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Current Opinion in Chemical Biology

# Primordial membranes: more than simple container boundaries

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Cellular membranes, which are self-assembled bilayer structures mainly composed of lipids, proteins and conjugated polysaccharides, are the defining feature of cell physiology. It is likely that the complexity of contemporary cells was preceded by simpler chemical systems or protocells during the various evolutionary stages that led from inanimate to living matter. It is also likely that primitive membranes played a similar role in protocell 'physiology'. The composition of such ancestral membranes has been proposed as mixtures of single hydrocarbon chain amphiphiles, which are simpler versions of modern lipids. In this review, we discuss the origins, self-assembly patterns, potential functions of these amphiphiles, and their possible roles in protocell activities, as well as their possible evolution towards modern lipids.

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**Current Opinion in Chemical Biology** 2017, **40**:78–86

This review comes from a themed issue on **Synthetic biomolecules**

Edited by **Peter H Seeberger** and **Beate Koksch**

http://dx.doi.org/10.1016/j.cbpa.2017.07.009



## Introduction

Lipid membranes play essential roles in contemporary cells by compartmentalizing cellular machinery and by forming a semi-permeable link to the environment. The membrane defines the unit cell and its internal volume. This barrier also acts to preserve the integrity of the cell in varying environments. But membranes are more than just passive containers. They mediate the interactions of cells with the environment including the harvesting of energy, material and other resources, and the interaction with other cells including potential pathogens. Such functionalities are essential mechanisms for cells to avoid equilibrium and death.

Modern membranes are modified to link the physicochemical nature of the lipid bilayers with cellular dynamics. The material and informational flux through a cell is often controlled by various proteins and lipid conjugates integrated into the membrane. For example, transmembrane proteins govern signal transduction pathways. Furthermore, lipid bilayers define sub-compartments within the cell interior that are crucial for metabolic processes, for example, energy conversion either from processed chemicals or primary energy sources, such as light, or the maturation of cellular chemical products.

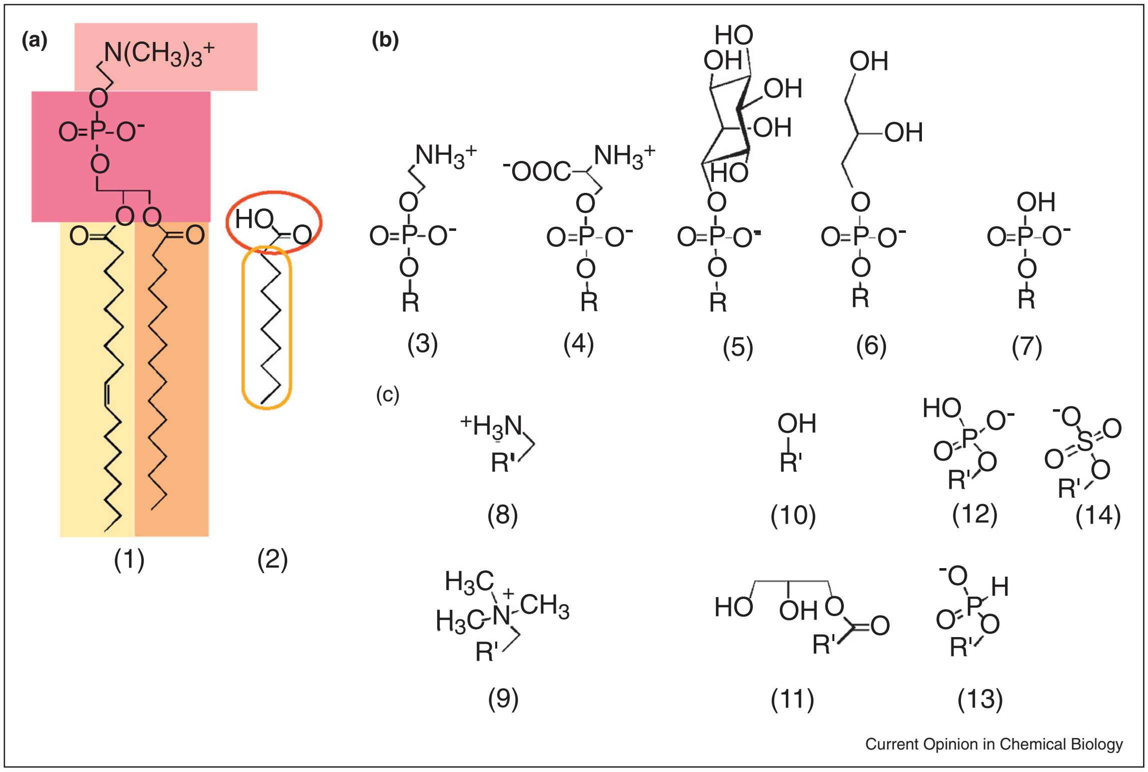
The sophisticated complexity of contemporary biochemistry and membranes seems to be the product of years of evolution [1]. Cells must have therefore been preceded by simpler systems, so called protocells, whose physical, organizational and functional nature is highly debated. Still, because of the central role of the lipid membrane compartmentalization in cellular life, one may hypothesize that the emergence of life is linked to the spontaneous formation of chemical systems [2••] that had the capacity to confine or compartmentalize chemical reaction networks together with a form of information [3,4]. The necessary condition of a confining membrane in addition to essential factors like information and metabolism is the impetus for research on primitive amphiphiles and their self-assembled structures.

### Membrane compositions

Modern membranes consist of complex mixtures of various lipids, most prominently phospholipids (Figure 1a and b). These molecules (Figure 1a **1**) are synthesized from four different parts by at least three enzymes [5]. Such a multi-step synthesis is plausible through chemical syntheses [6••], but only with low yields [7]. From the point of view of primitive membrane formation, this complexity seems to suggest that these molecules have been optimized over a long evolution to perform their tasks. However, the formation of lipid membranes itself still relies on spontaneous self-assembly processes that are not defined by genetic information, but related to the dual nature (or amphiphilic nature) of the lipid molecules.

This observation has implications for the research on plausible primitive membranes as it clearly indicates that the presence of simple amphiphilic molecules on the early Earth, such as fatty acids, might have been sufficient for the formation of primitive membranes by self-assembly (Figure 1). This process would allow the compartmentalization of chemicals and chemical reaction networks, forming the basis for protocellular systems.

**Figure 1**




Chemical structures of lipid and single chain amphiphiles (SCAs). **(a)** Prototypical representatives of phospholipids and SCAs. 1-Palmitoyl, 2-Oleyl-*sn*-glycero-PhosphoCholine (POPC, **1**) is a typical representative of the modern zwitterionic phospholipids. Its structure can be broken down to 4 pieces (four colored rectangles): two hydrocarbon chains (usually 14–18 carbons long and partially unsaturated, orange and yellow boxes), a glycerol phosphate (dark pink) and a choline (light pink), all linked together through ester bonds. Decanoic acid (**2**) is a fatty acid (FA), and one of the prototypical models for primitive amphiphiles. The red circle and the orange capsule highlight the hydrophilic headgroup moiety of the molecule and its hydrophobic moiety, respectively. Note that both POPC hydrocarbon chains are FAs. **(b)** Most common headgroups of phospholipids and **(c)** their potential precursors in primitive membranes. Besides the phosphocholine headgroups (1), phosphoethanolamine (3), phosphoserine (4), phosphoinositol (5), phosphoglycerol (6) and phosphatidic acid (7); R is a di-alkanoate glycerol. These species represented at least 75% of all lipids in mammalian cells [5]; ammonium/amines (8), trimethylammonium (9), hydroxyl (10), glycerol ester (11), phosphate (12), phosphite (13) and sulfate (14) headgroups for SCAs. R′ represents a hydrocarbon chain substituent. The hydrocarbon chain length of SCAs could have varied from medium chain (8–12 saturated carbons, MCFAs) to longer partially unsaturated chains. Indeed, longer saturated chains (≥14 carbons) tend to be in gel state below 45 °C (i.e., a state that generally does not favor their suspension in an aqueous medium). The molecule arrangement in (b) and (c) underlines the similarities between lipid and amphiphile headgroups that could suggest similar functions and potentially ancestry. Note that molecules 8, 9, 10 do not form bilayer structures on their own, but rather serve as co-surfactant (section Self-assembly).

## Possible origins of single hydrocarbon amphiphiles

According to origin of life scenarios, organics including single hydrocarbon amphiphiles (SCAs) could have had two origins: extraterrestrial and endogenous [8]. In brief, complex organic mixtures delivered by meteorites and interstellar dust particles accumulated on the early Earth's surface, at an estimated rate of $10^8$ kg of organics per year [9]. For instance, certain carbonaceous chondrite meteorites contain large amounts of SCAs, in particular fatty acids (FA) with single saturated hydrocarbon chain up to 12 carbons long (Figure 1a-2) [10], along with related chemicals that may have served as chemical precursors for FAs, other amphiphiles or co-surfactants. Additionally, special environments such as Earth's atmosphere, hydrothermal fields and ocean thermal vents found on the Earth could have produced complex organic molecules (for a proposal of parallel and nested synthetic pathways for essential biomolecules see [11]). Amphiphiles, especially FAs and related compounds, have been successfully synthesized as fraction of complex product mixtures via Fischer–Tropsch like reactions (Figure 2a) from simple precursors ($CO_2$, $H_2$) [12].

Phosphate and phosphite amphiphiles are also plausible via leaching phosphorus from nickel/iron-rich meteorites [20] (anoxic corrosion). The phosphorus is transformed via redox chemistry to phosphate and phosphite, which could have then reacted with alkyl alcohol forming amphiphiles (Figures 1c and 2a). It is worth noting here that no source of potentially prebiotic amphiphiles likely delivered pure