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Chapter 21

Archaea

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Introduction

Just about half a century ago, all prokaryotes, i.e., cells without nucleus, were classified within one kingdom: *Monera*. However, in the late 1970s, scientists were starting to recognize that this classification system, based predominantly on morphological and metabolic traits, underestimated the vast diversity of prokaryotic life. Around the same time, the pioneering work of Carl Woese and George Fox led to the discovery that prokaryotes were, in fact, composed of two fundamentally different domains of life—the *Bacteria* and the *Archaea* (originally referred to as "Eubacteria" and "Archaebacteria," respectively) [1]. Woese and coworkers used the RNA components of the ribosome to reconstruct the first phylogenetic tree of life based on molecular data [2], which divided cellular organisms into three separate domains of life

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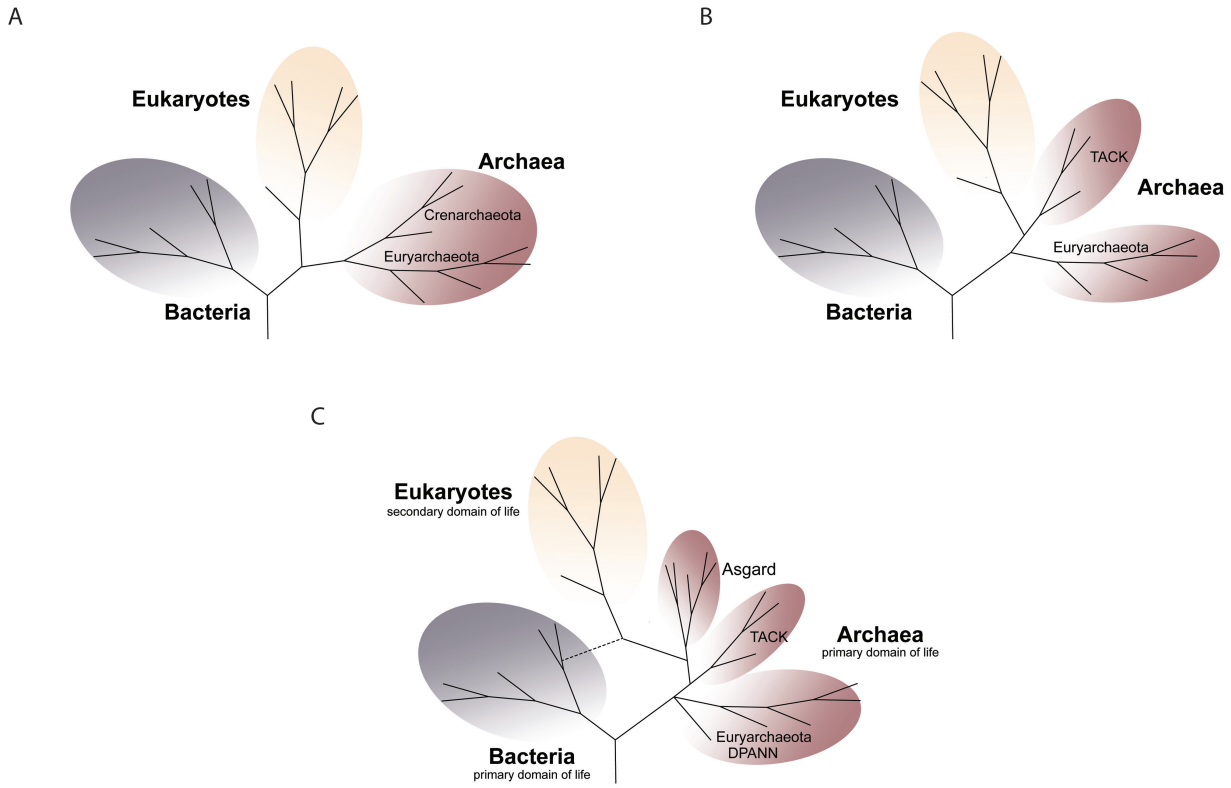

FIGURE 21.1 Schematic depictions of the relationship of *Archaea* with *Bacteria* and eukaryotes in the tree of life. A: Upon the discovery of *Archaea* as a separate domain, the tree of life was divided into three major domains. B: However, phylogenetic analyses of core informational proteins suggested later that eukaryotes may have evolved from within the *Archaea*, challenging the three-domain topology. C: Recent research, among others enabled by the discovery of the Asgard archaea, has shed further support on the branching of eukaryotes from within the *Archaea* (in terms of universal marker proteins). In turn, it has been suggested that the tree of life has two primary domains of life—the *Archaea* and *Bacteria*—and one secondary domain of life, which evolved from the former (see text for more details).

(Figure 21.1A)—the *Bacteria*, *Archaea*, and *Eukarya*, the latter of which comprised all organisms with a true nucleus [2]. At that time, it was suggested that *Archaea*, in spite of their superficial similarity to *Bacteria*, may be more closely related to eukaryotes than *Bacteria*. In fact, they seemed to harbor simplified versions of eukaryotic informational processing machineries (replication, transcription, translation, and cell division), in addition to unique characteristics such as ether-bound isoprenoids rather than ester-bound fatty acid-based lipids (Table 21.1). Subsequent research on *Archaea*, accompanied by extensive methodological developments in environmental microbiology, sequencing technologies, physiology, cell biology, and phylogenetics, has further changed our view on the diversity of life, the tree topology, as well as the ecological and evolutionary importance of *Archaea*. In particular, the use of cultivation-independent techniques, such as metagenomics and single-cell genomics, which allow us to obtain genomes of uncultivated organisms directly from environmental samples [3, 4], have been a key element leading to our changed perception of archaeal diversity and distribution. While *Archaea* have originally been viewed as comprising predominantly "extremophilic" organisms inhabiting environments with high temperature, salinity, and high or low pH, they are now known to be ubiquitous in all environments on Earth, including marine waters and freshwater lakes, sediments, soils (including plant roots), aquifers, and the human microbiome to name a few [5–7]. With their widespread ecological distribution and important metabolic capabilities, *Archaea* are recognized as key players in a wide variety of biogeochemical processes, including the sulfur, nitrogen, and carbon cycles [8]. For instance, *Archaea* include the only known organisms able to conserve energy through the anaerobic production or consumption of methane in processes referred to as methanogenesis and anaerobic methane oxidation, respectively. Since methane is an extremely potent greenhouse gas, with a global-warming potential about 25 times greater than carbon dioxide, these *Archaea* have an essential role in the global carbon budget and consequently climate change [9]. Finally, the study of archaeal phylogenetic diversity and evolution has fundamentally changed our understanding of the eukaryotic cell (see below) [10].

Archaea and the Tree of Life

Since the discovery of the *Archaea* as a separate domain of life (Figure 21.1A), their relationship to *Bacteria* and eukaryotes has been a matter of debate and is regarded to be of fundamental importance for our understanding of the origin of eukaryotes. Eukaryotic cells are highly compartmentalized and it has long been recognized that eukaryotic compartments, such as mitochondria (the site of ATP generation via oxidative phosphorylation) and chloroplasts (the organelles in which photosynthesis occurs in plants), evolved as a result of endosymbiosis, i.e., mitochondria and chloroplasts seem to be derived from Alphaproteobacteria

TABLE 21.1

Comparison of Selected Characteristics of the Major Domains of Life

Characteristic	Bacteria	Archaea	Eukarya
Membrane-enclosed nucleus	No	No	Yes
Chromosomal structure	Circular	Circular	Linear
Peptidoglycan in cell wall	Yes	No	No
Membrane lipids	Ester-linked	Ether-linked	Ester-linked
Glycerol	Glycerol-3-phosphate	Glycerol-1-phosphate	Glycerol-3-phosphate
Ribosomes (mass)	70S	70S	80S
Initiator tRNA	formylmethionine	methionine	methionine
Introns	No	No	Yes
Operons	Yes	Yes	No
RNA polymerase	One (4 subunits)	One (8–12 subunits)	Three (12–14 subunits)
Transcription factors required	No	Yes	Yes
TATA box in promoter	No	Yes	Yes

and Cyanobacteria, respectively (e.g., reviewed in [11]). In contrast, the nature of the host cell taking up the progenitors of these compartments was unknown until recently; while some hypotheses suggested that this cell was a proto-eukaryote that already resembled extant eukaryotic cells, others point out that the host was an archaeon or even bacterium [11–13]. For a long time, the prevailing view was that *Archaea* and eukaryotes represent two independent sister lineages in the tree of life [2, 14], and it was unclear how the shared ancestor of *Archaea* and eukaryotes looked like. However, while certain phylogenetic analyses have supported this model, others have suggested alternative scenarios, in which eukaryotes evolved from within the *Archaea* ([15] and reference therein).

The use of cultivation-independent genomic approaches combined with improved phylogenetic methods and more realistic evolutionary models have recently led new insights into the evolutionary history of the Archaea, their placement in the tree of life and eukaryogenesis. In particular, these analyses have provided increasing support for eukaryotes branching from within the *Archaea* [10, 15] instead of as a sister lineage as originally assumed (Figure 21.1 B–C). Though eukaryotes initially appeared to branch close to the TACK superphylum (discussed later in this chapter) [16] (Figure 21.1B), it was challenging to pinpoint a specific archaeal lineage as being more closely related to eukaryotes than the others. The position of eukaryotes among *Archaea* became clearer with the recent discovery the Asgard archaea—a novel archaeal superphylum [17, 18] (discussed later in this chapter). Phylogenomic analyses revealed that Asgard archaea form a sister group of eukaryotes (Figure 21.1C) and harbor an extended set of proteins that were previously assumed to be specific to eukaryotes [17, 18] (discussed later in this chapter). Together, these findings indicate that eukaryotes may have evolved from a symbiosis between an archaeal host cell and a bacterial endosymbiont, and also provide greater evidence in support of a two-domain tree of life [19–22], with *Archaea* and *Bacteria* representing two primary domains and eukaryotes being a secondary domain [15, 23]. Although the exact placement of eukaryotes with respect to the different members of the Asgard archaea remains to be elucidated, continued exploration of Asgard archaeal diversity will allow to further refine the position of Archaea and eukaryotes in the tree of life.

Archaeal Cell Biology and Eukaryotic Signature Proteins (ESPs)

In agreement with their close relationship to eukaryotes, *Archaea* encode informational processing machineries that closely resemble those of eukaryotic representatives. Although *Archaea* harbor a single circular chromosome like *Bacteria*, their replication machinery includes various components homologous (i.e., shared by common ancestry) to those of eukaryotes, while most functionally equivalent complexes in *Bacteria* are unrelated [24, 25]. For instance, *Archaea* and eukaryotes share homologous subunits comprising the origin of replication complex (ORC), a replicative helicase unit referred to as the CMG (Cdc45, MCM, GINS) complex, and the active replisome, which includes a two-subunit primase, a DNA polymerase sliding clamp and clamp loader, and DNA polymerases [24]. Yet, some *Archaea* also encode components that are absent from both eukaryotes and *Bacteria* and others that are shared with *Bacteria*. For example the two-subunit DNA polymerase D [24, 26] is unique to *Archaea* while the NAD+-dependent DNA ligase, the DNA gyrase, and the DNA primase DnaG are homologous to bacterial enzymes [25]. In many cases, archaeal complexes seem to represent a simplified version of their counterparts in eukaryotes [25], the latter of which often encode additional paralogous enzymes (i.e., those that evolved by gene duplication), whose evolution involved subfunctionalization [24]. For instance, while *Archaea* collectively encode three families of polymerase B, eukaryotes harbor the four polymerase B family enzymes referred to as Pol alpha, beta, gamma and delta [24, 26]. Notably, all of these eukaryotic enzymes seem to have evolved from two distinct archaeal polymerase B family homologs [18, 26]. Another interesting example represents the nucleosome: *Archaea* harbor histone-like proteins, which form a homodimeric histone complex in part homologous to the heterodimeric nucleosome of eukaryotes [27, 28].

Archaeal transcription also shares several features in common with eukaryotes. While many archaeal genomes encode gene clusters reminiscent of bacterial operons, the archaeal transcription machinery represents a simplified version of their eukaryotic counterparts [29]. For instance, the archaeal DNA-dependent RNA polymerase (RNAP) consists of 12-13 subunits, which are homologous to the subunits of the three eukaryotic RNA polymerases (RNAP I-III) [29]. In contrast, RNAP of Bacteria consists of only five subunits, two of which are distantly related to archaeal RNAP subunits 1 and 2 (i.e., RpoA and RpoB). Transcription initiation, which is based on the same molecular mechanisms across the domains, also involves homologous transcription factors in *Archaea* and eukaryotes [29].

Similarities in the translational machinery between *Archaea* and eukaryotes are also evident. Archaeal ribosomes are of

comparable size to bacterial ribosomes (70S), but share various ribosomal subunits uniquely with eukaryotes [30]. Additionally, translation in *Archaea* is initiated by an initiator tRNA carrying methionine and several translation initiation factors, as is seen in eukaryotic organisms but contrasts with the use of formylmethionine by bacteria. Further, a 22nd amino acid, pyrrolysine, has been identified uniquely in certain members of the *Archaea*, in particular methanogens [31].

Notably, *Archaea* not only share homologous replication, transcription, and translation machineries with eukaryotes, but have also been found to encode various so-called eukaryotic signature proteins (ESPs) [32], i.e., proteins that are generally absent from bacterial genomes while being central to the integrity and functioning of eukaryotic cells. These proteins include, for instance, components of the eukaryotic cytoskeleton (such as actin and tubulins), cell division and vesicle trafficking machineries, endosomal sorting complexes required for transport (ESCRT), as well as the proteasome and ubiquitin system [10].

In particular, members of the TACK archaea (discussed later in this chapter) including among others the *Cren-*, *Aig-* and *Thaumarchaeota* have early on been found to encode certain ESPs that were absent from *Euryarchaeota* [15, 16, 33–35]. For instance, while *Euryarchaeota* use FtsZ as major cell division protein, many *Cren-* and *Thaumarchaeota* harbor a cell division system (also referred to as cdvABC system) that includes homologs of eukaryotic ESCRT-III and an ATPase related to vacuolar protein sorting-associated protein 4 (Vps4) [36–39]. Furthermore, archaeal actin homologs referred to as crenactin, which are distantly related to eukaryotic actins, have been discovered in *Thermoproteales*, as well as in *Korarchaeota* [40]. Yutin and coworkers identified distant homologs of eukaryotic tubulins—the artubulins—in the genomes of two species of *Thaumarchaeota*, "*Candidatus Nitrosoarchaeum limnia*" and "*Candidatus Nitrosoarchaeum koreensis*" [41], and an analysis of the "*Candidatus Caldiarchaeaum subterraneum*" composite genome revealed the presence of a presumably fully functional ubiquitin-like protein modifier system [42].

The discovery of the Asgard archaea [17, 18], the currently most closely related archaeal sister lineage of eukaryotes, has recently revealed a variety of additional ESPs in *Archaea*. For instance, Asgard archaea not only encode additional homologs of eukaryotic informational processing machineries but also harbor simplified versions of the eukaryotic oligosaccharyl-transferase-complex and ubiquitin modifier system. Furthermore, they encode an extended set of small GTPases [17, 18], which are key regulators in eukaryotic cells with a central role in vesicle trafficking machineries [43]. Additional central components homologous to eukaryotic vesicle transport and tethering were identified in the genomes of the *Thorarchaeota* [18]. Further, Asgard archaea harbor protein domains homologous to the key domains of the three major eukaryotic ESCRT machinery complexes (ESCRT I-III) and a diversity of cytoskeleton-related proteins that are much more similar to their eukaryotic counterparts than those previously identified in *Archaea*. These include the lokiactins found across the Asgard representatives, as well as *bona fide* tubulins in *Odinarchaeota* [10, 17, 18]. Notably, Asgard archaea also encode actin-regulating proteins, such as the profilins [18], which were recently shown to be functionally equivalent to those of eukaryotes [44].

Altogether, archaeal information processing machineries as well as an extended set of ESPs in members of the TACK and in particular the Asgard archaea, further testify to the archaeal origin of the eukaryotic cell. Importantly, the study of these complexes in *Archaea* can help to provide a better understanding of eukaryotic cell biology and provide insight into the relative timing of the evolution of cellular complexity.

Archaeal Cell Membranes and Cells Walls

The composition of archaeal cell membranes differs fundamentally from those of *Bacteria* and eukaryotes [45]. For instance, the glycerol used to make archaeal phospholipids is a stereoisomer of the glycerol used to build bacterial and eukaryotic membranes, i.e., while *Archaea* use glycerol-1-phosphate, eukaryotes and bacteria have glycerol-3-phosphate. Furthermore, *Archaea* harbor isoprenoid side chains instead of the fatty acid side chains found in Bacteria and eukaryotes. These isoprenoids are bound to the glycerol backbone by ether linkages contrasting with the ester linkages formed between the bacterial and eukaryotic glycerol and fatty acid moieties. Archaeal isoprenoid side chains in the two monolayers of the lipid bilayer can be linked, thereby giving rise to transmembrane phospholipids. The isoprenes can also form five-carbon ring structures, which may function in the stabilization of the membranes of archaeal species that live in high temperature environments. More than 100 different ether-type polar lipids, such as phospholipids and glycolipids, have been identified in *Archaea* [46].

Different archaeal representatives differ with regard to their cell walls. In contrast to *Bacteria*, *Archaea* lack peptidoglycan and are thus naturally resistant to antibiotics that impair the synthesis of peptidoglycan, such as penicillins. Some species of methanogenic *Archaea* contain cell walls of pseudopeptidoglycan (pseudomurein) that superficially resemble bacterial peptidoglycan but contain different components (e.g., N-acetyltalosaminuronic acid instead of and N-acetylmuramic acid) and have β-1,3 instead of β-1,4-glycosidic bonds. Yet, most archaeal species lack pseudomurein and instead harbor cell walls made of proteins, glycoproteins, or polysaccharides [47]. For instance, a common cell wall structure found in *Archaea* is composed of a paracrystalline surface layer, termed S-layer, consisting of protein or glycoprotein moieties arranged in hexagonal patterns. Finally, some *Archaea*, such as certain members of the order *Thermoplasmatales*, lack cell walls altogether.

Taxonomic Diversity of *Archaea*

The *Archaea* were originally divided into two major phyla, termed *Crenarchaeota* and *Euryarchaeota* [2]. However, recent advances in culture-independent, high-throughput sequencing techniques have uncovered a large diversity of novel archaeal lineages, most of which remain uncultivated [5]. Many of these newly discovered archaeal lineages are only distantly related to established lineages within the *Cren-* and *Euryarchaeota*, which has led to the proposal of many additional archaeal phyla and superphyla during the past years [7]. Figure 21.2 summarizes the

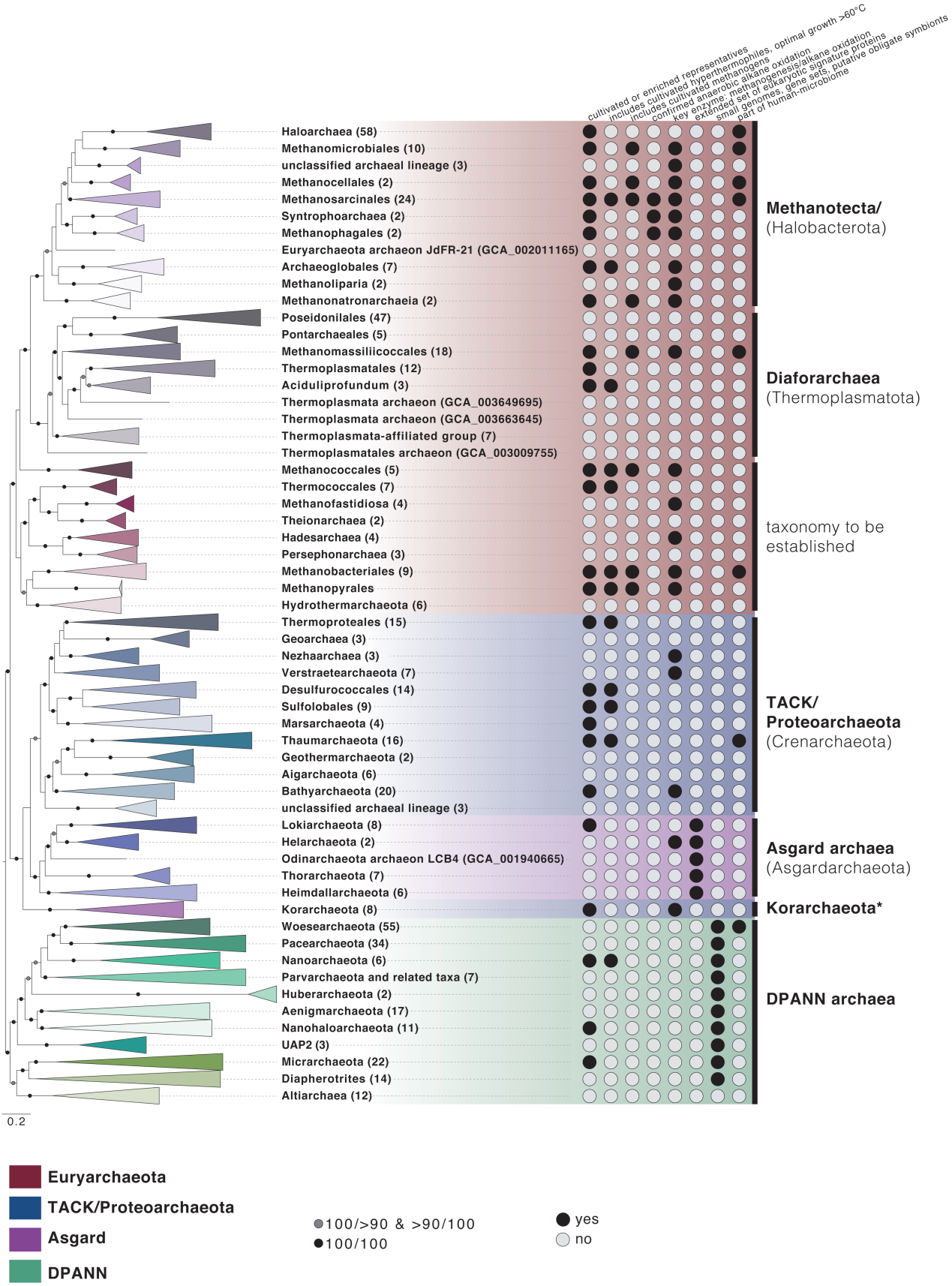

FIGURE 21.2 Depiction of the phylogenetic diversity of the *Archaea* and the presence/absence of key features. The unrooted phylogenetic tree was inferred with maximum likelihood using the IQ-tree software (with the C20+LG+F+R mixture model) and was based on an alignment of 11399 positions from a representative set of 569 archaeal taxa. Highly supported clusters (assessed by ultrafast bootstraps [220] and SH-like approximate-likelihood ratio test [221]) are indicated with gray or black dots based on their branch support values (see figure inlet). Taxa were predominantly named according to Adam et al. [7] (bold face), but alternative names suggested by GTDB (https://gtdb.ecogenomic.org/) are indicated in parenthesis when available. Numbers in brackets indicate the number of genomes/taxa per cluster. The presence and absence of certain features are shown with black and gray circles for each major taxonomic lineage (see figure inlet). Please note that the last column only reports those archaeal taxa that have been confirmed to be part of the human archaeome.

current understanding of the archaeal phylogeny, including established and proposed phyla, classes, and orders, as well as their general physiological grouping and certain features discussed below. However, please note that there is currently no consensus on how to best classify archaeal lineages. Therefore, a widely accepted taxonomy of the *Archaea* remains to be established [5]. In particular, there are currently two main classification schemes used: the classification suggested by Adam and coworkers that is implemented in NCBI [7] and the system introduced by the developers of the Genome Taxonomy Database (GTDB) (https://gtdb.ecogenomic.org/). The latter of these was suggested to provide a standardized and rank-normalized genome-based classification system, which was recently used to revise the bacterial taxonomy [48].

Euryarchaeota

The *Euryarchaeota* (Figure 21.2) comprise various cultivated and well-characterized archaeal species including the globally important methanogens (i.e., methane producers) as well as anaerobic methane-oxidizing Euryarchaeota (ANME) [49, 50]. Methanogens and ANME play a key role in the carbon cycle by anaerobically producing or consuming the potent climate gas, methane [8, 9, 50–52]. However, research during the past years has shown that the *Euryarchaeota* are a phylogenetically and physiologically much more diverse radiation than originally thought [5, 7]. Indeed, it remains to be elucidated whether *Euryarchaeota* comprise a monophyletic group or phylogenetically distinct divisions, some of which may be more closely related to the TACK and Asgard archaea [7, 53, 54]. In the following, we provide an overview of the major lineages comprising canonical and recently discovered lineages affiliating with the *Euryarchaeota*.

Methanotecta

The *Methanotecta* (Figure 21.2), a recently proposed superclass [7], comprise the so-called class II methanogens (*Methanosarcinales*, *Methanomicrobiales*, *Methanocellales*), several phylogenetically distinct ANME archaeal lineages, the *Haloarchaeota*, *Archaeoglobales*, as well as the more recently described archaeal orders referred to as *Methanonatronarchaeia*, *Syntrophoarchaeales*, *Methanoliparales*, and *Methanophagales*. We present major features of these different lineages below.

Methanomicrobiales

The order *Methanomicrobiales* comprises several families, such as the *Methanocalculaceae*, *Methanoregulaceae*, *Methanospirillaceae*, *Methanomicrobiaceae*, and *Methanocorpusculaceae* (e.g., reviewed in [55]), and can be found in a variety of anoxic habitats, including wetlands, soil, oceans and freshwater, landfills, rice paddies, as well as associated with animals [50]. Members of the *Methanomicrobiales* have diverse cell shapes, ranging from rods to cocci to plates, including motile and nonmotile species, and grow between 0°C and 60°C [55]. Cells are often surrounded by glycoprotein-containing S-layers. Many *Methanomicrobiales* use hydrogen and carbon dioxide to form methane and all species are obligate anaerobes. They can use formate and alcohol but not acetate and methylated C1-compounds as substrates for methanogenesis, distinguishing them from the *Methanosarcinales* [9, 55].

Methanosarcinales

The *Methanosarcinales* are closely related to the *Methanomicrobiales* and include families such as the *Methanosarcinaceae*, *Methanotrichaceae* (formerly *Methanosaetaceae*), and *Methermicoccaceae* (Table 21.1), as well as the *Methanoperedenaceae* (ANME-2d). While this order comprises diverse methanogenic organisms, it also includes representatives of the anaerobic methane-oxidizing *Euryarchaeota* ANME-2 and -3 lineages [50, 52, 56]. Similar to the *Methanomicrobiales*, representatives of the *Methanosarcinales* are found in a range of anoxic habitats [50]. Yet, in contrast to other methanogenic orders, the *Methanosarcinales* are known for their much wider substrate range for methanogenesis, i.e., members of this group not only use hydrogen and formate as substrates but also a variety of methylated compounds and acetate [8, 9]. Considering that methanogenesis based on acetate may contribute up to two-thirds of methane released to the atmosphere, members of this group have important roles in the global carbon cycle [8, 51]. Representatives of the ANME-2 and -3 lineages use the reverse methanogenesis pathway to anaerobically oxidize methane [52]. While some ANME-2 members can grow independently using nitrate, nitrite, or Fe(III) as electron acceptors [57–59], other ANME-2 grow in syntrophic consortia with bacterial partners (especially sulfate reducers) that serve as external electron sinks [52, 60]. Members of these groups are particularly abundant in the sulfate-methane transition zone in marine sediments and play an important role in the global carbon cycle by reoxidizing a large fraction of the methane produced in marine sediments before it can enter the atmosphere [52, 61].

Methanophagales (ANME-1)

The *Methanophagales* comprise another lineage of anaerobic methane-oxidizing archaea, also known as the ANME-1 lineage. While originally thought to affiliate with the *Methanosarcinales*, they were recently shown to represent a sister lineage of the *Syntrophoarchaeales* [7] (Figure 21.2 and later in this chapter). Similar to the ANME-2 and -3 lineages that belong to the *Methanosarcinales*, members of this group occur in diverse marine, terrestrial, and freshwater environments [62], are particularly abundant in the sulfur-methane transition zone [61], and use the reverse methanogenesis pathway for the anaerobic oxidation of methane (AOM) [63]. While ANME-1 has not been cultivated thus far, various lines of research have suggested that members are able to oxidize methane in syntrophy with sulfate-reducing bacteria (SRB) through direct electron transfer [52, 60, 64].

Methanocellales

Methanocellales represents a more recently described order of hydrogenotrophic methanogens that were originally referred to as Rice Cluster I (RC-I) [65] due to their initial discovery in rice paddy fields, where they are important producers of methane [66]. The first representative of this order, *Methanocella paludicola*, was isolated from an anaerobic,

propionate-containing enrichment culture [65] and represents a nonmotile anaerobe with rod-shaped cells thriving at temperatures between 25°C and 40°C [65]. While the isolate performs methanogenesis using hydrogen, carbon dioxide, and formate, it uses acetate as a carbon source. Hydrogen is provided by its syntrophic partner, the bacterium *Syntrophobacter fumaroxidans* [67]. Similar metabolic features were found in other representatives of this order, including *M. arvoryzae* [68] and *M. conradii* [69].

Syntrophoarchaeales

Syntrophoarchaeales (sometimes assigned to the *Methanosarcinales*; Table 21.1) represent a recently discovered group of anaerobic, alkane-oxidizing archaea usually found in hydrocarbon-rich sediments [70, 71]. For example, the first two representatives of this lineage, *Syntrophoarchaeum butanivorans* and *Syntrophoarchaeum caldarius*, were originally isolated from hydrothermal- and hydrocarbon-rich marine sediments of the Guaymas Basin [71, 72]. Notably, *Syntrophoarchaeales* grow by the anaerobic oxidation of butane as well as propane, which are thought to be metabolized using the reverse methanogenesis pathway also operating in ANME archaea [73]. In particular, they encode subunits homologous to the Methyl-Coenzyme M Reductase (MCR) complex, which represents the key enzyme of methanogens catalyzing the demethylation of CH_3-S-CoM to methane [51]. In *Syntrophoarchaeales*, MCR is thought to be used in reverse and to mediate the first step of the breakdown of short-chain alkanes eventually yielding carbon dioxide as an end product [71]. As indicated by the names of members of this group, studied representatives grow syntrophically with the sulfate-reducing bacterium *Candidatus* Desulfofervidus auxilii.

Archaeoglobales

The *Archaeaoglobales* comprises species belonging to the genera *Archaeoglobus*, *Ferroglobus*, and *Geoglobus* [74]. The *Archaeoglobus* sp. is believed to be predominantly composed of strictly anaerobic and hyperthermophilic members, growing optimally at 80°C and neutral pH. The best studied representatives are autotrophs and/or organotrophs and can reduce sulfate or sulfite during respiration [75]. Species of *Ferroglobus* grow by oxidation of $Fe(II)S^{2-}$ and H_2 [75], whereas *Geoglobus* grows anaerobically in the presence of acetate and ferric iron [74]. Recently, genomes of so far uncultivated members of the *Archaeoglobi* were reconstructed from environmental samples and shown to encode MCR-like protein complexes similar to those of methanogens and ANME archaea [76, 77]. Based on genomic inferences, it was suggested that the respective organisms may be able to grow by the oxidation of methane or alternative short-chain alkanes.

Methanoliparales

Methanoliparales is an uncultivated lineage within the *Methanotecta* that phylogenetically places between *Archaeoglobales* and a cluster comprising *Syntrophoarchaeales* and *Methanophagales*. *Methanoliparales* were first discovered in two metagenomes from a petroleum-enrichment culture and an oil seep and are represented by two metagenome-assembled genomes: *Candidatus Methanoliparum thermophilum* NM1a and *Candidatus Methanolliviera hydrocarbonicum* NM1b [78]. Genomic analyses suggest that *Methanolipirales* are methanogens that encode the Wood-Ljungdahl carbon fixation pathway and are capable of beta-oxidation. Interestingly, both genomes code for two distinct MCR complexes, which may be involved in methanogenesis and the oxidation of alkanes, respectively.

Haloarchaeota

Halobacteria, herein referred to as *Haloarchaea*, are a diverse group of *Archaea*, most of which are adapted to high salinity. Salt requirements of these species range from 1.5 to 5.2 M NaCl, although most strains grow best between 3.5 and 4.5 M NaCl, at or near the saturation point of salt (36% w/v salts). In order to maintain osmolarity of their cells in high-salt environments, haloarchaeal members accumulate up to 5 M intracellular levels of KCl to counterbalance high extracellular salt concentration. As a result, the entire intracellular machinery, including enzymes and structural proteins, must be adapted to high salt levels. The proteins of all haloarchaeal species have a very low isoelectric point and the genomes contain high GC contents that are well above 60% [79].

Some species of *Haloarchaea* are motile by means of tufts of flagella, although many species are nonmotile [75]. *Haloarchaea* comprise various aerobic or facultative anaerobes and show diverse morphologies and shapes, including rods, cocci, and a multitude of pleomorphic forms [75, 80]. The lack of turgor pressure within haloarchaeal cells enables the cells to tolerate the formation of corners, and as such, some species are even triangular or square-shaped [75, 80]. Cell envelopes of coccoid *Haloarchaea* are stable in the absence of salt, while, noncoccoid species maintain their integrity only in the presence of high concentrations of NaCl or KCl [75]. Non-coccoid species have a proteinaceous cell envelope with glycoprotein subunits forming a hexagonal pattern [75]. Species of *Haloarchaea* are abundant in salt lakes, inland seas, and evaporating ponds of seawater, such as the Dead Sea and solar salterns. *Haloarchaea* often tint the water column and sediments in bright colors due to the presence of retinal-based pigments. Some of these pigments are capable of the light-mediated translocation of ions across cell membranes. The best known halobacterial pigment is bacteriorhodopsin, which is an outwardly directed proton pump. Bacteriorhodopsin is involved in energy conservation and is the only nonchlorophyll-mediated light energy transducing system known to date [79]. Other retinal-based pigments found in *Haloarchaea* include halorhodopsin, which is an inward chloride pump involved in osmotic homeostasis, as well as sensory rhodopsin I and II (SRI and SRII, respectively). SRI and SRII can mediate positive and/or negative phototaxis [79].

Methanonatronarchaoeta

Another lineage of halophilic archaea are the *Methanonatronarchaeota*, which were first recovered from hypersaline anoxic lake sediments [81] and are currently represented by isolates from two distinct subgroups: the soda lake isolate *Methanonatronarchaeum thermophilum* AMET and the salt lake isolate *Candidatus Methanohalarchaeum thermophilum*

HMET [82]. *Cand. M. thermophilum* has motile, coccoid cells that are around 0.4 µM in diameter and are surrounded by an S-layer. These anaerobic organisms tolerate a range of pH (between 6.5 and 8 [HMET] and 9.5 and 9.8 [AMET]) and grow optimally at a temperature of 50°C and salt concentrations of 4 M by accumulating high concentrations of potassium inside their cells for osmotic balance ("salt-in strategy") [81, 82]. *Cand. M. thermophilum* is a heterotrophic methanogen that grows with C1-methylated compounds as electron acceptors, such as methanol or trimethylamine, and formate or hydrogen as electron donors [81]. The 16S rRNA gene analyses indicate that *Methanonatronarchaeota* are the first cultured representatives of the SA1 group, which is commonly found in hypersaline environments [81, 83]. Yet, the exact placement of *Methanonatronarchaeota* in the archaeal tree of life is still debated. While initial phylogenetic analyses placed this lineage sister to *Haloarchaea* [81], recent analyses have suggested that the *Methanonatronarchaeota* form an early diverging lineage of the *Methanotecta* [84].

Diaforarchaea

The *Diaforarchaea* comprise a recently suggested superclass [7] that includes the *Thermoplasmata* and related lineages, such as the diverse and abundant Marine Group II and III archaea [85, 86], now also known as the *Poseidoniales* and *Pontarchaeales*, respectively, as well as a recently discovered new order of methanogens, the *Methanomassiliicoccales* [87].

Thermoplasmatales

The *Thermoplasmatales* comprise the genera *Acidiplasma, Thermoplasma, Picrophilus, Cuniculiplasma,* and *Ferroplasma. Cunicuplasma, Thermoplasma,* and *Ferroplasma* are the only cultivated archaeal representatives that lack cell walls [75, 88]. Species of *Thermoplasma* are facultative anaerobes and obligate heterotrophs, using elemental sulfur for respiration. Most members of this group are thermoacidophiles and grow optimally at 60°C and pH 2 [75]. For instance, representatives may be found in self-heating coal refuse piles and in acidic solfatara fields [75].

Members of the *Picrophilus* are the most acidophilic organisms known so far [89]. They form irregular cocci that are 1–1.5 µm in diameter and contain S-layer cell walls [75]. *Picrophilus* are thermophilic and hyperacidophilic and grow at temperatures between 47°C and 60°C and pH ranges of 0–3.5 [75]. Their ability to grow at pH values near 0 and at high temperatures has shifted the physicochemical boundaries at which life was considered to exist.

In contrast to other members of the *Thermoplasmatales*, *Ferroplasma* are not thermophilic and can grow autotrophically using ferrous iron as energy and inorganic carbon as a carbon source. Representatives can be found in a variety of acidic environments with stable chemical conditions, such as ore deposits, mines, and acid mine drainage systems (natural or man-made), as well as in areas with geothermal activity [90, 91]. Representatives of this family are cell wall-lacking extreme and obligate acidophiles that are able to grow at pH values around 0. Together with members of *Picrophilum*, they comprise a group of the most extreme acidophilic organisms known, members of which tolerate high concentrations of iron, copper, zinc, and other metals [91].

Aciduliprofundales

Aciduliprofundales, formerly named the "deep-sea hydrothermal vent euryarchaeota 2" (DHVE2) lineage, is currently represented by the cultivated *Aciduliprofundum boonei* [92, 93]. As the original name suggests, *Aciduliprofundales* are predominantly found across hydrothermal vents, where they can represent up to 15% of the archaeal community [92–94]. *A. boonei* is an anaerobic heterotroph that ferments peptides and is able to reduce elemental sulfur or ferric iron at a pH between 3.3 and 5.8 (optimum pH 4.6) and an optimal growth temperature of 70°C [92]. This organism is motile with a single flagellum and has pleomorphic cells of about 0.6–1 µM in diameter that are surrounded by a single S-layer.

Methanomassiliicoccales

The order *Methanomassiliicoccales* represents the first lineage of the *Thermoplasmata* known to comprise methanogenic members [87], several of which have been isolated, such as *Methanomassiliicoccus luminyensis* [95, 96], *Candidatus Methanomethylophilus alvus* [97], and *Candidatus Methanoplasma termitum* [98]. *Methanomassiliicoccales* are widely distributed in wetlands and sediments as well as the gastrointestinal tracts of animals including those of humans and cows [87, 99, 100]. Members of this group comprise H_2-dependent methylotrophic methanogens, which are able to use methylated amines [100] including mono-, di-, and trimethylamines for methanogenesis. Considering that the latter compounds have been implicated in human disease, gut-associated members of the *Methanomassiliicoccales* may play an important role in human health [100].

Poseidoniales

The *Poseidoniales* [101], formerly Marine Group II (MG II), lack any cultured representatives and are mainly known from 16S rRNA gene diversity assays and genomic analyses. *Poseidoniales* are often found in the photic zone of marine waters and can present up to 15% of archaeal cells in the Atlantic ocean [102–104]. They are further divided into *Candidatus Poseidonaceae* (MGIIa) and *Candidatus Thalassarchaeacea* (MGIIb), whose abundances seasonally fluctuate, i.e., members of MGIIa and MGIIb are more abundant in the summer and winter, respectively [105]. Members of this group comprise aerobic heterotrophs with the potential to utilize a range of substrates such as proteins, peptides, amino acids, fatty acids, carbohydrates, xenobiotics, and agar [101, 106–110]. In addition, some representatives of the class *Ca. Poseidoniia*, found in the photic zone, encode proteorhodopsin indicative of a photoheterotrophic lifestyle [101, 107, 110].

Pontarchaeales

The order *Pontarchaeales*, or Marine Group III, are often found in the deep ocean, while being less abundant in the photic zone [102, 111]. Based on genomic data, it was inferred that deep-sea *Pontarchaeales* likely represent motile heterotrophs that might degrade proteins, carbohydrates, and lipids [112]. In contrast, surface dwelling members of the *Pontarchaeales* seem to encode photolyase and rhodopsin genes and in turn may be photoheterotrophs [111]. Notably, both the *Pontarchaeales* and the *Poseidoniales* lack the key archaeal lipid biosynthesis gene encoding glycerol-1 phosphate dehydrogenase, such that it is currently unclear whether members of these orders encode

canonical archaeal lipids [45]. In particular, the presence of genes for glycerol-3 phosphate dehydrogenase, which is essential in the synthesis of bacterial lipids, has led to the suggestion that these *Archaea* may have mixed membranes [45, 101].

Other Euryarchaeota

The following section provides an overview of additional lineages affiliating with the *Euryarchaeota*, including methanogenic lineages that have been extensively studied in the past. However, some analyses indicate that at least some of these orders may be more closely related to the TACK and Asgard archaea [7, 53, 54].

Methanococcales

As the name implies, the *Methanococcales* include representatives with coccoid shapes and proteinous cell walls [75]. All members of this lineage are thought to be strict anaerobes that obtain energy by the reduction of CO_2 to methane [9] and comprise mesophilic (e.g., *Methanococcus*) to thermophilic (e.g., *Methanothermococcus*) to hyperthermophilic (e.g., *Methanocaldococcus*) taxa [75].

Thermococcales

Members of the *Thermococcales* represent anaerobic heterotrophs that utilize a wide range of organic compounds, including amino acids, a variety of sugars, and organic acids such as pyruvate. When available, they can use elemental sulfur as the terminal electron acceptor. Extensive research has been carried out on the metabolism of cultivated representatives and led to the discovery of unique enzymes and pathways [113]. Certain members of the *Thermococcales* represent important model organisms. For example, the hyperthermophilic *Pyrococcus furiosus*, which grows anaerobically at temperatures near 100°C using carbohydrates and peptides as carbon and energy sources [75], has been extensively used to study thermostable enzymes and adaptations to high-temperature environments [114].

Methanobacteriales

The *Methanobacteriales* comprise another lineage of methanogenic archaea that reduce CO_2 or methyl compounds with H_2, formate, or secondary alcohols as electron donors. They include rod-shaped, lancet-shaped, or coccoid members, which contain cell walls made of pseudopeptidoglycan. *Methanobacteriales* are widely distributed in nature and are found in anaerobic habitats such as aquatic sediments, soil, anaerobic sewage digesters, and the gastrointestinal tracts of animals to name a few [50, 75].

Methanopyrales

The *Methanopyrales* consists of a single genus, *Methanopyrus*, comprising rod-shaped members with cell walls made of pseudopeptidoglycan [75]. Known *Methanopyrus* are hyperthermophilic, and grow between 84°C and 110°C, with optimal growth at 98°C. Similar to other methanogenic lineages, members of this group have a chemolitoautotrophic lifestyle converting CO_2 and H_2 to methane [9, 75]. While it has proven difficult to resolve the exact phylogenetic placement of the *Methanopyrales* relative to other archaea, it has recently been suggested that this lineage forms a monophyletic clade together with the *Methanobacteriales* and the *Methanococcales* referred to as *Methanomada* [7]. However, it remains to be determined whether these so-called group 1 methanogens [9] are indeed closely related phylogenetically (Figure 21.2).

Methanofastidiosales

Methanofastidiosales represent a recently discovered and thus far uncultivated archaeal lineage (also known as WSA2 or Arc I), whose members are present in diverse environments including sediments, groundwater, and bioreactors [115–117]. Metagenomic approaches have enabled the reconstruction of genomes of representatives of the *Methanofastidiosales* from wastewater-treatment bioreactors [117]. While members of this group encode key genes for methanogenesis, they lack genes related to carbon-fixation pathways and were suggested to solely use methylated thiols as substrates for methanogenesis [117].

Theionarchaeota

Theionarchaea (formerly Z7ME43) represents another clade of uncultivated archaea, which forms a sister lineage of the *Hadesarchaea* (see next) and was originally discovered in water-filled limestone sinkholes in northeastern Mexico [118]. This clade is currently represented by two genomes that were recovered from the White Oak River Estuary in North Carolina [119]. Genomic analyses indicated that *Theionarchaea* might conserve energy by peptide fermentation.

Hadesarchaea

The *Hadesarchaea*, which were originally referred to as the South-African Gold Mine Miscellaneous Euryarchaeal Group (SAGMEG), are distributed in a variety of anoxic environments, including the terrestrial subsurface as well as marine sediments, which cover a wide span of temperatures [120–123]. The first genomes of members of this clade were reconstructed from the water column of the White Oak River estuary [123] as well as Yellowstone National Park (YNP) hot spring sediments and indicated the capability of anaerobic CO oxidation potentially coupled to nitrite or H_2O reduction [123]. Notably, another genome of a member of the *Hadesarchaea* was recently obtained from a hot spring metagenome and shown to encode a *mcr*-like operon. Based on phylogenetic analyses of MCR subunits as well as genomic analyses, it was suggested that these *Hadesarchaea* may represent alkane-oxidizing archaea similar to members of the *Syntrophoarchaeales* [124] and perhaps some representatives of the *Bathyarchaeota* [50].

Persephonarchaea

The Mediterranean Sea Brine Lakes 1 (MSBL1) clade, now referred to as the *Persephonarchaea* [7], is another lineage of uncultivated archaea that is closely related to the *Hadesarchaea*. The *Persephonarchaea* are commonly found in marine hypersaline environments [125, 126] and comprise potential anaerobic mixotrophs that may conserve energy through sugar fermentation but may also be able to fix inorganic carbon [127]. Genomic inferences suggest that MSBL1 archaea synthesize trehalose as putative osmolyte to encounter the high salt conditions in their environment [127].

Hydrothermarchaeota

The *Hydrothermarchaeota* [7], also known as the Marine Benthic Group-E (MBG-E), were originally discovered in marine deep-sea

sediments [128] and represent an uncultivated archaeal lineage widely distributed in deep subseafloor environments. Genomes from members of this group have been reconstructed from metagenomes of the Juan de Fuca Ridge flank, Guaymas Basin hydrothermal sediments, and the Mid-Atlantic Ridge of the South Atlantic Ocean [129–131]. Genomic analyses have indicated that *Hydrothermarchaea* are metabolically versatile [131] and include putative anaerobic chemolithoautotrophs that use carbon monoxide and/or hydrogen as electron donors as well as a variety of electron acceptors including nitrate and sulfate [132, 133].

The TACK Superphylum

The TACK superphylum was originally introduced to describe the *Crenarchaeota* and the related phyla referred to as the *Thaumarchaeota, Aigarchaeota*, and *Korarchaeota* [16]. During the past years, many additional lineages affiliating with the TACK archaea have been discovered through metagenomics and single cell genomics approaches and the TACK lineage has therefore been suggested to be referred to as the *Proteoarchaeota* [134]. However, a consensus has yet to be reached regarding both the naming as well as the validity of using a superphylum as a taxonomic level. In the following sections, we introduce canonical and recently discovered clades belonging to the TACK archaea.

Crenarchaeota

The *Crenarchaeota* includes a diversity of (hyper-) thermophilic archaeal species, many of which have been discovered through cultivation-based approaches before the onset of the genomics era in microbiology and now represent important model organisms. This taxon is composed of a single class, the *Thermoprotei*, which is subdivided into three to five subclades, the *Thermoproteales, Sulfolobales, Desulfurcoccales* as well as the *Fervidicoccales* and *Acidilobales*. However, the latter two may in fact belong to the *Desulfurococcales* (Figure 21.2). Cultured crenarchaeal species are morphologically diverse, and include rods, cocci, filamentous, and disk-shaped cells. Almost all cultured species are obligate (hyper-) thermophiles, with optimal growth temperatures ranging from 70°C to 113°C and many members are also acidophiles and capable of metabolizing sulfur. Representatives of the *Crenarchaeota* thrive in environments such as hot solfataras, volcanic areas, as well as hydrothermal vents at the bottom of the ocean. A variety of metabolic capabilities have been described in the different members of the *Crenarchaeota*. For instance, some *Thermoproteales* are chemolithoautotrophs, using carbon dioxide as a carbon source and conserving energy by the conversion of hydrogen and elemental sulfur to hydrogen sulfide. Others respire various organic substrates using oxygen, sulfur, nitrate, or nitrite as electron acceptors [75]. Many members of the *Desulfurococcales* are strict anaerobes and neutrophiles to weak acidophiles, growing optimally at pH 5.5–7.5 [135]. Representatives of the *Sulfolobales* are acidophilic hyperthermophiles, which can grow lithoautotrophically by oxidizing sulfur or chemoheterotrophically on simple reduced carbon compounds using sulfur derivatives as electron acceptors. Notably, the *Crenarchaeota* include several members that have been shown to be hosts of the small-celled *Nanoarchaeota* [136–140] (see later in this chapter). In particular, the biocoenosis between *Ignicoccus hospitalis*, a member of the *Desulfurococcales*, and its nanoarchaeal ectosymbiont, *Nanoarchaeum equitans*, has been extensively studied and provides important insights into archaeal cell biology and cell-cell communication [141]. For instance, investigation of *I. hospitalis* has revealed remarkable cellular features including the presence of two outer membranes surrounding a large periplasmic space as well as an endomembrane system reminiscent of eukaryotic cells [142].

Thaumarchaeota

Environmental 16S rRNA-based surveys in the early 1990s have led to the discovery of uncultivated archaeal lineages distantly related to the *Crenarchaeota* in moderate marine and terrestrial ecosystems. The subsequent cultivation of the first representatives of these so-called mesophilic *Crenarchaeota* (also MG1) from marine and terrestrial environments [143] and the study of the first genomes of members of this group [144, 145], revealed that they form a separate phylum within the *Archaea* referred to as the *Thaumarchaeota* that distantly affiliates with the *Crenarchaeota*. Most cultivated *Thaumarchaeota* are chemolithoautotrophic ammonia-oxidizing archaea (AOA), which play an important role in the nitrogen and carbon cycles in both aquatic and terrestrial environments [146]. However, the reconstruction of genomes of deep-branching *Thaumarchaeota* has recently led to the suggestion that not all members of this group are AOA but instead represent chemoorganotrophs that may reduce oxygen, nitrate, or sulfur [147]. This notion was recently confirmed with the isolation of the thermoacidophilic, sulfur- and iron-reducing organoheterotrophic *Conexivisphaera calidus*, a potentially early diverging member of the *Thaumarchaeota* [148].

Aigarchaeota

The *Aigarchaeota* represent another proposed candidate phylum that comprises species of the Hot Water Crenarchaeotic Group I (HWCGI), members of which have not been cultivated so far. Genomic analyses of the first representatives of this group have suggested that the *Aigarchaeota* comprise both facultative and obligate anaerobes, which may respire a variety of organic substrates and perhaps also hydrogen and carbon monoxide using oxygen or oxidized sulfur or nitrogen compounds as electron acceptors [42, 149–152]. Furthermore, several representatives seem to have the ability to fix inorganic carbon. *Aigarchaeota* seem to predominantly inhabit thermally heated terrestrial and marine ecosystems, including hot springs, subsurface aquifers, and mine fracture waters [150, 152].

Korarchaeota

The *Korarchaeota* comprises a group of uncultivated *Archaea* that had already been discovered in the late 1990s in terrestrial and marine thermal environments [153]. The first member of this clade, referred to as "*Ca. Korarchaeum cryptofilum*," was shown to comprise ultra-thin, needle-shaped cells measuring up to 100 µm in length. Genomic analyses indicated that this organism represents a peptide fermenter with a unique set of informational processing genes, which early on indicated that it comprises the first member of a distinct archaeal phylum [154]. Recently, genomes of additional members of the *Korarchaeota* have been recovered from

deep-sea hydrothermal vent sediments [130] and hot spring environments [18, 124, 155] providing novel insights into the metabolic features of this clade. Notably, genomic analyses revealed that certain members of the *Korarchaeota* harbor the key genes for methanogenesis, [155] which may for instance enable methanogenesis from methanol and hydrogen or the coupling of the anaerobic oxidation of methane with sulfite reduction [155].

Bathyarchaeota

Bathyarchaeota were originally discovered through 16S rRNA gene surveys in hot springs [153] and were referred to as Miscellaneous Crenarchaeota Group (MCG) [156] due to their distant affiliation with cultivated *Crenarchaeota*. This extremely diverse phylum is now subdivided into at least 25 subgroups, which are defined at family and order level [157]. Notably, members of this putative phylum-level lineage can be found in a diversity of anoxic marine, terrestrial, and hydrothermal environments including marine sediments and often represent the most abundant archaeal community members [157–159]. Based on genomic analyses, it is inferred that many *Bathyarchaeota* are heterotrophs with a wide substrate range including acetate, proteins, and aromatic compounds such as lignin [157, 160]. However, the *Bathyarchaeota* also includes putative acetogenic species [161] as well as organisms with *mcr* genes [162], which are closely related to those of *Syntrophoarchaea* [71]. In turn, it has been suggested that some members of the *Bathyarchaeota* may be able to mediate the anaerobic oxidation of short-chain alkanes [50].

Geoarchaeota

Geoarchaeota, also Novel Archaeal Group 1 (NAG1), are often found in hypoxic to oxic, hot, acidic, iron-rich springs [163–165] and represent a lineage of thus far uncultivated archaea which seem to be closely related to or part of the Crenarchaeota [164, 166]. Based on genomic inferences, it has been suggested that the *Geoarchaeota* are likely motile and might conserve energy through the oxidation of carbon monoxide, peptides, and/or carbohydrates using oxygen as a terminal electron acceptor [149, 164].

Verstraetearchaeota

Verstraetearchaeota were originally discovered in deep South-African Gold mine microbial communities through 16S rRNA gene surveys and were referred to as Terrestrial Miscellaneous Crenarchaeota Group (TMCG) [120]. Members of this group seem to be widely distributed and are also found in hydrocarbon-rich environments, sediments, soil, and wetlands [167]. First insights into the metabolic features of members of this group were derived from genomes assembled from anoxic digesters, named *Methanomethylicus sp.* and *Methanosuratus sp.* [167]. Subsequently, additional representatives were discovered and referred to as *Methanohydrogenales* and *Methanomediales* [168]. Notably, the *Verstraetearchaeota* comprise members with *mcr*-gene operons most similar to those found in methanogenic *Euryarchaeota*. In turn, based on genomic inferences, it was suggested that the *Verstraetearchaeota* likely include anaerobic methylotrophic as well as hydrogenotrophic methanogens [167–169].

Nezhaarchaeota

Nezhaarchaeota are a recent addition to the TACK superphylum represented solely by uncultivated members, whose genomes were assembled from hot spring metagenomes and hydrothermal sediments [77]. Notably, the *Nezhaarchaeota* encode a MCR protein cluster and are potential hydrogenotrophic methanogens [77].

Marsarchaeota

The *Marsarchaeota*, or "Novel Archaeal Group 2" (NAG2), are typically found in geothermal, iron oxide-rich mats [163]. The first genomes of members of this lineage were recently recovered from thermal (50–80°C) and acidic (pH 2.5–2.5) microbial mats from Yellowstone National Park [170] and led to the suggestions that the *Marsarchaeota* are aerobic chemoorganotrophs that degrade lipids, peptides, and carbohydrates and may be able to reduce ferric oxide.

Geothermarchaeota

The *Geothermarchaeota* represents one of the most recent additions to the *Archaea* and is thus far only represented by uncultivated members, whose genomes have been reconstructed from metagenomes from the Juan de Fuca Ridge subseafloor [129] and hydrothermal vent sediments in the Guaymas Basin [130]. Little is yet known about the lifestyle and ecological roles of *Geothermarchaeota*, and in-depth genomic analyses will be necessary to infer their metabolic potential.

The Asgard Superphylum

The Asgard superphylum is a recently described archaeal radiation, which comprises several different archaeal clades of high taxonomic rank (likely phylum-level) [17, 18]. Notably, phylogenetic and comparative genomic analyses have indicated that this archaeal clade includes the closest archaeal sister lineage of eukaryotes (discussed previously in this chapter). Members of this superphylum have originally been discovered in sediments all around the world, in which they can comprise a significant fraction of the microbial diversity. In the following, we briefly introduce the major metabolic features of the currently known members of the Asgard archaea, i.e., the *Loki-*, *Thor-*, *Odin-*, *Hel-*, and *Heimdallarchaeota*.

Lokiarchaeota

The *Lokiarchaeota* represents an archaeal lineage originally referred to as the Deep Sea Archaeal Group (DSAG) or Marine Benthic Group B (MBGB) archaea, which are abundant in diverse marine sediments [94, 171]. For example, the *Lokiarchaeota* comprise up to 10% of the microbial community in cold sediments near Loki's Castle hydrothermal vent field from which the first metagenomes were obtained [17, 18]. Members of the *Lokiarchaeota* might be autotrophs using the Wood-Ljungdahl pathway for carbon fixation [172]. However, genomic analyses also revealed the potential for the use of a variety of organic carbon substrates, suggesting that representatives of the *Lokiarchaeota* may predominantly rely on fermentative growth [20]. In fact, the successful cultivation of the first *Lokiarchaeote*, *Candidatus*

Prometheoarchaeum syntrophicum, revealed that this organism ferments amino acids enabled through a syntrophic interaction with hydrogen- or formate-consuming partner organisms [22].

Thorarchaeota

The *Thorarchaeota* share many metabolic features with the *Lokiarchaeota* [20, 173, 174]. Currently known representatives harbor a variety of genes likely encoding proteins involved in the usage of organic substrates. Furthermore, they encode the Wood-Ljungdahl pathway, which could be used for carbon fixation or serve as an electron sink during growth on organics. In contrast to currently known *Lokiarchaeota*, members of this group also harbor a putative NADH dehydrogenase that may enable respiratory growth in addition to fermentation [20]. Based on current environmental survey data, the *Thorarchaeota* seem less abundant than the *Lokiarchaeota* but occur in a wide variety of anoxic environments [18].

Heimdallarchaeota

Thus far known representatives of the *Heimdallarchaeota* are metabolically diverse and differ from other Asgard lineages [20]. While genomic analyses indicate that they are able to utilize a large variety of organic substrates similar to other members of the Asgards, they do not seem to be fermentative organisms and current members lack the Wood-Ljungdahl pathway. Instead, they encode a membrane-bound electron chain, which allows growth using oxygen and nitrite as electron acceptors [20, 21]. *Heimdallarchaeota* are currently thought to comprise the archaeal lineage most closely related to the archaeal ancestor of eukaryotes. However, though found in a variety of environmental samples including anoxic sediments and oxygenated waters, they are generally less abundant than the *Loki-* and *Thorarchaeota*.

Odinarchaeota

Odinarchaeota are currently represented by a single genome, which was obtained from a hot spring metagenome [18]. Similar to other members of the Asgard superphylum, *Odinarchaeum* encodes the ability to use organic compounds as growth substrates [20]. Yet, it lacks the key enzyme of the Wood-Ljungdahl pathway and instead encodes membrane-bound hydrogenases, which suggests that the thermophilic *Odinarchaeum* may conserve energy through fermentation of organic substrates to hydrogen, acetate, and carbon dioxide. Members of the *Odinarchaeota* are thought to predominantly inhabit thermal environments such as hot spring sediments and hydrothermal vents [18].

Helarchaeota

The *Helarchaeota* represent the most recently discovered clade within the Asgard archaea [175]. While they harbor similar gene sets as the *Loki-* and *Thorarchaeota*, currently known representatives of this lineage also contain *mcr*-gene clusters. Phylogenetic analyses of the encoded proteins revealed their close relationship with proteins of *Syntrophoarchaea* opening the possibility that certain members of the Asgard archaea have the potential to anaerobically oxidize short-chain alkanes, perhaps in syntrophy with microbial partners [175]. However, the environmental distribution of the *Helarchaeota* and the functional importance of this potential alkane metabolism in Asgard archaea remain to be determined.

The DPANN Superphylum

The DPANN superphylum is the fourth major radiation in the *Archaea*, besides the *Euryarchaeota*, TACK, and Asgard archaea [149, 176, 177]. Currently, this radiation is assumed to comprise a large diversity of distinct archaeal clades most of which seem to predominantly include members with extremely small genomes and cell sizes that are thought to depend on partner organisms for growth and survival [177]. While first defined in reference to the *Diapherotrites, Parvarchaeota, Aenigmarchaeota, Nanoarchaeota,* and *Nanohaloarchaeota* (DPANN) [149], additional lineages such as the *Micrarchaeota, Pacearchaeota, Woesearchaeota*, and *Huberarchaeota* are now also considered members of this group [177, 178]. Furthermore, the *Altiarchaeota* [179], representatives of which do not have reduced genomes, are sometimes considered to belong to the DPANN [177, 180]. However, the boundaries between certain clades of DPANN and other archaea (in particular the *Euryarchaeota*) are not well defined and it remains to be established which lineages indeed belong to a monophyletic (i.e., sharing a common ancestor) DPANN clade [180].

Nanoarchaeota

The first representative lineage of the DPANN archaea was already discovered in 2002, i.e., long before the DPANN radiation was known. In particular, Huber and coworkers discovered a small-celled organism in cultures of the crenarchaeaum, *I. hospitalis,* which they referred to as *N. equitans* [136]. Initially, it was suggested that this organism is the first representative of a novel phylum called *Nanoarchaeota* or may represent a highly derived member of the *Euryarchaeota* [136, 181]. However, upon the genomics-based discovery of additional archaeal lineages represented by organisms with small genomes, which affiliated with *Nanoarchaeota*, it was proposed that the *Nanoarchaeota* belong to the DPANN radiation [149].

Notably, the nanosized hyperthermophilic *N. equitans* is obligately host-dependent and grows as an ectoparasite on the surface of *I. hospitalis* [182, 183]. It lacks genes for many major metabolic pathways and in turn depends on its host for the acquisition of diverse metabolites likely including lipids, amino acids, and ATP. In line with this, the genome of *N. equitans* represents one of the smallest known genomes of any extracellular organism (480 kb) [184]. However, compared to the genomes of many bacterial endosymbionts, the genome of *N. equitans* does not show evidence of pseudogenes and contains a full complement of tightly packed genes encoding informational processing machineries [184]. Similar trends have recently been seen in other representatives of the DPANN radiation [177]. Members of the *Nanoarchaeota* have been found in a variety of thermal environments ranging from hydrothermal vents to hot springs and are now assumed to infect a variety of different crenarchaeal hosts. For instance, additional *Nanoarchaeaota*, such as *Candidatus Nanobsidianus stetteri*, *Candidatus Nanopusillus acidilobi*, and *Candidatus Nanoclepta minutus* have recently been successfully co-cultivated with their crenarchaeal hosts referred to as

Acidolobus sp., Acidilobus sp. 7A, and *Zestosphaera tikiterensis*, respectively [138, 185, 186].

Overview of Other Putative DPANN Clades

Most of the other DPANN clades are represented by genomes reconstructed through metagenomics or single-cell genomics approaches. However, recent cultivation efforts have led to the enrichment of the first co-culture of a member of the *Nanohaloarchaeota* with its haloarchaeal host, i.e., *Ca. Nanohaloarchaeum antarcticus* and *Halorubrum lacusprofundi* [187], and of members of the *Micraarchaeota* members with their putative archaeal partners belonging to the *Thermoplasmatales* [188, 189]. Even though *Ca. N. antarcticus* has a larger genome and metabolic gene repertoire than *N. equitans*, it seems to obligately depend on its host for growth and survival [187].

Additional insights into the diversity and metabolic potential of members of the various DPANN clades predominantly derive from genomic inferences [6, 177, 180]. For instance, the *Woese-* and *Pacearchaeota* seemingly represent extremely diverse DPANN lineages whose members differ in the extent of genome reduction and metabolic capabilities. However, all representatives lack major and essential metabolic pathways indicating obligate host dependency. Few representatives of the DPANN, such as members of the *Diapherotrites* [190], may be able to conserve energy through fermentation. But the lack of some biosynthetic pathways indicates that they still depend on the external acquisition of certain amino acids, vitamins and/or cofactors [177, 180].

While much has to be learned about the DPANN archaea, the discovery of this large diversity of putative archaeal symbionts and the occurrence of certain representatives in almost all environments on Earth indicates that the future investigation of this radiation will be crucial for our understanding of both the evolution and ecology of *Archaea* and their impact on global nutrient cycles.

Altiarchaeota and its Symbiont—A Member of the Huberarchaeota

The *Altiarchaeota* represent a lineage variably affiliating either with the DPANN archaea or *Euryarchaeota* [6, 135, 177, 179, 180, 191] in phylogenetic analyses depending on the type of analysis (e.g., with regard to model choice) and data used. *Altiarchaeota* (formerly also referred to as SM1 *Euryarchaeota*) were originally discovered in a cold (~10°C), sulfurous Moor in Germany [135] but can also be found in sulfidic springs [192, 193], marine sediments, hot springs, and aquifers [191]. Notably, some members of the *Altiarchaeota* are found in microbial consortia that display a unique morphology described as a "string-of-pearls," which is several millimeters in length and consists of tiny white pearls (0.5–3 mm diameter) connected by thin threads [135]. The outer part of the pearl is composed of bacteria, such as the *Gammaproteobacterium Thiotrix uunzi* [194] or the *Epsilonproteobacterium* IMB1 [195], while the inside is dominated by *Altiarchaeota* [135]. The large size of the consortium allows for the effective enrichment of *Altiarchaeota* on polyethylene nets that can consist of ~98% of archaeal cells and ~2% bacteria [196]. Other representatives of the *Altiarchaeota* occur in almost single-member biofilms (~5% bacteria, ~95% *Altiarchaeota*) in sulfidic springs [192, 193].

Notably, *Altiarchaeota* have not only been found in symbiosis with bacteria but represent the hosts of members of the *Huberarchaeota*, a recent addition to the DPANN superphylum [178, 197]. Similar to other DPANN archaea, known members of the *Huberarchaeota* have reduced genomes and lack proteins related to energy metabolism, regeneration of redox equivalents and nucleotide biosynthesis indicating that they depend on a variety of compounds from their hosts.

The first insights into the metabolism of the Altiarchaeota came from the metagenome-assembled genome (MAG) of *Candidatus* Altiarchaeum hamiconexum, which was reconstructed from a cold, sulfidic spring in Germany [179]. Genomic analyses suggested this representative is an anaerobic autotroph, potentially capable of growth on carbon dioxide and possibly acetate, formate, and carbon monoxide [179]. *Ca.* A. hamiconexum is a biofilm-forming, nonmotile organism with coccoid cells (0.4–0.7 μM in diameter) and a double membrane [179]. Cells can be surrounded by up to 100 hair-like proteinaceous appendages of 2–3 μM length, so-called hami, which mediate adhesion to various surfaces [198]. However, representatives of the *Altiarchaeota* from sediments lack genes encoding proteins involved in hami formation and show specific adaptations to their respective environments [191].

Archaea as Part of the Human Microbiome

For a long time, it was thought that *Archaea* played minor roles in the microbiomes of humans and other mammals and true archaeal pathogens remain to be discovered. The first archaeon associated with humans was described in 1982, the methanogenic *Methanobrevibacter smithii*, which was isolated from human feces [199] suggesting that the methane exhaled by a certain proportion of humans may be produced by methanogens residing in the gastrointestinal tract [200]. Since then, several archaeal species have been identified to be associated with the intestinal, oral, gut, nasal, vaginal, lung, and skin microbiota of both humans and other animals [201–203]. However, their roles in human health and disease remain poorly understood [201–205]. In the following, we summarize current knowledge regarding the diversity and function of human-associated archaea.

Oral Archaeome

Methanogenic archaea are part of the oral archaeome with *Methanobrevibacter oralis* being the most frequently detected species [205, 206]. Notably, *M. oralis* seems to be correlated with periodontitis severity, supporting a potential pathogenic role of methanogenic archaea [206–208]. While no direct experimental evidence has demonstrated the virulence pattern of *M. oralis* and other oral archaeal species, the unique metabolism of methanogenic archaea provides insight into possible drivers of oral disease. For instance, methanogens in periodontal pockets may serve as an H_2 sink, which would favor the proliferation of syntrophic pathogenic microbes [206–209]. Recent investigation into microbial communities in the oral cavity has shown significant positive correlations between the abundance of methanogens with that of *Prevotella intermedia*, a known bacterial pathogen involved in periodontal infections such as periodontitis, gingivitis, and necrotizing ulcerative gingivitis [208].

The relationship between these two groups in periodontal pockets is still unknown, but indirect and direct associations between the methanogens and the local environment may be driving the proliferation of *P. intermedia* through a series of possible syntrophic interactions [208]. A current key research interest is to further determine the immediate role of archaea in the pathogenesis of periodontal infections [206, 210]

Gut Archaeome

To date, three species of methanogenic archaea have been cultivated and isolated from gut-derived samples, i.e., from human stool: *M. smithii*, *Methanosphaera stadtmanae*, and *Methanomassiliicoccus luminyensis* [95, 199, 211]. With the help of molecular tools, two candidate-species, *Candidatus Methanomassiliicoccus intestinalis* and *Candidatus Methanomethylophilus alvus*, in addition to several unknown members of the orders *Methanosarcinales*, *Methanobacteriales*, *Methanococcales*, *Methanomicrobiales*, and *Methanopyrales*, have been shown to inhabit the human gastrointestinal tract [202]. Further, the presence of methanogens in biopsy samples suggests that they may be associated with the mucosal lining in addition to their presumed presence in the lumen [202]. *M. smithii* is the major archaeal component in the human gut, while *M. stadtmanae* and *M. luminyensis* are less frequently detected species [201, 202] and appear to play an important role as H_2-consumers in the complex microbial ecosystem of the gut [201, 205, 209]. Fermentative microorganisms produce short-chain fatty acids and H_2, the former being consumed by the host and the latter being scavenged and consumed by the archaea. This removal of H_2 from the system by methanogens makes the fermentative processes kinetically more favorable and continuously drives this cyclical syntrophy [201, 202, 205]. Furthermore, there is evidence that methanogens may be involved in inflammatory bowel disease, irritable bowel syndrome, colorectal cancer, diverticulosis, and obesity [201, 205]. However, it is unclear whether methanogens directly or indirectly contribute to the development of gastrointestinal disorders and without doubt, more research is needed to unravel the role of archaea in intestinal disorders [204, 212]. For instance, it has also been suggested that some human-associated archaea may be mutualistic, providing health benefits and influencing host metabolism [202, 213].

Not all gut-associated archaea are methanogens however [202]. For instance, a halophilic archaeon belonging to the halobacteria, *Haloferax massiliensis*, was recently isolated from a human stool sample, reigniting the debate over whether halophiles may colonize the gut [214, 215]. Other studies have revealed a diversity of halobacteria-related sequences in fecal samples collected from healthy Korean people, with analyzed sequences representing *Halorubrum alimentarium* and *Halorubrum koreense*. Interestingly, both *H. alimentarium* and *H. koreense* had previously been isolated from salt-fermented sea foods suggesting native cuisine and eating habits may contribute to the propensity of these organisms in the gut environment [201, 216].

Global Human Archaeome

Technological advancements in high-throughput sequencing have further improved insights into the human microbiome and revealed unexpected diversity of representatives from archaeal phyla that had not previously been detected in human habitats, including members of the DPANN archaea. In particular, members of the *Woesearchaeota* appear to be present in the human lung, and while it is speculated that they may exhibit parasitic/symbiotic lifestyles, their environmental role remains unclear [202]. Analytical exploration into the distribution of archaeal signatures in the human body has revealed site-specific patterns that shape a preliminary biogeographical view of the human archaeome: (1) *Thaumarchaeota* on the skin, (2) methanogenic *Euryarchaeota* in the gut, (3) mixed skin-gut nasal archaeal communities, and (4) *Woesearchaeota* inhabiting the lungs [202].

While *M. smithii*, *M. oralis*, *M. stadtmanae*, *M. luminyensis*, and *H. massiliensis* are the only archaeal species that have been successfully isolated and cultivated from human habitats, efforts are underway to culture more archaeal species associated with humans in order to better understand their roles as potential pathogens or commensal members with potentially positive physiological impacts. For instance, a major step toward a better understanding of the function and dynamics of human-associated archaea may be gained through the Human Microbiome Project [209, 217].

Concurrent with efforts to culture archaeal species infecting humans and elucidate their potential roles in human pathogenesis, there are several initiatives aiming to identify antimicrobial agents that are effective against *Archaea*. Research shows that archaea are resistant to antibiotics used to treat bacterial infections, in part due to morphological and physiological features that impede the action of many bacterial-targeting antimicrobial agents. *In vivo* and *in vitro* experiments have indicated susceptibility of several archaeal groups to certain protein synthesis inhibitors, including fusidic acid and imidazole derivatives [218]. Nonetheless, antibiotic-resistant archaea may become indirectly susceptible to antimicrobial treatments when relying on chemically susceptible bacterial partners within their complex communities. To date, there are a limited number of antimicrobials that target archaea directly. Greater exploration into archaea as causative agents of human disease would also require further investigation into antiarchaeal compounds and treatments [210, 218].

Summary

Thought to be of limited ecological relevance originally, *Archaea* are now known to inhabit a wide range of ecosystems and to play a key role in major biogeochemical cycles [8]. Furthermore, *Archaea* have proven to be of fundamental importance for our understanding of the evolution of complex eukaryotic cells [10] and have emerged as important model systems. Notably, representatives of the *Archaea* are now known to form a stable part of the human microbiome and may even be involved in disease. Unique metabolic and cellular features of *Archaea* are being utilized in a variety of biotechnological applications as well as the development of novel adjuvants in the use of vaccines utilizing the unique membrane lipids of archaeal membranes [219]. Considering that a large fraction of *Archaea* of high-taxonomic rank likely still awaits discovery [5], the coming years will certainly witness further insights into the role of *Archaea* in ecological food webs, the evolution of life and human biology.

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