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Abstract

Host-associated microbial communities have an important role in shaping the health and fitness of plants and animals. Most studies have focused on the bacterial, fungal or viral community, but have often neglected the archaeal component. The archaeal community, the so-called archaeome, is now growingly recognized as an important component of host-associated microbiomes. It is composed of various lineages, including mainly Methanobacteriales and Methanomassiliicoccales (Euryarchaeota), as well as representatives of the Thaumarchaeota. Host-archaeome interactions were mostly delineated from methanogenic archaea in the gastrointestinal tracts, where they contribute to substantial methane production, and are potentially also involved in disease-relevant processes. In this Review, we discuss the diversity and potential role of archaea associated with protists, plants and animals. We also present our current understanding of the archaeome in humans, the specific adaptations involved in interaction with the resident community as well as the host, and its role in health and disease.

Introduction

Eukaryotes are inhabited by microorganisms, and there is increasing appreciation that this resident microbial community interacts with their host, and influences host fitness and functionality. These communities likely evolved over millions of years of coexistence with their hosts, leading to the holobiont concept [1–4].

Most studies have focused on host-associated bacteria, but archaea have generally been neglected, despite the fact that they are also consistent members of microbiomes associated with diverse hosts, including protists, plants, animals and humans. Specifically, we know for almost half a century that methanogenic archaea thrive in the human gastrointestinal tract (GIT) [5], and the first representative, *Methanobrevibacter smithii*, was isolated nearly 40 years ago [6].

Archaea were originally discovered and isolated from extreme ecosystems, including volcanic environments, salt lakes and other biotopes that are characterized by extreme temperatures, pH values or ion concentrations. However, over the past decades, cultivation-independent studies have revealed that archaea are universally distributed and could be among the most abundant and active microorganisms in moderate environments such as the ocean water column [7–11]. The domain Archaea includes a vast diversity of lineages, some of which are mostly composed of uncultured representatives [12,13]. These lineages are gathered into at least four large clades, namely the Euryarchaeota, the TACK (**T**haumarchaeota, **A**igarchaeota, **C**renarchaeota, **K**orarchaeota) superphylum, the DPANN (**D**iapherotrites, **P**arvarchaeota, **A**enigmarchaeota, **N**anoarchaeota) clade and the Asgard archaea (Fig. 1). Currently known host-associated archaea are phylogenetically diverse, but are mostly composed of methanogens and, more recently, Thaumarchaeota (Fig. 1). Today, research on the human archaeome (defined as the archaeal component of the human-associated microbial community) is still in its infancy. This is due to various reasons, including methodological issues resulting from their specific biology (Box 1), which also leads to a general lack of knowledge about archaea in the microbiome research

community. Recent studies provide new insights into the human archaeome, including, for example, the discovery of novel host-associated lineages, such as the Methanomassiliicoccales, which might have a beneficial impact on human health [14,15], the discovery of archaea on the human skin and their possible link to age and skin physiology [16,17], the finding that human archaea are recognized by the immune system and are involved in proinflammatory processes [18,19]. In addition, the development of specific archaea-targeting methods has updated the biogeography of the human archaeome and revealed previously undetected members [20,21]. Furthermore, novel insights were also gained into the role of archaea in plant physiology and the plant-specific profile of the archaeome [22], their association with animal skin [23] and the GIT of primates [24], which has fueled the debate on archaeome host-adaptation and co-evolution.

With novel methods in place, even if still imperfectly adapted to the archaeome (Box 2), many fundamental questions about the contribution of archaea to the microbiome and host physiology can now be addressed (see Refs. [25–36]).

In this Review, we aim to provide a comprehensive view of the current knowledge on the host-associated archaeome, including humans, protists, plants and animals. In addition, we highlight the potential role of archaea in human health and disease, and explore the question of whether pathogenic archaea exist. Finally, we identify knowledge gaps that remain to be addressed and advise next steps for research on the archaeome.

Protist, plant and animal archaeomes

The archaeome of anaerobic protists.

Similarly to bacteria, archaea (namely members of the orders Methanobacteriales, Methanomicrobiales, Methanosarcinales and possibly Methanomassiliicoccales[37]) can live in the cytoplasm of anaerobic ciliates,

amoebas and flagellates [38]. These endosymbiotic methanogens interact closely with hydrogenosomes, which are specific organelles of protists that generate H_2 by oxidizing pyruvate and malate during carbohydrate degradation [39]. Methanogens benefit from the H_2 for methanogenesis, and in return, they improve the energy gain of the host cell by maintaining a low H_2 concentration [40] (Box 1). In sediments and wetland soils, where free-living sulfate-reducing or iron-reducing bacteria are more competitive for H_2 than free-living methanogens, endosymbiotic methanogens can remain active by benefiting from an exclusive source of H_2 produced by hydrogenosomes. In such contexts, endosymbiotic methanogens can be responsible for the largest part of the methane production in these environments [41,42].

Adding another order of complexity to the holobiont concept, methanogenic archaea can also be endosymbionts (and ectosymbionts [43]) of protists living inside the gut of termites [44], cockroaches [45], amphibians [46] and ruminants (reviewed in Refs. [47,48]), where they have a role in host digestion together with the rest of the microbiota [49] (Fig. 2). In addition to the H_2 produced by their host cell, endosymbiotic methanogens also benefit from O_2 depletion by protists, as most methanogens are extremely oxygen sensitive organisms (Box 1), during ruminant feeding [50]. In support of this assumption, methane emissions from ruminants are positively correlated with protist concentrations [51], and defaunation experiments (that is, removal of protists) led on average to an 11% reduction of methane emissions, albeit with a great variability between studies (from no effect up to 37% reduction [47,52]). Thus, this variability suggests that the relationships between methane emissions and protists also include complex and not well understood factors [53,54].

Whether endosymbiotic archaea form stable association with their host or are the result of random engulfment of free-living archaea by the protist has been debated [37,55,56]. On one hand, archaea–protist associations are not maintained on long evolutionarily periods as shown by the absence of co-speciation patterns between the host and the archaea [46]. On the other hand, specific associations are supported by the observations that geographically distant representatives of the same protist species host similar methanogens,

whereas different protist species in the same location host different methanogens [38,57,58]. Moreover, recent genomic analyses of endosymbiotic archaea have revealed only little differences with their free-living counterparts [59,60], but the nature of these variations seems partly similar between evolutionary distant endosymbiotic archaea, which suggests convergent adaptations to this lifestyle[58]. In addition, the high level of genes undergoing pseudogenization in these genomes probably indicates a recent and still ongoing process of adaptation [58]. Together, these studies suggest that endosymbiotic archaea form stable associations with their host, probably at the strain level, but are periodically replaced by a novel archaeal symbiont. However, most of these observations derive from associations between archaea and free-living protists, and the question still remains open for host-associated protists.

The plant archaeome.

Microbial communities of plants have an essential role as they can affect plant growth, productivity, adaptation, diversification and health [61]. Overall, archaea are differently distributed in the rhizosphere , endosphere and phyllosphere . Micro-niche differentiation is supported by the competition with bacteria and fungi as well as abiotic factors, including nutrient availability and exposure in the phyllosphere, the presence of root exudates in the rhizosphere, and the more stable conditions in the soil [62]. For the widespread leafy green plant arugula (rocket salad), the diversity of archaea was found to be lowest in the phyllosphere, which indicates unfavorable habitat conditions, whereas the diversity of archaea in the soil and rhizosphere was much richer, and may thus be the preferred habitat [62].

However, knowledge on the interaction of archaea and plants is very restricted and based on a few specific types of plant–archaeome interactions. The most prominent example of plant-associated archaea are methanogens residing in the anaerobic rhizosphere of rice in oxygen-depleted wetlands [63], mostly represented by Methanocellales, Methanosaetaceae and Methanoregulaceae [64]. A large part of the methane produced in the rice rhizosphere is derived from the breakdown of organic compounds produced by the plant [63,65], and it primarily escapes to the atmosphere via the plant gas vascular system, thus bypassing bacterial aerobic methanotrophs [66]. Although methane emission in rice fields is a subset of the overall plant-mediated methane emission in wetlands, it is responsible for 10% of the global budget of atmospheric methane [67].

Signatures of ammonia oxidizing Thaumarchaeota were also found to be abundant in leaves of Mediterranean olive trees [68], which reveals cultivar-specific abundance patterns. Similar observations were made in tomato plants, where the abundance of the archaeal community (Thaumarchaeota (60%), Methanosarcina (12.6%), Methanoculleus (3.4%); Fig. 3) was found to be dependent on plant genotype and habitat. Notably, the archaeal abundance and diversity was comparably low in seeds, and no indications of plant-mediated vertical transmission of archaeal microbiome components was detected [69].

Plants in alpine bogs harbor a substantial archaeal community that is composed of 60 different genera [22]. Notably, metagenomic analyses revealed potential archaeal functions in, for example, the promotion of plant growth through auxin biosynthesis, nutrient supply, and protection against oxidative and osmotic stress. Additional genetic capacities for CO_2 and N_2 fixation were also observed. Similar functions were reported for the arugula, with mainly Thaumarchaeota and Euryarchaeota detectable and visible in both the rhizosphere and phyllosphere [62]. In particular, '*Candidatus* Nitrosocosmicus' (Thaumarchaeota) seems to be involved in positive interaction with plants, as *Nitrosocosmicus oleophilus* MY3 was found to colonize root surfaces of *Arabidopsis thaliana* plants and to trigger systemic resistance against the plant pathogens *Pectobacterium carotovorum* subsp. *carotovorum* SCC1 and *Pseudomonas synringae* pv. tomato DC3000 [70].

The animal archaeome.

Known symbiotic associations of archaea with animals include sponges, insects and vertebrates. The first representative genome of Thaumarchaeota, namely '*Candidatus* Cenarchaeum symbiosum', was retrieved from a marine sponge, which lives in close symbiosis with its archaeal inhabitant [71,72]. In some cases, Thaumarchaeota even dominate the microbial communities associated with sponges [73]. It was suggested that these archaea might remove nitrogenous host-waste products and, in turn, provide carbon to the host [71].

Methanogenic archaea, and in particular *Methanobrevibacter* species, are extraordinarily well-adapted to interact with animal hosts and non-archaeal components of their microbiomes. By their consumption of various small fermentation end-products, *Methanobrevibacter* species are flexible supporters of syntrophic interactions. *Methanobrevibacter* species are the predominant archaea in gastrointestinal tracts (GIT) of various ruminants and non-ruminants, such as cattle, yak, sheep, reindeer, goat, buffalo, deer, pigs, wallabies, rhinos, chicken, iguanas, termites and many others (see Ref. [25]) (Figs. 2,3). Other methanogenic archaea (*Methanosphaera, Methanosarcina, Methanomassiliicoccus* and *Methanimicrococcus* species) have also been

identified in various animals (for example, cattle, sheep, goat, deer, horses, pigs, kangaroos, rhinoceros, hoatzin, iguana and termites), but they are usually less abundant (Fig. 4). Due to the resulting massive methane production and impact on global warming (Fig. 2), methanogenic archaea–ruminant and archaea–termite symbiosis is the subject of active research. It has been estimated that a single cow emits up to 700 L of methane per day [74] (on average 150.7 g/day; see Ref. [25]), and these studies also aim to reduce methane emission [75]. In addition, the activity of methanogenic archaea negatively affects the weight gain and efficiency of feeding, so that a reduction of the methanogenic archaea load (generally ~4%) in the rumen is a sought outcome [76]. Also, the termite archaeome is a substantial contributor to biotic methane emission. It is estimated that approximately 20 Tg (Teragram) of methane are produced by those insects globally each year [77], but the overall contribution is considered rather low (1%-3 % of total methane budget). This discrepancy is explained by the observation that 20%-80% of the termite-produced methane is depleted by bacterial methanotrophs which reside in the mound or soil in close proximity to the termites [77].

A recent study assessed archaeal diversity in great apes faecal samples, which detected more than 200 archaeal taxa, with the highest diversity observed for orangutans [24]. More specifically, Methanobacteriales, Methanomassiliicoccales and Thaumarchaeota were all detected in the GIT of the analyzed primates. Notably, it was proposed that the diversification of great apes correlated with a decline of archaeal diversity in the GIT [24], which potentially indicates a diet-associated loss of archaeal taxa during primate evolution, and improved fitness of remaining taxa.

Besides archaeal communities in the GIT, various animals also carry methanogens, Haloarchaea and Thaumarchaeota on their skin (Fig. 3). The relative abundance of skin archaea was found to be species-specific[23] and reached up to 26% of archaeal sequence proportions (averaged) in cape elands (Fig. 3). However, the overall archaeal proportion in this study was ~0.1% of all retrieved sequences, even though a non-archaea-specific approach was used, and thus the archaeal load might have been underestimated.

Interestingly, and although the functional capability of the detected archaea is largely unknown, the variety of skin-associated archaea in mammals was very similar to the skin archaeome found in humans (see below; Fig. 3).

Current available information suggests that only specific archaeal clades are prone to interaction with hosts and non-archaeal components of their microbiomes (Figs. 3, 4). Thaumarchaeota (also referred to as Nitrososphaeria; with many unclassified representatives) are mainly associated with the host outer or exposed surfaces (such as, human and animal skin, or the plant's phyllosphere), whereas methanogenic archaea (Methanobacteriales, Methanosarcinales, Methanomicrobiales, Methanomassiliicoccales) are frequently found in anoxic areas (mostly the GIT of animals and humans). Both archaeal groups consume metabolic end-products of the host and the associated bacteriome, and exhibit specific functions which can protect or negatively affect the host.

In addition, the consistent detection of halophilic archaea (particularly *Halococcus*; Fig. 4) in animals (and plants) raises many questions on the origin and the type of interaction [27], particularly as it was discussed for humans that halophilic archaea could be contaminants from salted food[78].

This is also true for the unclassified '*Candidatus* Woesearchaeota' (DPANN) which have also been identified in human samples, mainly from the respiratory tract [20]. The function of Woesearchaeota in the environment remains elusive, but due to the metabolic deficiencies, a probable dependency on syntrophic microorganisms has been discussed[79]; details on their potential role in the human body are completely unknown to date.

The human archaeome

The human microbiome carries numerous archaea, in particular on skin, in the respiratory tract and the GIT. Whereas the specific role of non-methanogenic archaea in the human body remains to be explored,

methanogens maintain numerous syntrophic relationships with the resident bacteria. Due to their dependence on bacterial metabolic activity for their own substrate availability, methanogens could be indicators for the microbiome status *per se* [32,80,81]. Despite limited knowledge on host interactions, archaeal genomes and experiments with cultured methanogen representatives reveal a profound adaptation strategy to the human GIT.

Presence, abundance and activity of archaea in the human microbiome.

Archaea are substantial components of the human microbiome and include a wide diversity of lineages, including Methanobacteriales, Methanomassiliicoccales, Methanomicrobiales, Methanosarcinales, Halobacteriales, Thaumarchaeota (Nitrososphaeria), and members of the DPANN clade [15,20,35] (Figs. 1, 3).

In the GIT, the most prevalent and abundant archaea are representatives of the Methanobacteriales and the Methanomassiliicoccales [15]. Methanobacteriales are mainly represented by two species, namely *Methanobrevibacter smithii* and *Methanosphaera stadtmanae*, having a prevalence of up to 97.5% and 23%, respectively [82]. Human gut-associated Methanomassiliicoccales consist of at least nine species, the most common being '*Candidatus* Methanomassiliicoccus intestinalis', '*Candidatus* Methanomethylophilus alvus', Mx-02, Mx-03 and Mx-06, with a prevalence of up to 80% [15]. Together, these methanogens contribute to an average human body methane emission of about 0.35 l per day [83]. Considering a world population of 7.5 billion people, the total human methane emission would be equivalent to 410 ± 113 Gg per year (Fig. 2). Although this seems to be a high amount, it represents less than 0.2 % of the overall anthropogenic emitted methane [84].

Several factors influence the presence, abundance and diversity of archaea in the human gut. For example, the percentage of people emitting breath methane above 1 ppm correlates with geography and ethnicity, which indicates an influence of host genetics and life history, gut microbiota composition and diet. Of note, the

methods used to measure breath methane have been frequently debated [85], as inconsistent values can be obtained based on test methodology (for example, prior subject challenge with carbohydrates), selected cut-off values, and correction of raw measurements or interpretation. As summarized in a recent publication [83], only 15% of the Japanese population [86] but more than 70% of rural Africans [87,88] were shown to emit methane levels above the 1 ppm threshold. Interestingly, compared to native Africans, African Americans showed statistically significant lower methane emission and methanogen diversity [89,90], which suggests a negative effect of western diet or lifestyle on the GIT archaeome.

In Western adult populations, around 40%-60% of individuals were found positive following the methane breath test (with a threshold of 1 ppm)[91] and thus are estimated to carry more than 10^7-10^8 methanogens per gram of stool [92,93], which corresponds to a minimum of 0.03%-0.3% of the gut microbiota. However, the proportion of methanogens can greatly vary above this level and reach up to 14% of the gut microbiota in extreme cases, as found in a Russian cohort via untargeted metagenomic analyses [81].

Another important factor is age, correlating positively with the diversity and abundance of gut-associated archaea in several human populations [83,94]. Whether this increase is due to host physiological changes, such as the prolonged gastrointestinal transit time with age, and/or multiple acquisitions during human life, remains unclear. Another factor is host genetics, as the abundance of *M. smithii* has been found to be more similar between monozygotic twins than between dizygotic twins [95–97], and correlates positively with a SNP in a long noncoding RNA of the human genome [98]. However, the presence and activity of methanogens is also associated with non-archaeal members of the host microbiome. For instance, the prevalence of Methanomassiliicoccales, which reduce trimethylamine (TMA) with H_2 for methanogenesis, was found to correlate positively with the number of different TMA-producing pathways present in the bacterial microbiome [15]. Similarly, a correlation of *M. smithii* with certain bacterial taxa from the Firmicutes was noted. In particular, Christensenellaceae, representing a highly heritable clade [99,100] were found to be associated with

a high abundance of *Methanobrevibacter*. *Christensenella* representatives support *M. smithii* through efficient H_2 transfer via close physical interactions, as shown in co-culture experiments with *C. minuta* [100]. In these experiments, the hydrogen consumption by *M. smithii* shifted the *C. minuta* metabolism towards acetate production rather than butyrate production, an effect that was less pronounced with *Bacteroides thetaiotaomicron,* a taxon not correlating with *M. smithii* abundance in the human gut. Interestingly, non-bacterial microbiome members such as *Candida* fungi were also found to co-occur with *M. smithii*, which suggests additional syntrophic relationships [101].

Besides methanogens, Halobacteriales (for example, *Haloferax massiliense*) have been detected and isolated from human stool samples, including from patients suffering from inflammatory bowel disease (IBS) [35,78,102,103]. However, the impact of halophilic archaea on the human microbiome and the host remains unclear, and their presence has been discussed as possibly transient and associated with consumption of salt-containing food products [104].

The overwhelming majority of studies on human-associated archaea were conducted on stool samples, and knowledge on specific body sites is still sparse. It seems likely that the GIT contains a larger diversity of archaea than that identified from stool samples, as signatures of Methanomicrobiales, Methanobacterium and DPANN were reported in biopsy samples but not in the stool [20,90]. Moreover, similar to bacteria, human-associated archaeal communities group based on the body location, with Thaumarchaeota signatures predominating on the skin, methanogens in the GIT, a mixed Thaumarchaeota or methanogens landscape for the upper respiratory tract, and DPANN (Woesearchaeota) in the lung [20]. On the skin, two studies revealed that archaea generally represent 0.1% to 1% of the microbiota [16,17]. Interestingly, the positive correlation between age and abundance of archaea observed for the gut also holds true for the skin [17].

Adaptations to the human host and interaction with the immune system.

As discussed above, archaea in the human gut are generally dominated by a few specific taxa (Fig. 3). These taxa are rarely reported from environments outside of the animal GIT, which suggests a high degree of specialized adaptation. Such adaptations are mirrored by a number of specific traits differentiating archaea residing in the GIT from free-living ones. These traits include, for example, modifications of the cell surface (for improved adhesion and biofilm formation), and the possession of bile salt hydrolases, to defeat the host defense mechanisms (Fig. 5).

M. smithii, *M. stadtmanae* and host-associated Methanomassiliicoccales encode a large number of membrane-bound adhesin-like proteins (ALPs) that have been suggested to be involved in binding to different host sites and syntrophic commensal bacteria [15,105–107]. As the expression levels of *M. smithii* ALPs are influenced by environmental conditions (for example, the presence of bacteria or substrate availability), it has been suggested that *M. smithii* has a high ability to colonize different microniches in the gut [96,105]. It could be hypothesized that the specific physical interaction of *M. smithii* with *C. minuta* [100] is promoted by some of these ALPs. Methanobacteriales and Methanomassiliicoccales ALPs comprise different protein domains [15,96], possibly indicating different niche adaptations and evolutionary origins. Phylogenetic approaches revealed that several of the *M. smithii* ALPs have been probably acquired by horizontal gene transfer (HGT) [96,108]. Methanomassiliicoccales have probably also acquired their ALPs via HGT, as the type they possess has not been found in other archaea but is present in high numbers in several gut-associated bacteria [15].

Besides ALPs, diverse glycosyltransferases seem to have been acquired via HGT in *Methanobrevibacter* and *Methanosphaera* species. These glycosyltransferases could account for a modification of polysaccharides present at the cell surface, which could improve adherence to abiotic and biotic surfaces [105,107,108]. Supporting this observation, *M. stadtmanae* cells strongly adhere to human immune and epithelial cells [109], and easily

aggregate into biofilm structures, most probably due to secretion of extracellular polysaccharides [109]. Incidentally, oral biofilms were reported to contain *Methanobrevibacter oralis* (in at least every second patient suffering from periodontal disease [110]), and members of the *Methanomassiliicoccus* genus [111].

Bile acids are important regulators of the human microbiome and exert a strong selective pressure on the microbial population. Microorganisms have developed strategies to counteract bile toxicity via bile salt hydrolases (BSHs) which are also important for secondary bile acid synthesis. Similar to various bacteria, several gut methanogens, *M. smithii*, *M. stadtmanae* and C*a. M. alvus*, could detoxify this molecule using BSH. Methanobacteriales and Methanomassiliicoccales BSH are distantly related and could have been acquired via independent HGT events [112], probably from Firmicutes in the case of Methanobacteriales [113]. *M. oralis* (mainly present in the mouth) and Methanomassiliicoccales from an environmental clade lack BSH [35,112] , an observation which supports the acquisition of this enzyme due to a very specific adaptation to the intestine.

The innate immune system is the very first line of host defense against microorganisms, including the production and release of antibacterial compounds such as antimicrobial peptides (AMP), along with cytokines. These are excreted by epithelial cells right after the recognition of microorganism-associated molecular patterns (MAMPs) of bacteria, such as flagellins, peptidoglycan and lipopolysaccharides (LPS). Although probably not directly the target, human archaea are exposed to the various AMPs secreted by the host to control the bacterial microbiota. Notably, susceptibilities against AMPs were found to be substantially different among mucosa-associated methanogenic strains [19,114], with pseudomurein-containing archaea, such as *M. stadtmanae*, being more resistant against the lytic effects of AMPs than, for example, members of the Methanosarcinales or Methanomassiliicoccales.

In recent years it was clearly shown that archaea interact and activate the human immune system. Activation of human immune cells, as well as pro-inflammatory cytokine responses by peripheral blood mononuclear

cells and by monocyte-derived dendritic cells, initiated by phagocytosis and endosomal lysis, was demonstrated [18]. Strong response, that is high release of pro-inflammatory cytokines including interleukins as well as interferons, was exclusively observed when stimulating with *M. stadtmanae* cells [18,115]. Interestingly, the other two GIT archaeal isolates tested, *M. smithii* and *Methanomassiliicoccus luminyensis,* showed only mild responses, if at all [18,19]. As *M. smithii* has the capacity to produce glycans that mimic those found in the human gut [105], it is attractive to hypothesize that those host-like glycans enable *M. smithii* to escape from the host immune system. Although these studies demonstrated not only innate, but also adaptive immune response by human immune cells in response to *M. stadtmanae*, initially no specific receptor involved was identified. Only recently it was demonstrated that RNA of *M. stadtmanae* is a potent immune stimulator, and Toll-like receptor (TLR) 7 and TLR8 were identified as the involved pattern-recognition receptors, respectively [116]. Moreover, this molecular interaction led to TLR8-dependent triggering of the NLRP3 inflammasome in a new and alternative path of inflammasome activation. To the best of our knowledge, archaea do not trigger any other innate immune receptor and may thus be unique among microbial stimulators in triggering RNA-dependent signaling only. Hence, this TLR8-dependent alternative inflammasome activation may be archaea-specific.

Archaea in human health and disease.

By using the indirect detection of methanogenic activity via methane breath tests, possible correlations between the occurrence of methanogens in the human GIT and various diseases have been analyzed since the late 70s [117]. Since then, the relationship of methanogen abundance (cultivation-, quantitative PCR (qPCR)- and next-generation sequencing (NGS)-based analyses) or breath methane content with disease has been assessed in various (gastrointestinal) diseases and physiological states of the host. These include colon cancer, diverticulosis, diabetes, obesity and anorexia, inflammatory bowel diseases and many others (summarized in

Refs. [28,35,118]). However, due to the above mentioned methodological issues of bacteria-centric methods or other pitfalls (Box 2), available information is contradictory and the involvement of archaea in human health and disease remains often blurry [31,35,118].

When they are subject to dysbiosis or infection, several sites of the human body are known to present higher prevalence and abundance of methanogenic archaea. For example, *M. smithii* was reported in the vagina only in patients suffering from vaginosis, but was absent in healthy individuals [119,120]. Moreover, *M. smithii* was found in individuals with muscle abscesses [104], pneumonia [121] and urinary tract infections [122], and, together with *M. oralis,* in patients with refractory sinusitis [123]. *M. oralis* was also reported in brain abscesses [111,124], and has been associated with periodontitis [110,125] or peri-implantitis [126]. Interestingly, *M. oralis* is more prevalent and abundant in severe periodontitis, but was not detected in healthy sites adjacent to periodontal pockets and was no longer present after healing, which highlights the specific association of *M. oralis* with the inflamed site [110]. All these dysbioses and infections consist in a strong increase or *de novo* colonization by anaerobic fermentative bacteria. This shift to anaerobic fermentative bacteria is accompanied by an increase of archaea that can reach a high proportion of the whole microbial community, namely up to ~25% in brain abscesses [111,124] and 18% in severe periodontitis [110]. Although methanogens are never the only microorganisms present at these infected sites, they are likely to promote the outgrowth of fermentative bacteria involved in the inflammation by lowering H_2 concentrations (Box 1). In fact, other hydrogen-consuming microorganisms such as sulfate-reducing bacteria show an increased abundance in severe periodontitis and could fulfill the same role as methanogens [127]. Thus, methanogenic archaea might participate in such polymicrobial diseases through syntrophic interactions, representing one component of a 'unit of pathogenicity' besides bacterial partners[128,129]. Interactions of methanogenic archaea with pathogenic bacteria could actually occur in various diseases and not be limited to syntrophic partnerships. Indeed, a recent genome survey revealed that more than 200 pathogens have genes involved in hydrogen consumption or production [130]. This suggests a potential

dual role for methanogens, as syntrophic partners of fermentative pathogens and as potential competitors of the hydrogenotrophic ones.

Beyond this indirect role, it is unknown whether archaea can be directly involved in inflammation at these infected sites. Some indications exist for *M. oralis*, as it has only been detected in inflamed areas so far. In this respect, it has also been shown that the pro-inflammatory potential of archaea varies among species as, for example, *M. stadtmanae* triggers a stronger immune response than *M. smithii* and *M. luminyensis* using monocyte-derived dendritic cells [29]. Moreover, increased abundance of *M. stadtmanae* was found to frequently correlate with disease and inflammation, in particular in inflammatory bowel disease [118,131]. In combination with its observed high pro-inflammatory potential, activation of the inflammasome, as well as strong B-cell and T-cell responses within the draining lymph nodes due to *M. stadtmanae* entering the bloodstream [18,115,132], suggest a potential involvement in the development and or manifestation of disease. By contrast, a recent publication showed an association between *M. stadtmanae* carriage and a lower risk of asthma in young children, which is indicative for a beneficial role for *M. stadtmanae* [132].

Besides the direct interaction of archaeal cells and the immune system, the gaseous product of methanogenic archaea, methane, could have by itself a physiological effect on the host, as indicated by a recent growing number of studies. For example, a direct influence of methane on gut motility was shown, leading to a reduced faeces transit time by up to 59%. This slow-down is possibly caused by a direct action of methane on the cholinergic pathway of the enteric nervous system [133], possibly explaining also the association of methanogens with constipation (IBS-C type) [134,135]. Constipation, or longer faeces transit times, also ease the colonization of microorganisms with longer generation time, such as preferred syntrophic partners of methanogens (for example, Clostridiales cluster XIV) [136], and methanogens themselves [137]. Treatment with statins, which specifically inhibit the archaeal fatty acid synthesis pathway, is considered as a possible way to improve constipation and associated disorders [138]. Other recent works, performed with methane-rich saline in rodent

models, indicate that methane might be involved in other important processes [139], such as enhanced exercise capacity [140], increased secretion of GLP-1 (glucagon-like peptide-1, which has a role in insulin secretion and appetite suppression) [141], or anti-inflammatory and neuroprotective effects [142]. Whether the methane formed by methanogens directly in the GIT also has these effects remains to be analyzed.

In addition to these potential positive effects of methane (which need to be re-evaluated in the human setting with biogenic methane supplied by methanogens), several other positive roles for archaea have been proposed. For example, Thaumarchaeota found on the skin could contribute to oxidation of ammonia compounds delivered by sweat, and thus lower the skin pH. Their presence has in fact been linked with drier skin [17], but details on beneficial, commensal or opportunistic pathogenic activities are still missing. Another important positive role of members of the Methanomassiliicoccales in human health could be through their utilization of TMA as a substrate for methanogenesis. TMA is generated during dietary compound degradation by intestinal bacteria and is then oxidized into trimethylamine-oxide (TMAO) in the liver [143,144]. TMAO is involved in the development of cardiovascular and chronic kidney diseases [144,145], and TMA itself is associated with a genetic metabolic disorder, trimethylaminuria [146]. Methanomassiliicoccales species with the genetic potential to use TMA were found to be associated with a lower concentration of fecal TMA when compared to subjects without Methanomassiliicoccales or with Methanomassiliicoccales not capable of TMA consumption [15]. The removal of TMA by Methanomassiliicoccales before it enters the bloodstream could therefore help prevent the development of diseases and metabolic disorders associated with this dietary nutrient.

The anaerobic TMA-degradation pathway, which requires the 22nd proteinogenic amino acid pyrrolysine [147–149], is shared by only a few bacteria and some archaea, and in the human GIT it currently seems to be unique to the Methanomassiliicoccales [147–149]. Therefore, the prevention of these diseases could rely on the supplementation of TMA-consuming Methanomassiliicoccales (so-called 'archaebiotics' [14]). As a proof-of-concept, a single inoculation of *M. luminyensis* B10 (the so-far unique isolate of Methanomassiliicoccales[150])

significantly lowered the concentration of plasma TMAO in standard C57BL/6 laboratory mice through a 30-days experiment, despite a very poor colonization [151,152]. *M. smithii* and two TMA-using methanogenic archaea (non-human and environmental) also showed a protective effect on a mouse model prone to atherosclerosis [151].

Do archaeal pathogens exist?

Despite the above described possible involvement of methanogenic archaea in several polymicrobial diseases [129], archaeal pathogens according to Koch's postulates and their *per se* pathogenicity have not been identified to date.

Nonetheless, in theory, archaea have all the preconditions to develop into pathogens: they are genetically and metabolically diverse, widespread in the environment, capable to engage in warfare with their close relatives by various anti-archaeal compounds (such as sulfolobicin [153]), have been interacting with different hosts for millions of years, and they are recognized by the host immune system [30,31]. Thus, it was proposed that the current lack of identified archaeal pathogens might simply reflect a lack of knowledge due to our current inability to correctly detect them in disease patterns [30].

By contrast, it has also been proposed that no archaeal pathogens exist, and this may be due to various reasons. One hypothesis is that archaea use different cofactors than eukaryotes, and as such they have no inherent advantage in becoming pathogens to acquire resources from their target [154]. However, archaea could take advantage by acquiring other metabolites than vitamins [155].

Another hypothesis for the absence of archaeal pathogens was attributed to the fact that they have unique viruses, and thus cannot acquire virulence factors from bacterial and eukaryotic viruses; besides, the abundance of archaeal lytic viruses may prevent the maintenance of virulence factors in the mobile genetic

pool [156]. However, lysogenic or integrated viruses can also carry virulence factors, and current knowledge of the diversity and genetic pool of archaeal viruses is highly incomplete, covering only a few non host-associated lineages [157]. Even less information is available on the virome of host-associated archaea and its interplay with that of host-associated bacteria and eukaryotes.

Another prospect is that the emergence of pathogenesis is a rare event that occurred only in a few bacteria and eukaryotes, but never in archaea [156]. Amongst the very few bacterial pathogens (estimated less than 1% of all bacterial species [158]), pathogenic Gram-negative proteobacteria deliver virulence factors into their target cells by using specialized molecular needles such as type III secretion systems, which are absent from archaea. However, many Gram-positive pathogens exist, and they deliver their virulence factors by other machineries that can also be found in the archaea, and so there is *de facto* no reason why an archaeon could not have acquired the capability to use one of these systems to deliver virulence factors to a eukaryotic cell.

As discussed in previous chapters, only a few lineages of the archaea have engaged the association with eukaryotic hosts (Fig.1). This small number of transitions from a free-living to a host-associate lifestyle in archaea may have narrowed the chances to develop virulence in a certain time frame, in particular when considering that a minimum of 42 independent events of adaptations to the host-associated lifestyle occurred in bacteria [159].

This opens another question: why would archaea be inherently less capable than bacteria to adapt to a host-associated life? The answer may be linked to a common ecological trait of the Archaea as proposed previously [160]: the adaptation to chronic energetic stress. This trait relies primarily on the specific membranes of archaea that enables them to dominate in extreme environments by minimizing their maintenance energy and outcompete or be as competitive as bacteria in niches with low available energy. According to this hypothesis,

the inherent tendency of archaea to thrive under chronic energy stress would therefore be incompatible with the rapid adaptability that is a distinguished feature of many pathogens [160]. Moreover, this ancestral trait may have restricted the environmental distribution of many archaea to specific niches, such as extreme environments and/or deep anoxic sediments, where they are unlikely to encounter a potential eukaryotic host.

In conclusion, it is striking that nearly 40 years after the first description of human-associated archaea, we still have no evidence for one of their members being the primary cause of a disease. The reasons for this are still unclear and probably lie in a combination of all the above-mentioned hypotheses, including the fact that the archaea that are the most strongly associated with the animal host, notably methanogens, depend indeed on the availability of metabolites (H_2, methyl compounds) produced by other resident bacteria, and as such, may be unable to act as independent pathogens.

Conclusions and outlook

Summarizing the current knowledge, it is evident that archaea are abundant, diverse and active components of numerous microbiomes in plants, animals, and humans. The current body of literature indicates that their presence has a substantial influence on their hosts and other members of the microbiome. However, it is still unclear whether these interactions rely on archaea-specific traits or properties shared with and/or acquired from other microbiome components. Either way, such adaptations are likely to be the result of a long-term co-evolution. From a host perspective, and beyond the enigma of the absence of pathogenic archaea, the extent to which their interactions are beneficial, neutral or deleterious is still unknown. Moreover, no data are available on the intra-species and interspecies level communication between archaea and both their

syntrophic partners and hosts. Open questions are also how and when archaea are acquired during the lifetime of their hosts, and why their diversity and abundance seem to increase with age. These questions are central but still unanswered due to methodological limitations and complex confounding factors affecting archaeal distribution (for example, host age or ethnicity). More efforts are therefore required to characterize and capture the diversity of host-associated archaea by using targeted approaches on well-characterized populations. There is also an urgent need for growing, isolating and characterizing a higher number of host-associated archaeal strains, which will provide key knowledge on their physiology, besides that inferred from genome or metagenome sequences alone. This would also reveal the determinants that enabled certain archaea to successfully colonize their host. Finally, it will be important to study archaea–host associations through the development of plant and animal models with defined microbiomes. In addition to the above-mentioned perspectives, future research on human health will need to include more clinical studies, and take into consideration the inflammation potential of archaea and their interaction with the immune system, especially of archaea that are strongly associated with inflamed body sites. These studies should also address the role of archaeal metabolisms and their products, such as the influence of methane on the human body.

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Fig. 1: Archaeal diversity. Shown is a schematic of the current tree of Archaea based on the most recent phylogenomic analyses[12,13,161,162], and host-associated clades, including Methanosarcinales, Methanomassiliicocci, Thaumarchaeota, Halobacteria, Methanocellales, Methanomicrobiales, Methanobacteria and Woesearchaeota, are highlighted. Host-associated archaea are phylogenetically diverse, but are mostly composed of methanogens and, more recently, Thaumarchaeota. The most basal phylogenetic relationships, including the monophyly of Euryarchaeota and DPANN, are still under debate[12].

Fig. 2: Methane emission in cattle in comparison to other animals. Methane (CH_4) is formed by the methano-archaeal components of the rumen and protist microbiome. The archaea syntrophically consume hydrogen (H_2), a product of anaerobic fermentation, and hereby support the metabolic activity of bacteria and protists. The methanogens can be free-living in the rumen, but specifically members of the orders Methanobacteriales, Methanomicrobiales, Methanosarcinales and possibly Methanomassiliicoccales can live as endosymbionts in the cytoplasm of anaerobic protists. These endosymbiotic methanogens utilize the H_2 that is generated by hydrogenosomes following the oxidation of pyruvate for methanogenesis. Methane is mainly emitted by eructation of cattle and by flatulence. The shows a comparison of the global methane emission rates of cattle[163,164], termites[165], sheep [163,164], goats [163,164], pigs [166] (considering one billion pigs worldwide (The Food and Agriculture Organization [www.FAO.org]), humans [83], chicken [167] (considering 23 billion chicken worldwide; The Food and Agriculture Organization [www.FAO.org]) in million tons per year (mtpa). Methane levels from cattle released into the atmosphere are the highest amongst the livestock, and represent one of the largest sources of anthropogenic methane emissions.

Fig. 3: Archaeal taxa detected in human, animal and plant samples. 16S rRNA gene sequences from isolated strains, publicly available clone sequences (for example, Ref. [16]), reconstructed metagenome assembled genomes (MAGs) from human microbiomes [15,168] and sequences from amplicon-based studies of animals [23,24], humans [17,20] and plants [22,62,68,69] were quality filtered (no singletons, length > 100bp, alignment score > 30, alignment identity > 40%; [169]), grouped at 97% similarity, and processed through SILVA SINA classification. Trees were calculated via RAxML, on the backbone of three neighbour sequences per query which were used to stabilize the tree ('add to neighbours tree' option; neighbor representatives are shown in the tree with an unlabeled node) (for a detailed overview please see supplementary figures). For the human archaeome tree (top panel), lineages found in only one publication are not shown; this filtering was not applied for the animal archaeome tree (bottom left panel) and plant archaeome tree (bottom right panel) due to the small number of available studies. Output was completed with meta-information (sample origin, isolate) using Itol [169]. Thaumarchaeota (correspond to Nitrososphaeria, in shades of orange), Woesearchaeota (in very soft red), and Halobacteriales (in shades of grey), Methanomicrobiales (in shades of red), Methanocellales (in shades of dark blue), Methanosarcinales (in shades of blue), Methanomassiliicoccales (in shades of purple), and Methanobacteriales (in shades of green), were found in all groups in different sample types (that is, skin, gastrointestinal tract (GIT) (including faeces, gut biopsies and rumen samples), respiratory tract and oral cavity samples), as well as green plant and/or seed samples, as indicated by the circles outside, which is linked to an individual archaeal representative.

Fig. 4: Detailed information on five archaeal genera found in humans, animals and plants. The reported association of *Halococcus*, *Methanobrevibacter*, *Methanosphaera*, *Methanosarcina* and *Methanoculleus* with specific animals and plants in specific sample types is displayed. The sub-class taxonomic information is given for groups of animals and plants. Figure is based on the data of Fig. 3. GIT, gastrointestinal tract.

Figure 5: Interaction of the gastrointestinal archaeome with the host and the bacterial microbial community. The host provides a stable biotope, including nutrition, to the archaeal community and regulates the composition of the microbial community through antimicrobial peptides (AMPs) and bile acids. In addition, the host has been shown to release pro-inflammatory cytokines in response to some archaeal components. Archaea in the human gut may exhibit a high degree of specialized adaptation, which are mirrored by a number of specific traits, such as reduced and/or adapted physiological capacity (not shown) and defense mechanisms (adhesin-like proteins (ALPs), glycans, bile salt hydrolases and biofilm formation. Methanogenic archaea produce methane, a potential neuro- and immunomodulator (see main text), which is excreted by the host, contributing to the global methane emission (see figure 2), and affecting human physiology, such as gut motility. The host-associated bacteriome provides substrates for the archaeome (including formate, trimethylamine (TMA), methanol, H_2 and CO_2). Moreover, the bacteriome may be a source of genetic material for archaeal members of the microbiome via horizontal gene transfer (HGT), allowing the acquisition of traits like ALPs, glycosyltransferases and bile salt hydrolases (BSHs). The interactions of the bacteriome with the host are not shown in this simplified schematic.

Text box 1: The unique biology of Archaea

At first glance, archaea resemble bacteria, as they lack a nucleus and organelles, possess circular genomes, an operon-based gene arrangement, and ribosomes of 70S type (see the table). However, archaea are evolutionarily distantly related to bacteria, which is reflected in their divergent 16S rRNA sequences. Moreover, they share many traits with eukaryotes, particularly their molecular machineries for transmission and manipulation of genetic information (for example, RNA and DNA polymerases).

Archaea also possess specific structural characteristics, such as unique membrane lipids (C_5 isoprenoid units ether-coupled to L-glycerol at the (*sn*)-2,3 position)[170,171]. Their cell envelopes never contain bacterial-like peptidoglycan or lipopolysaccharides but can be composed of protein, pseudomurein or modified heteropolysaccharides. In some cases, even only single or double membranes without additional layers function as an outer shell[172]. Consequently, archaea are not affected by antibiotics that target peptidoglycan, such as β-lactams, but are susceptible to antimicrobials that are also active against both bacteria and eukaryotes, such as metronidazole[34].

For motility, archaea use unique rotating flagella ('archaella') that are not homologous to those of bacteria and eukaryotes, but evolutionarily and structurally related to type IV pili[173]. Archaeal surfaces can additionally bear pili or fimbriae, cannulae, fibers or even grappling hook-bearing hami[174]. Many of these cell surface structures enable them to interact with surfaces, other (microbial) cells or viruses [175]. Also, most archaea have a single membrane, and lack the specific machineries that many Gram-negative bacteria use to deliver toxins into eukaryotic target cells, such as type III secretion systems [170].

Archaea can survive challenging conditions by switching to extreme slow growth or dormancy, but capacity to form spores has not been observed to date. They are widespread in various ecosystems and include autotrophs, heterotrophs, phototrophs, chemotrophs, organotrophs and lithotrophs, aerobes and anaerobes.

Archaea are considered to comply with chronic energy stress, and are thus well adapted to nutrient-limiting ecological niches [160].

Some of the archaea-specific pathways correspond to functions that are also present in bacteria (sugar metabolism, CO_2 fixation and biosynthetic pathways) but involve archaea-specific enzymes [176,177]. This is exemplified by ammonia-oxidation[178], a capacity with high ecological impact in marine and soil environments, whose pathway is distinct from its bacterial counterpart owing to the lack of heme-based enzymes [179]. Methane metabolisms (methanogenesis and methanotrophy), are widely distributed among archaea [162], and involve a specific enzymatic complex, the methyl-coenzyme M reductase. Methanogenesis is a unique metabolic trait of archaea that results in methane production *via* four main pathways: two of them commonly use hydrogen as electron donor (hydrogenotrophic pathways), that is, CO_2-reducing and methyl-reducing methanogenesis, whereas the other two do not require an external hydrogen source and include methylotrophic and acetoclastic methanogenesis [180,181]. Methanogens are strict anaerobes and are widely distributed in various environments, such as freshwater and marine sediments, (wetland) soils and the digestive tract of animals. Methanogenesis relies on a limited number of simple compounds (for example, H_2, CO_2, formate, methyl-compounds and acetate), that are metabolic by-products of organic matter degradation in anoxic environments. By keeping H_2 concentrations low, methanogens enable secondary fermentation (for example the utilization of volatile fatty acids, lactate and alcohol) to remain thermodynamically favorable and they increase the energy yield of primary fermenters using complex molecules such as carbohydrates[182]. Thus, by contributing to the overall efficiency of energy retrieval during digestion of organic matter, methanogens are considered to represent key-stone microorganisms in anoxic ecosystems. The contribution of methanogenesis to climate change is observed with concern, as most of biologically produced, atmospheric methane originates from archaeal metabolism (~69%; Ref. [67]). Methanotrophic archaea play an important role in the mitigation of methane emissions to the atmosphere, particularly from marine sediments. In contrast to

bacterial methanotrophy, the archaeal pathway relies on the reverse use of the enzymes involved in methanogenesis. Moreover, some archaea couple methane oxidation with the direct reduction of electron acceptors not used by bacteria, such as iron and manganese oxides, nitrate, humic acids [183–185] or with indirect electron transfer to sulfur compounds via sulfate-reducing bacteria [186].

Feature	Bacteria	Archaea	Eukaryotes
Nucleus	no	no	yes
Organelles	no	no	yes
Spliceosomal introns	no	no	yes
Chromosome shape	Circular and linear	Circular	Linear
Operons	yes	yes	Rare
RNA polymerase	Bacteria-like	Eukaryote-like	Eukaryote-like
DNA polymerase	Bacteria-like	Eukaryote-like	Eukaryote-like
Ribosome type	70S	70S	80S
Translation start (amino acid)	Formylmethionine	Methionine	Methionine
Histones	no	yes	yes
Peptidoglycan	yes	no Pseudo PG in some	no
Motility	Bacteria-type flagellum	Archaea-type flagellum (archaellum)	Eukarya-type flagellum
Lipopolysaccharide	yes	no	no
Membrane lipids	Ester-links (glycerol-1-phosphate backbone)	Ether-links (glycerol-3-phosphate backbone)	Ester-links (glycerol-1-phosphate backbone)
Methanogenesis	no	yes	no
Oxygenic	yes	no	yes

photosynthesis			
Spores	yes	no	yes
Human pathogenicity	yes	no	yes

For entries denoted as 'yes' the specific trait is present in either all or some members.

Text box 2: Methodological challenges for studying the archaeome

Due to the different physiological, structural and molecular properties of archaea, bacteria-centric methodologies applied to complex microbial communities often fail to detect the contribution of the archaeome. This concerns many aspects (see the figure), including visualization (for example, nucleic acid-based fluorescence *in situ* hybridization), cultivation and molecular quantitative analyses. For example, numerous commercial DNA extraction kits contain lysozyme, an enzyme that breaks bacterial peptidoglycan, but not archaeal pseudo-peptidoglycan. Moreover, due to the hardy nature of the (methano-)archaeal cell wall, in particular that of Methanobacteriales such as *Methanobrevibacter*, *Methanosphaera* and *Methanobacterium*, additional physical treatment, for example extended bead-beating, application of additional detergents or pseudo peptidoglycan endopeptidases [187], is necessary for efficient cell lysis. Also, most of the so-called 'universal' 16S rRNA primers fail to cover the broad archaeal diversity and are thus unable to detect certain archaeal lineages in specific sample types [21,118], such as tissue samples. Moreover, 16S rRNA gene copy per genome of bacteria (mean: 4.9) outnumbers that of archaea (mean: 1.7), resulting in lowering the estimation of real archaeal representation by 16S rRNA gene profiling or quantitative PCR [188]. Disadvantageous bacteria:archaea ratios, particularly in the case of massive eukaryotic DNA background in the samples, also challenge primer-independent, shotgun-based metagenomic studies. This could be overcome by

a physical enrichment of archaeal cells, or the depletion of host DNA using molecular capturing methods. Finally, due to the limited availability of well annotated genomes in underrepresented archaeal phyla, current databases often fail to correctly assign archaeal sequences [118]. Other issues concern the cultivability of non-extreme archaea in general [189], and the still unclear medical relevance of archaea.

Glossary:

Holobiont: A multicellular Eukaryote together with its associated microbial communities.
Endosymbiotic: Endosymbiontic microorganisms live in the cells of another organism.
Ectosymbionts: Microorganisms living on the surface of another organism in a symbiotic relationship.
Pseudogenization: Conversion of a gene into a nonfunctional gene-like sequence in a symbiotic relationship.
Rhizosphere. Soil area around a plant root, influenced by root exudates and inhabited by a specific population of microorganisms.
Endosphere. Internal regions of plant tissues, which are inhabited by endophytic microorganisms.
Phyllosphere. All above-ground parts of plants, serving as habitat for microorganisms.
Heritable: Proportion of variance in the phenotype which can be attributed to genetic differences between individuals.
Biofilm: Microbial consortium attached to a surface or interface and organized in an extracellular matrix
Horizontal gene transfer: A process by which genetic material is acquired from another organism (as opposed to vertical inheritance where genetic information is transmitted from parent to offspring).
Glycosyltransferases: Enzymes that catalyze the transfer of glycosyl (sugar) residues to an acceptor molecule
Microorganism-associated molecular patterns: Conserved molecules characteristic for microbes, which are recognized by the immune system.

Table of content:

The archaeal community, the archaeome, is now growingly recognized as an important component of host-associated microbiomes. In this Review, Moissl-Eichinger and colleagues discuss the diversity and potential role of archaea associated with protists, plants and animals, and they highlight the potential role of archaea in human health and disease.

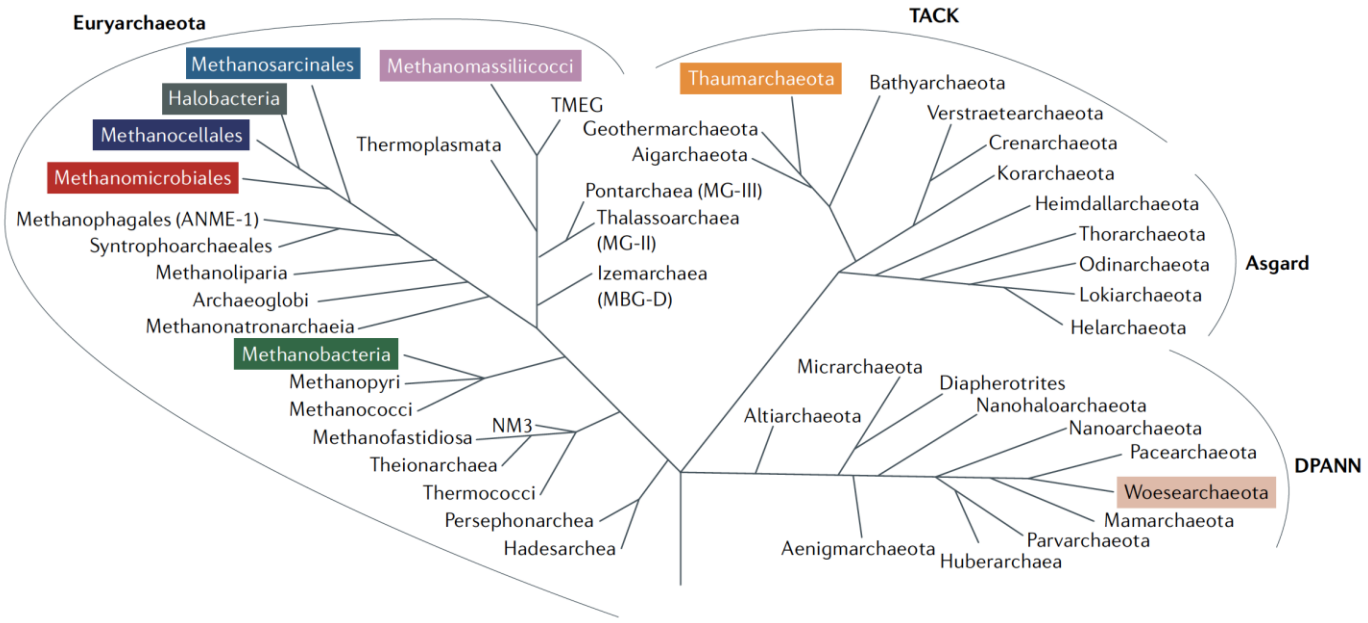
Euryarchaeota
TACK
Methanosarcinales
Methanomassiliicocci
Halobacteria
Methanocellales
Methanomicrobiales
Thermoplasmata
TMEG
Methanophagales (ANME-1)
Syntrophoarchaeales
Methanoliparia
Archaeoglobi
Methanonatronarchaeia
Pontarchaea (MG-III)
Thalassoarchaea
(MG-II)
Izemarchaea
(MBG-D)
Methanobacteria
Methanopyri
Methanococci
Methanofastidiosa
NM3
Theionarchaea
Thermococci
Persephonarchea
Hadesarchea
Thaumarchaeota
Bathyarchaeota
Geothermarchaeota
Aigarchaeota
Verstraetearchaeota
Crenarchaeota
Korarchaeota
Heimdallarchaeota
Thorarchaeota
Odinarchaeota
Lokiarchaeota
Helarchaeota
Asgard
Micrarchaeota
Diapherotrites
Altiarchaeota
Nanohaloarchaeota
Nanoarchaeota
Pacearchaeota
Woesearchaeota
Mamarchaeota
Parvarchaeota
Aenigmarchaeota
Huberarchaea
DPANN

Figure 1

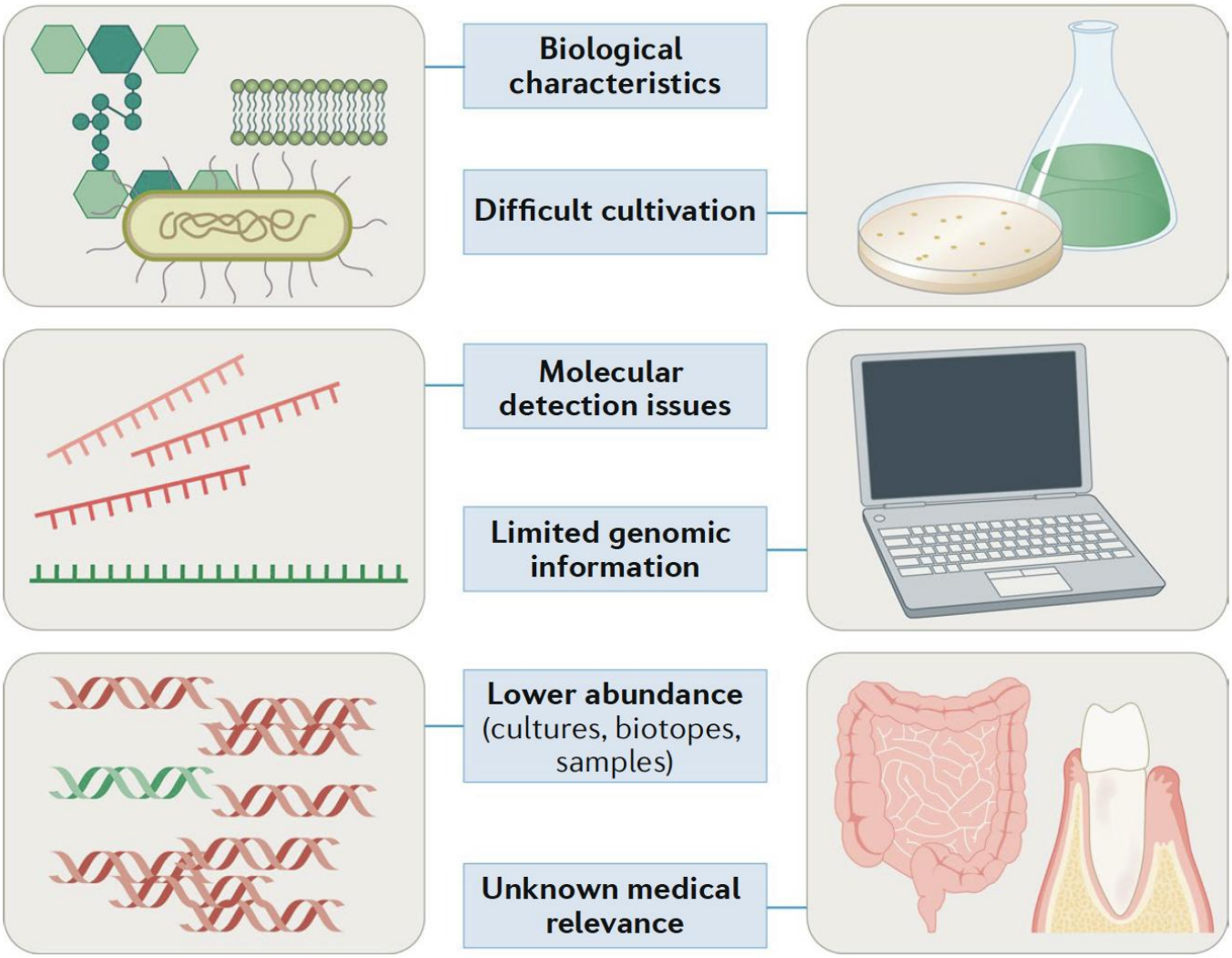
Biological characteristics
Difficult cultivation
Molecular detection issues
Limited genomic information
Lower abundance (cultures, biotopes, samples)
Unknown medical relevance

Figure Box 2

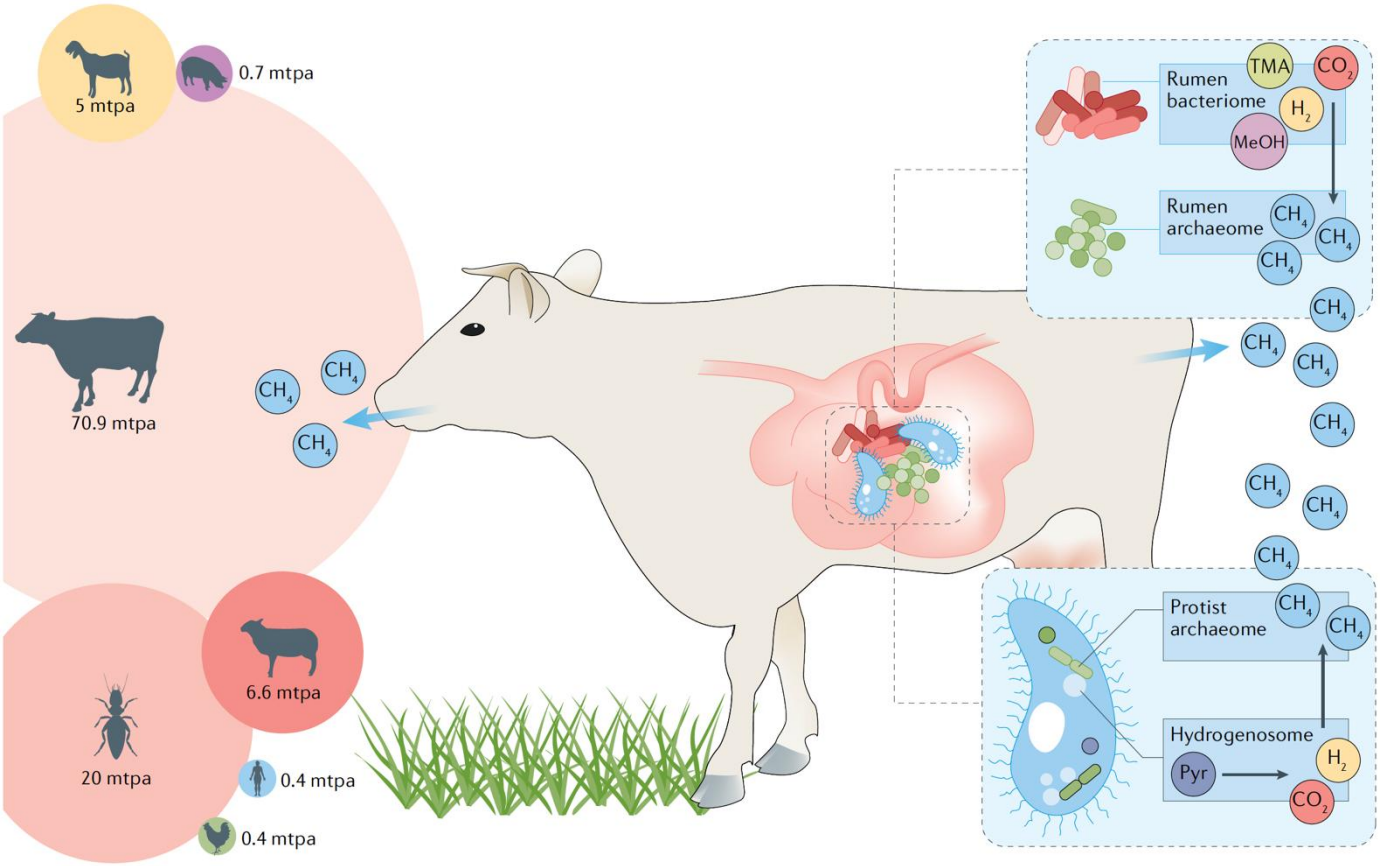
5 mtpa
0.7 mtpa
70.9 mtpa
6.6 mtpa
20 mtpa
0.4 mtpa
0.4 mtpa
CH4
Rumen bacteriome
TMA
CO2
H2
MeOH
Rumen archaeome
Protist archaeome
Hydrogenosome
Pyr

Figure 2

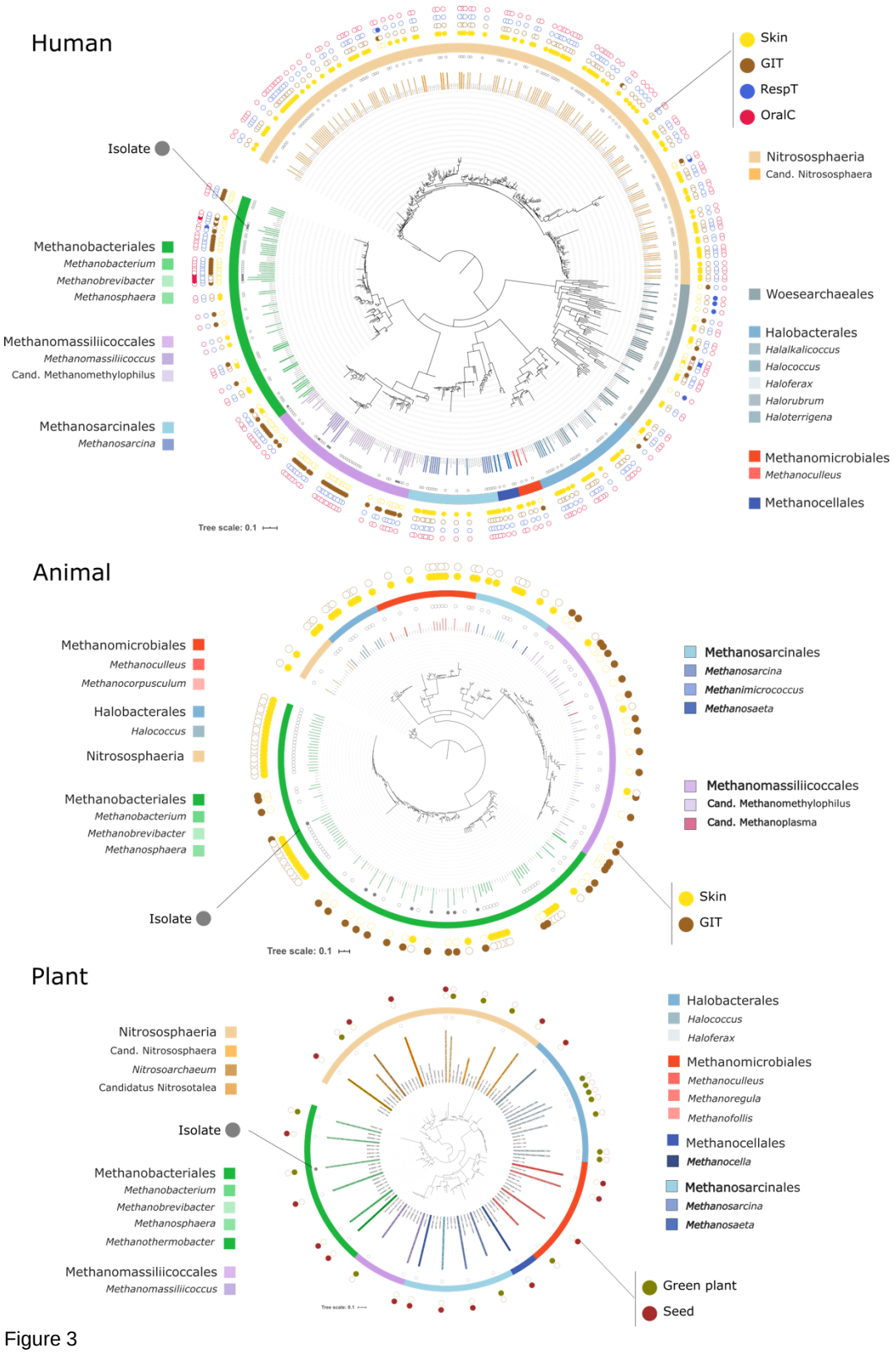
Human
Skin
GIT
RespT
OralC
Isolate
Nitrososphaeria
Cand. Nitrososphaera
Methanobacteriales
Methanobacterium
Methanobrevibacter
Methanosphaera
Woesearchaeales
Halobacterales
Halalkalicoccus
Halococcus
Haloferax
Halorubrum
Haloterrigena
Methanomassiliicoccales
Methanomassiliicoccus
Cand. Methanomethylophilus
Methanomicrobiales
Methanoculleus
Methanosarcinales
Methanosarcina
Methanocellales
Tree scale: 0.1
Animal
Methanomicrobiales
Methanoculleus
Methanocorpusculum
Halobacterales
Halococcus
Nitrososphaeria
Methanobacteriales
Methanobacterium
Methanobrevibacter
Methanosphaera
Isolate
Methanosarcinales
Methanosarcina
Methanimicrococcus
Methanosaeta
Methanomassiliicoccales
Cand. Methanomethylophilus
Cand. Methanoplasma
Skin
GIT
Tree scale: 0.1
Plant
Nitrososphaeria
Cand. Nitrososphaera
Nitrosoarchaeum
Candidatus Nitrosotalea
Isolate
Methanobacteriales
Methanobacterium
Methanobrevibacter
Methanosphaera
Methanothermobacter
Methanomassiliicoccales
Methanomassiliicoccus
Halobacterales
Halococcus
Haloferax
Methanomicrobiales
Methanoculleus
Methanoregula
Methanofollis
Methanocellales
Methanocella
Methanosarcinales
Methanosarcina
Methanosaeta
Green plant
Seed

Figure 3

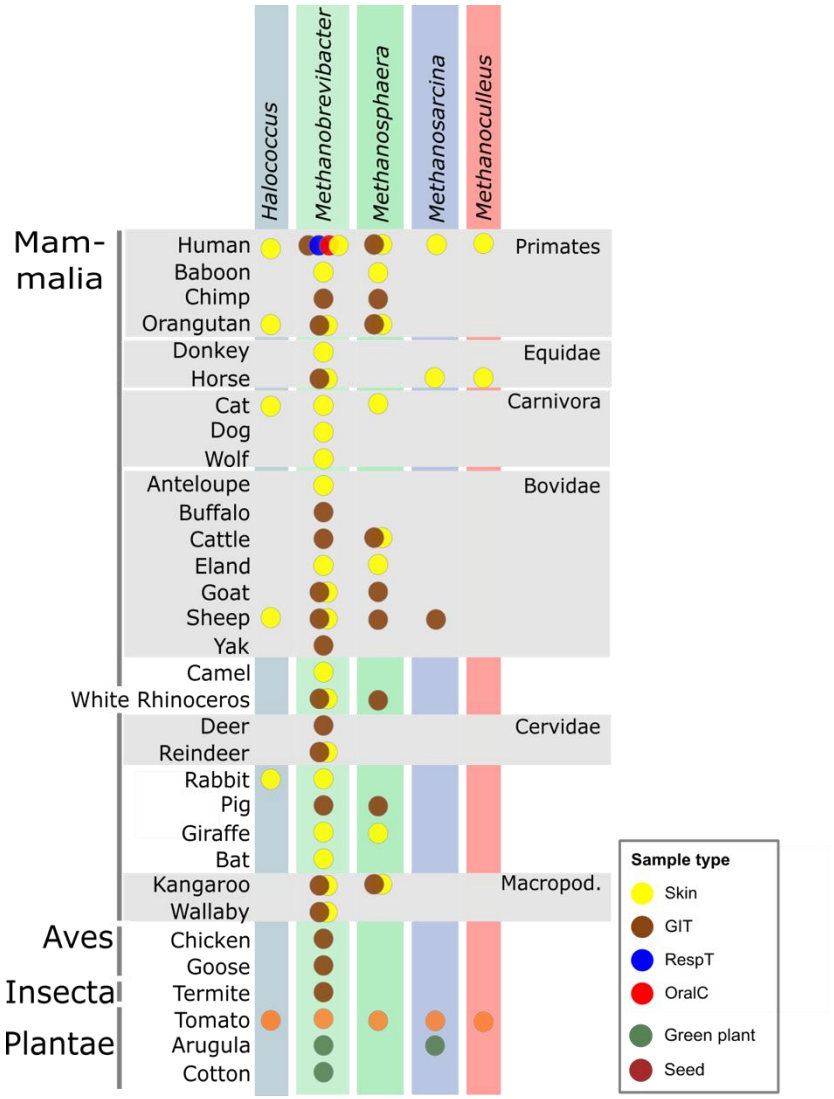

Figure 4

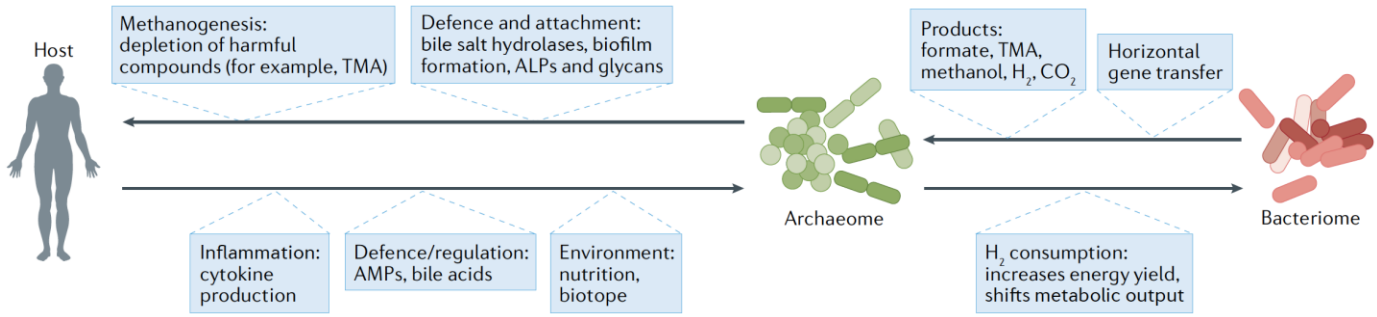

Figure 5