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The astrochemical evolutionary traits of phospholipid membrane homochirality

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Abstract

Compartmentalization is a key prerequisite for the evolution of life. Present-day phospholipid membranes exhibit a high level of complexity and species-dependent homochirality, the so-called *lipid divide*. However, it is very likely that less stable yet more dynamic systems, promoting out-of-equilibrium environments, facilitated the evolution of life at its early stages. The composition of the preceding primitive membranes and the evolutionary route towards complexity and homochirality, however, still remain unexplained. Organic-rich carbonaceous chondrites are evidence of the ample diversity of interstellar chemistry, which may have largely enriched the prebiotic milieu on the early Earth. This Review thoroughly evaluates the detections of simple amphiphiles — likely ancestors of membrane phospholipids — in extra-terrestrial samples and analogues, along with potential pathways to form primitive compartments on the primeval Earth. The chiroptical properties of chiral backbones of phospholipids provide a guide for future investigation into the origins of phospholipid membrane homochirality. We highlight a plausible common pathway towards homochirality of lipids, amino acids, and sugars starting from enantioenriched monomers. Finally, given their high recalcitrance and resistance to degradation, lipids are one of the best candidate biomarkers in exobiology.

Key words: *chirality, membrane, lipids, amphiphiles, compartments, biomarkers, circularly polarized light, extant and extinct extra-terrestrial life*

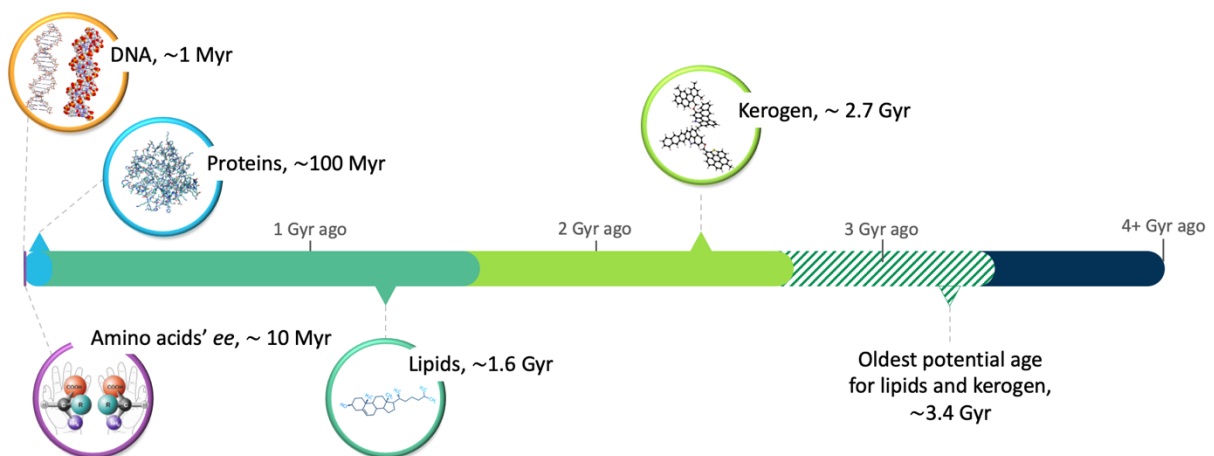
I. Introduction

The origin of biological membranes is a complex and intriguing topic closely tied to the broader question of the origin of life itself. Given the wide diversity of lipids, the ease with which they self-assemble, their ability to compartmentalise along with the potential of autocatalytic activity, lipids would have been pivotal at the dawn of self-organization and early metabolism, both necessary for life to arise and develop.¹ While numerous experiments have explored different challenges on how life originated on Earth, there is a lack of experimental studies addressing the dichotomy of biological membrane structure and their inherent chirality. Finding an answer to this question is crucial not only for understanding life on Earth but also for detecting life, whether extant or extinct, in space.

Carbonaceous chondrites, rich in chemical compounds composed of C, H, N, O, P, and/or S,² are evidence of the complexity of interstellar chemistry. This rich chemistry occurs in denser

44 regions of the interstellar medium, so-called molecular clouds—nurseries of stars and planets—
 45 where interstellar dust, water ices, and molecules are detected.^{3–5} Interstellar dust grains are
 46 primarily composed of carbonaceous and silicate material of varying size between 1 nm and
 47 1 μm .⁶ Making up only about 1% of the total mass of the interstellar medium, dust grains are
 48 the cradle for the synthesis of complex organic molecules (COMs) in space that cannot be
 49 produced by gas-phase chemistry. Most complex organics, including prebiotically relevant
 50 species, are proposed to form through radical chemistry in icy mantles mixed with porous
 51 grains.^{3,7} During planetary system formation, the solid cloud material containing embedded
 52 COMs becomes incorporated into various celestial bodies, including planetesimals, comets,
 53 and asteroids.³ Thence, the exogenous delivery may have largely contributed to the pool of
 54 organic molecules on the early Earth.⁸ However, it also implies that any monomeric building
 55 block of life is very likely to be present in extra-terrestrial bodies, which hinders the
 56 identification of biosignatures of putative life in space. Any specific biomolecule detected in
 57 space therefore cannot be considered a biosignature *per se*. A recent review by Glavin et al.⁹
 58 distinguished the following attributes: (1) *chiral asymmetry*, (2) *light isotopic composition*,
 59 and (3) *strong structural isomer preference*, the combination of which may provide a strong
 60 hint for the presence of past extra-terrestrial life. Nevertheless, since abiogenesis was an
 61 evolutionary process rather than a one-off event, unambiguous classification of signatures
 62 between biotic or abiotic appears even more intricate.

63



64

65 **Fig. 1 Schematic timeline of the geological longevity of major molecular biosignatures.** The timeline shows the
 66 oldest recovery ages in the geological records. Lipids and kerogen outlast DNA, amino acids' enantiomeric excess
 67 (*ee*) and proteins by more than an order of magnitude, making them the most valuable biosignatures when
 68 searching for past life in space.¹⁰

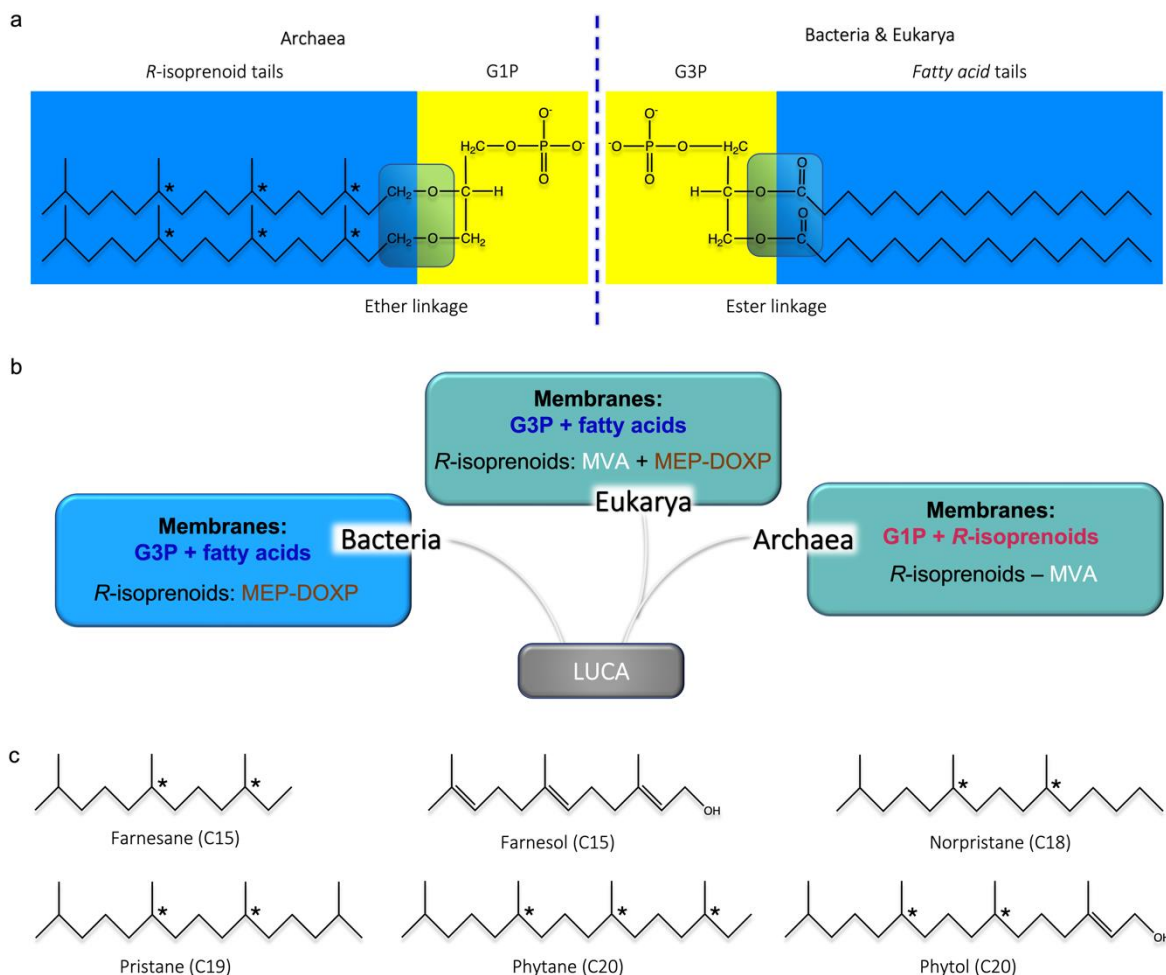
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70 Studying contemporary life forms on Earth has enabled scientists to identify four common
 71 features of life: (1) *nucleic acids*, (2) *proteins*, (3) *membranes* composed of amphiphilic
 72 molecules—lipids, and (4) *biological homochirality*. Lipids exhibit exceptional resistance to
 73 degradation under various environmental conditions, surpassing both DNA and proteins,
 74 along with their monomeric building blocks—sugars and amino acids. (**Fig. 1**).^{10,11} This
 75 characteristic positions lipids as promising biomarkers for ancient life. However, was the

76 molecular machinery of the most primitive organisms the same as we know it from present-
77 day life? This is particularly debatable in the case of membrane lipids which are known to be
78 species specific. While in general bacterial and eukaryal membranes' phospholipids are fatty
79 acid esters linked to *sn*-glycerol-3-phosphate (G3P), archaeal phospholipids are commonly
80 built on the backbone of the opposite handedness, namely *sn*-glycerol-1-phosphate (G1P),
81 and contain ether-linked isoprenoid derivatives (20–40 carbons), which if chiral are present
82 exclusively in the *R*-configuration (**Fig. 2a**).¹² Despite the high level of scientific interest, the
83 membrane composition of the last universal common ancestor (LUCA) and the so-called *lipid-*
84 *divide* remain an unresolved puzzle so far. A growing body of evidence suggests that the first
85 membranes were built of simple amphiphiles rather than complex phospholipids.^{13–15}
86 However, their composition, chirality, and the transition from the primitive membranes to
87 the ones of present-day life is underexplored. This is where the organic content analyses of
88 carbonaceous chondrites, as well as experiments simulating prebiotic species synthesis in
89 interstellar ices and on the early Earth, become of high importance. These can help us to not
90 only elucidate what prebiotic material with potential to form primitive membranes could
91 have been available on the primitive Earth, but also to identify what lipid-like species of
92 abiotic origin can be expected to be found in the search for life on Mars¹⁶ or in space in
93 general. Furthermore, studying the self-assembly and chirality interplay between primitive
94 amphiphiles, complex phospholipids as well as amino acids and sugars, is inescapable for
95 unravelling the origins of species-dependent homochirality of phospholipid membranes.
96 At the emergence or evolution of life, the stereospecificity of amino acid–phospholipid
97 interactions might have guided a pre-selection of life's machineries. Stereosensitivity is a
98 hallmark of ligand–receptor recognition in many biological processes, due to the specific and
99 complementary bonds between the ligand and the receptor binding site. Consequently,
100 enantiospecific interactions are broadly exploited in miscellaneous pharmaceutical concepts.
101 Thorough understanding of interactions of drugs with chiral biological molecules is needed to
102 not only efficiently direct the drug delivery, but also to avoid unwanted side-effects arising
103 from non-target stereospecific interactions.¹⁷ Nanoencapsulation of drugs into vesicles and
104 micelles represents an efficient means for protecting the active compounds throughout the
105 transit, channelling the drug release and decreasing potential side toxicity.¹⁸ The most
106 common building blocks of drug delivery vectors are phospholipids. Analogously to biological
107 membranes, phospholipids' structure critically affects the biophysical properties of liposomes
108 and hence their functionality. The type of headgroups, carbon chain length, branching,
109 symmetry, degree of saturation as well as intra- and intermolecular interactions affect the
110 membrane thickness, fluidity, phase transition temperature, and drug release rate. Generally,
111 the shorter hydrocarbon chain, the higher degree of unsaturation or branching are likely to
112 result in reduced drug retention times due to looser membrane packing.^{19,20} Archaeal
113 phospholipid based liposomes–archaeosomes–have been increasingly investigated for
114 potential application in pharmaceuticals thanks to their robustness against extreme
115 temperatures, pH, oxidative conditions, pressure, etc.^{21,22} Probing enantioselectivity and
116 other properties of chiral amphiphilic membranes such as permeability, stability, etc. has,

117 therefore, important implications not only for elucidating the origin of life, but also in e.g.
 118 designing new drug delivery systems, biosensing, as well as for testing drug effects or
 119 antibiotic resistance and selectivity.²³

120



121
 122 **Fig. 2 The membrane lipid divide.** **a** Characteristic phospholipid composition of archaea vs. bacteria and eukarya.
 123 **b** Scheme of the phylogenetic tree of three clades of life. The chirality of the phospholipid backbones, the
 124 ester/ether linkages, and side chains are, however, not strictly delineated within the three domains. The *R*-
 125 isoprenoids, found ubiquitously in all three domains, are synthesized through distinct enzymatic pathways: the
 126 mevalonate pathway (MVA) and the 2-*C*-methyl-*D*-erythritol 4-phosphate/1-deoxy-*D*-xylulose 5-phosphate
 127 (MEP-DOXP) pathway. **c** The most common branched hydrocarbons. Farnesane (C15) is an ancient analogue of
 128 farnesol, esterifying alcohol in bacterial chlorophylls. Norpristane (C18), pristane (C19), and phytane (C20) were
 129 previously detected in the Murchison meteorite.²⁴ Most chlorophylls contain phytol (C20) side chains (*R*-
 130 configurations), and are considered the main source of pristane (*meso*-configuration after separation) and
 131 phytane on Earth. Another source of pristane (*meso*-configuration after separation) are tocopherols possessing
 132 phytol tails (*R*-configurations).²⁵

133

134 II. Species-specific traits of membrane phospholipids

135 Terrestrial life is based on carbon chemistry operating in aqueous media. While liquid water
 136 appears indispensable for driving prebiotic reactions, the emergence of life was very likely
 137 conditioned by compartmentalization. Membranes not only create protective boundaries to

138 the outer environment sequestering critical cellular biopolymers, they also secure energy
139 gradients, communication, controlled transport of molecules across the membrane, and are
140 involved in metabolism. Such rich functionality stems from their complex organization,²⁶
141 which is a consequence of their protracted evolution. A clear trait of the evolution is a distinct
142 composition of archaeal, versus bacterial and eukaryal membrane phospholipids encoded in
143 their biosynthetic machineries. In general, glycerol-1-phosphate dehydrogenase (G1PDH)
144 catalyses the formation of G1P from dihydroxy acetone phosphate (DHAP) in archaea, while
145 G3PDH and glycerol kinase (GK) catalyse the formation of G3P from DHAP and glycerol,
146 respectively, in bacteria and eukarya.²⁷ This distinction is, however, not mutually exclusive.
147 Fatty acid phospholipid synthesis was identified in certain types of archaea,^{28,29} while some
148 bacteria were found to produce ether-linked lipids^{30,31} and even possess genes for synthetic
149 pathways of archaeal ether-bound isoprenoid lipids.³² Given these interlinks between the two
150 branches of lipid membranes, it was hypothesised that membranes were first of mixed
151 chirality and it was the intrinsic instability of heterochiral membranes which triggered the
152 *lipid divide*.^{33,34} However, it was proven later on that heterochiral membranes can be even
153 more robust than homochiral ones.^{35,36}

154 Interestingly, the branched hydrocarbon chains with the *R*-configuration on their
155 stereocentres are present in all three clades of life (**Fig. 2b,c**), and are found in chlorophylls
156 and tocopherols of cyanobacteria, algae, and higher plants, as well as in steroids, carotenoids,
157 ubiquinones etc.,^{25,37,38} which points towards their common origins. The isoprenoid chains are
158 in present life synthesised from isopentenyl pyrophosphate (IPP) and the isomeric form
159 dimethylallyl pyrophosphate (DMAPP). Two distinct enzymatic pathways lead to these
160 precursors, notably the mevalonic (MVA) pathway named after its intermediate *R*-
161 mevalonate and the 2-C-methyl-D-erythritol 4-phosphate/1-deoxy-D-xylulose-5-phosphate
162 (MEP-DOXP) pathway starting from D-glyceraldehyde-3-phosphate and pyruvate. While the
163 MVA channel is fully responsible for the synthesis of IPP and DMAPP in archaea and non-
164 photosynthetic eukarya, the MEP-DOXP is present in bacteria, algae, and plants (**Fig. 2b**).
165 Interestingly, the three final steps of the MVA synthetic route in archaea and eukarya differ
166 as the three corresponding enzymes in archaea do not share a common sequence homology
167 with those of eukarya³⁸. It is, therefore, likely that the distinct enzymatic pathways for the
168 synthesis of branched hydrocarbons always leading to the *R*-configurations are a result of
169 speciation, while the roots of ubiquitous homochiral isoprenoid chains were already anchored
170 abiotically or in an alternative enzymatic route of a common ancestor.

171 It is widely accepted that archaea and bacteria evolved from the last universal common
172 ancestor. Despite extensive research into the genetic traits and membrane compositions of
173 archaea and bacteria, a clear-cut theory about the composition of LUCA's membrane is still
174 missing. It also remains open whether LUCA's membrane phospholipid synthesis was
175 enzymatic or not, the elucidation of which could help to resolve the question about the origin
176 of the chiral lipid divide.¹⁷ Several hypotheses and reviews have been centred around
177 discussing these research questions and the reader is referred to references ^{12,17,27,34,38,39}.

178

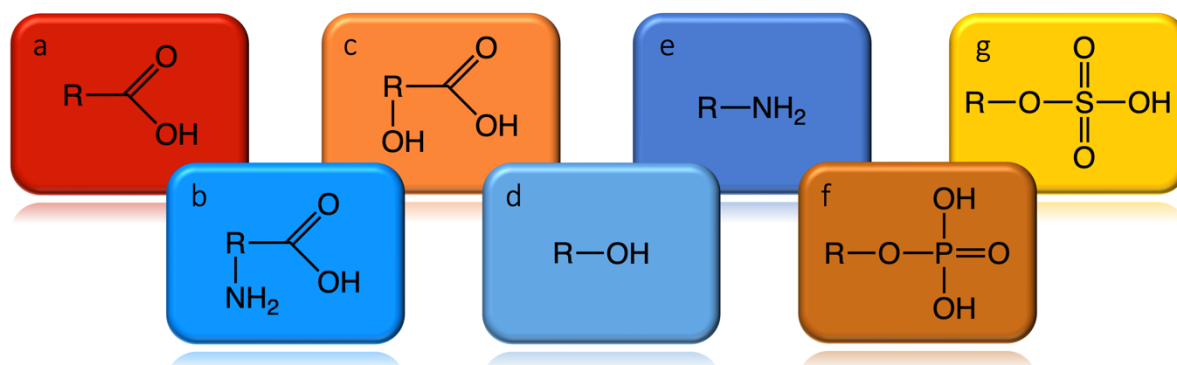
179 **III. Amphiphilic compartments as primitive membranes**

180 Given the distinct membrane phospholipid suits, archaea and bacteria employ different
181 mechanisms to maintain cell integrity upon extreme conditions.³⁸ Such robust membrane
182 morphology is undoubtedly a result of long evolution and is optimal for extant life. However,
183 it is very likely that more dynamic systems facilitating growth, division, recombination, and
184 transfer of molecules aided the emergence and/or evolution of life at the early stages by
185 creating out-of-equilibrium environments. Amphiphilic molecules (**Fig. 3**) were found to
186 spontaneously form vesicles in aqueous environments. This is driven by hydrophilic
187 interactions between polar head groups, which also form hydrogen bonds with water
188 molecules, and van der Waals forces between hydrophobic hydrocarbon tails, which are
189 repelled by water molecules. The formation and stability of vesicles is affected by the type of
190 amphiphiles, their concentration, temperature, pH, and salinity of the solution.⁴⁰⁻⁴⁴ As
191 opposed to double chain phospholipid vesicles, single-chain fatty acid vesicles exhibit
192 enhanced dynamics, mainly thanks to their lower hydrophobicity. This, however, comes at
193 the expense of lower stability especially at low concentrations.⁴⁵ The addition of small
194 amounts of alcohol or glycerol monoesters to fatty acid vesicles was found to enhance their
195 stability, manifested by their self-assembly at lower concentrations, and better resistance to
196 basic pH^{42,46} and elevated temperatures.^{44,46} Prebiotic nucleobases⁴⁷ and amino acids⁴⁸ were
197 shown to bind to and stabilise decanoic acid vesicles in the presence of 10 mM Mg²⁺ salt.
198 Isoprenoids were also found to improve the stability of fatty acid vesicles in the presence of
199 salts, however, about 30-times higher concentrations are necessary to allow membrane
200 formation.⁴⁹ The level of binding and the effect of amino acids or dipeptides on the growth,
201 size, leakiness, and susceptibility to flocculation of prebiotic vesicles further depends on
202 chirality, structure/sequence, or length, thence creating selective environments for
203 Darwinian evolution at the cellular level to start.

204 An alternative scenario for the emergence of the first proto-cellular systems is based on
205 liquid-liquid phase separation of oppositely charged polyelectrolytes in aqueous solution, so-
206 called coacervation. Depending on their charge with respect to the charge of these
207 membrane-less structures, phospholipid liposomes were found to coat coacervates (same
208 charge) or form fibre networks within them (opposite charge).^{50,51} However, given
209 phospholipids' relative structural complexity, the transition from membrane-less coacervates
210 would have been more likely driven by a self-assembly of fatty-acid membranes around them
211 as a potential intermediate step towards present-day phospholipid bilayers.^{52,53}

212 Wet-dry cycling processes representative of night-day cycles on the early Earth have
213 manifested unprecedented efficiency in the emergence of membrane-forming proto-
214 amphiphilic systems, notably polyesters synthesised from hydroxycarboxylic acids,⁵⁴ *N*-acyl
215 amino acids synthesised from amino acids and phospholipids⁵⁵ or amino acids and
216 monoglycerides,⁵⁶ and amino acid-fatty alcohol esters synthesised from homonymous
217 components.¹⁴ Importantly, *N*-acyl amino acids can also serve as a substrate for peptide
218 formation similarly to depsipeptides comprised of amino acids and hydroxycarboxylic acids⁵⁷
219 or thiopeptides formed from amino acids and mercaptoacids.⁵⁸ Therefore, such one-pot

220 reactions from a common set of prebiotically relevant reactants would have spontaneously
221 and simultaneously driven the emergence of two key pre-requisites of life, proto-peptides
222 and primitive membranes. The robustness of proto-amphiphilic vesicles towards extreme pH
223 or the presence of metal ions can be enhanced in the presence of oleic acid or
224 monoglyceride.⁵⁶ Such a scenario of mixed amphiphilic membranes appears prebiotically
225 more plausible considering the diversity of organics delivered by meteorite impacts^{2,59,60} or
226 possibly synthesised on the early Earth.^{61–64}
227



228
229 **Fig. 3 Schematic structures of simple amphiphiles. a** Monocarboxylic acids, **b** amino acids, **c** hydroxycarboxylic
230 acids, **d** alcohols, **e** amines, **f** phosphates, and **g** sulphates.
231

232 Lipids comprise more than 60% of the soluble organic matter in meteorites,⁶⁵ likely enhancing
233 the importance of their contribution to the pool of organics synthesised on the primitive
234 Earth. Microscopic studies by Dworkin et al.⁶⁶ manifested the potential of forming vesicles
235 from self-assembling amphiphilic molecules synthesised upon astrophysical conditions in UV
236 irradiated interstellar/pre-cometary ice analogues composed of H_2O , CH_3OH , NH_3 , and CO , as
237 well as from those found in the extracts of Murchison. Unfortunately, insufficient amount of
238 material prevented compositional analysis in the study. Nevertheless, numerous amphiphiles
239 have already been identified, both in carbonaceous chondrites and simulated interstellar/pre-
240 cometary ices. **Supplementary Tables 1–7** list the detections of aliphatic monocarboxylic
241 acids, hydroxycarboxylic acids, alcohols, amines, and alkyl phosphorus- and sulphur-bearing
242 molecules. An exhaustive review of amino acid detections has been recently reported by
243 Glavin et al.⁹ While a rich variety of straight-chain and branched monocarboxylic acids,
244 ranging from C1 to C20 units, has been identified, only short chain alcohols (**Supplementary**
245 **Table 3**) have been reported so far. The presence and formation pathways of their long-chain
246 counterparts remain to be elucidated. However, the synthesis of long-chain aliphatic
247 hydrocarbons, extending up to C27, under astrophysical conditions has already been
248 manifested by numerous detections in carbonaceous chondrites (**Supplementary Table 7**).
249 Among prebiotically relevant molecules, amino acids have been extensively studied,⁹
250 followed by hydroxycarboxylic acids (**Supplementary Table 2**). In contrast, the identification
251 of amines in simulated interstellar ices (**Supplementary Table 4**), as well as alkyl phosphorus
252 (**Supplementary Table 5**) and sulphur-bearing (**Supplementary Table 6**) compounds, both in
253 extra-terrestrial samples and ice analogues, lags behind.

254 IV. Emergence of phospholipid membrane homochirality

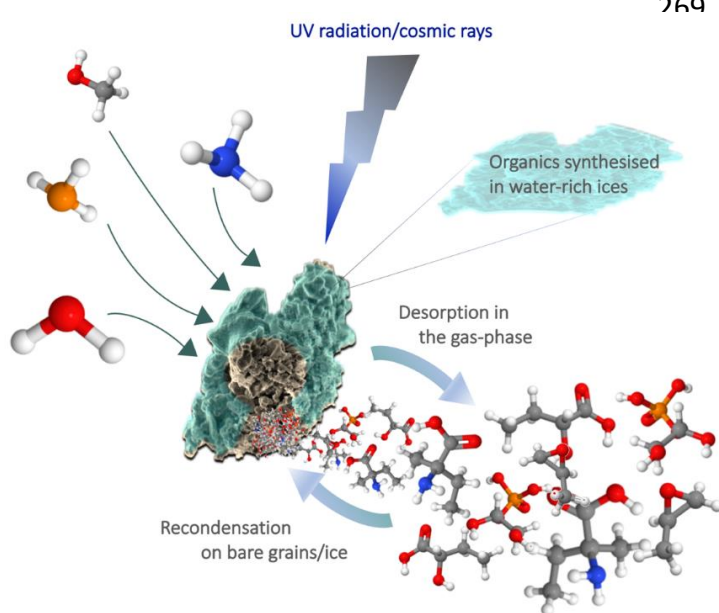
255 Homochirality is often considered a pre-requisite for life based on its critical role for molecular
256 recognition and replication.⁶⁷ Importantly, the presence of enantiomerically enriched species⁹
257 in carbonaceous chondrites points to the astrophysical roots of symmetry breaking. So far,
258 the *astrophysical circularly polarized light (CPL) scenario* provides the most conclusive proof
259 for explaining the origin of chiral bias in space.⁶⁸ Despite significant scientific interest, the
260 species-dependent homochirality of phospholipid membranes has remained unexplained.

261

262 Box 1

263 Astrophysical circularly polarized light scenario

264 Cosmic rays and stellar radiation liven up cold dark interstellar regions transforming simple
265 molecules such as water, methanol, ammonia, methane, carbon monoxide or dioxide, frozen
266 onto interstellar dust particles into complex organic molecules. Throughout their lifetime
267 these molecules can undergo phase transitions as indicated in the figure, while concurrently
268 being subject to further chemical transformations triggered by radiation.^{3,6,69}



269 Circularly polarised light (CPL) in the interstellar medium is a likely trigger of symmetry breaking of chiral organics in space.¹²⁷ Stereospecific interactions of ultraviolet CPL with chiral amino acids or their precursors, known to generate a subtle chiral bias, are broadly discussed to be linked to the L-enantiomeric excesses of amino acids detected in multiple carbonaceous chondrites.⁹ It is plausible that the Solar System remnants containing CPL enantioenriched chiral molecules seeded the early

285 Earth during the late heavy

286 bombardment period, with a systematic chiral imbalance that would have shaped the
287 evolution of life's homochirality.^{60,70} The single chirality of amino acids in proteins (L-) and
288 sugars in nucleic acids (D-) is the basis for the build-up of functional biopolymers necessary
289 for life.

290 The most likely sources of CPL in space, detected several times in the infrared range in
291 different star-forming regions,^{71,72} are reflection nebulae associated with high-mass young
292 stellar objects.⁷³ Modelling of dichroic extinction or scattering of light on magnetically aligned
293 non-spherical dust particles has proven the potential to generate circular polarization.^{74,75} It
294 is assumed that our Sun was formed alongside a heavier star which might have acted as a
295 source of CPL for asymmetric photochemistry during the early stages of protoplanetary disk
296 evolution. The peripheral regions of the protoplanetary disk would have received the highest
297 flux of external UV CPL, while being well shielded from the unpolarized UV radiation of the

298 young Sun. Mixing and diffusion of the dust within the disk would have secured exposure of
299 a greater amount of material to chiral photons eliciting more asymmetric interactions, while
300 shielding the already CPL-enantioenriched species from the destruction due to UV
301 overexposure.⁷³ Our recent study on propylene oxide, the first chiral molecule detected in
302 space, has indicated that our presolar nebula would have likely been irradiated by left-handed
303 CPL.⁷⁶

304 The potential of UV CPL in generating chiral enrichment to amino acids has been
305 experimentally confirmed in two types of simulation experiments. The analysis of room-
306 temperature residues of interstellar ice analogues, prepared from a mixture of H₂O, CH₃OH
307 and NH₃ cooled down to 80 K and irradiated by monochromatic UV circularly polarized light,
308 demonstrated the formation of a number of chiral amino acids with enantiomeric
309 enrichments of up to 2.5%.^{73,77} Irradiation of racemic amino acids by monochromatic CPL in
310 aqueous solution,^{78,79} approximating water-rich solvation shell in interstellar ices, as well as
311 in solid phase thin films,^{80–82} mimicking molecules condensed on bare interstellar grains,
312 confirmed the asymmetric photolysis reaching up to about 5% enantioenrichment of the
313 remaining material. Further investigations of CPL interactions with other chiral organics and
314 deeper elucidation of the circular polarisation of stellar radiation will hone our understanding
315 of the conditions of the astrophysical circularly polarized light scenario and its implications
316 for the origin and evolution of biological homochirality.

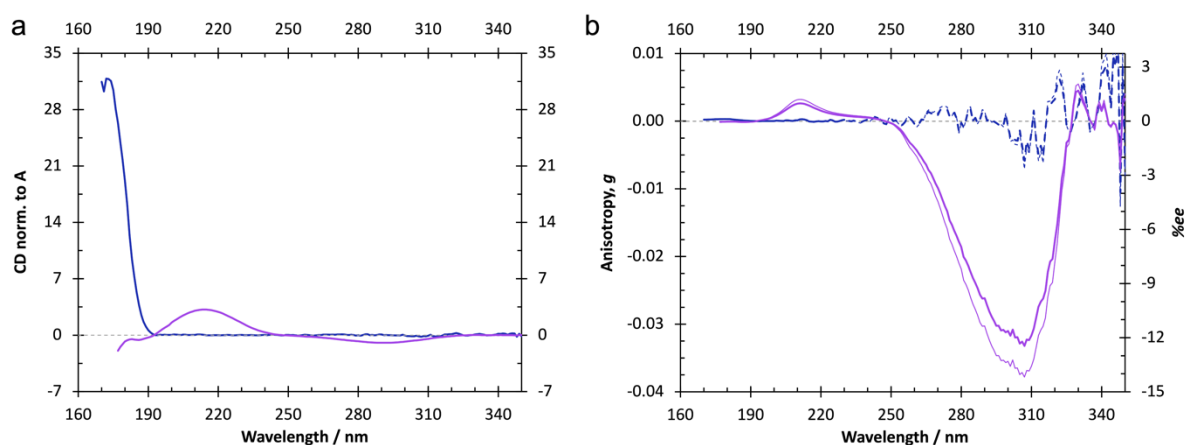
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318 Exogeneous delivery would very likely have been an important source of organo-phosphorous
319 compounds, given constrained bioavailable phosphorus in terrestrial water and the
320 thermodynamically unfavourable nature of phosphorylation reactions on biomolecules in an
321 aqueous environment in the absence of enzymes.⁸³ In support of this are several detections
322 of phosphorus-bearing molecules in space, notably phosphine (PH₃),^{84–86} PO, and PN^{87,88} as
323 well as organophosphorus compounds in carbonaceous chondrites and simulated
324 astrophysical ices (**Supplementary Table 5**). Finally, the abiotic synthesis of glycerol
325 phosphate has been confirmed in electron irradiated simulated interstellar ices composed of
326 PH₃, CH₃OH, CO₂, and H₂O.⁸⁹ Given the relative complexity of present membrane
327 phospholipids, it is unlikely that these would have been synthesised in extra-terrestrial
328 environments. Instead, chiral backbones and shorter chain phospholipid derivatives could
329 have been delivered, preceding their function in the early stages of life evolution. Several
330 potential paths for the prebiotic phospholipid synthesis on the early Earth have been unveiled
331 to date, encompassing the synthesis of (lyso)phosphatidic acids and naturally occurring 2-
332 amino alcohol-bearing head groups (choline, ethanolamine, serine, threonine, etc.), which
333 are crucial intermediates in the build-up of complex phospholipids. In particular, it has
334 recently been discovered that stepwise *N*-methylation of ethanolamine leads to the
335 formation of choline.⁹⁰ Ethanolamine has been found toward the molecular cloud G+0.693–
336 0.027 in the Sagittarius B2 complex in the Galactic Center⁹¹ as well as in the Almahata Sitta
337 meteorite⁹² and in a UV irradiated interstellar ice analogue.⁹³ Furthermore, several detections
338 of serine and threonine in carbonaceous chondrites and simulated interstellar ices are
339 reviewed in reference ⁹⁴.

340 To ultimately commence an experimental search of the potential astrophysical origins of
 341 homochirality of membrane phospholipids, we recorded electronic circular dichroism (ECD)
 342 and anisotropy spectra of the phospholipid backbones *sn*-glycerol-1/3-phosphate
 343 (G1P/G3P).⁹⁵ While ECD provides information about the wavelength-dependent differential
 344 absorption of UV circularly polarized light by enantiomers of chiral molecules ($\Delta\varepsilon = \varepsilon_L - \varepsilon_R$; ε_L
 345 and ε_R are extinction coefficients of left- and right-CPL, respectively), the fractional difference
 346 in the absorption given by the anisotropy factor g ($g = \Delta\varepsilon/\varepsilon$, where $\varepsilon = (\varepsilon_L + \varepsilon_R)/2$ is the
 347 extinction coefficient) reflects on the enantiomeric excess (ee) inducible by preferential UV-
 348 photon induced photolysis of the more absorbing enantiomer.⁹ Consequently, the
 349 enantiomeric excess (ee) inducible by asymmetric photodecomposition by monochromatic
 350 UV CPL can be approximated as

$$351 \quad | \%ee | \geq \left(1 - (1 - \xi)^{\frac{|g|}{2}} \right) \times 100\% \quad (1)$$

352 where ξ is the extent of reaction and the sign of ee follows the sign of g .⁹⁶ Based on the
 353 anisotropy spectra of G1P/G3P reported in Bocková et al.⁹⁵, the asymmetric photolysis of
 354 G1P/G3P by monochromatic circularly polarized light at wavelengths corresponding to the
 355 anisotropy spectra extrema would introduce a chiral bias of less than 0.5%, even at photolysis
 356 rates as high as 99.99%. This suggests rather low efficiency of chirality transfer from chiral
 357 photons to phospholipid backbones, especially when compared to the experimentally
 358 induced optical purities in amino acids via UV CPL. In an astrophysical scenario, stellar
 359 circularly polarized light covers a broad range of wavelengths and is only partially polarized,
 360 thus averaging out to even smaller net chiral photon induced ee -s. Thence, it is rather
 361 improbable that the homochirality of phospholipid backbones would stem from the direct
 362 asymmetric interactions of G1P/G3P with circularly polarized light. It is more plausible that
 363 alternative processes have been involved in the development of lipid homochirality.
 364

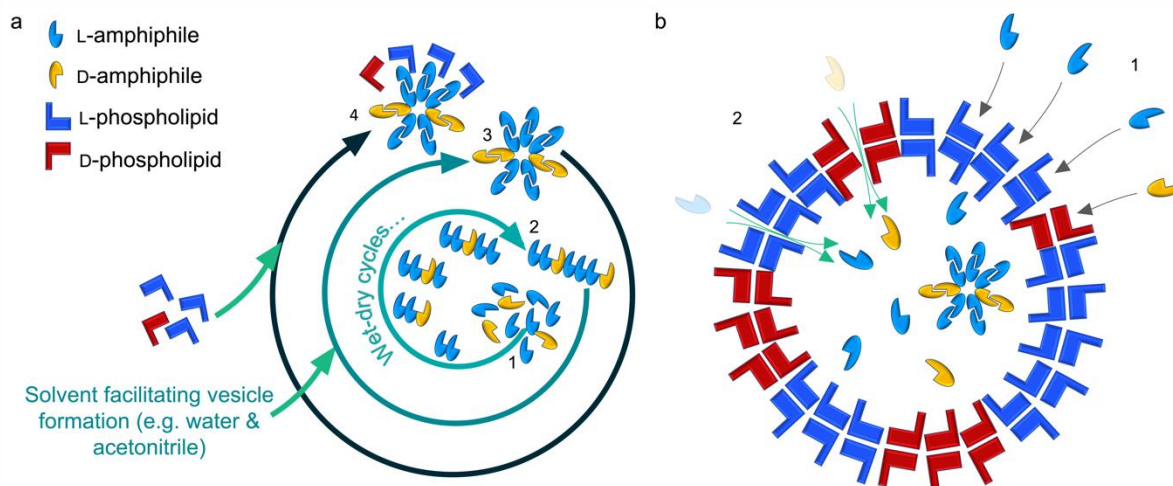


365
 366 **Fig. 4 Chiroptical properties of *sn*-glycerol-1-phosphate lithium salt (blue) in aqueous solution reveal the small**
 367 **enantioselective sensitivity of the chiral backbone of glycerophospholipids to circularly polarized light as**
 368 **opposed to *D*-glyceraldehyde-3-phosphate (purple).** **a** Electronic circular dichroism, and **b** anisotropy spectra
 369 (thick lines) and the ee inducible by asymmetric photolysis by monochromatic circularly polarized light at the
 370 extent of reaction $\xi=0.9999$ (thin lines).⁹⁵
 371

372 Interestingly, replacing the terminal carbon with a hydroxy group of the G1P moiety by an
373 aldehyde group was found to significantly affect the chiroptical properties (**Fig. 4**), enhancing
374 the magnitude of the asymmetry factor up to ~ 0.03 . This can lead to *ee*-s of up to $\sim 14\%$ at the
375 asymmetric photolysis rate of 99.99%.⁹⁵ Thus, the delivery of enantioenriched
376 glyceraldehyde-phosphate to the early Earth might have shaped the evolution of homochiral
377 phospholipids via synthetic pathways that have yet to be explored. The structural analogues
378 of glyceraldehyde-phosphate, notably glycerol phosphate and glyceraldehyde, were
379 previously detected in simulated interstellar ices^{89,97,98} and carbonaceous chondrites⁹⁹,
380 suggesting that astrochemical synthesis and extra-terrestrial supply of glyceraldehyde-
381 phosphate is highly plausible. So far reported prebiotically relevant synthetic routes leading
382 to phospholipids were recently reviewed by Fiore et al.¹⁰⁰ and Aleksandrova et al.⁹⁰
383 An alternative route by which phospholipids could have acquired their homochirality is
384 through interactions with simpler amphiphiles.¹⁵ Although enantioselective adsorption of
385 amino acids on homochiral liposomes¹⁰¹ and their oligomerization¹⁰² have been observed
386 previously, a major shortcoming of the scenario in which the chiral information is transferred
387 from phospholipids to amino acids is how the phospholipids' homochirality would have arisen
388 in the first place. Nevertheless, chirality-specific interactions between amino acids and
389 phospholipids have been clearly evidenced, indicating the potential of the assembly of
390 phospholipids around polypeptide chains. It is, however, very likely that the chirality transfer
391 would have been initiated already before the synthesis of homochiral peptides.
392 As discussed in Section III, wet-dry cycling appears to be an efficient means for the synthesis
393 of vesicle forming proto-amphiphilic systems that can simultaneously serve as substrates for
394 primitive peptides. Moreover, polyester microdroplets comprised of hydroxycarboxylic acids
395 were found to scaffold self-assembly of phospholipid amphiphiles around them.⁵⁴ Our recent
396 findings showed that UV CPL of the same helicity and photon energy can simultaneously
397 induce L-enantiomeric excesses in amino acids and hydroxycarboxylic acids in the conditions
398 approximating water-rich interstellar ices' environment as a cradle of prebiotic organic
399 species.¹⁰³ In addition to numerous detections of L-enriched amino acids in carbonaceous
400 chondrites,⁹ L-excesses of much less studied hydroxycarboxylic acids were for lactic acid also
401 detected in several meteoritic samples.¹⁰⁴ Taken together, a potential route towards the
402 emergence of protocells might have started from CPL L-enriched amino and hydroxycarboxylic
403 acids brought to the early Earth via meteorites, micrometeorites, or interplanetary dust
404 particles.^{60,70} A small chiral excess generated by CPL could have been potentially amplified
405 during parent bodies alteration processes.¹⁰⁵
406 In wet-dry cycles on the primeval Earth, L-enriched depsipeptides would spontaneously
407 emerge from L-enriched amino and hydroxycarboxylic acids (**Fig. 5a**).^{57,106,107} A combination
408 of ester bond-formation and ester–amide bond exchange during the dry/hot phase and
409 dispersion of reactants and ester bond hydrolysis during the wet/cool phase would have led
410 to the enrichment of depsipeptides with amino acids.⁵⁷ A preference for homochiral chain
411 growth as opposed to racemic was demonstrated by Blocher et al.¹⁰⁸ by studying
412 polycondensation from a pool of racemic tryptophan *N*-carboxyanhydrides. In experiments

413 by Blair and Bonner,¹⁰⁹ polymerization of a scalemic mixture of leucine *N*-carboxyanhydrides
414 yielded an oligomer with a higher enantiomeric excess of the dominant enantiomer than in
415 the original scalemic mixture. The oligomer was then partially hydrolysed, leaving even more
416 enantiomerically enriched unhydrolyzed polyleucine residues. Moreover, hydrolysis of
417 scalemic leucine oligomers proceeded more readily than for the homochiral chains. Despite
418 the specific conditions in the above-mentioned experiments lacking prebiotic relevance, they
419 provide a precedent that polymerization and hydrolysis are capable of chiral amplification. A
420 repetitive sequence of polymerizations and hydrolyses in environmentally driven wet-dry
421 cycles, both critically involved in the formation of proto-peptides, would have been,
422 therefore, likely favouring the L-enrichments of built-up oligomers.

423 Hydroxycarboxylic acid rich depsipeptides would have very likely self-assembled into vesicles
424 like polyesters⁵⁴ and facilitated the adsorption of first phospholipids (**Fig. 5a**), either primitive
425 ones or those synthesised on the early Earth from both terrestrial and extra-terrestrial
426 substrates. Various enantiospecific interaction mechanisms between enantiomers of chiral
427 molecules that direct a plethora of biorecognition processes have been characterised to
428 date,^{110–112} including a recent finding of a spin-dependent exchange interaction due to the
429 chiral-induced spin selectivity (CISS) effect,¹¹³ which results in a stronger binding force
430 between same enantiomers than between optical antipodes. Furthermore, numerous reports
431 of adsorption enantioselectivities of chiral minerals and clays, organic crystals, and metal
432 surfaces can be found in the literature.¹¹⁴ Consequently, it is likely that L-enriched
433 depsipeptides would have transferred their chiral preference to phospholipids. Such
434 enantioenriched phospholipid membranes could have further aided the enantioselective
435 adsorption¹⁰¹ and oligomerization¹⁰² of amino acids leading to even more L-enriched proto-
436 peptides (**Fig. 5b**). In addition, phospholipid bilayers were found to be enantioselectively
437 permeable for amino acids and dipeptides¹¹⁵ which would have further enhanced the chiral
438 excess of the encapsulated material (**Fig. 5b**). Since it is the headgroup chirality which governs
439 such permeation, even primitive phospholipids with shorter carbon chains could have served
440 as such chiral filters. Racemization of the non-encapsulated free chiral moieties, possibly in
441 combination with self-disproportionation mechanisms such as phase transitions, would have
442 ensured continuous re-supply of the L-enantiomers.¹¹⁶ The build-up of enriched oligomers
443 would have then served as a trigger for template-directed stereospecific adsorption and
444 oligomerization, hence continuously increasing the length and the chiral excess of newly built
445 oligomers towards homochirality.



446
 447 **Fig. 5 Schematic illustrating a potential pathway from enantio-enriched amphiphiles towards the build-up of**
 448 **homochiral phospholipid membranes and proto-peptides. a** 1 – pre-concentration of initially CPL L-enriched
 449 amphiphiles (e.g. hydroxycarboxylic/amino acids) on the primitive Earth, 2 – polymerization of the amphiphiles
 450 upon wet-dry cycling, 3 – self-assembly of polymers into vesicles, 4 – scalemic amphiphilic vesicles scaffolding
 451 the enantioselective self-assembly of phospholipids. **b** An L-enriched scalemic phospholipid vesicle encapsulating
 452 an L-enriched amphiphilic vesicle. 1 – Enantioselective adsorption and 2 – enantioselective permeation of amino
 453 acids.

454 Clearly, this is a simplified illustrative example of how CPL L-enriched amino and
 455 hydroxycarboxylic acids, and a racemic pool of phospholipids could have led to homochiral
 456 peptides and phospholipid membranes. However, the prebiotic pool would have contained
 457 many more species, including sugars, incorporation of which would have been necessary for
 458 the emergence of primitive genetic information carriers and metabolism. The experiments by
 459 Sacerdote and Szostak¹¹⁷ exhibited varying degrees of lipid bilayer permeability to sugars and
 460 sugar alcohols. While the membrane permeability showed no chiral preference to the
 461 enantiomers of xylose, ribose permeated more readily than other aldopentoses or hexoses.
 462 A potential chirality transfer pathway from amino acids to sugars was reported by Breslow
 463 and Cheng.¹¹⁸ In addition to hydroxycarboxylic acids and amino acids, other amphiphilic
 464 molecules (Section III) would very likely have been involved too, though specific mechanisms
 465 and conditions are yet to be elucidated. Still, the hitherto identified chirality interplay
 466 between lipids, amino acids, and sugars suggests that homochirality of all the three branches
 467 of key building blocks could have evolved prebiotically and simultaneously.

468
 469 **V. Lipids as biomarkers in the quest for extra-terrestrial life**

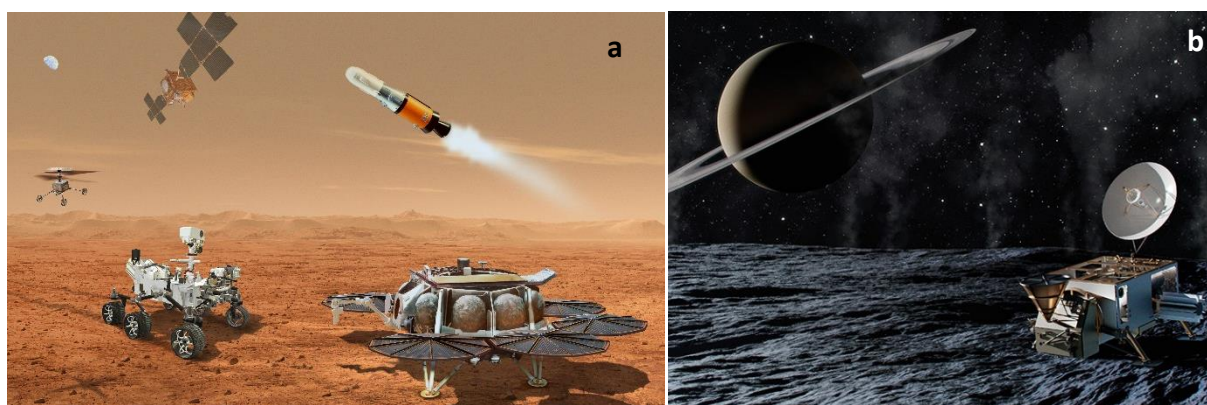
470 Life displays discernible differences in chemical composition, stereochemical preferences,
 471 and a confined chemical space when compared to non-living organic matter. This provides a
 472 foundation for identifying potential biomarkers of extant or extinct life in space.^{9,119–121} On
 473 Earth, even-carbon numbered fatty acids (C_{14} – C_{20}), odd carbon-numbered hydrocarbons, and
 474 specific acyclic isoprenoids such as C_{15} , C_{20} , and C_{25} are characteristic of biologically derived
 475 lipids. Unlike nucleic acids and proteins, lipids consist of only two basic building blocks without
 476 a hydrolysable linkage, making them resistant to depolymerization.^{119,120} The presence of

477 repeating constitutional sub-units, along with features like homochirality, ubiquity and geo-
478 stability, particularly hydrocarbons,²⁵ positions these molecules as excellent biomarkers for
479 potential extra-terrestrial life.

480 Given the similarities in the evolutionary processes of Earth and Mars, the quest for potential
481 Martian life has been a subject of 14 space missions since NASA's Viking mission in 1976.^{11,59}
482 Instruments such as the SAM (Sample Analysis at Mars) on the Curiosity rover, which landed
483 in the Gale Crater in 2012, the SHERLOC (Scanning Habitable Environments with Raman &
484 Luminescence for Organics & Chemicals) on the Perseverance rover, active in the Jezero
485 Crater since 2021, and the MOMA (Mars Organic Molecule Analyser) on the Rosalind Franklin
486 rover, scheduled to be launched in 2028, hold the potential to detect lipids.^{11,25} In the
487 challenging environmental conditions that Mars has endured over billions of years, the
488 detection of any complex organic species in surface or shallow subsurface samples is likely to
489 have been thwarted.¹¹ However, the drilling capabilities of the Rosalind Franklin rover,
490 reaching up to about 2 meters in depth, present the highest potential yet for directly
491 uncovering molecular biosignatures on Mars.¹²⁰ Adding to its uniqueness, the MOMA
492 instrument holds enantio-resolution capabilities through its gas-chromatograph (GC),
493 equipped with a chiral capillary column (CP Chirasil-Dex CB, Agilent). Notably, a Chirasil-Dex
494 column has demonstrated the ability to resolve enantiomers of the branched chiral
495 hydrocarbon 4-methyloctane in a conventional laboratory gas-chromatography mass
496 spectrometry instrument.²⁵ Further testing on the ground-based duplicate (Testbed Model)
497 is necessary to confirm the enantio-resolving capability of the MOMA Flight Model system. It
498 should be noted that lipids serve as biomarkers not only in Mars exploration, but also beyond.
499 The LDI-MS (Laser Desorption Ionization Mass Spectrometry) instrument of the proposed
500 Enceladus Orbilander mission allows for simultaneous detection of lipids, amino acids and
501 polycyclic aromatic hydrocarbons.¹²² Additionally, the SUDA (Surface Dust Analyzer)
502 instrument of the Europa Clipper mission planned for launch in October 2024, based on
503 laboratory analogue experiments, can identify bacterial lipids, DNA, metabolic
504 intermediates,¹²³ as well as fatty acids, amino acids and peptides while distinguishing
505 between biotic and abiotic origins.^{124,125}

506 The *in-situ* detection of lipids, as well as any organics in general, faces limitations imposed by
507 the challenges of space instruments in reliably identifying such targets in the harsh conditions
508 beyond Earth.¹¹ To gain further insights into the potential existence of past and/or present
509 extraterrestrial life, sophisticated state-of-the-art laboratory instruments will play a crucial
510 role in analysing samples returned from Mars (Mars Sample-Return, MSR) and its moon
511 Phobos (Martian Moons eXploration, MMX). In contrast, the recently completed successful
512 asteroid sample return missions, such as Hayabusa2 (from the asteroid Ryugu) and OSIRIS-
513 REx (from the asteroid Bennu), have provided the most intact extraterrestrial pieces of the
514 Solar System ever to reach Earth. These missions are invaluable for establishing a baseline for
515 the complexity and diversity of lipids that can be produced abiotically in extraterrestrial
516 environments. At the same time, they will offer the most credible information regarding the

517 organics that could have contributed to the prebiotic milieu and hence enlighten our research
518 into the origin of life on the early Earth.
519



520 **Fig. 6 Schematics illustrating two conceptual space missions that could enable the identification of potential**
521 **extraterrestrial lipids. a** This illustration shows a concept of the Mars Sample Return Campaign for multiple
522 robots that would team up to ferry to Earth samples of rocks and soil being collected from the Martian surface
523 by NASA's Mars Perseverance rover. The Perseverance rover would deliver its samples directly to the Sample
524 Retrieval Lander. The lander would also carry and deliver to Mars two NASA helicopters to serve as an alternate
525 way to deliver a set of samples stashed on the surface by Perseverance. **Credits:** NASA/JPL-Caltech. **b** Encealdus
526 Orbilander: An artistic representation of the spacecraft designed for orbital exploration around Saturn's moon
527 Enceladus, poised to unveil the mysteries of its icy surface and subsurface environments. The ideal arrival times
528 aim to strike a balance between Jupiter flyby opportunities in the late 2030s and optimal solar illumination at
529 the high southern latitudes of Enceladus, where plume material is abundant. As a result, the mission concept is
530 set to commence in 2030. **Credits:** NASA/Johns Hopkins APL

531

532 **VI. Conclusion**

533 While studying contemporary cells has unprecedented importance in identifying common
534 features of all life forms in our biosphere, the complexity of present-day life, which is a result
535 of several billions of years of evolution, can well mask its most primitive origins. This is
536 undoubtedly the case of phospholipid membranes, which are clearly distinguished in bacteria
537 and eukarya as opposed to archaea. While there has been ample discussion about how and
538 when the *lipid divide* occurred, resolving these questions seeks targeted experiments.

539 The extra-terrestrial supply of phosphorous-bearing organics likely significantly contributed
540 to the source of bioavailable phosphorous on Earth. Still, the complexity of membrane
541 phospholipids and low efficiency of chirality transfer from chiral photons to chiral backbones
542 of glycerophospholipids suggests that an extra-terrestrial delivery of enantioenriched
543 phospholipids is unlikely to have occurred. In the present review, we have highlighted a
544 potential precursor of phospholipid backbones, glyceraldehyde-phosphate, which could, after
545 efficient enantioenrichment by stellar CPL, trigger the synthesis of enantioenriched
546 phospholipids on the early Earth. The experiments centred at identifying prebiotically
547 plausible synthesis pathways are the subject of future studies. In addition, we discussed an
548 alternative path towards homochiral membranes starting from enantioenriched amphiphiles.
549 Numerous amphiphiles are expected to have been present on the early Earth, the assembly

550 of which upon wet-dry cycling might have shaped not only the evolution of membranes but
551 also primitive peptides. Here, laboratory astrochemistry experiments aimed at
552 enantioselective photosynthesis of amphiphilic species and their analysis in extra-terrestrial
553 samples, both return and meteorites, will be central. Enantioselective interactions between
554 simple chiral amphiphiles, amino acids, sugars, and phospholipids on the primeval Earth are
555 likely to have simultaneously led towards homochiral protocells. Specific processes and
556 driving forces are to be identified and will be of great importance, also for strengthening our
557 search for traces of past and/or present primitive life in space.

558
559

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