The search for archaeal pathogens

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Archaea were only classified as a separate kingdom in the late 20th century. Archaea are associated with the ancient origins of life on earth and were assumed to inhabit only extreme environments like hydrothermal vents and salt lakes. However, the surprising discovery that Archaea are widespread and include mesophiles has led to the question of what role these organisms might play in human health and disease. In contrast to hundreds of bacterial species, only a few archaeal species have been identified in humans. These are predominantly the methanogens found in the oral cavity and the gastrointestinal tract. In addition, an extreme halophile in colonic tissue and a thermoacidophile in subgingival plaque have been detected. Although these organisms appear to have less stringent growth requirements than many extremophiles, they may inhabit extreme microniches that could exist within the human body. In addition to these Archaea that are members of the phylum Euryarchaeota, faecal samples were found to contain phyla of the Crenarchaeota, whose divergence from Euryarchaeota is far greater than phyla within bacteria or Eukarya. Many of these were identified as Sulfolobales, of which the only cultured examples are thermoacidophiles. How these organisms have adapted to their human environments remains unknown. This review presents the diversity of Archaea identified in human samples, as well as factors limiting their detection. The known associations of Archaea with disease that may indicate a possible cause will be explored. Finally, a comparison will be made with known pathogens to address the possibility that Archaea could evolve virulence and cause disease.

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Introduction

Archaea were initially mischaracterized as a group belonging to bacteria under the assumption that all prokaryotes were alike. Archaea were not classified as a separate domain until the late 20th century. Propagating this confusion is nomenclature like the class 'Methanobacteria'; in fact, all methanogens belong to the Archaea. As the domain name implies, Archaea are associated with their archaic origins and were assumed to inhabit only extreme environments like hydrothermal vents and salt lakes – far from any clinical relevance. The surprising discovery that Archaea are in fact widespread and include mesophiles among their ranks has led to the question of whether they might have a role in human health and disease [1]. Over the last two decades, there has been an increasing interest in the field, but without a satisfactory answer.

Although a definite archaeal pathogen has yet to be identified, this does not mean they do not exist [2]. Thus, an examination of the diversity of Archaea identified in human samples, as well as factors limiting their detection, is merited. Exploration of the known associations of Archaea with disease may hint at possible cause. Finally, comparison to known pathogens will enable a theoretical consideration of the ability of Archaea to cause disease or to evolve virulence.

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Archaeal diversity in the human microbiome

Only a handful of archaeal species have been identified in humans, in stark contrast to more than 700 types of bacteria [2]. The most prevalent are the obligate anaerobes, methanogens (produce methane). The overwhelmingly predominant species, and the only Archaea cultured from humans so far, are *Methanobrevibacter smithii*, *Methanobrevibacter oralis*, and *Methanosphaera stadtmanae*. *M. oralis* is the predominant archaeal species in the oral cavity, whereas *M. smithii* and, to a lesser extent, *M. stadtmanae* are common to the gastrointestinal tract [3]. Other, less ubiquitous methanogens have also been identified through nucleic acid-based methods [4].

Other types of Archaea have also been detected in clinical samples, but the isolated nature of these reports makes it difficult to assess whether they are common members of the human microbiome. Diverse members of the family Halobacteriaceae and a novel phylotype of the class Thermoplasmata were detected in colonic tissue and subgingival plaque, respectively [5,6]. These discoveries were surprising because they are extreme halophiles and thermoacidophiles, respectively. Thus, these organisms appear to represent novel species with less stringent requirements for growth than their better-characterized (but still mysterious) extremophilic relatives. Additionally, they may inhabit extreme microniches within the human body. For example, folds in colonic tissue provide pockets of higher salt that may be attractive to halophiles [5].

Archaea inhabiting humans are not limited to the phylum Euryarchaeota, to which all of the previous examples belong. Faecal samples were found to contain multiple phylotypes of Crenarchaeota [7], whose profound divergence from Euryarchaeota is unparalleled among phyla of Bacteria or Eukarya [1]. The majority of sequences clustered within the order Sulfolobales, of which the only cultured examples are thermoacidophiles [7]. Once again, the question of how these organisms have adapted to their human environments remains unknown. Our knowledge of archaeal diversity in the human body is expanding, but is far from complete (Fig. 1).

Detection of Archaea

The identification of Archaea in clinical samples, requisite to establishing pathogenicity, is complicated by the unique characteristics of this domain. Archaea are notoriously difficult to culture. They often possess unusual requirements for growth due to their unique proteins and pathways. Like other microbes that rely on complex interactions, many species may be impossible to culture in isolation. Even previously isolated species can be difficult to culture in routine microbiology laboratories. Furthermore, even culture-independent molecular methods can yield misleading results. For example, sequence similarity between some archaeal and eukaryotic genes may result in promiscuous binding of PCR primers. Cross-hybridization of archaeal 16S primers with human DNA can occur, preventing accurate identification [2]. Additionally, inherent stability of archaeal structures may complicate detection with standard methods. Through a combination of harsher mechanical and chemical lysis, a recent study detected *M. smithii* in 95.7% and *M. stadtmanae* in 29.4% of faecal samples, significantly exceeding all previous published data [8]. Thus, the inconsistent detection of Archaea may be due to an ineffective protocol, belying their significance and prevalence in the human microbiome.

Methanogens and disease

In every part of the human body that Archaea have been found to colonize, methanogens have been associated with disease.

(1) In the oral cavity, methanogens have been identified in patients with a variety of polymicrobial infections, both periodontal and endodontic, for which no single pathogen has been established [2]. For example, Archaea were detected in the root canals of many patients with apical periodontitis. They always occurred in conjunction with bacteria, hinting at a potential syntrophic relationship in which the metabolic pathways of both species are inextricably linked [9]. A mechanism for this has been supported by multiple studies [2,3,10] (Fig. 2). Notably, clinical symptoms were more prevalent in cases of co-infection with Archaea versus bacteria alone [9]. Furthermore, sera from patients with aggressive periodontitis reacted with components of *M. oralis* – the first demonstration of IgG antibodies generated *in vivo* in response to archaeal antigens [11]. The production of circulating antibodies against methanogens, as well as their correlation with clinical symptoms, may indicate that these organisms actively contribute to oral disease, rather than merely colonizing anaerobic niches provided by pathogenic plaque biofilms [3].
(2) Levels of methanogens in the lower gastrointestinal tract, often detected by breath methane, are correlated with a variety of disorders ranging from colorectal cancer to inflammatory bowel disease to diverticulosis [3]. Additionally, gut methanogens may contribute to the cause of obesity. Germ-free mice colonized with *M. smithii* and a common gut bacterium exhibited increased adiposity compared with control mice colonized with the gut bacterium alone or in

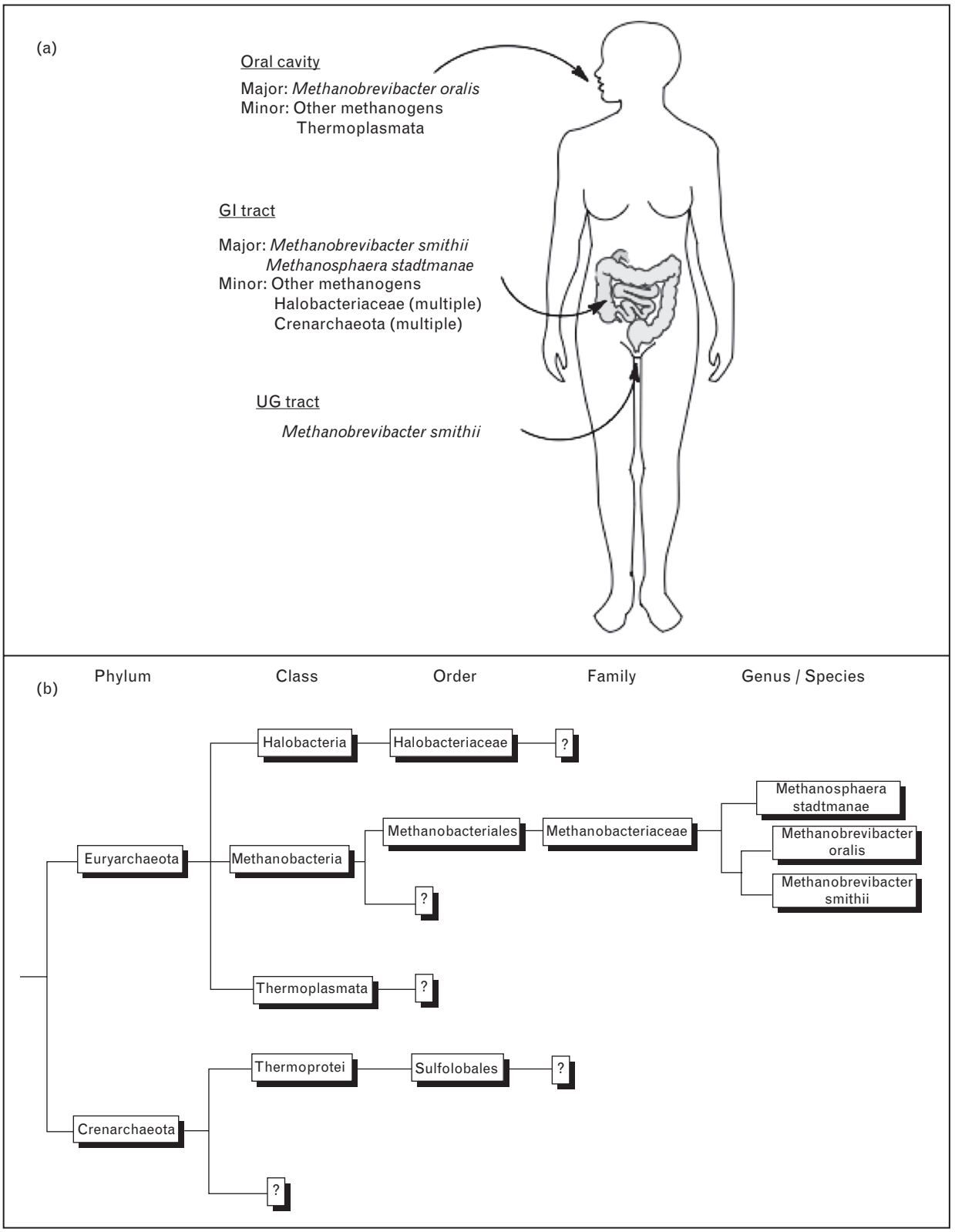

Fig. 1. Representation of some of the diversity of Archaea identified in human samples thus far: (a) by site of discovery and (b) by cladogram. Note that the latter is based solely on taxonomy (as reported by the *NCBI Taxonomy Database*) and distances do not necessarily reflect accurate evolutionary distances. Rather, the diagram is meant to illustrate the dearth of a complete picture of archaeal diversity in humans. Question marks indicate that one or more archaeotes of this type have been detected, but more specific classification may not be available [3–7]. GI, gastrointestinal; UG, urinogenitary.

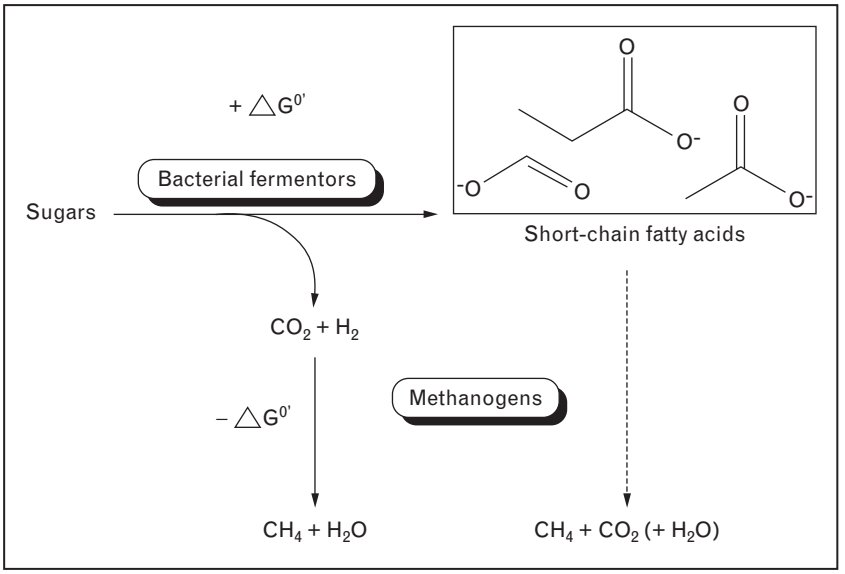

Fig. 2. Illustration of potential syntrophic interactions between methanogens and fermenting bacteria. Various pathways have been described for how methanogens exploit the products of fermentation, benefiting the bacteria in turn. The major pathway, left, decreases the partial pressure of H_2, which might otherwise inhibit bacterial fermentation and growth. Furthermore, the production of methane from CO_2 and H_2 is highly exergonic, and some of this free energy is believed to be available to bacteria living in close association. Some methanogens are also capable of using certain SCFAs produced by fermentation as carbon sources for methanogenesis, depicted at right [3,10]. SCFAs, short-chain fatty acids.

conjunction with a sulphate-reducing bacterium. This is due to syntrophic interactions between these species, similar to those described in the oral cavity. Co-colonization with *M. smithii* increased bacterial fermentation of polysaccharides to particular short-chain fatty acids (SCFAs), generating CO_2 and H_2 gases. Whereas both the methanogen and the sulphate reducer respire H_2, only *M. smithii* is also capable of consuming SCFAs as carbon sources for methanogenesis, further favouring fermentation. The increased production of SCFAs results in higher calorific absorption, upregulation of enzymes for lipogenesis, and, ultimately, increased storage in adipose tissue [10].

(3) Finally, methanogens have been associated with disease in the urinogenitary tract where *M. smithii* was found in vaginal samples from patients with bacterial vaginosis, but not in healthy controls [12].

Although none of these examples reflect the canonical sort of pathogenesis, in which a single virulent strain directly causes damage to the host, this may simply be too reductionist to encompass the range of mechanisms that organisms have evolved for causing disease. Through syntrophic interactions with other microbes (Fig. 2), methanogens may act as keystone species for complex communities that are more than the sum of their parts, by enabling certain species to thrive and outcompete others for limited resources. Depending on how the microbial community equilibrates, disorder may result [2,3]. However, correlation with disease does not prove causation. If the definition of pathogenicity was to be re-evaluated, it would need to include a means of establishing this type of communal pathogenicity [3].

Route to pathogenesis

In addition to the role of methanogens in syntrophic interactions, do Archaea have virulence factors that are directly capable of pathogenesis? Here, comparison with known pathogens may be informative. The classic route to pathogenesis follows several key steps. By considering the hypothetical ability of Archaea to complete each step in light of current research, their potential to serve as direct pathogens may be evaluated.

(1) We know that the initial step of access and entry to the host occurs as diverse Archaea have been shown to colonize humans [13]. The existence of archaeal mesophiles among diverse phyla indicates that the ability to thrive at human temperatures has arisen multiple times, and may not be difficult to evolve [1]. A potential access route for Archaea is through diet; various Archaea have been detected in table salt [5] and fermented foods [14]. Some of the host's defences to prevent entry do not pose a threat for Archaea. For example, they are insensitive to lysozyme, a bactericidal enzyme in tears and saliva, which degrades peptidoglycan found in bacteria but not in Archaea [1].

(2) The next step is attachment to host tissues, which may be facilitated by cell surface structures such as flagella. Although disparate in evolutionary origin from their bacterial counterparts, archaeal flagella have been identified in organisms like *Pyrococcus furiosus* [15]. These structures enable swimming and the formation of stable, biofilm-like structures through adherence to each other and to a variety of surfaces. Thus, the potential function of archaeal flagella as virulence factors is manifest. Furthermore, most sequenced Archaea possess clusters of Tad-like genes that are involved in tight adherence and identified in many pathogenic bacteria [16]. Nonspecific adherence may also be facilitated by the enrichment in intrinsic disorder of archaeal proteins that may contribute to virulence by aiding attachment and invasion of host cells [17,18].

(3) Persistence and proliferation in the host depend on successful competition with preexisting microbiota and other potential colonizers for limited resources [13]. Obtaining essential nutrients from the host may limit Archaea from becoming pathogens. Although archaeal metabolism usually requires unique cofactors that humans cannot synthesize [19], many Archaea can synthesize their own cofactors, thus eliminating the requirement for an exogenous source [20]. Additional benefits may also be derived from the host apart from vitamins, such as metabolites, nucleic acids, or amino acids, as well as utilizing host machinery for gene replication and expression [21]. For example, *M. smithii* in the gut is exquisitely adapted to scavenge ammonium and compete effectively for host nitrogen sources [20]. Additionally, host tissue provides a site for advantageous interactions with other microbiota. As previously described, methanogens metabolize H_2 and other products of bacterial fermentation, effectively competing with sulphur-reducing bacteria for these resources [3]. The extremophilic nature of some Archaea may also aid in competing for limited resources by enabling the colonization of niches that would be too acidic or too salty for nonextremophiles [5].

(4) As the invader continues to proliferate, evasion of the host immune system may become necessary. Studies with vesicles of archaeal polar lipids (archaeosomes) that are unique to this domain show that they are potent vaccine adjuvants, which could prevent their proliferation and pathogenesis [13]. Mice vaccinated with archaeosomes containing BSA, which is not normally antigenic, developed immunity against it. Multiple archaeosomes based on various archaeal species were superior to nonarchaeal liposomes and to conventional adjuvants like alum [22]. However, *in vivo*, the archaeal membrane is not exposed to the immune system, as this is enveloped by an outer S-layer. This is composed of identical protein subunits modified by glycosylation and isoprenylation [23]. Because such posttranslational modifications are prevalent in eukaryotes, this archaeal property could enable molecular mimicry of human host structures and thus evasion of the immune response. For example, *M. smithii* in the gut produces surface glycans that resemble gut mucosal glycans [20]. In addition, the nonspecific binding promoted by intrinsic disorder in some archaeal proteins could inhibit the generation of high-affinity antibodies, thus preventing an effective immune response [17].

(5) Finally, by definition, pathogenesis requires that some trait of the invader result in damage to the host. Opposing the potential for pathogenicity, archaeal homologues of classic virulence factors like toxin biosynthesis genes have not been identified. Currently, sequence data from Archaea reveal an absence of a type III secretion system that is associated with Gram-negative bacterial pathogens, through which effector molecules are injected directly into host cells [13]. However, Archaea do possess alternate secretion pathways that could have a similar function [23]. An alternative mode of toxin production has already been described, namely, the volatilization of metals and metalloids into more toxic compounds. Methanogenic gut isolates can react with a variety of metal(loid) substrates to produce volatile derivatives more efficiently than do various bacteria. Permethylated bismuth was shown to have a toxic effect on commensal gut bacteria and may contribute to pathogenesis [24].

Pathogenicity may occur through over stimulation of the immune system [13]. Evidence that Archaea may cause this has been demonstrated *in vitro*. Chaperonin subunits from *M. oralis* were demonstrated to be highly antigenic and to contain sufficient sequence identity to human group II chaperonins to result in cross-reaction between subunits of both domains. This may lead to the generation of auto-antibodies *in vivo*, potentially causing chronic inflammation and autoimmune disease. A similar cross-reaction between human group I chaperonins and Hsp60, a highly antigenic bacterial chaperonin, has been associated with autoimmune diseases like rheumatoid arthritis [25].

Thus, even our limited knowledge of Archaea has revealed multiple genes with potential to serve as virulence factors, though pathogenicity may be limited by characteristics of archaeal structures and pathways.

Evolution of pathogenicity

If the traits possessed by Archaea are insufficient to enable pathogenesis, does a barrier lie in the evolution of pathogenicity? It has been recently postulated that Archaea are precluded from evolving virulence due to the lack of multidomain viruses [26]. This is based on

several assumptions. First, gene pools of bacterial and archaeal viruses are proposed to be mutually exclusive due to insurmountable differences across domains in morphology of membrane receptors and of the viruses themselves. Second, bacterial pathogenicity is proposed to depend on acquisition of virulence factors from bacteriophage as part of a complex system in which phage essentially exploit bacteria as vehicles with which to infect eukaryotes. Thus, Archaea are unable to acquire bacterial virulence factors through phage-mediated lateral gene transfer (i.e., transduction). The authors assume that this model of pathogenicity is so complex that Archaea are unable to evolve virulence independently [26].

However, this postulation has numerous issues. First, there is evidence of viral domain crossover in both directions. Phylogenetic and structural analysis demonstrated the presence of archaeal-derived proteins in some phage genomes [27]. Similarly, the genome of a haloarchaeal virus was found to derive elements from bacteriophage and nonhalophilic bacteria [28]. Thus, viruses may serve as vectors for horizontal gene transfer (e.g., of virulence factors) across domains, as well as between extremophiles and nonextremophiles. Additionally, Gill and Brinkman's [26] hypothesis revolves around the oversimplification that pathogenicity is necessarily derived from a complex interplay between phage, bacterium, and host. Although this model has been demonstrated for pathogens like *Vibrio cholera* [26], virulence factors are not all associated with mobile genetic elements, and lateral gene transfer is not always through a viral vector. Interdomain conjugation through pili has been demonstrated, and naked DNA may also be taken up by cells [29]. In fact, there are numerous examples of lateral gene transfer between Archaea and pathogenic bacteria. Multiple putative virulence factors with archaeal origin have been identified in various pathogenic bacteria based on phylogeny [30]. For example, *Escherichia coli* O157 : H7, implicated in hemorrhagic colitis, has acquired a number of genes through lateral gene transfer with Archaea. Of particular interest is a gene for a bifunctional catalase peroxidase. Because it is absent from nonpathogenic strains of *E. coli* and similar to proven virulence factors in other pathogens, this gene likely represents the emergence of a bacterial virulence factor from an archaeal source [31]. However, examples like this raise the (yet unanswerable) question of why these genes do not serve as virulence factors for the Archaea in which they originate.

Conclusion

Gill and Brinkman make the case that, based on the proportion of known pathogenic bacteria (538 out of 151 154) and the number of known species of Archaea, we would expect to have identified roughly 16 archaeal pathogens to date. The 'expected' number of archaeal pathogens was calculated by Gill and Brinkman [26], but their analysis assumes equivalent diversity among discovered bacterial and archaeal species. However, the search for novel Archaea has historically been focused on extreme environments inhospitable to potential human colonizers. Based on this reasoning, the lack of an archaeal pathogen is statistically significant [26]. Note, however, that this analysis assumes equal diversity among known bacteria and Archaea. Yet until relatively recently, Archaea were believed to comprise solely extremophiles, causing scientists to focus their search in extreme environments [1]. As a result, our knowledge of archaeal diversity may be skewed toward extremophiles, which are less likely to be clinically relevant.

With insufficiencies in methods of detection and few examples of cultured Archaea, the lack of a clear-cut pathogen is perhaps not unsurprising. Although a direct archaeal pathogen is yet to be identified, a conclusive obstacle to pathogenicity has not yet been substantiated. Multiple routes to pathogenesis have been postulated. Methanogens may indirectly cause damage to the host through syntrophic interactions, modulating complex microbial communities that may cause disease. For these diseases, then, it is no longer a search for an archaeal pathogen but rather refinement of techniques to establish pathogenicity and, perhaps, a paradigm shift to a more holistic definition [3]. Indirect pathogenesis may also result from horizontal gene transfer of novel virulence factors from Archaea to bacteria [30]. Alternately, Archaea may act as direct pathogens through the synthesis of toxins like volatile metal derivatives [24] or through overstimulation of the immune system [25].

Factors such as unique metabolic needs, antigenicity of membrane lipids, and some division between viral gene pools may limit pathogenicity [19,22,26]; however, no insurmountable hurdle to direct pathogenesis or evolution of pathogenicity by Archaea has been established. In fact, sequential analysis of the various steps to virulence reveals that many Archaea possess characteristics that could render them adept pathogens. Over half of sequenced archaeal genes remain unclassified [13]. As our knowledge of archaeal diversity and gene function increases, will virulence factors or new obstacles to pathogenicity emerge? Either way, this research has important implications for understanding not only the least characterized domain of life, but also virulence in general. The search for an archaeal pathogen continues!

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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