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Isoprenoid biosynthesis in Archaea – Biochemical and evolutionary implications

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Abstract

Isoprenoids are indispensable for all types of cellular life in the Archaea, Bacteria, and Eucarya. These membrane-associated molecules are involved in a wide variety of vital biological functions, ranging from compartmentalization and stability, to protection and energy-transduction. In Archaea, isoprenoid compounds constitute the hydrophobic moiety of the typical ether-linked membrane lipids. With respect to stereochemistry and composition, these archaeal lipids are very different from the ester-linked, fatty acid-based phospholipids in bacterial and eukaryotic membranes. This review provides an update on isoprenoid biosynthesis pathways, with a focus on the archaeal enzymes. The black-and-white distribution of fundamentally distinct membrane lipids in Archaea on the one hand, and Bacteria and Eucarya on the other, has previously been used as a basis for hypothetical evolutionary scenarios, a selection of which will be discussed here.
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Keywords: Archaea; Membrane; Lipids; Isoprenoids; Glycerol phosphate; Evolution

1. Introduction

1.1. Archaea

A major scientific milestone was the discovery of Woese et al. (1990) that the evolution of life on earth has resulted in three distinct types of living systems: Archaea, Bacteria and Eucarya. At first glance, the morphology of organisms that belong to the archaeal and bacterial domains are very similar, apparently lacking the complex composition of eukaryotic cells. Because of their morphological similarity, the co-existence of two fundamentally different types of prokaryotes was not recognized before the introduction of molecular classification techniques in the 1970s. Comparison of ubiquitous sequences such as the building blocks of the protein synthesis machinery (ribosomal RNA and protein) was used to compose universal phylogenetic trees. These analyses strongly suggested that early in the cellular evolution two domains diverged within the prokaryotes: the Archaea and the Bacteria (Forterre et al., 2002). The division of life into three domains has since been supported by a wealth of data from various aspects including differences in membrane lipid structure (Koga and Morii, 2005), information processing machinery (Barry and Bell, 2006; Werner, 2007) and genome sequence comparisons (Snel et al., 1999). Although the distribution of the Archaea was initially presumed to be confined to extreme environments (high temperature, high salt concentration, extreme pH), it has become clear that they are ubiquitous in nature, present in ecosystems ranging from soil to oceans (Pace, 1997; Schleper et al., 2005).

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1.2. Archaeal membrane lipids

In all domains of life, isoprenoids are key molecules exhibiting a variety of functions in the cell membrane. Isoprenoids include steroids (e.g. cholesterol), protecting pigments (e.g. carotenoids), light-responsive co-factors (e.g. retinal), respiratory electron carriers (e.g. quinones), and membrane lipids. In Archaea, isoprenoid compounds are utilized for the synthesis of ether-linked membrane lipids that are structurally very different from the membrane lipids of bacteria and eukaryotes (Kates et al., 1963, 1966; Kates, 1993; Sehgal et al., 1962; De Rosa et al., 1986; Koga et al., 1993). The phospholipids of bacteria/eukaryotes consist of a glycerol moiety linked to linear hydrophobic fatty acids via ester bonds (Fig. 1A). The majority of the fatty acids consist of 16–18 carbon atoms. In contrast, the hydrophobic portion of archaeal membrane lipids consists of chains of isoprene molecules with regularly branching methyl groups (Fig. 1B). These phytanyl groups are covalently bound to glycerol molecules through ether bonds, and the most commonly observed membrane lipid, diphytanylglycerol diether (archaeol), contains phytanyl chains consisting of 20 carbons. Membrane lipids with acyl chains of different lengths (e.g. C25) have also been observed (De Rosa et al., 1982; Morii et al., 1999). One of the most unique structures of archaeal membrane lipids concerns the tetraether lipids, diphytanyldiglycerol tetraether (caldarchaeols) (Fig. 1C) (Langworthy, 1977). These membrane lipids consist of two hydrophilic groups connected by 40-carbon hydrophobic isoprene chains, allowing the formation of monolayer membranes. Furthermore, some archaeal species have been found to contain pentacyclized tetraether lipids (Gulik et al., 1985). In addition to the structural differences in the hydrophobic moieties, the archaeal and bacterial/eukaryotic membrane lipids also strictly differ in stereochemistry. Whereas the eukaryotes and bacteria utilize 1,2-*sn*-glycerol, archaea adopt the opposite stereochemistry, using 2,3-*sn*-glycerol backbones (Kates, 1993; De Rosa et al., 1986; Koga et al., 1993). This difference in stereochemistry is strict with no known exception in any one of the three domains. As such, membrane lipids are the most clear-cut biological markers for the identification of archaea (Brassell et al., 1981; Sturt et al., 2004). In terms of the head groups that are attached to the glycerol, archaeal membrane lipids have been found to utilize various compounds including sugars, amines, phosphate, sulfate, alcohols and amino acids, which are also generally found in the phospholipids of bacteria and eukaryotes (Daiyasu et al., 2005).

1.3. Membrane lipid composition and its adaptation in Archaea

The relative amounts of the various lipid structures in the archaeal membrane have been found to vary widely, depending on the particular organism and the environmental conditions (Koga and Morii, 2005; Macalady et al., 2004; Ulrih et al., 2009). For example, the Halobacteriales only possess bilayer (mainly C20) membrane lipids. *Aeropyrum pernix* utilizes only C25 archaeols (Morii et al., 1999). On the other hand, the genera *Pyrobaculum*, *Thermoplasma* and *Sulfolobus* mainly utilize caldarchaeols (C40), including those with cyclopentane ring structures. Intriguingly, the membrane lipid composition of different members of the genus Thermococcales appears to be highly variable (Sugai et al., 2004).

An interesting observation has been that the compositions of membrane lipids in various archaeal species change and respond to environmental factors. In the hyperthermophilic archaea *Thermococcus kodakarensis* and *Archaeoglobus fulgidus*, it has been reported that increasing growth temperature leads to an increase in the ratio of caldarchaeols to archaeols (Lai et al., 2008; Matsuno et al., 2009). In *Methanocaldococcus jannaschii*, it has also been observed that archaeols decreased and caldarchaeols and macrocyclic archaeols increased with increasing growth temperature (Sprott et al., 1991). Analysis of members of the

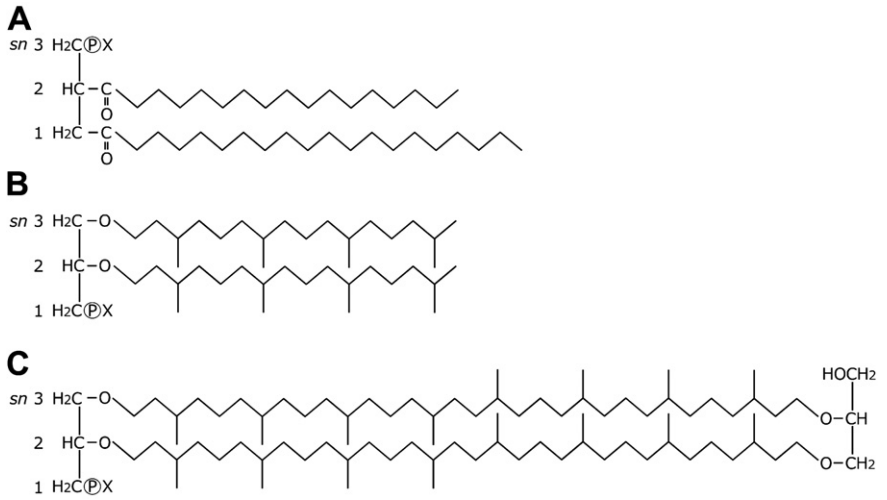

Fig. 1. Membrane lipid structures from archaea and bacteria/eukaryotes. (A) Typical structure of the phospholipids of bacteria/eukaryotes consisting of a glycerol moiety linked to linear hydrophobic fatty acids via ester bonds. (B) Structure of diphytanylglycerol diether (archaeol), a common membrane lipid of the Archaea. (C) Structure of diphytanyldiglycerol tetraether (caldarchaeol), a tetraether lipid found in archaea. X represents polar head groups.

thermoacidophilic archaea Thermoplasmatales and Sulfolobales revealed that the number of cyclopentane rings in the caldarchaeols increases at elevated growth temperatures (De Rosa et al., 1980; Shimada et al., 2008; Uda et al., 2001). Moreover, in the psychrophilic archaea *Halorubrum lacusprofundi* and *Methanococcoides burtonii*, it has been reported that decreasing temperature leads to an increase in the ratio of unsaturated isoprenoid side chains (Gibson et al., 2005; Nichols et al., 2004). In *Ignicoccus* sp., it has been observed that compared to cells grown at optimal growth temperatures, tetraether formation decreased in cells grown at either higher or lower temperatures (Jahn et al., 2004). With this wealth of data, it appears that both the euryarchaeotes and crenarchaeotes generally have the ability to alter their membrane lipid composition depending on the growth conditions. The molecular basis underlying the thermo-sensing and the subsequent adjustments of the membrane lipid side chains remain to be elucidated.

After the discovery of the unique archaeal membrane lipids, it had been proposed that the unique structural features of these lipids could provide an advantage to survive in the hostile, extreme environments where many archaea had been isolated (Gliozzi et al., 1983; Kates, 1993). As the ester group is much more susceptible to hydrolysis, the ether-linked archaeal lipids can be considered much more chemically stable at high temperatures or extreme pH than the ester-linked lipids. Furthermore, the branched chain structures are presumed to allow a more densely-packed supramolecular structure, suggesting that membranes consisting of archaeal lipids are more stable and less permeable than those of bacteria/eukaryotes. Experimental evidence agrees well with the idea that ether-linked isoprenoid membrane lipids are well suited to support life in extreme environments (Brown et al., 2009; Chong, 2010; Komatsu and Chong, 1998). However, there is no strict correlation between ether-linked isoprenoid membrane lipids and extremophilicity. It is now known that archaea thriving at non-extreme environments also harbor the same ether-linked membrane lipids. Although some thermophilic bacteria such as members of the hyperthermophilic *Aquifex* and *Thermotoga* have been demonstrated to possess some ether lipids in their membranes, the majority of their membrane consists of ester-based fatty acid lipids with the bacterial-type stereochemistry (Sinninghe Damsté et al., 2007). It should be noted that the ether-linked membrane lipids in these bacteria utilize linear fatty alcohol chains, not isoprenoid chains, and adopt the same stereochemistry as the ester-type lipids, opposite that of the archaeal membrane lipids.

2. Biosynthesis of isoprenoids and archaeal membrane lipids

2.1. Isoprenoid biosynthesis pathway

The biosynthesis of isoprenoid compounds can be divided into two phases; the first phase that generates the two basic building blocks, and the second phase that combines the building blocks to generate the isoprenoid compounds. The two basic building blocks are both five-carbon compounds, isopentenyl diphosphate (IPP) and its isomer dimethylallyl diphosphate (DMAPP). Two pathways are known through which these precursors are biologically synthesized. One is the mevalonate pathway which is found in eukaryotes, archaea and some bacteria, and the other is the pyruvate-glyceraldehyde 3-phosphate (pyruvate-GAP) pathway, which is the major pathway utilized in bacteria and chloroplasts. The latter route is also referred to as the 2-*C*-methyl-*D*-erythritol 4-phosphate (MEP) pathway (not described here; for review, see Eisenreich et al., 2004; Hunter, 2007).

The typical mevalonate pathway (Fig. 2) comprises seven enzyme reactions and is responsible for the conversion of acetyl-CoA to IPP and DMAPP. Biosynthesis initiates with the condensation of two acetyl-CoA molecules to form acetoacetyl-CoA (catalyzed by acetoacetyl-CoA thiolase), and the subsequent condensation of yet another acetyl-CoA generating 3-hydroxy-3-methylglutaryl CoA (HMG-CoA synthase). Thereafter, HMG-CoA is reduced to mevalonate (HMG-CoA reductase), which is then subjected to two phosphorylating reactions to form phosphomevalonate (mevalonate kinase) and diphosphomevalonate (phosphomevalonate kinase). Finally, the latter compound is decarboxylated to generate the first building block, IPP (diphosphomevalonate decarboxylase), and this is partly isomerized to produce the second building block, DMAPP (isopentenyl diphosphate delta-isomerase).

In the second phase (Fig. 2), DMAPP acts as the seed compound for a series of condensation reactions with IPP catalyzed by prenyltransferases. A single condensation reaction thus results in the elongation of the isoprenoid chain by 5 carbons. In this reaction, the release of the pyrophosphate group of DMAPP generates a carbocationic intermediate which is then attacked by the double bond of IPP. A subsequent loss of a proton from the original C2 carbon of IPP results in the formation of the double bond of geranyl diphosphate. Since the latter product is also an allyl diphosphate, it can in turn react with another molecule of IPP and further extend the isoprenoid chain. Prenyltransferases are named on the basis of the number of condensation reactions they permit, geranyl diphosphate synthase (single reaction), farnesyl diphosphate synthase (two reactions), geranylgeranyl diphosphate synthase (three reactions), and farnesylgeranyl diphosphate synthase (four reactions). Enzymes that catalyze even more rounds of condensation reactions are involved in the generation of quinone-like molecules (6–10 reactions) and natural rubber.

2.2. Archaeal enzymes involved in isoprenoid biosynthesis

As described above, the mevalonate pathway is present in all three domains of life. The majority of the corresponding enzymes in the bacterial and eukaryotic pathways are homologous to one another. Biochemical studies of the archaeal enzymes are still at an early stage, and further research will be necessary to obtain a complete and thorough

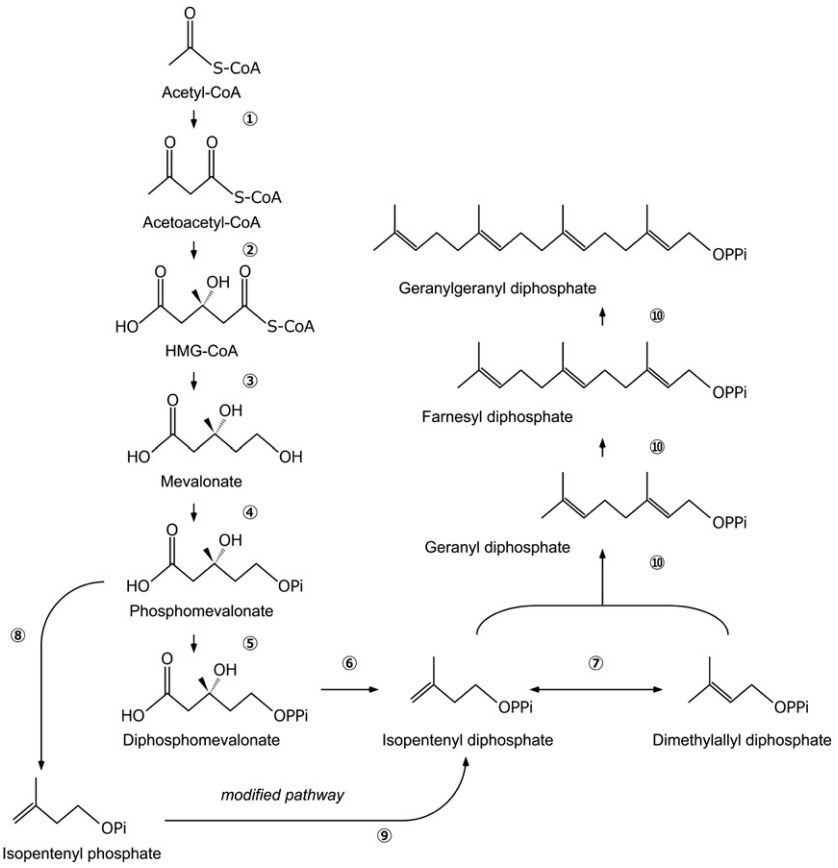

Fig. 2. Diagram illustrating the reactions of the mevalonate pathway. The classical pathway found in bacteria/eukaryotes is indicated along with the modified pathway proposed in archaea. Enzymes responsible for the numbered reactions are as follows; 1, acetoacetyl-CoA thiolase; 2, HMG-CoA synthase; 3, HMG-CoA reductase; 4, mevalonate kinase; 5, phosphomevalonate kinase (PMK); 6, diphosphomevalonate decarboxylase (DMD); 7, isopentenyl diphosphate isomerase (IDI); 8, predicted phosphomevalonate decarboxylase (PMD); 9, isopentenyl phosphate kinase (IPK); 10, prenyltransferase.

understanding of the archaeal mevalonate pathway. Initial studies on the individual enzymes are summarized below. *Nanoarchaeum equitans*, which is an obligate symbiont with a condensed genome, does not possess genes involved in isoprenoid biosynthesis and it has been suggested that it depends on its partner *Ignicoccus* for lipid biosynthesis (Podar et al., 2008; Waters et al., 2003; Jahn et al., 2004). The absence of particular genes on the *N. equitans* genome will thus be excluded from our discussion below. The distributions of the individual genes, based on the integrated microbial genomes (IMG) system (Markowitz et al., 2009), are shown in Table 1.

2.2.1. Acetoacetyl-CoA thiolase (COG0183)

The enzyme has been purified and characterized from *Halobacterium* strain ZP-6, and the N-terminal amino acid sequence is similar to that of the deduced amino acid sequence of a putative thiolase gene on the *Halobacterium* sp. NRC-1 genome (Liu et al., 2002). Homologs of this gene are present on all of the archaeal genomes, and some harbor multiple paralogs.

2.2.2. HMG-CoA synthase (COG3425)

An archaeal HMG-CoA synthase has not been characterized to date. Genes homologous to bacterial and eukaryotic genes are present on the archaeal genomes, and rather than the archaeal enzymes forming a cluster with one another on the phylogenetic tree, they cluster together with the enzymes from the other two domains (Jiang et al., 2008). This has led to the proposal that HMG-CoA synthases were already present in ancestral cells before the archaea diverged with other forms of life, and that HMG-CoA synthases have an ancient descent (Jiang et al., 2008).

2.2.3. HMG-CoA reductase (COG1257)

Two classes of HMG-CoA reductases have been identified in bacteria/eukaryotes, and both are present in the archaea (Friesen and Rodwell, 2004; Hedl et al., 2004). As in the case of the enzymes from bacteria and eukaryotes, the archaeal class-I HMG-CoA reductase is NADP-dependent. Enzymes from *Halobacterium halobium*, *Haloferax volcanii*, and *Sulfolobus solfataricus* have been biochemically characterized (Bischoff and Rodwell, 1996; Bochar et al., 1997; Cabrera et al., 1986). The class-II enzymes, which are NAD-dependent, have been identified in *A. fulgidus* and biochemically examined (Kim et al., 2000). The enzyme prefers NAD but also accepts NADP as a cofactor (Kim et al., 2000). The class-I homologs are distributed among the majority of the archaea. In contrast, the class-II enzymes are limited to the members of

the Archaeoglobales, the Thermoplasmatales and the Thaumarchaeota, as well as to several other archaeal species.

2.2.4. Mevalonate kinase (COG1577 and COG2605)

The mevalonate kinase from *M. jannaschii* (COG1577) has been characterized, and its crystal structure has been determined (Huang et al., 1999; Yang et al., 2002). The enzyme is homologous to the bacterial/eukaryotic enzymes, and corresponding genes can be found on all of the published archaeal genome sequences except for the Thermoplasmatales. The Thermoplasmatales instead appear to possess a predicted kinase related to the GHMP kinase (Galactokinase, Homoserine kinase, Mevalonate kinase and Phosphomevalonate kinase) superfamily (COG2605) that is found only in this order.

2.2.5. Phosphomevalonate kinase, diphosphomevalonate decarboxylase and isopentenyl diphosphate isomerase

These three enzymes are responsible for the synthesis of the two basic building blocks, IPP and DMAPP, from phosphomevalonate. Intriguingly, whereas homologs of the aforementioned enzymes of the mevalonate pathway are present in the Archaea, homologs of these three enzymes are not found in the majority of the Archaea. Identification of the enzymes responsible for the conversion of phosphomevalonate to IPP and DMAPP is a current topic of research, and will be discussed below.

2.2.6. Prenyltransferase (COG0142)

The genome sequences suggest that the archaea all harbor a geranylgeranyl diphosphate synthase, except for *A. pernix*. Whereas the eukaryotes harbor specific enzymes that are responsible for individual elongation reactions (C5–C10, C10–C15 and so on), homologs of these enzymes cannot be identified on the archaeal genomes. Geranylgeranyl diphosphate synthases have been studied from numerous archaea including *Thermococcus*, *Pyrococcus*, *Methanothermobacter* and *Sulfolobus* (Chen and Poulter, 1993, 1994; Fujiwara et al., 2004; Masuchi et al., 1998; Ohnuma et al., 1994; Tachibana et al., 1993). These enzymes can be identified by the presence of a bulky Phe or Tyr residue near the FARM (first aspartate rich motif) motif highly conserved in prenyltransferases (Wang and Ohnuma, 1999). The Phe/Tyr residues have been shown to limit the degree of isoprenoid elongation to C20 (Ohnuma et al., 1996; Wang and Ohnuma, 1999). In addition to the geranylgeranyl diphosphate synthases, some archaea have been shown to also harbor a farnesylgeranyl diphosphate synthase (Tachibana, 1994; Tachibana et al., 2000). The archaeal farnesylgeranyl diphosphate synthase was first identified in *Natronomonas pharaonis* (Tachibana, 1994). This organism possesses C20–C25 diether membrane lipids in addition to the C20–C20 archaeols, suggesting that the farnesylgeranyl diphosphate synthase is responsible for the synthesis of the C25 isoprenoid chains. The enzyme from *A. pernix* has also been studied (Tachibana et al., 2000). Consistent with the presence of C25 archaeols in this archaeon (Morii et al., 1999), the enzyme exhibits farnesylgeranyl diphosphate synthase activity.

2.3. Synthesis of the glycerol moiety, ether bond linkage and further modification of the isoprenoid chains for archaeal membrane lipids

The stereostructure of the glycerophosphate backbone in archaea is glycerol-1-phosphate (G-1-P), while bacteria and eukaryotes utilize glycerol-3-phosphate (G-3-P) backbones (Fig. 1). Nishihara and Koga (1995, 1997), Nishihara et al. (1999) have identified and characterized an enzyme from *Methanothermobacter thermautotrophicus* which is involved in G-1-P formation from dihydroxyacetone phosphate (DHAP) (Fig. 3). The enzyme, G-1-P dehydrogenase (COG0371), displays similarity to glycerol dehydrogenase, alcohol dehydrogenase Type IV, and dehydroquinate synthase (Daiyasu et al., 2002). The enzyme from *A. pernix* has also been studied biochemically in detail (Han et al., 2002; Han and Ishikawa, 2005). As stated above, another typical archaeal feature concerns the formation of ether bonds between the G-1-P backbone and the isoprenoid side chains, instead of the ester bonds found in bacteria and eukaryotes. Two enzymes are involved in ether bond formation (Zhang et al., 1990; Zhang and Poulter, 1993). First, (*S*)-3-*O*-geranylgeranylglyceryl phosphate synthase (COG1646) catalyzes ether bond formation between the *sn*-3 hydroxylgroup of G-1-P and geranylgeranyl diphosphate (C20). The enzymes from *M. thermautotrophicus* and *Thermoplasma acidophilum* have been characterized (Chen et al., 1993; Nemoto et al., 2003; Soderberg et al., 2001). Furthermore, the crystal structure of the enzyme from *A. fulgidus* has been determined (Payandeh et al., 2006). Second, (*S*)-2,3-di-*O*-geranylgeranylglyceryl phosphate synthase (COG0382) catalyzes ether bond formation between the *sn*-2 hydroxy group of geranylgeranyl G-1-P and geranylgeranyl diphosphate. The activity of this reaction has been confirmed in the recombinant protein from *S. solfataricus* (Hemmi et al., 2004). This gene belongs to the UbiA prenyltransferase family. As an exception, the available genomes of Thaumarchaeota do not possess an orthologous gene.

After the G-1-P backbone is connected with two isoprenoid side chains via ether bonds, cytidine-diphosphate (CDP) is attached by CDP-archaeol synthase. Although the activity of CDP-archaeol synthase has been detected in *M. thermautotrophicus*, the gene has not yet been identified (Morii et al., 2000). Finally, reduction of the unsaturated isoprenoid side chains is generally catalyzed by geranylgeranyl reductase (GGR, COG0644). Identification and enzymatic characterization were first performed on the enzyme from *T. acidophilum* (Nishimura and Eguchi, 2006), and further studies have also been reported for the enzymes from *A. fulgidus* and *Sulfolobus acidocaldarius* (Murakami et al., 2007; Sato et al., 2008). Almost all archaea harbor multiple paralogs (~8 genes) of GGR on their genomes. These are considered to be involved in the reduction of other isoprenoid compounds that the Archaea possess besides membrane lipids (see below). Some archaea possess tetraether polar lipids which are synthesized from two diether polar lipids, but the enzyme(s)

Table 1
Distribution of homologs related to membrane lipid biosynthesis in the Archaea.

		1	2	3	4	4	5	6	7	7	10	A	B	C	D	8*	8*	9
Classification	Species	COG0183	COG3425	COG1257	COG1577	COG2605	COG3890	COG3407	COG1443	COG1304	COG0142	COG0371	COG1646	COG0382	COG0644	COG1355	COG1586	COG1608
Crenarchaeota																		
Desulfurococcales	*Aeropyrum pernix*	5	1	1	1	0	0	0	0	1	1	1	1	2	5	1	2	1
	Desulfurococcus kamchatkensis	1	1	1	1	0	0	0	0	1	1	1	1	1	2	1	1	1
	Hyperthermus butylicus	1	1	1	1	0	0	0	0	1	2	1	1	2	4	2	2	1
	Ignicoccus hospitalis	2	1	1	1	0	0	0	0	1	2	1	1	2	3	1	2	1
	Staphylothermus marinus	1	1	2	1	0	0	0	0	1	1	1	1	1	2	1	2	1
Sulfolobales	*Metallosphaera sedula*	8	1	1	1	0	1	1	0	1	2	1	1	2	7	1	2	1
	Sulfolobus acidocaldarius	11	1	1	1	0	1	1	0	1	2	1	1	2	6	1	2	0
	Sulfolobus islandicus	12(13)	1	1	1	0	1	1	0	1	2	1	1	2	6	1	2	1
	Sulfolobus solfataricus	10	1	1	1	0	1	1	0	1	2	1	1	2	7	1	2	1
	Sulfolobus tokodaii	8	1	1	1	0	1	1	0	1	2	1	1	2	6	1	2	0
Thermoproteales	*Caldivirga maquilingensis*	2	1	1	1	0	0	0	0	2	2	1	1	1	5	1	2	1
	Pyrobaculum aerophilum	7	1	1	1	0	0	0	0	1	2	1	1	2	5	1	2	1
	Pyrobaculum arsenaticum	4	1	1	1	0	0	0	0	1	2	1	1	2	5	1	2	1
	Pyrobaculum calidifontis	5	1	1	1	0	0	0	0	1	2	1	1	2	5	1	2	1
	Pyrobaculum islandicum	4	1	1	1	0	0	0	0	1	2	1	1	2	5	1	2	1
	Thermofilum pendens	1	1	1	1	0	0	0	0	1	2	1	1	2	5	1	2	1
	Thermoproteus neutrophilus	2	1	1	1	0	0	0	0	1	2	1	1	2	5	1	2	1
Thaumarchaeota																		
Cenarchaeales	*Cenarchaeum symbiosum*	2	1	1	1	0	0	0	1	0	2	1	1	0	4	1	0	1
Nitrosopumilales	*Nitrosopumilus maritimus*	2	1	1	1	0	0	0	1	0	2	1	1	0	4	1	0	1
Euryarchaeota																		
Archaeoglobales	*Archaeoglobus fulgidus*	15	2	1	1	0	0	0	0	2	2	1	1	3	4	1	1	1
	Archaeoglobus profundus	2	1	1	1	0	0	0	0	1	2	0	1	3	3	1	1	1
Halobacteriales	*Haloarcula marismortui*	7	2	1	1	0	0	1	1	0	2	1	1	2	7	0	0	1
	Halobacterium salinarum	3	1	1	1	0	0	1	1	2	2	2	2	2	4	0	0	1
	Halobacterium sp. NRC-1	3	1	1	1	0	0	1	1	4	2	2	2	2	4	0	0	1
	Halomicrobium mukohataei	3	1	1	1	0	0	1	1	0	2	1	2	2	8	0	0	1
	Haloquadratum walsbyi	3	1	1	1	0	0	1	1	1	2	1	1	2	4	0	0	1
	Halorhabdus utahensis	1	1	1	1	0	0	1	1	0	3	1	1	1	6	1	0	1
	Halorubrum lacusprofundi	4	1	1	1	0	0	1	1	0	2	2	1	2	4	0	0	1
	Haloterrigena turkmenica	16	4	1	1	0	0	1	1	3	2	1	2	5	5	0	0	1
	Natronomonas pharaonis	8	2	2	1	0	0	1	1	2	3	1	1	3	4	0	0	1
Methanococcales	*Methanocaldococcus fervens*	1	1	1	1	0	0	0	0	1	1	1	1	1	3	1	1	1
	Methanocaldococcus jannaschii	1	1	1	1	0	0	0	0	1	1	1	1	1	3	1	1	1
	Methanocaldococcus vulcanius	1	1	1	1	0	0	0	0	1	1	1	1	1	3	1	1	1
	Methanococcus aeolicus	1	1	1	1	0	0	0	0	1	1	1	1	1	2	1	1	1
	Methanococcus maripaludis	1	1	1	1	0	0	0	0	1	1	1	1	1	2	1	1	1
	Methanococcus vannielii	1	1	1	1	0	0	0	0	4	1	1	1	1	2	1	1	1
Methanocellales	*Methanocella paludicola*	1	1	2	1	0	0	0	0	1	3	1	2	2	3	1	0	2
	Methanocella sp. RC-I	1	1	2	1	0	0	0	0	1	3	1	2	4	2	1	0	1
Methanosarcinales	*Methanococcoides burtonii*	1	1	1	1	0	0	0	0	1	2	1	1	6	5	1	0	1
	Methanosaeta thermophila	1	1	1	1	0	0	0	0	1	2	1	1	3	5	1	0	1
	Methanosarcina acetivorans	1	1	1	1	0	0	0	1	1	2	1	1	6	8	1	0	1
	Methanosarcina barkeri	1	1	1	1	0	0	0	1	1	2	1	1	7	7	1	0	1
	Methanosarcina mazei	1	1	1	1	0	0	0	1	1	2	1	1	4	6	1	0	1

Methanobacteriales	*Methanobrevibacter ruminantium*	1	1	1	1	0	0	0	0	1	1	1	1	1	3	1	0	1
	Methanobrevibacter smithii	1	1	1	1	0	0	0	0	1	1	1	1	1	1	1	0	1
	Methanothermobacter thermautotrophicus	1	1	1	1	0	0	0	0	1	1	1	1	4	3	1	0	1
	Methanosphaera stadtmanae	1	1	1	1	0	0	0	0	1	1	1	1	1	5	1	0	1
Methanomicrobiales	*Methanocorpusculum labreanum*	1	1	1	1	0	0	0	0	1	1	1	1	1	2	1	1	1
	Methanoculleus marisnigri	1	1	1	1	0	0	0	0	1	2	1	1	4	4	1	1	1
	Candidatus Methanoregula boonei	1	1	1	1	0	0	0	0	1	1	1	1	1	2	1	0	1
	Methanosphaerula palustris	1	1	1	1	0	0	0	0	1	1	2	1	3	3	1	0	1
	Methanospirillum hungatei	1	1	1	1	0	0	0	0	1	1	1	1	1	2	1	2	1
Methanopyrales	*Methanopyrus kandleri*	1	1	1	1	0	0	0	0	1	1	1	1	1	2	1	0	1
Thermococcales	*Pyrococcus abyssi*	1	1	1	1	0	0	0	0	1	1	1	1	1	2	1	1	1
	Pyrococcus furiosus	1	1	1	1	0	0	0	0	1	1	1	1	1	2	1	1	1
	Pyrococcus horikoshii	1	1	1	1	0	0	0	0	1	1	1	1	1	2	1	1	1
	Thermococcus gammatolerans	1	1	1	1	0	0	0	0	1	2	1	1	3	2	1	1	1
	Thermococcus kodakaraensis	1	1	1	1	0	0	0	0	1	1	1	1	2	2	1	1	1
	Thermococcus onnurineus	1	1	1	1	0	0	0	0	1	1	1	1	3	2	1	1	1
	Thermococcus sibiricus	1	1	1	1	0	0	0	0	1	1	1	1	2	2	1	1	1
Thermoplasmatales	*Picrophilus torridus*	4	1	1	0	1	0	2	0	2	2	1	1	3	5	1	1	1
	Thermoplasma acidophilum	5	1	1	0	2	0	3	0	1	2	1	1	2	4	1	1	1
	Thermoplasma volcanium	5	1	1	0	2	0	3	0	1	2	1	1	2	3	1	1	1
Korarchaeota	*Candidatus Korarchaeum cryptofilum*	2	1	1	1	0	0	0	0	1	2	1	1	2	4	1	2	1
Nanoarchaeota	*Nanoarchaeum equitans*	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0

Numbers (1−10) and letters (A−D) correspond to those indicated in Figures 2 and 3.

* Proposed, but not experimentally examined.

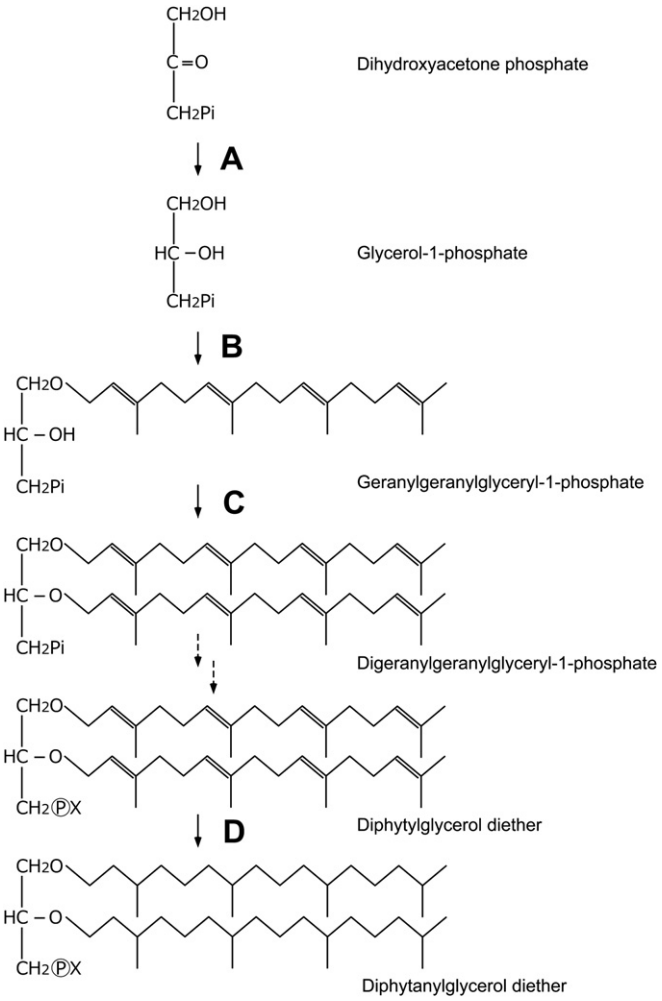

Fig. 3. Diagram illustrating the reactions involved in membrane lipid synthesis in the archaea. Enzymes responsible for the indicated reactions are as follows; A, glycerol-1-phosphate dehydrogenase; B, (*S*)-3-*O*-geranylgeranylglyceryl phosphate synthase; C, (*S*)-2,3-di-*O*-geranylgeranylglyceryl phosphate synthase; D, geranylgeranyl reductase (GGR). X represents polar head groups.

responsible for this C−C bond reaction have not yet been identified.

2.4. Conversion of phosphomevalonate to isopentenyl diphosphate, dimethylallyl diphosphate

As described above, homologs of four of the seven enzymes of the classical mevalonate pathway are generally found in the archaea, and many have been characterized biochemically. A very common and most intriguing feature of the archaea is that genes homologous to those encoding the classical phosphomevalonate kinase (PMK), diphosphomevalonate decarboxylase (DMD), and isopentenyl diphosphate isomerase (IDI) are missing on their genomes. Smit and Mushegian (2000) proposed several candidates for these enzymes by computational reconstruction of the pathway. A bacterial homolog of one of the candidate genes for IDI from *Streptomyces* sp. that was originally annotated as FMN-dependent dehydrogenase, was found to encode a protein with IDI activity (Kaneda et al., 2001). This enzyme (IDI-2), designated as a Type-II IDI (COG1304), does not display primary structure similarity to the Type-I eukaryotic IDI (IDI-1, COG1443). Interestingly, IDI-2 homologs are found on almost all archaeal genomes, and can be presumed to be the predominant type in the Archaea. Supporting the role of this protein as the archaeal IDI, several archaeal IDI-2 homologs have recently been demonstrated to catalyze the predicted isopentenyl diphosphate isomerase reaction (Dutoit et al., 2008; Siddiqui et al., 2005; Yamashita et al., 2004; Barkley et al., 2004). Introduction of the *M. thermautotrophicus* Type-II enzyme gene into an isopentenyl diphosphate isomerase-deficient strain of *Escherichia coli* resulted in functional complementation, suggesting that the gene encodes an IDI (Barkley et al., 2004). In some exceptional cases, such as in *Halobacterium* sp. NRC-1, both types seem to be present. Analysis of the *Halobacterium* type-I enzyme has confirmed that it exhibits IDI activity (Hoshino and Eguchi, 2007). Whereas the eukaryotic enzymes depend on Mg^{2+} or Mn^{2+} for activity, the *Halobacterium* type-I enzyme requires Co^{2+} (Hoshino and Eguchi, 2007). Moreover, recent complete genome analyses suggest that some of the Halobacteriales and Thaumarchaeota only possess Type-I IDI.

As for PMK and DMD, among the several candidates proposed as PMK by Smit and Mushegian (2000), the homolog from *M. jannaschii* has been shown not to display PMK activity, but rather isopentenyl phosphate kinase (IPK) activity (Grochowski et al., 2006). This result led to the proposal that archaea utilize a modified mevalonate pathway. This modified pathway has been proposed to utilize phosphomevalonate decarboxylase (PMD, which has not yet been identified) to convert phosphomevalonate to isopentenyl phosphate and IPK to convert isopentenyl phosphate to IPP (Grochowski et al., 2006). Besides the *M. jannaschii* enzyme, IPKs from *T. acidophilum* and *M. thermautotrophicus* have also been characterized, and their X-ray structures have been determined (Chen and Poulter, 2010; Mabanglo et al., 2010). The X-ray structure of the *M. jannaschii* IPK has revealed an important role of the His60 residue in both substrate and product stabilization (Dellas and Noel, 2010). The archaeal IPK protein (COG1608) is a new member of the amino acid kinase (AAK) superfamily, which also includes aspartokinase and glutamate-5-kinase (Dellas and Noel, 2010). By contrast, mevalonate kinase and phosphomevalonate kinase belong to the GHMP kinase superfamily, which includes galactokinase and homoserine kinase. The IPK homolog is conserved in almost all of the archaeal genomes except for those of *S. acidocaldarius* and *Sulfolobus tokodaii*. As the candidate of PMD, a predicted dioxygenase (COG1355) was proposed because the gene is often clustered with genes involved in isoprenoid biosynthesis, and has not yet been characterized (Grochowski et al., 2006). Although almost all Halobacteriales do not possess the COG1355 gene, they instead possess a putative bacteria-type DMD (COG3407) gene. This gene may encode a protein with PMD activity, or the Halobacteriales may harbor a unique PMK that functions with the bacteria-type DMD to generate isopentenyl diphosphate.

Alternatively, Smit and Mushegian (2000) had proposed a gene (SAM decarboxylase homolog, COG1586) as DMD, which may be a candidate for the missing PMD. The gene is missing not only in Halobacteriales, but also in Thaumarchaeota and many methanogens. Examination of the *in vivo* function of the IPK gene will surely be an important topic to address, as well as the identification of the missing PMD.

2.5. Mevalonate pathway in Sulfolobales

Sulfolobales have a complete set of the classical mevalonate pathway genes. PMKs (COG3890) from Sulfolobales are similar to the homologs from eukaryotes. The Sulfolobales DMDs (COG3407) also resemble their eukaryotic counterparts in primary structure. If the IPK is a signature of the modified pathway in archaea, *S. acidocaldarius* and *S. tokodaii* can be expected to use the classical pathway because they do not possess homologs of the IPK gene. It will be interesting to reveal whether a single pathway or both pathways are or can be used in *S. solfataricus*, *Sulfolobus islandicus* and *Methallosphaera sedula*, as these organisms apparently harbor homologs of both the classical pathway enzymes and IPK. As archaea that harbor the classical pathway genes are exceptional, the genes may have been obtained via horizontal gene transfer (Boucher et al., 2004). If so, how, when, and from where the Sulfolobales obtained these two classical genes remains to be determined. It has also been proposed that the classical mevalonate pathway was present in the archaeal ancestor, and that the modified pathway evolved in the archaea afterwards, allowing gene loss of the classical PMK, DMD and IDI (Lombard and Moreira, 2010). In this scenario, the classical enzymes of Sulfolobales are not a result of horizontal gene transfer, but rather a result of vertical inheritance.

2.6. Other isoprenoid compounds

Isoprenoid compounds in the Archaea are not limited to their membrane lipids. Some Halobacteriales possess retinal, which is the cofactor of bacteriorhodopsin (proton pump), halorhodopsin (chloride pump) and two kinds of phototactic sensors, sensory rhodopsin and photorhodopsin. In addition, C50 carotenoids such as bacterioruberines (involved in photo protection) and different types of quinones, squalenes (steroid precursor) and dolichol have been detected in archaea.

2.6.1. Carotenoids

The carotenoids are found in all domains of life in which they play distinct physiological roles, including UV protection, anti-oxidant activity and regulation of membrane fluidity. The majority of carotenoids is synthesized from lycopene (C40). Zeaxanthin glycosides have been detected in a *Sulfolobus shibatae* mutant subjected to multiple cycles of UV treatment (Grogan, 1989; Kull and Pfander, 1997). Although Kull and Pfander (1997) discussed the function of zeaxanthin glycosides as membrane reinforcers, Hemmi et al. (2003) considered that they act as radical scavengers in *Sulfolobus*, because the phenotype of the mutant is photoinductive. Recently, Götz et al. performed a microarray analysis to detect genes that respond to UV irradiation in *S. solfataricus* and *S. acidocaridarius*. The results indicated that carotenoid biosynthesis genes are transcribed and up-regulated in both organisms in response to UV irradiation (Götz et al., 2007).

2.6.2. Quinones

Many respiratory quinones in archaea contain fully or partially saturated isoprenoid chains, e.g. menaquinone, caldariellaquinone, sulfolobusquinone, thermoplasmaquinone. In *A. fulgidus*, four paralogs of GGR involved in the saturation of the geranylgeranyl group are found on its genome, and one of them has been shown to exhibit menaquinone reductase activity (Hemmi et al., 2005). Almost all archaea possess multiple paralogs of GGR. As mentioned above, saturated isoprenoid chains are found not only in the respiratory quinones but also in the membrane lipids in archaea. Hence, all archaea should at least harbor the genes involved in the production of membrane lipids, while some may have additional GGR homologs responsible for the synthesis of other isoprenoid-derived compounds. Many of the archaeal GGR homologs are highly similar or close relatives to their counterparts in plants and cyanobacteria, while others are closely related homologs of the *A. fulgidus* menaquinone-specific reductase, suggesting that the latter are involved in the biosynthesis of respiratory quinones (Hemmi et al., 2005). In *S. solfataricus*, hexaprenyl diphosphate synthase has been characterized (Hemmi et al., 2002). The enzyme produces C30 isoprenoid side chains and is expected to be responsible for producing caldariellaquinone, a C30 isoprenoid derivative (Hemmi et al., 2002; De Rosa et al., 1977). Interestingly, the enzyme belongs to a phylogenetic cluster whose members consist mainly of eukaryotic short chain prenyltransferases (Hemmi et al., 2002).

2.6.3. Methanophenazine

Methanosarcina mazei harbors two prenyltransferase homologs. While both have the FARM (first aspartate rich motif) motif, only MM1767 harbors the Phe/Tyr residue, suggesting that MM1767 is responsible for C20 isoprenoid synthesis, whereas MM0789 takes part in the production of longer isoprenoid chains (Ogawa et al., 2010). As only archaeols (C20 lipids) are found in the membrane of *M. mazei*, it is most likely that MM1767 participates in lipid biosynthesis, whereas MM0789 is involved in the biosynthesis of methanophenazine (C25 isoprenoid chains), an electron carrier involved in methanogenesis (Ogawa et al., 2010).

3. Evolution

3.1. Evolution of the isoprenoid biosynthesis pathway in the Archaea

Judging from gene distribution among the Archaea, the mevalonate pathway was most likely present in the last common ancestor of the Archaea. The first two enzymes of the pathway, acetoacetyl-CoA thiolase and HMG-CoA synthase,

are present on all the sequenced archaeal genomes. Each of these enzymes constitutes a single homologous protein family. As they are also related with their bacterial/eukaryotic counterparts, the two enzymes may have been present in the universal common ancestor. As to HMG-CoA reductase, two classes of enzymes, that are structurally related to one another, are present in the Archaea. Since all archaea harbor at least one of the two classes of enzymes, HMG-CoA reductase can also be considered to have an ancient history. Mevalonate kinase is present in the majority of the Archaea. The enzyme may have been present in the archaeal ancestor, and lost in the ancestors of the Thermoplasmatales. Similar interpretations can be proposed for isopentenyl diphosphate isomerase (Type II) and isopentenyl phosphate kinase, as both are present on almost all of the archaeal genomes with only a few exceptions. Although the archaeal phosphomevalonate decarboxylase has not yet been identified, the wide distribution of the known mevalonate pathway enzymes, including the archaea-specific isopentenyl phosphate kinase, among the Archaea suggest that the modified archaeal mevalonate pathway is an ancient trait of this domain.

As to isoprene condensation, all archaea harbor at least one prenyltransferase that belongs to COG0142. The four enzymes that lead to archaeol generation, G-1-P dehydrogenase (COG0371), (*S*)-3-*O*-geranylgeranylglyceryl phosphate synthase (COG1646), (*S*)-2,3-di-*O*-geranylgeranylglyceryl phosphate synthase (COG0382) and geranylgeranyl reductase (COG0644) are all present in the majority of the archaea with only a few exceptions. We observe that G-1-P dehydrogenase is not encoded on the *Archaeoglobus profundus* genome, and the (*S*)-2,3-di-*O*-geranylgeranylglyceryl phosphate synthase gene is apparently missing from the genomes of Thaumarchaeota. Nevertheless, the wide distribution of the genes involved in the archaeal mevalonate pathway and those responsible for membrane lipid biosynthesis strongly suggests that the archaeal ancestor already harbored the ability to synthesize archaeols via these pathways.

3.2. Archaeal membrane lipids and evolution

Elucidating the origin of life is one of the most fundamental questions in the life sciences. Although many hypotheses have been and are still being proposed, we are not even close to a stage in which a single scenario can be generally accepted. When one attempts to envision a single cell as a last universal common ancestor (LUCA), the differences in lipid structure between the archaea and bacteria/eukaryotes pose a tremendous problem. Below, a selection of evolutionary scenarios has been briefly summarized.

Glansdorff et al. (2008) note the possibilities that LUCA was already sophisticated; a community consisting of eukaryote-like, non-thermophilic, entities (protoeukaryotes) with membrane lipids consisting of fatty acids connected to G-3-P backbones. In this scenario, the Archaea evolved by "thermoreduction" (Forterre, 1995), a reductive evolution under selection for adaptation to high temperatures, with the Archaea obtaining isoprenoid ether lipids at the beginning of this process. By contrast, the Bacteria emerged as a separate group from the LUCA by reductive evolution in a non-thermophilic form, allowing the fatty acid ester lipids from the LUCA community to be maintained. A secondary, convergent adaptation towards thermophilicity occurred in the Bacteria, leading to the formation of a variety of membrane lipids, some with ether bonds, but still with a G-3-P backbone.

Koga et al. (1998), Koga and Morii (2005, 2007) have proposed that glycerol phosphate was first synthesized chemically from DHAP in a non-chiral manner, perhaps on a pyrite surface. This would lead to the abiotic accumulation of a racemic mixture of G-1-P and G-3-P. Later on, stereospecific dehydrogenases emerged that catalyze the conversion of DHAP to either G-1-P or G-3-P. Eventually, proto-cells utilizing the individual G-1-P or G-3-P evolved, representing the ancestors of the Archaea or Bacteria, respectively.

The scenario proposed by Wächtershäuser (2003, 2006) envisions a pre-cell, first proposed by Kandler (1994), that contained a racemate of chiral membranes supplied by either non-enzymatic reactions or by non-stereospecific enzymes. The emergence of a stereospecific dehydrogenase would then lead to the enrichment of a single enantiomer, which is energetically favorable considering that homochiral membranes display higher degrees of stability compared to heterochiral membranes. In this way the bacteria and archaea could have diverged from the pre-cells in an independent manner. The main difference of this scenario with the previous one is that cell-like entities were present prior to the occurrence of stereospecific enzymes. Peretó et al. (2004) have carefully investigated the evolution of G-1-P dehydrogenase and G-3-P dehydrogenase genes, and have provided the genetic background from which these two activities evolved in the pre-cells.

Martin and Russell (2003), Koonin and Martin (2005) have proposed that the earliest biological metabolism may have evolved not within lipid membranes, but in geochemical compartments, such as iron monosulphide bubbles present in hydrothermal environments. This scenario allows the individual emergence of bacteria and archaea from these compartments when the respective lipid biosynthesis pathways evolved.

If the Archaea and Bacteria emerged individually, the isoprenoid lipid membranes of the first archaeal cells may have presented an advantage to these cells. This would certainly be the case if these cells were hyperthermophilic, which is supported by phylogenetic analyses of the archaeal domain. Besides molecular phylogeny, predictions on the environment of our planet in the era when life occurred, and biochemical analyses of mutant proteins designed to represent ancestors of present day proteins, suggest that cells evolved as a thermophilic form of life (Di Giulio, 2003a,b; Shimizu et al., 2007; Watanabe et al., 2006; Stetter, 1996). The presence of the stable, isoprenoid membranes may have been the reason why the archaea could, at a later stage in evolution, invade into and adapt to various extreme environments. In this hypothesis, the membranes were not obtained in response to the extreme environments; it was the presence of the isoprenoid

membranes that allowed the archaea to colonize various extreme environments. By contrast, the range of environments in which the bacteria with their ester bonded membranes could thrive, and to which they eventually could adapt, was more limited. The fact that the archaea that thrive in "normal" environments also utilize isoprenoid membranes may simply reflect that these membranes do not pose a disadvantage under these conditions.

4. Conclusion

Every known cellular organism belongs to one of the three domains of life. In many cases distinct organisms occupy similar niches, and as such it is unavoidable that they influence each other, either positively (syntrophy) or negatively (competition, predation). Apart from physiological interactions, also genetic exchange (HGT) has been crucial for the evolution of life. Numerous researchers have proposed a variety of models to explain the early events in the evolution of cellular life, including the divergence of archaea and bacteria. However, we are still far from a solid consensus scenario. The intriguing black-and-white distinction of lipid structure in archaea and bacteria might turn out to be the key in elucidating some more details on this mystery. An integrated approach of bioinformatics, biochemistry and genetics is expected to identify many of the missing links in the biochemical pathways. Moreover, in the course of future synthetic biology projects, it will be extremely challenging to engineer a bacterium with archaeal membrane lipids or vice versa. This will allow us to identify unknown biological functions or mechanisms that are linked to the use of ester- or ether-based lipids or their stereochemistry.

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