

## Search for the Most Primitive Membranes: Some Remaining Problems

Yoichi Nakatani · Nigel Ribeiro · Stéphane Streiff ·  
Laurent Désaubry · Guy Ourisson

Received: 25 June 2012 / Accepted: 22 August 2012 /  
Published online: 19 October 2012  
© Springer Science+Business Media Dordrecht 2012

**Keywords** Membranes · Vesicles · Terpenoids · Polyprenyl phosphates

### Introduction

A cell enclosed by a membrane is the common unit of structure shared by all living organisms. The understanding of the origin of membranes is therefore central to an understanding of the origin of life. We have earlier observed that terpenoids (isoprenoids) are universal, necessary constituents of all living organisms and postulated an original scenario for the early formation of membranes and their evolution. It is possible to arrange known membrane terpenoids in a phylogenetic sequence (Ourisson and Nakatani 1994) and a retrograde analysis led us to propose that polyprenyl phosphates, the root of all membrane terpenoids, might have themselves been precursors of archaeal membrane lipids and that they might be a candidate for the most primitive membrane constituents (Fig. 1).

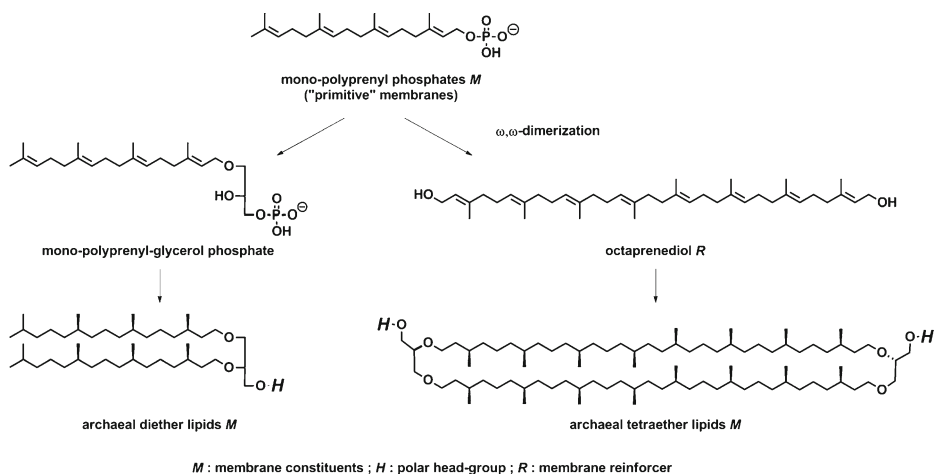
We will discuss how we examined our hypothesis and what problems are remaining.

### Vesicle Formation of Polyprenyl Phosphates, Role of Reinforcers of Polyprenols

We have first synthesized polyprenyl phosphates bearing different isoprenyl C5 units, and demonstrated by fluorescence microscopy that these lipids do spontaneously form vesicles in water in a wide pH range, when the chain contains 15 to 30 C-atoms (Pozzi et al. 1996; Streiff et al. 2007; Ribeiro et al. 2007), respecting the lipophilicity/hydrophobicity ratio for vesicle formation (Israelachvili et al. 1977). Osmotic swelling of a suspension of unilamellar vesicles using stopped-flow/light scattering methods enabled us to evaluate the water permeability of polyprenyl phosphate vesicles with or without polyprenyl alcohol (polyprenol). The addition of acyclic, mono-, di-, or tri-cyclic polyprenols reduced the water

---

Y. Nakatani (✉) · N. Ribeiro · S. Streiff · L. Désaubry · G. Ourisson  
Institut de Chimie, Université de Strasbourg, 1, rue Blaise Pascal, 67008 Strasbourg, France  
e-mail: nakatani@unistra.fr



**Fig. 1** Search for the precursors of archaeal lipids: polyprenyl phosphates, a candidate for the most primitive membranes

permeability. These results imply that polyprenols might have been reinforcers of primitive membranes made of polyprenyl phosphates.

### Hypothetical Pathways for the Abiotic Formation of Primitive Membranes

Above observations led us to postulate a scenario for the abiotic formation of primitive membranes (Ourisson and Nakatani 1999, 2006) (Fig. 2).

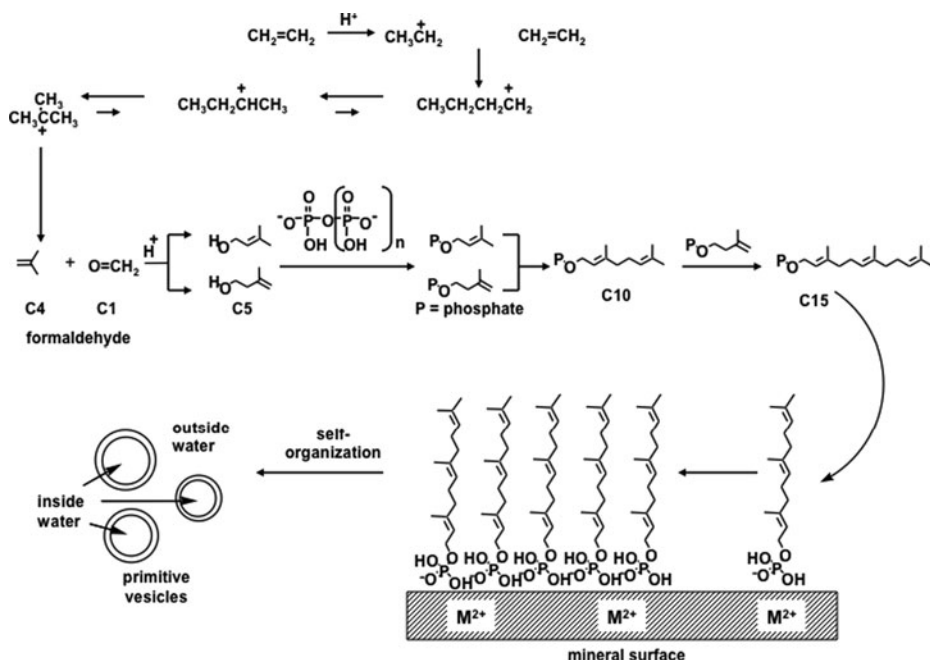
#### Prebiotic Synthesis of Polyprenols from C5 Isopentenol

The abiotic formation of polyprenyl phosphates requires the formation of the polyprenols, followed by their phosphorylation. Going backwards, the synthesis of the polyprenols requires only the recurrent acid-catalyzed condensation of the C5 units of isopentenol. We showed that a clay, montmorillonite K-10, mediates the condensation of isopentenol (C5) with isoprenol (C5) to generate a mixture of isomeric C10 prenols (Désaubry et al. 2003). These steps have been repeated, and led from C10 to C15 prenols. These results support our hypothesis that polyprenols may have been formed in prebiotic conditions as shown here.

#### Polymerisation of C5 Prenyl Units

We proposed that the condensation reaction of C5 units might have proceeded as the head-to-tail elongation by anchoring one end of the molecule to a solid mineral surface through a phosphate group (Ourisson and Nakatani 1994). Once critical length and concentration have been achieved, polyprenyl phosphates would peel off the surface to form vesicles (Fig. 2).

In contemporary organisms, the stepwise condensation of C5 phosphate units is achieved by specific prenyl-transferases (Porter and Sandra 1981). It is probably not a coincidence, but a reminiscence, that the modern biosynthesis of polyprenols involves pyrophosphates at all stages.



**Fig. 2** Hypothetical pathways for the abiotic formation of primitive membranes

### Origin of the C5 Units and the Local Concentration

What compounds might be the starting materials of the C5 units, and how and where could the C5 units be obtained in abiotic conditions? It is also clear that a minimal concentration (cmc) must be attained locally before self-organization of lipids into vesicles in water.

Biochemically, the isopentenyl C5 units are formed either by the mevalonic pathway or by the nonmevalonic pathway (Rohmer et al. 1993). Both are too complex to have close prebiotic analogues. However, these C5 units could be derived from simpler precursors (Fig. 2). Indeed, they can be obtained industrially by acid catalyzed Prins reaction from formaldehyde and isobutene (Blomquist and Verdol 1955). Isobutene could be obtained by olefin homology on zeolite, either from methanol (C1) and ethylene (C2) or from ethylene alone at high temperature (Cui et al. 2008; Oikawa et al. 2006). These abiotic conditions are potentially prebiotic: isobutene, ethylene and formaldehyde do occur in volcanic gases (Capaccioni et al. 2004; Minissale et al. 2007; Tassi et al. 2009; Capaccioni et al. 2011; Kiyosu and Asada 1995; Oro 1994).

### The Prevalence of Phosphates and the Phosphorylation of Alcohols

Phosphates are present in all head-groups of membrane lipids. The indispensable role of phosphates in many aspects of biochemistry is attributed to the specific properties of this group (Westheimer 1987). But, this ubiquitous role of phosphates is in sharp contrast with the low abundance of phosphorus in the Earth's crust (0.12 %). Furthermore, the phosphorylation of an alcohol is a difficult task (Baba et al. 1990). How could polyprenols be phosphorylated in abiotic conditions and how did polyprenyl phosphates reach a minimal concentration to form vesicles in water? The phosphorylation of polyprenols may have

initially involved phosphorous pentoxide, produced by volcanoes (Yamagata et al. 1991). The concentration of oligophosphate ions in water resulting from the weathering of magmatic rocks could be very much increased by their concentration in layered minerals (Arrhenius et al. 1997). Recently, carboxylic-phosphoric mixed anhydrides (Biron and Pascal 2004) and one imidoyl phosphate were shown to phosphorylate alcohols (Powner and Sutherland 2011). Phosphitylation of alcohols followed by oxidation could be an alternative pathway for the formation of phosphates (Yoza et al. 1992; De Graaf and Schwartz 2000; Bryant et al. 2010).

### Phospholipidic Head-Groups

The next stage of elaboration from polyprenyl phosphates could have been to change the head-group. There are several plausible ways in which the mono-polyprenyl phosphates might have been converted, for example via mono-polyprenyl-glycerol phosphates, to the corresponding di-polyprenyl-glycerol phosphates, the types of lipids found in *Halobacterium* (Ourisson and Nakatani 1994) (Fig. 1). These scenarios should be verified experimentally.

### Conclusion

We postulated that primitive membranes may have been formed by polyprenyl phosphates from very simple precursors. These polyprenyl phosphates could then have evolved step-wise into the constituents of modern membranes. However, a major problem remains: it is not at all clear how one would have obtained sufficient amounts of the required starting materials in a confined space, and we are left with three hypotheses:

- Charles Darwin's poetic hypothesis of the lagoon by the side of the sea,
- Environments of hydrothermal vents (Martin et al. 2008),
- Terrestrial geothermal fields (Mulkiđjanian et al. 2012).

**Acknowledgments** Y.N. (nakatani@unistra.fr) and G.O. are greatly indebted to our co-workers, listed in many publications from our laboratory.

### References

- Arrhenius GB, Sales BS, Mojzsis ST, Lee T (1997) *J Theor Biol* 187:503–522
- Baba Y, Tsuchiaki M, Yoza N (1990) *Trends Org Chem* 1:53–75
- Biron J-P, Pascal R (2004) *J Am Chem Soc* 126:9198–9199
- Blomquist AT, Verdol JA (1955) *J Am Chem Soc* 77:77–80
- Bryant DE, Marriott KER, Macgregor SA, Kilner C, Pasekc MA, Kee TP (2010) *Chem Commun* 46:3726–3728
- Capaccioni B, Taran Y, Tassi F, Vaselli O, Mangani G, Macias JL (2004) *Chem Geol* 206:81–96
- Capaccioni B, Aguilera F, Tassi F, Darrah T, Poreda RJ, Vaselli O (2011) *J Volcanol Geotherm Res* 208:77–85
- Cui Z-M, Liu Q, Ma Z, Bian S-W, Song W-G (2008) *J Catal* 258:83–86
- De Graaf RM, Schwartz AW (2000) *Orig Life Evol Biosph* 30:405–410
- Désaubry L, Nakatani Y, Ourisson G (2003) *Tetrahedron Lett* 44:6959–6961
- Israelachvili JN, Mitchell DJ, Ninham BW (1977) *Biochim Biophys Acta* 470:185–201
- Kiyosu Y, Asada N (1995) *Geochem J* 29:231–241
- Martin W, Baross J, Kelley D, Russell MJ (2008) *Nat Rev Microbiol* 6:805–814
- Minissale A, Mattash MA, Vaselli O, Tassi F, Al-Ganad I, Selmo E, Shawk NM, Tedesco D, Poreda R, Ad-Dukhain AM, Hazzae MK (2007) *Appl Geochem* 22:799–820

- Mulkidjanian AY, Bychkov AY, Dibrova DV, Galperin MY, Koonin EV (2012) PNAS 109:E821–E830
- Oikawa H, Shibata Y, Inazu K, Iwase Y, Murai K, Hyodo S, Kobayashi G, Baba T (2006) Appl Catal Gen 312:181–185
- Oro J (1994) In: Bengtson S (ed) Early life on earth, Nobel Symposium N° 84. Columbia U. P., New York, pp 48–59
- Ourisson G, Nakatani Y (1994) Chem Biol 1:11–23
- Ourisson G, Nakatani Y (1999) Tetrahedron 55:3190–3283
- Ourisson G, Nakatani Y (2006) In: Gargaud M, Barbier B, Martin H, Reisse J (eds) Lectures in astrobiology, Vol. 1: Part 2, 29–48, Springer-Verlag, Berlin, Heidelberg
- Porter JWS, Sandra L (1981) Biosynthesis of isoprenoid compounds first edition. Wiley, New York
- Powner MW, Sutherland JD (2011) Phil Trans R Soc B 366:2870–2877
- Pozzi G, Birault V, Werner B, Dannenmuller O, Nakatani Y, Ourisson G, Terakawa S (1996) Angew Chem Int Ed Engl 35:177–180
- Ribeiro N, Streiff S, Heissler D, Elhabiri M, Albrecht-Gary AM, Atsumi M, Gotoh M, Désaubry L, Nakatani Y, Ourisson G (2007) Tetrahedron 63:3395–3407
- Rohmer M, Knai M, Simonin P, Sutter B, Sahn H (1993) Biochem J 295:517–524
- Streiff S, Ribeiro N, Wu Z, Gumienna-Kontecka E, Elhabiri M, Albrecht-Gary AM, Ourisson G, Nakatani Y (2007) Chem Biol 14:313–319
- Tassi F, Aguilera F, Vasselli O, Medina E, Tedesco D, Delgado Huertas A, Poreda R, Kojima S (2009) Bull Volcanol 71:171–183
- Westheimer FH (1987) Science 235:1173–1178
- Yamagata Y, Watanabe H, Saitoh M, Namba T (1991) Nature 204:516–519
- Yoza N, Ueda N, Tokushige N, Miyajima T, Baba Y, Tshako M, Tateda A (1992) Inorg Chim Acta 202:237–239