periodontitis have a relatively high periodontal and peri-implant concentration of MA compared with controls, and oral MA such as *Methanobrevibacter oralis* have been associated with the development of periodontitis [17, 47–50]. Efficient treatment of periodontal disease reduces the abundance of MA (*Methanosaeta concilli*, *Methanosaeta lacustris*, *Methanobrevibacter arboriphilus*, and *Methanobrevibacter smithii*) in the oral cavity [51, 52].

Gut microbiota of periodontitis patients were reported as enriched in *Euryarchaeota*, an archaeal phylum comprising all MA [53].

Atherosclerosis

Trimethylamine N-oxide (TMAO) production and its possible use by MA might underlie a pathophysiological link between MA and atheroma formation [41]. Increasing levels of circulating TMAO are associated with a higher risk of atherosclerosis. *M. smithii* engrafted in the gut microbiota of a mouse model of atherogenesis was associated with TMAO consumption and therefore lower levels of circulating TMAO [41]. Multiple MA might exert protective roles against atherogenesis, as high levels of gut *M. luminyensis* were also associated with a decreased prevalence of atherosclerosis [42].

Other Conditions

MA involvement as human pathogens is rapidly emerging. We have recently shown their role in anaerobic abscesses [56–58, 62], refractory rhinosinusitis [55], and urinary tract infections [54].

Mechanistic Data on the Crosstalk Between Methanogenic Archaea and the Immune System

The association between MA and disease provided an incentive for studying the immune correlates of MA (Fig. 2). Several lines of evidence are currently available.

Biofilm Production

The production of biofilms is viewed as a model of evasion from host immune response [43, 66]. Archaea, including MA, have been demonstrated to produce biofilms. Bang et al. evaluated the general ability of three MA strains, *M. smithii, M. stadtmanae*, and the Gö1 strain of *Methanosarcina* (*M.*) *mazei* to grow on different surfaces and form biofilms [43]. The growth of the methanoarchaeal strains and their biofilm production were assessed with phase-contrast microscopic examination. A distinct behavior was found, with *M. smithii* producing biofilms up to a 40 μm height, while biofilms formed by *M. stadtmanae* did not exceed 2 μm [43]. These results showed that MA strains living in the intestine can create biofilms under static conditions, in agreement with the reported interaction of these MA strains with intestinal bacteria [14].

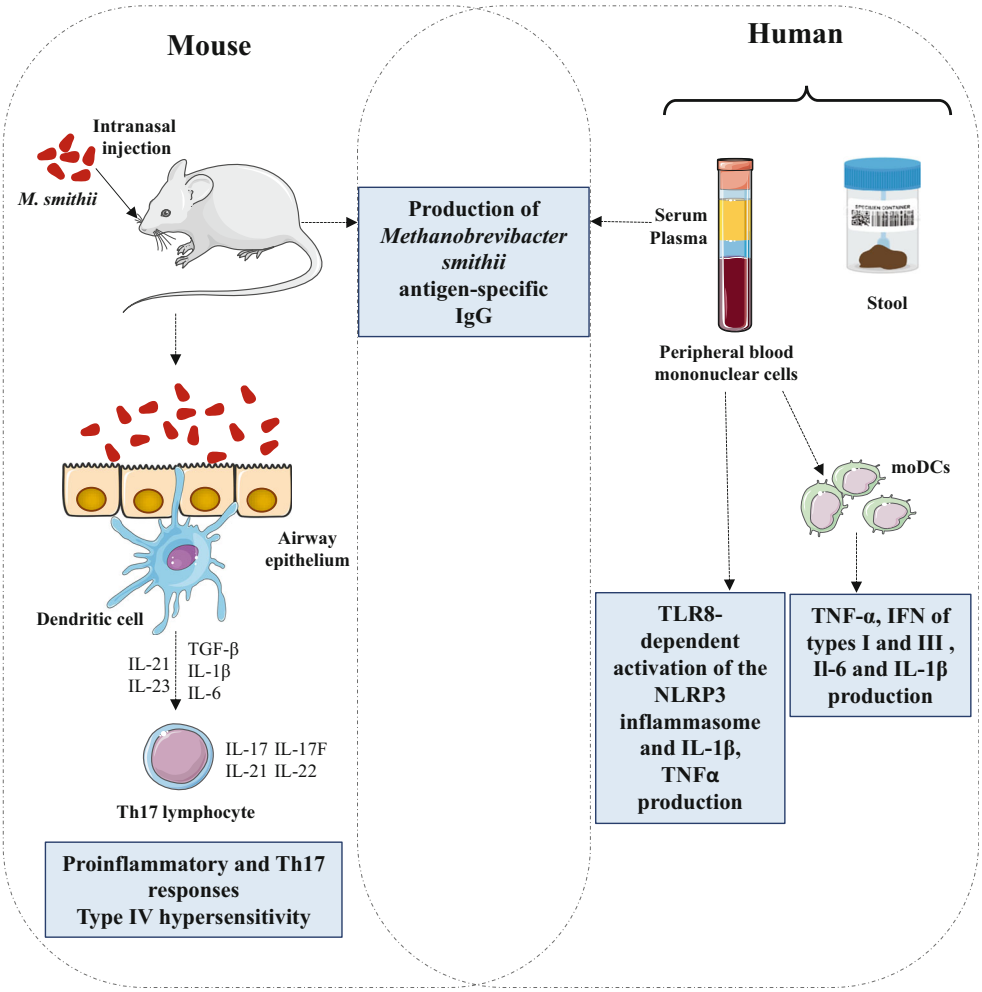

Fig. 2 Methanogenic Archaea and host immune responses. Currently available data regarding the crosstalk between methanogenic Archaea and the host's immune responses are illustrated as a function of murine versus human host. IL, interleukin; moDC, monocyte-derived dendritic cells; NLRP3, NOD-like receptor family, pyrin domain containing 3; TGF, transforming growth factor; TNF, tumor necrosis factor; TLR, toll-like receptor

Immune Recognition

Monocyte-derived dendritic cells (moDCs) phagocytose *M. smithii* and *M. stadtmanae* and degrade them following acidification of the endosome [44]. Cell surface ligands of both MA and moDCs remain elusive, but it has been shown that intracellular archaeal RNA released after *M. stadtmanae* degradation in the phagolysosome behaves as a microbial-associated molecular pattern (MAMP) and is recognized by toll-like receptors (TLR) 7 and 8 [45]. This recognition activates the signaling cascade resulting in nuclear translocation of transcription factors IRF and NFκB followed by NLRP3-induced inflammasome activation, moDC activation, and triggering of innate and adaptive immune responses [45, 46].

Innate Immune Responses

In humans, the release of proinflammatory cytokines TNF-α and Il-1β was investigated in healthy donors using peripheral blood mononuclear cells (PBMC) and moDCs exposed to *M. stadtmanae*, *M. smithii*, *and M. luminyensis* [44, 67]. Again, the proinflammatory response was significantly higher with *M. stadtmanae* than with *M. smithii* or *M. luminyensis* [44]. This finding held true for PBMC from IBD [36]. In addition, Bang et al. found that *M. stadtmanae* and *M. smithii* interfered with moDC expression of antimicrobial peptide genes [44]. Phagocytosis of the microorganisms and endosomal acidification were a prerequisite for moDC activation. The same experiments conducted with the Caco-2/BBe intestinal epithelial cells did not result in cytokine induction, suggesting that recognition of *M. smithii* and *M. stadtmanae* might be restricted to immune cells [44].

In a C57/BL6 murine model of exposure to inhaled *M. smithii* or *M. stadtmanae*, dose-dependent accumulation of leukocytes was demonstrated [68]. Histopathological assessment showed perivascular infiltrates of mononuclear cells and granulocytes, peribronchial infiltrates of mononuclear cells, macrophage accumulation, and thickening of alveolar septa. Overall, these effects were more prominent in *M. stadtmanae*–exposed mice. The same team further investigated *M. stadtmanae*–induced responses, showing that the granulocytic response comprised significant fractions of neutrophils and eosinophils [69].

More recently, the discovery of *M. stadtmanae* RNA recognition by TLR-7 and TLR-8 in moDCs led to the investigation of subsequent interferon (IFN) production and the demonstration of significant amounts of IFN-α14, IFNβ, and IFN-λ1 (IL-29) by moDCs and PBMC from healthy donors stimulated with *M. stadtmanae* RNA [45].

Adaptive Immune Responses

In humans, exposure of moDC to *M. stadtmanae* and *M. smithii* led to phagocytosis of the microorganisms, followed by cellular maturation demonstrated by the upregulation of costimulatory molecules CD86 and CD197 which are associated with subsequent adaptive immune responses [44]. The magnitude of this effect was similar with both MA. Mice exposed to *M. smithii* or *M. stadtmanae* inhalation displayed dose-dependent lung accumulation of myeloid DCs, identified as CD11c + autofluorescence^{low} CD11b + MHC^{hi} [68]. Inhalation of *M. smithii* induced a tenfold accumulation of myeloid DCs as compared with saline inhalation, while *M. stadtmanae* was more effective, resulting in a 25-fold increase in DC accumulation; however, the activation status of such DC infiltrates was not addressed in this study [68]. Cytokine response to inhaled *M. stadtmanae* was reported in a recent study from the same team, with significant increases in T CD4 cells expressing IL-13 and IL-17 but not IFNγ in exposed mice [69].

The adaptive immune responses induced by *M. stadtmanae* and *M. smithii* comprise specific IgG1 and IgG2a, which were demonstrated in mice using the intranasal delivery model. The magnitude of IgG responses did not differ between the two MA species. *M. stadtmanae* also induced a non-significant increase in levels of serum total IgE [68, 69].

IgG responses to *M. stadtmanae* and *M. smithii* were also investigated in IBD patients compared to healthy donors. Detectable IgG responses to both MA were found in healthy controls and IBD patients, as well as increased levels of IgG directed against *M. stadtmanae* in IBD patients [36].

Lipid Adjuvanticity

The term "archaeosome" was coined for spontaneous or synthetic liposomes composed of archaeal lipids [70]. The polar ethers typical of archaeal membrane lipids are chemically stable and display adjuvant activities [70, 71]. Early experiments showed that bovine serum albumin immunization was more effective when *M. smithii*–derived archaeosomes were employed, as compared with conventional liposomes [72]. The adjuvant properties of MA-derived archaeosomes for oral and injected vaccines have since been confirmed in multiple experimental designs [71, 73].

Taken together, these data are accumulating pieces of evidence of the salient interactions between MA and the host immune system.

MA and Allergic and Atopic Diseases

Allergy, also known as allergic immunological hypersensitivity, is defined as allergic hypersensitivity, where "allergic" indicates a proven or strongly suspected immunological mechanism and "hypersensitivity" is defined as "objectively reproducible symptoms or signs, initiated by exposure to a defined stimulus at a dose tolerated by normal subjects" [74]. Direct evidence of a link between Archaea and allergy is scarce, despite abundant evidence on microbiome, allergy, and the immune system [75, 76]. To our best knowledge, only two types of studies have provided experimental data so far.

The first report on the association of MA and human allergic conditions was published in 2019. In a subsample of the KOALA birth cohort in the Netherlands, 472 school-aged children were assessed for *M. smithii* and *M. stadtmanae* using qPCR in stool samples [77]. *M. smithii* was detected in 78.2% of the children, and *M. stadtmanae* in 8.3%. *M. stadtmanae* was associated with a significantly lower risk of asthma with an odds ratio (OR) of 0.32 (0.08–0.98). A dose-effect was found as the OR for asthma decreased in children with a higher abundance of *M. stadtmanae*. The authors reported a trend to lower risk for eczema and sensitization to airborne and food allergens in children with positive qPCR for gut *M. stadtmanae*. No significant association was found for *M. smithii*. The authors speculated that the higher immunogenicity of *M. stadtmanae* could provide a link to the current understanding of the hygiene hypothesis, as induction of antimicrobial responses in early life might confer protection against allergy development.

However, an association between a positive qPCR for gut *M. smithii* and the consumption of organic dairy products (specified by the authors as raw milk, processed milk, and yogurt) had been previously reported in the same pediatric population [78]. *M. smithii* DNA was indeed present in raw and to a lesser extent in processed milk, without significant differences between conventional and organic products, while *M. stadtmanae* DNA was not detected in milk samples. None of the two MA species were detected in yogurt, the consumption whereof was also significantly associated with gut *M. smithii* presence. Differences in the composition of organic versus conventional dairy products, e.g., higher contents of omega-3 fatty acids, relative omega-6 to omega-3 fatty acids content, have nots been considered in this study. Despite the fact that probiotic intake must be analyzed at the strain level for its potential beneficial effect [75], it is often considered that organic food may be related to health benefits, including less prevalent atopic/allergic conditions [79]. This perception is supported by a few reports, including one performed in 2-year-old children from the same KOALA cohort and showing a protective association (OR 0.64) between strictly organic dairy consumption and the presence of eczema [80]. Overall, these data suggest that the actual association of MA with the

development of atopic/allergic conditions needs to be studied as a functional network of nutrients, bacteria, and MA acting at specific time points of the immune system maturation. The use of MA culturomics might improve the relevance of data which are currently mostly derived from qPCR experiments.

Finally, there is indirect evidence for MA involvement in the pathogenesis of lung hypersensitivity reactions. Occupational hypersensitivity pneumonitis is defined as "an immunologic lung disease resulting from lymphocytic and frequently granulomatous inflammation of the peripheral airways, alveoli, and surrounding interstitial tissue which develops as the result of a non-IgE-mediated allergic reaction to a variety of organic materials or low molecular weight agents that are present in the workplace" [81]. High concentrations of up to 10^8 Archaea/m^3, mainly *Methanobrevibacte*r and *Methanosphaera* genera, have been detected in bioaerosols from farms, swine confinement buildings, and poultry barns (but not house dust) and might constitute a source of hypersensitivity events [82–84]. In a mouse model, inhaled *M. stadtmanae* triggered lung inflammation and a type IV hypersensitivity response with predominant Th-17 production and bronchial hyperreactivity [68, 69].

Moreover, concomitant presence of *M. stadtmanae* and bacterial products (endotoxin or peptidoglycan) in environmental dust samples triggered synergistic stimulation of bone marrow–derived DCs, evaluated through membrane CD86 and MHC upregulation and TNF production [83]. An interesting finding was the ability of environmental dust samples to activate DCs even with subthreshold levels of endotoxin, suggesting that MA—bacterial synergy evidenced with in vitro experiments also plays a role in vivo [84]. Overall, inhaled *M. stadtmanae* is a potent inducer of (i) cytokines associated with Th-17 (IL-17) and Th-1 (TNF), and to a lesser extent Th-2 (Il-13) hypersensitivity; (ii) neutrophilic, lymphocyte, and mononuclear/DCs accumulation in the perivascular spaces of the lung; and (iii) lung alterations comprising thickening of alveolar septa and bronchial hyperreactivity.

Indirect evidence for a protective role of MA against the development of atopic/allergic diseases comes from the growing body of knowledge about SCFA, their sources, and the timing of gut microbiota maturation. As explained above, gut fermentative bacteria feed on dietary fibers and produce SCFA and hydrogen [13, 14, 60, 61]. MA remove hydrogen, ensuring the continued digestion of dietary fibers and production of SCFA. SCFA exert immunomodulatory functions, not only in gut but also in distant sites such as lungs and hematopoietic bone marrow [85]. At the molecular level, a fiber-rich diet or experimental intake of SCFA triggers the development of lung DCs with impaired ability to induce Th2-type cytokines, while at the phenotype level, they are associated with protection against the development of lung allergic inflammation [85]. A "weaning reaction" has been recently described, consisting of an immune reaction triggered by changes in microbiota when exclusive milk feeding is progressively replaced with solid foods [86]. The normal weaning reaction leads to the generation of T regulatory cells and a healthy imprinting of later immune responses, associated with a lower risk of pathological inflammatory processes later in life. One of the major changes in gut microbiota during the weaning is a dramatic increase in *Clostridium* bacteria, which include fermentative bacteria and are associated with SCFA production. One can speculate that the presence of MA during the weaning reaction contributes to efficient SCFA production and therefore to the healthy long-term imprinting of the immune system. Indeed, MA have been demonstrated in human neonates as soon as the first hours of post-birth [30, 31, 59]. Finally, the precise timing of the weaning reaction and the inability to induce such changes later in life are reminiscent of the "neonatal window of opportunity", which shapes an individual's lifelong immunity, including resistance or susceptibility to atopic/allergic conditions [87, 88].

Conclusions

The spectrum of Archaea associations with human diseases is still expanding, progressively uncovering a full spectrum from beneficial microbiome members to genuine pathogenic microorganisms. On one hand, MA are part of the human microbiota as early as the neonatal period. They are responsible for the production of most of the methane in the intestine, which stimulates the fermentation of food by saccharolytic bacteria through removing the hydrogen end product. Their relationship with the immune system and their association with pathophysiologic processes are under investigation. The first reports on MA association with asthma and allergic manifestations are available. The increasing development of molecular, culturomic, and bioinformatic tools holds promise for further advances into the involvement and/or partnership of MA in human diseases, including atopic/allergic conditions. With respect to the latter, MA might bring not only further insight into pathophysiology but also a basis for personalized therapeutic intervention.

Acknowledgments We thank Professor Bernard La Scola for his help and advice in this review.

Author Contributions Y.S., S.M., J.L.M., M.D., P.C., and J.V. conceived and designed the paper. Y.S., S.M., G.G., M.D., and J.V. wrote the paper. All authors read and approved the final manuscript.

Funding Information Youssouf Sereme is supported by a "Fondation Méditerranée Infection" doctoral position. Soraya Mezouar was first supported by a "Fondation pour la Recherche Médicale" postdoctoral fellowship (SPF20151234951) and then by a "Fondation Méditerranée infection" postdoctoral fellowship. This work was supported by the French Government under the "Investissements d'avenir" (Investments for the Future) program managed by the "Agence Nationale de la Recherche" (reference: Méditerranée Infection 10-IAHU-03). This work was supported by the Région Provence-Alpes-Côte d'Azur and the European funding FEDER IHU PRIMMI.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests. Outside this work, J.V. declares the following conflicts of interest: speaker honoraria from MEDA Pharma-Mylan and Thermo Fisher Scientific and consultancy fees from Sanofi.

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