Opinion TRENDS in Biochemical Sciences Vol.29 No.9 September 2004

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Ancestral lipid biosynthesis and early membrane evolution

Juli Peretó[1,2], Purificación López-García[1] and David Moreira[1]

[1]Unité d'Ecologie, Systématique et Evolution, UMR CNRS 8079, Université Paris-Sud, 91405 Orsay Cedex, France
[2]Institut Cavanilles de Biodiversitat i Biologia Evolutiva i Departament de Bioquímica i Biologia Molecular, Universitat de València, 46100 Burjassot, Spain

Archaea possess unique membrane phospholipids that generally comprise isoprenoid ethers built on *sn*-glycerol-1-phosphate (G1P). By contrast, bacterial and eukaryal membrane phospholipids are fatty acid esters linked to *sn*-glycerol-3-phosphate (G3P). The two key dehydrogenase enzymes that produce G1P and G3P, G1PDH and G3PDH, respectively, are not homologous. Various models propose that these enzymes originated during the speciation of the two prokaryotic domains, and the nature (and even the very existence) of lipid membranes in the last universal common ancestor (cenancestor) is subject to debate. G1PDH and G3PDH belong to two separate superfamilies that are universally distributed, suggesting that members of both superfamilies existed in the cenancestor. Furthermore, archaea possess homologues to known bacterial genes involved in fatty acid metabolism and synthesize fatty acid phospholipids. The cenancestor seems likely to have been endowed with membrane lipids whose synthesis was enzymatic but probably non-stereospecific.

The origin of cell membranes is a major unresolved issue of evolution. Contemporary cells are bounded by membranes that are essentially made out of phospholipid bilayers (or monolayers in many thermophilic prokaryotes) into which different proteins are embedded. Phospholipids are AMPHIPATIC (see Glossary) molecules composed of a glycerol phosphate (GP) moiety and two lateral hydrocarbon chains (usually C_{14}–C_{20}). Despite this overall chemical composition, however, phospholipids present in archaea and bacteria differ radically.

In bacteria, as well as in eukaryotes, whose lipids are bacterial-like, G3P is bound to fatty acids by ester linkages. In archaea, by contrast, three important features distinguish membrane lipids in the most idiosyncratic way [1,2]. First, the phospholipid backbone is built on the opposite glycerol stereoisomer, G1P. Second, the hydrophobic side chains are generally isoprenoid derivatives instead of fatty acids. Third, isoprenoid chains are always bound to G1P by ether linkages. Of these three features, the most distinctive is the STEREOCHEMISTRY of GP, because ether-linked lipids are present both in eukaryotes (sometimes they account for up to 25% of the total lipids in animals), where they have various functions [3], and in a few thermophilic bacteria [4], and fatty acids have been recently found in archaea [5]. So far, there is no known exception to the G1P stereochemistry in archaea and the G3P stereochemistry in bacteria and eukaryotes.

The key dehydrogenase enzymes that synthesize G1P and G3P are the archaeal G1PDH and the bacterial/eukaryotic G3PDH enzymes, respectively (Box 1). The genes encoding these two enzymes are not homologous, and the proteins do not show structural similarity other than a small conserved NAD^{+}-binding motif [6]. Both enzymes clearly belong to two separate families, which raises interesting questions about the origin of membrane lipids in bacteria and archaea, and about the nature of the cell envelope in the last universal common ancestor or CENANCESTOR. Which stereoisomer came first: the archaeal-type G1P, the bacterial-type G3P, or both? How did HOMOCHIRAL membranes evolve? What type of lipid stereochemistry was present in the cenancestor? Did the cenancestor already possess phospholipid cell membranes?

Various hypotheses have been recently advanced to elucidate the emergence of phospholipid stereochemistry; some models even question whether the cenancestor had membrane lipids at all. Here, we briefly review current models put forward to explain how archaeal and bacterial lipids arose, and we comment on concurrent pieces of evidence that lend support to the idea that the cenancestor possessed lipid membranes. We propose that the two stereospecific activities, G1PDH and G3PDH, evolved by ENZYME RECRUITMENT from pre-existing enzymatic superfamilies that were present in the cenancestor.

Glossary

Amphipatic: Possessing a hydrophobic (water-repelling) and a hydrophilic (water-soluble) region.
Cenancestor: The most recent common ancestor of the taxa under consideration.
Chiral: A molecule is chiral (i.e. it has chirality) if its image in a plane mirror cannot be brought to coincide with itself.
Enantiomers: Synonymous with stereoisomers (see 'stereochemistry').
Enzyme recruitment: Development of a new enzymatic activity from a functionally related enzyme derived from gene duplication.
Heterochiral: Structures that are mixtures of different enantiomers.
Homochiral: Structures that are made out of the same enantiomer.
Racemic: Equimolecular mixtures of two enantiomers.
Stereochemistry: The spatial organization of molecules. Stereoisomers are mirror image forms of two molecules with the same molecular and structural formula.

Corresponding author: David Moreira (david.moreira@ese.u-psud.fr).
Available online 21 July 2004

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Box 1. Stereospecific biosynthesis of glycerol phosphate

Both glycerol phosphate isomers, *sn*-glycerol-1-phosphate (G1P) and *sn*-glycerol-3-phosphate (G3P), are derivatives of dihydroxyacetone-phosphate (DHAP), a glycolytic intermediate that can be obtained from different sources including exogenous glycerol (Figure I). In archaea, the NADH-dependent reduction of DHAP by G1P-dehydrogenase (encoded by *egsA*) yields G1P, the backbone of archaeal phospholipids. DHAP can be obtained from G3P by means of the triosephosphate isomerase (*tpiA*). Some heterotrophic archaea synthesize DHAP from glycerol via glycerol kinase (*glpK*) and a flavin-dependent G3P-dehydrogenase (*glp*).

In bacteria, the NADPH-dependent reduction of DHAP catalysed by the product of the gene *gpsA* is responsible of the stereospecific synthesis of G3P, the backbone of bacterial phospholipids. Bacteria can also generate DHAP from glycerol by using glycerol dehydrogenase (*gldA*) and dihydroxyacetone kinase (*dak*). In eukaryotes, the concerted activity of the cytosolic NAD^+-dependent dehydrogenase (*gpd*, belonging to the same gene family as *gps*) and the flavin-dependent mitochondrial dehydrogenase (*glp*) enables the transport of reducing equivalents from the cytosol to the mitochondrial electron chain – a process known as the 'GP shuttle'.

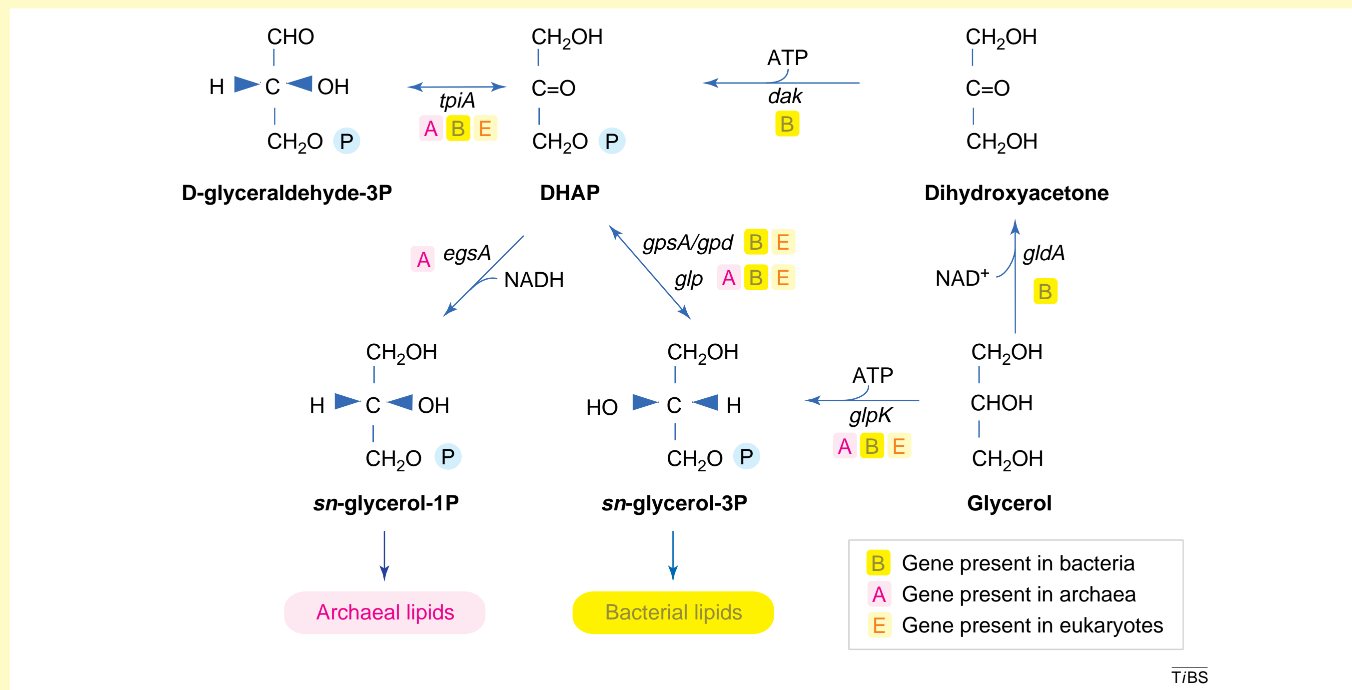

Figure I. Mechanisms of glycerol phosphate stereospecific biosynthesis in archaea and bacteria. (DHAP, dihydroxyacetone-phosphate).

Models of the origin of bacterial and archaeal membranes

Three different hypotheses have been recently proposed to explain the origin of G1P and G3P homochiral membranes in archaea and bacteria (Figure 1). First, Koga *et al.* [7] have proposed that GP was synthesized chemically in a non-chiral manner on pyrite surfaces [7], which would have been the first acellular metabolists, as proposed by Wächtershäuser [8]. A RACEMIC mixture of G1P and G3P could have accumulated in this way and used in phospholipid synthesis during the early emergence of cellular compartments. After this initial primitive racemic stage, archaea and bacteria would have acquired their respective homochiral membranes by the independent invention of G1PDH and G3PDH for catalysing the reduction of dihydroxyacetone phosphate (DHAP) to the opposite ENANTIOMERS G1P and G3P, respectively (Box 1). Later in evolution, eukaryotes, which would derive from an archaeal–bacterial symbiosis, would inherit their membrane lipids from bacteria [7].

Second, Martin and Russell have proposed that, before the advent of fully fledged prokaryotic cells, an early stage of chemical evolution took place in a network of geochemical three-dimensional cell-like compartments rather than on a bidimensional surface [9]. Their proposal is that iron monosulphide 'bubbles' of hydrothermal origin might have constituted the earliest metabolic compartments before the emergence of cells [10,11]. In their model, a complex, geochemically driven, prebiotic chemistry developed, leading to different evolutionary stages (the 'RNA', 'RNA–protein' and 'DNA' eras) that included, successively, the invention of key steps such as ribonucleotide synthesis, the peptidyl transferase reaction and the reduction of ribonucleotides to deoxyribonucleotides.

The universal cenancestor, although endowed with all the biochemical machinery to make DNA, RNA and proteins and in possession of a chemoautotrophic metabolism, was still a non-free-living entity in Martin and Russell's model [9]. Its cell-like compartments were surrounded by walls made out of iron monosulphide and peptides that interconnected these walls, forming a network. The absence of lipid membranes would explain why the archaeal and bacterial lipids are so different. The archaeal and bacterial biosynthetic pathways for membrane lipids and cell wall components would have been invented independently from this mineral-bounded ancestor, leading to both the emancipation of free-living cells from the mineral compartments by the acquisition of a

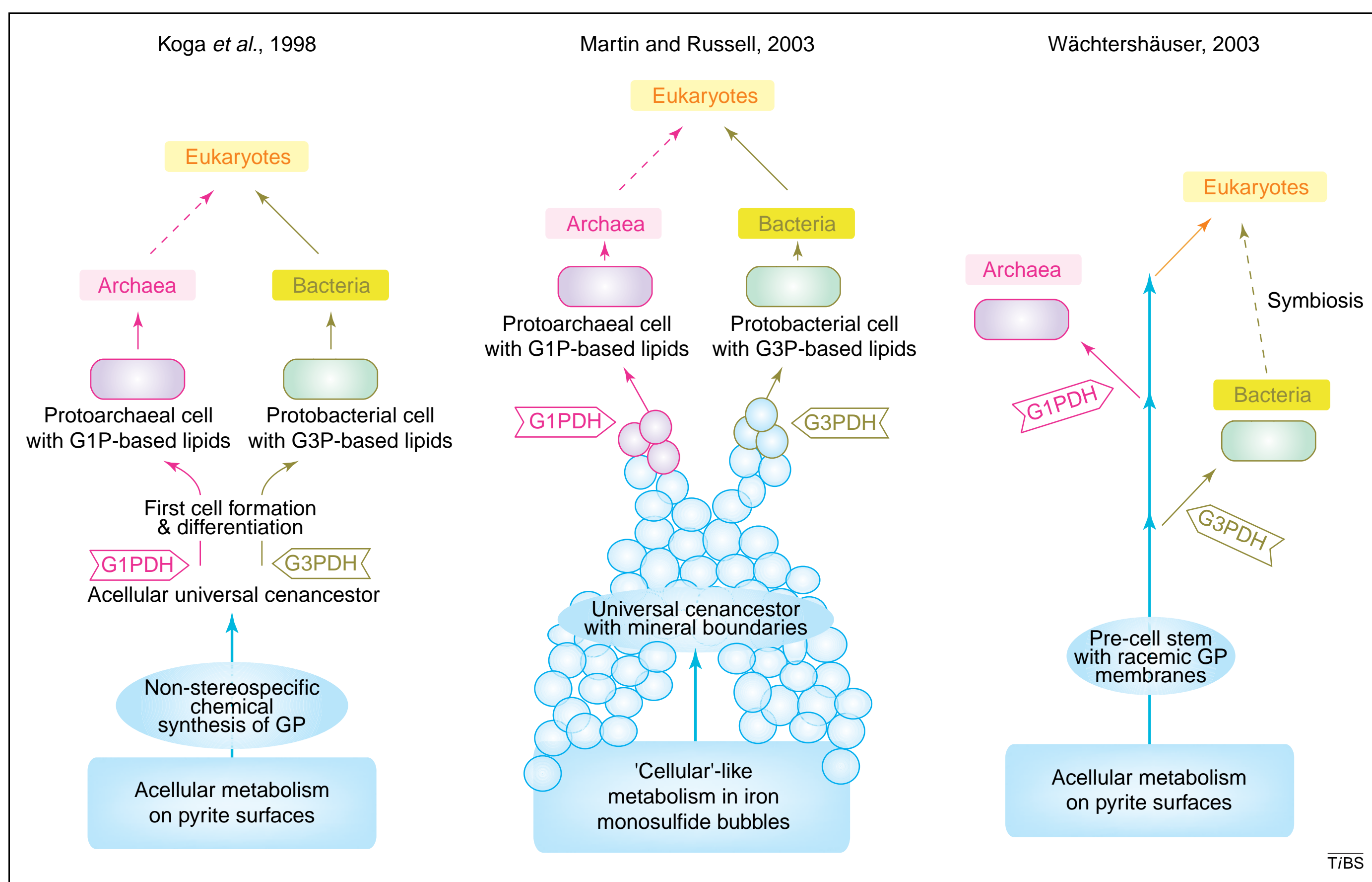

Figure 1. Models of the origin of archaeal and bacterial stereospecific membrane lipids. Shown are three recent schemes proposed by Koga *et al.* [7] (left), Martin and Russell [8] (middle) and Wächtershäuser [8] (right). Abbreviations: GP, glycerol phosphate; G1P, *sn*-glycerol-1-phosphate; G3P,*sn*-glycerol-3-phosphate; G1PDH, G1P-dehydrogenase; G3PDH, G3P-dehydrogenase.

lipid membrane and the emergence of the two distinct prokaryotic domains. As a result of an archaeal–bacterial symbiosis, eukaryotes would subsequently acquire their lipids from bacteria [9] (Figure 1).

Third, Wächtershäuser [12] has formulated a model that bears some resemblance to that proposed by Koga *et al.* [7] and incorporates previous ideas of Kandler's [13–15] 'pre-cell theory' to explain the emergence of the three domains of life. According to this theory, at some point during the early evolution of life, a pre-cell stage existed that was characterized by a population of entities bounded by a stable lipid membrane. This membrane was a bilayer of racemate chiral lipids synthesized inside the pre-cells by a series of non-enzymatic catalysts or by primitive non-stereospecific enzymes.

Little by little, and due to strictly physico-chemical forces, the pre-cell populations could have segregated in subpopulations enriched in either enantiomeric phospholipid. Subsequently, the higher stability of homochiral over racemic HETEROCHIRAL membranes would have shown a strong selective advantage, favouring the emergence of enzymes for the stereospecific synthesis of the GP backbone. The independent origin of biosynthetic enzymes for G1P and G3P would have led to the divergence of stable cellular lineages of one or the other CHIRAL type. In this way, bacteria would have diverged first, followed by archaea. Eukaryotes would have diverged later from a stem of ancestral pre-cells endowed with racemic lipid membranes after they acquired the G3P-specific biosynthetic pathway from bacterial symbionts [12] (Figure 1).

Although the three mentioned hypotheses highlight more or less explicitly the evolutionary importance of the emergence of the two key enzymes for the stereospecific biosynthesis of GP, none of them explains how they evolved. Thus, the origin of the phospholipid backbone chirality in archaea and bacteria remains enigmatic.

Genes for stereospecific synthesis of the phospholipid backbone

As we accumulate more complete genome sequences, particularly for prokaryotic species, it becomes possible to look for more- or less-distant homologues to our favourite gene (or gene family) in an attempt to infer evolutionary schemes explaining the origin of this gene according to its distribution and phylogeny. In this way, updated phylogenetic analyses for the genes encoding G1PDH and G3PDH and their homologues should help to elucidate whether the two genes could be far-distant, hardly distinguishable homologues and could thus share any kind of common ancestry, or whether, being unrelated, they had a common origin with other protein families that could reveal something about their origin and evolution.

The first sequence of the gene encoding G1PDH (*egsA*), the key enzyme for the synthesis of G1P in archaea, was obtained from *Methanothermobacter thermautotrophicus* in 1998 [7]. This gene was very different from the known

Figure 2. Phylogenetic trees of *sn*-glycerol-1-phosphate dehydrogenase (G1PDH), *sn*-glycerol-3-phosphate dehydrogenase (G3PDH) and their respective homologous protein families. Archaea are shown in pink, bacteria in green and eukaryotes in orange. Only a few representative eukaryotic sequences are shown for the alcohol dehydrogenase (ADH) and dehydroquinate synthase (DHQS) families. The trees were constructed by a Bayesian search [39] of one million generations by using a JTT model with a Γ law (eight rate categories). Ten thousand trees were sampled (1500 trees were discarded as 'burnin'). Numbers at nodes indicate posterior probabilities. The scale bar corresponds to the number of substitutions per 100 sites. Abbreviations: GDH, glycerol dehydrogenase; HACDH, 3-hydroxyacyl-CoA dehydrogenase; UDPGDH, UDP-glucose 6-dehydrogenase. EC numbers and gene names are given.

bacterial G3PDH gene (*gpsA*) [7]. Thus, G1PDH and G3PDH seemed to derive from different ancestral enzymes, despite their coincidences in substrate, coenzyme and class of reaction. Daiyasu *et al.* [6] reinforced this conclusion in a study of the tertiary structure of G1PDH; this enzyme shows structural similarity to three other protein families that also share amino acid sequence similarity. These include glycerol dehydrogenase (GDH), alcohol dehydrogenase (ADH) and 3-dehydroquinate synthase (DHQS).

Notably, the G1PDH family is integrated not only by archaeal sequences, but also by a few bacterial members whose function is unknown (Figure 2). These bacterial sequences include several Gram-positive species and the hyperthermophile *Thermotoga maritima*. This patchy distribution of G1PDH in bacteria, in sharp contrast to its ubiquity in all archaea, resembles the typical situation found in many genes that have been affected by horizontal gene transfer (HGT) [16,17]. In contrast to G1PDH, the other families seem to be typically bacterial, with only a few interspersed archaeal sequences.

No eukaryotic G1PDH sequences are known, but eukaryotes are well represented in the ADH and DHQS families (Figure 2). By contrast, GDH, which catalyses the first step in the metabolic incorporation of exogenous glycerol in

bacteria, has a homologue only in *Schizosaccharomyces pombe*, suggesting that this species acquired the gene by HGT. Although independent examples of HGT are easy to identify in the tree, they do not mask the phylogenetic origin of each family. Thus, the GDH family seems to be bacterial and the G1PDH archaeal. The ADH and DHQS families are widespread in bacteria and eukaryotes, but have only a few members in archaea, most probably from HGT.

The four dehydrogenase families show a great functional resemblance that includes the oxidoreduction of NAD^+. This is true even for DHQS (involved in the shikimate pathway for the synthesis of aromatic amino acids), whose functional and structural similarity to the other dehydrogenases was shown only recently [18,19]. These similarities are in agreement with phylogenetic analyses and support a common evolutionary origin [6]. Therefore, the universal cenancestor was probably endowed with at least one dehydrogenase of this superfamily that had the ability to carry out the NAD^+-dependent mechanism shown by all superfamily members today.

Although very distantly related, G3PDH seems to be homologous to two additional dehydrogenase families, the UDP-glucose 6-dehydrogenase (UDPGDH) and 3-hydroxyacyl-CoA dehydrogenase (HACDH) families [20]. Again, this link indicates that these three monophyletic families (Figure 2) belong to a large protein superfamily sharing a NAD^+-dependent oxidoreduction mechanism. G3PDH is ubiquitous in bacteria. It is also detected in the euryarchaeotal species *Archaeoglobus fulgidus* and *M. thermautotrophicus*, although its metabolic function in these archaea is unknown. Its presence in only two archaeal species that do not form a monophyletic group strongly suggests that they acquired the gene by HGT from bacteria in two independent events. A homologue of the bacterial G3PDH is also present in the cytosol of animals and fungi (*gpd*), functioning as part of the 'GP shuttle' (Box 1).

In contrast to G3PDH, the UDPGDH family shows a universal phylogenetic distribution. The metabolic function of this enzyme, which catalyses the twofold NAD^+-dependent oxidation of an alcohol to an acid [21], is related to the synthesis of numerous polymers including animal proteoglycans, plant hemicellulose and pectin, and prokaryotic cell walls and secreted polysaccharides. The presence of D-glucuronic acid as a main component in some archaeal cell walls [14] suggests that members of the UDPGDH family have a metabolic role in archaea. The HACDH family also shows a wide phylogenetic distribution, with remarkable structural and functional diversity, and is very often fused with other proteins to form multifunctional enzymes [22–24].

Thus, similar to G1PDH, G3PDH belongs to a dehydrogenase superfamily [20] with two members (UDPGDH and HACDH) that are universally distributed. This strongly suggests that at least one member of this superfamily was present in the universal cenancestor. In contrast to the good degree of sequence conservation shown by G1PDH and its related dehydrogenases, the sequence similarity found among G3PDH, UDPGDH and HACDH is much more limited. This implies that either the three families diverged earlier than the G1PDH-like dehydrogenases or that they evolved faster.

Enzyme recruitment from ancestral dehydrogenases at the origin of membrane stereochemistry

As discussed above, G1PDH and G3PDH, which define the specific stereochemistry of archaeal and bacterial membrane lipids, respectively, belong to two large dehydrogenase superfamilies with universal phylogenetic distribution. None of the subfamilies of the G1PDH-type is universal, although the overall occurrence of the superfamily is. It therefore seems that none of the G1PDH-related subfamilies was present in the cenancestor, but rather the cenancestor possessed an ancestral representative that might have had a nonspecific dehydrogenase activity. For the G3PDH-related subfamilies, by contrast, both UDPGDH and the HACDH are universal, which suggests that members of these two subfamilies were present in the cenancestor, although their precise function at that time is unknown.

Contemporary G1PDH and G3PDH enzymes with their present stereospecificity probably evolved by enzyme recruitment from those ancestral superfamilies. On the one hand, it is tempting to speculate that the archaeal G1PDH enzyme derived from a catabolic enzyme, such as GDH, by gene duplication and functional divergence. This divergence would have been followed by the loss of the original catabolic copy in many organisms because, whereas GDH still has a central role in bacteria growing in glycerol as a carbon source, heterotrophic archaea rely on a different pathway (glycerol kinase and a flavin-dependent G3PDH; Box 1) to incorporate glycerol [25]. On the other hand, we can easily imagine a parallel situation for the origin of the idiosyncratic bacterial G3PDH enzyme, although it could have also emerged by the recruitment of either of its two related universal families: namely, the UDPGDH family involved in cell wall component synthesis or the HACDH family that participates in the catabolism of diverse acyl-coenzyme A (CoA) compounds.

The genes required to evolve the G1PDH and G3PDH activities were already present in the cenancestor. Therefore, this ancestor might have developed the capacity to synthesize both G1P and G3P backbones, and its membrane might have been heterochiral. This possibility would be in agreement with the type of ancestral membrane proposed by Wächtershäuser [12], who postulated that membrane lipids might have been formed either by the action of inorganic transition metal catalysts or by nonspecific enzymes. The gene distribution and phylogeny of these enzymes seem, however, to be more consistent with the existence of non-stereospecific GP biosynthesis by enzymes belonging to two different superfamilies.

Three main possibilities could explain the evolution of these gene families and the concurrent prokaryotic divergence from a universal cenancestor endowed with dehydrogenases belonging to those superfamilies. First, the enzyme leading to the stereospecific synthesis of only G1P or G3P had already evolved in the cenancestor, which would imply that it had a homochiral membrane. The subsequent recruitment of the second stereospecific enzyme in a subpopulation could have then led to a selective advantage and to the speciation of either archaea

or bacteria with the loss of the ancestral enzyme in that subpopulation.

Second, both stereospecific activities had already evolved in the universal ancestor, which would imply that it had a heterochiral membrane (racemic or not). Archaeal and bacterial speciation would have paralleled the take over of each one of the stereospecific enzymes in the two lineages owing to the presumed increased stability of homochiral membranes.

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Third, none of the stereospecific activities were present in the ancestor, but it was able to synthesize both types of GP backbone nonspecifically. In this scheme, which we favour, evolution of the two specific G1PDH and G3PDH activities by recruitment of dehydrogenases already present in the universal cenancestor would have been one of the triggering factors determining the speciation of archaea and bacteria (Figure 3). Our model conforms and extends Wächtershäuser's hypothesis [12] by providing the genetic background from which the two enzymatic activities, G1PDH and G3PDH, evolved. It differs from that proposed by Koga *et al.* [7], however, in the explicit postulation of a universal cenancestor of cellular nature (compare Figures 1 and 3), which is also incompatible with the mineral-bounded cell ancestor proposed by Martin and Russell [9] (see below).

Did the universal cenancestor possess lipid membranes?

Because of the fundamental differences existing between archaeal and bacterial GP lipids, Martin and Russell [9] have proposed that the universal cenancestor lacked membrane lipids. G1PDH and G3PDH might, or might not, have existed at that time, although, as we have discussed above, related members had already evolved that could have been capable of non-stereospecific GP synthesis. In addition, a few genes encoding enzymes participating in isoprenoid biosynthesis also seem to be ancestral, although they do not define a complete pathway [26]. *Per se*, these elements do not constitute compelling evidence for the existence of phospholipid membranes in the cenancestor. A look into the ancestral gene content, however, provides two chief arguments that contradict Martin and Russell's [9] idea that the ancestor possessed mineral membranes. Indeed, several membrane-related genes that are broadly distributed in bacteria and archaea today can be traced back to the cenancestor.

First, the existence of universally conserved membrane proteins, such as V- and F-ATPases and the signal recognition particle, convincingly advocates an ancestor bounded by lipid membranes [27,28]. Ancestral operons found in archaea and bacteria include the genes encoding secE and secY – two essential subunits of a membrane-bound protein translocase [29].

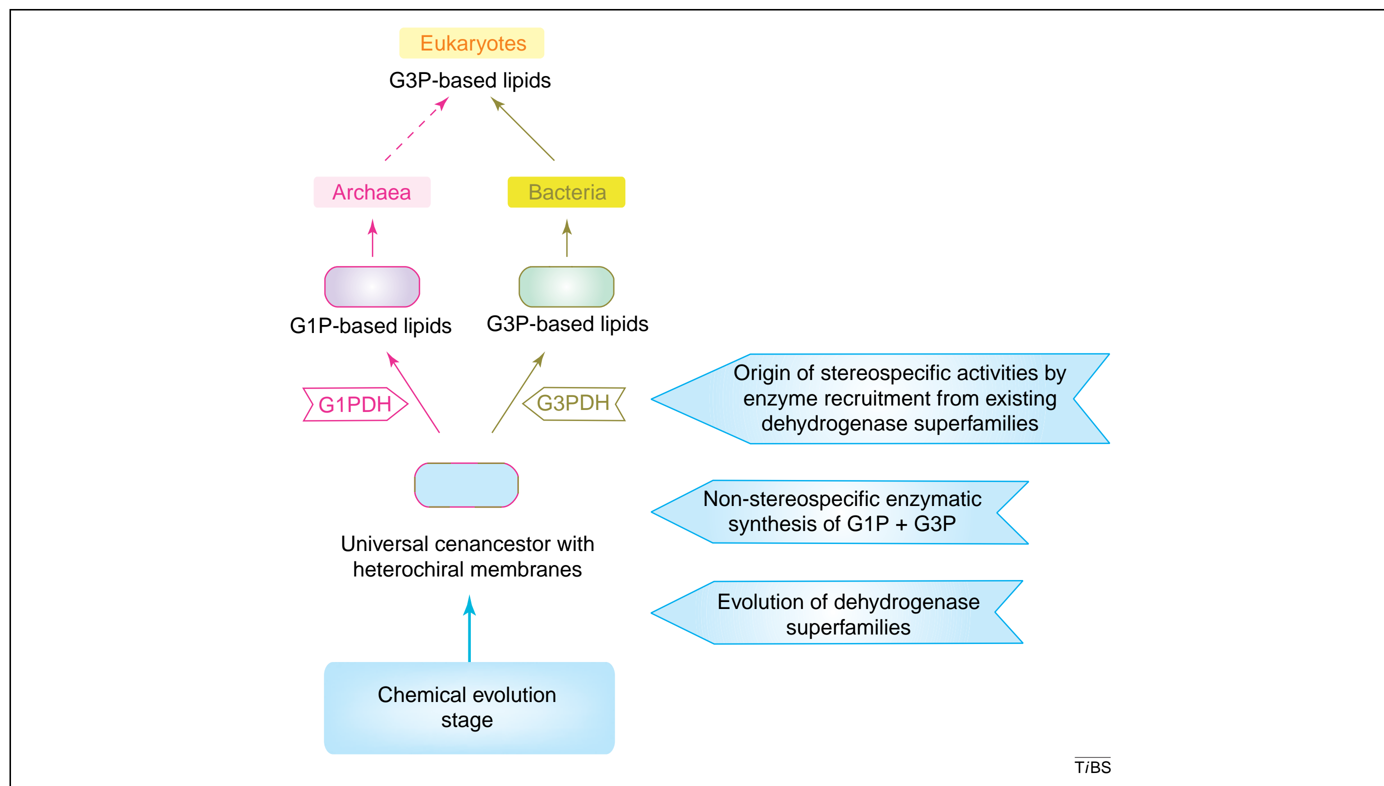

Figure 3. Favoured model of the evolution of lipid stereochemistry. Abbreviations: G1P, *sn*-glycerol-1-phosphate; G3P,*sn*-glycerol-3-phosphate; G1PDH, G1P-dehydrogenase; G3PDH, G3P-dehydrogenase.

Second, in contrast to the common view, fatty acid phospholipids are widespread in archaea. In *Methanothermus fervidus*, phospholipid fatty acids can account for up to 89% of total phospholipids; in other words, this archaeon contains up to 2.2 μmol of phospholipid fatty acids per gram of freeze-dried cells [5]. Typical bacterial species contain roughly 20–50 μmol of phospholipid fatty acids per gram of freeze-dried cells; therefore, the phospholipid fatty acid content of *M. fervidus* represents about 4–10% of that found in bacteria [5]. Furthermore, genes involved in fatty acid biosynthesis are found in the complete genome sequences of archaeal species. For example, they define the largest functional gene family in *Sulfolobus solfataricus* [30]. With the exception of a few genes (the acyl carrier protein, ACP, and its associated ACP-synthase, malonyl-CoA:ACP transacylase and 3-ketoacyl-ACP synthase II), all genes known to be involved in the bacterial fatty acid biosynthesis pathway [31] have more- or less-closely related homologues in archaea (Figure 4 and Supplementary Data).

Because archaea contain fatty acids and show an almost complete bacterial-like anabolic gene complement, those few functions must be performed by non-homologous proteins that remain to be identified. This situation is not exclusive to archaea, because several bacterial species also show 'missing' genes in the lipid biosynthesis pathway whose functions have been replaced by non-homologous genes (Refs [31,32] and Supplementary Data). Not only does the biosynthetic pathway exist in archaea, but also a homologous complete gene set of the bacterial β-oxidation pathway is found in several species (Figure 4 and Supplementary Data). Taken together, these data strongly support the idea that both the anabolic and the catabolic pathways for fatty acids are ancestral.

The parallel existence of both biosynthetic pathways for fatty acids and dehydrogenase families that were probably able to synthesize GP indicates that the universal cenancestor might have possessed the gene complement necessary to synthesize membrane lipids based on glycerol and fatty acids.

Perspectives

The evolutionary genesis of lipid membranes is still a mystery, and lipids are often omitted in early evolutionary models. A few authors have discussed the origin and evolution of lipids and their metabolic synthesis [8,33,34] but, in general, their propositions are theoretical bottom-up models. In any case, the presence of amphiphilic components, including long-chain acids and alcohols, in meteorites attests for their abiotic synthesis, which indicates that lipids might have been formed under prebiotic conditions before, and perhaps fostering, the emergence of cells [35]. By no means does this imply, however, that mineral surfaces did not have an essential role in very early steps of evolution.

As complete genome sequences are continuing to amass, the possibility to look for genes involved in lipid synthesis and to reconstruct the evolution of metabolic pathways is becoming a reality. At some point, this top-down approach should converge with theoretical propositions and, eventually, should corroborate or discard some

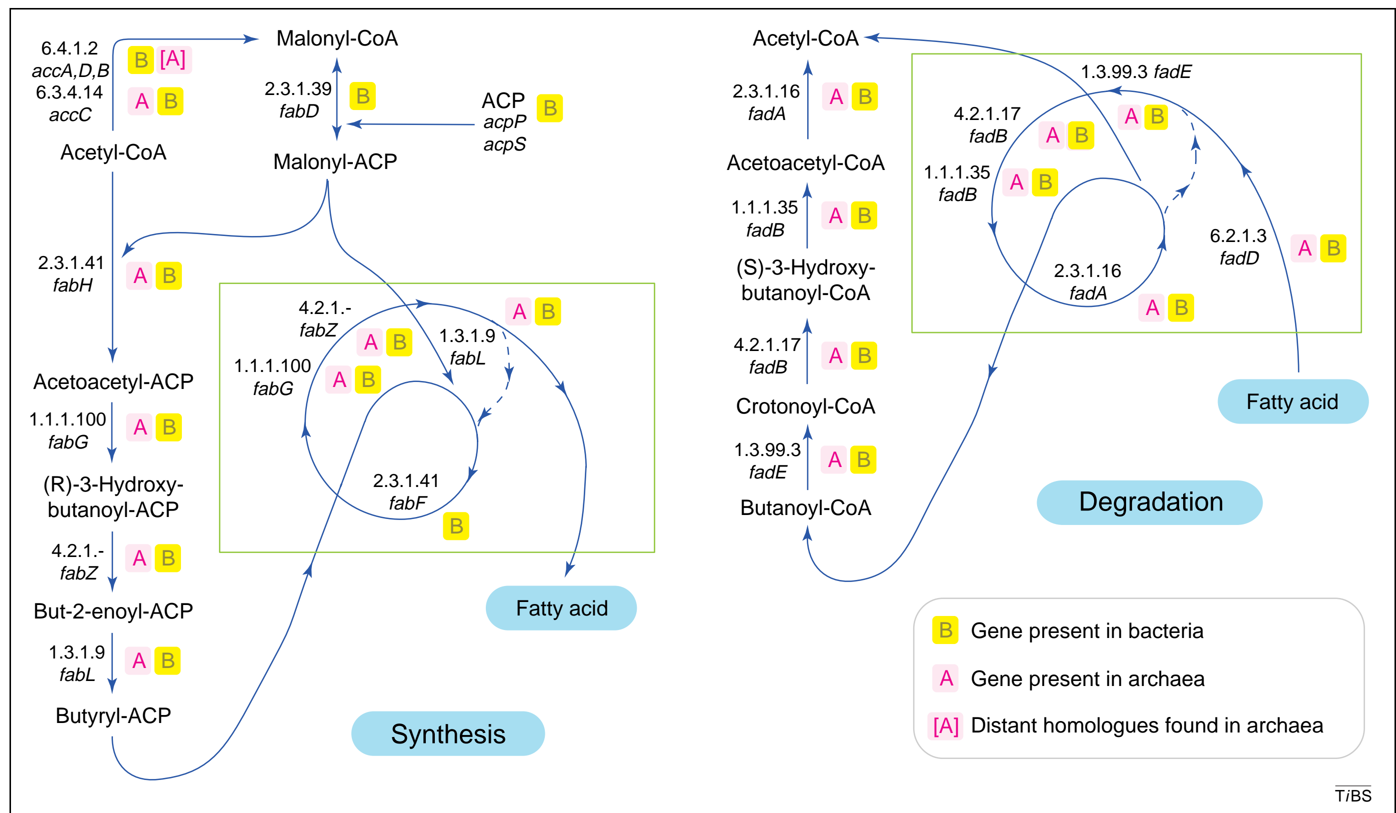

Figure 4. Pathways of fatty acid synthesis and β-oxidation in bacteria and archaea. Homologues of fatty acid metabolic genes were identified by BLAST and PSI-BLAST [40], starting from the Kyoto Encyclopaedia of Genes and Genomes (KEGG metabolic pathway database, http://www.genome.ad.jp/kegg/). For each catalytic step, the enzyme EC number and gene name (*Escherichia coli* nomenclature, except for *fabL*, which follows that of *Bacillus subtilis*) are given. Boxed regions correspond to elongation and β-oxidation cycles. Abbreviations: ACP, acyl-carrier protein; CoA, coenzyme A.

of them. Nevertheless, this task is still hampered by a lack of information. For example, there are still missing enzymes or proteins whose genes have not yet been identified (e.g. the gene corresponding to 3-ketoacyl-ACP synthase II or the archaeal ACP equivalent). In addition, much biochemical work is needed to prove suspected enzymatic specificities and even to verify that homochiral membranes are indeed more stable than heterochiral ones.

From the data that are currently available, we conceive the universal cenancestor to be a complex organism that had already evolved most of the essential biochemical pathways for energy production and for the biosynthesis of proteins, lipids and nucleic acids, although in many instances these pathways were probably not very specific or optimized. This situation also seems to be true for the DNA replication machinery, which is very different in archaea and bacteria but shares some common elements [36,37]. This dissimilarity has led some authors to propose that the cenancestor had an elementary pathway for DNA replication that evolved differently in both prokaryotic lineages. Notably, an intimate relationship exists between DNA replication and membrane phospholipids in bacteria, and DNA replication itself might occur at the cell membrane [38]. Not only might DNA replication and the stereospecific synthesis of membranes have paralleled each other in evolution, they might even have coevolved.

Acknowledgements

We acknowledge the constructive criticisms received from two anonymous reviewers. This work was supported by an ATIP grant from the Centre National de la Recherche Scientifique to P.L.G. J.P. enjoyed the hospitality of the Département d'Evolution et Systématique at the Université de Paris-Sud during a sabbatical leave of absence from the Universitat de València and was recipient of a postdoctoral fellowship from Generalitat Valenciana.

Supplementary data

Supplementary data associated with this article can be found at doi:10.1016/j.tibs.2004.07.002

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