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Phospholipids and glycolipids mediate proton containment and circulation along the surface of energy-transducing membranes

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ABSTRACT

Proton bioenergetics provides the energy for growth and survival of most organisms in the biosphere ranging from unicellular marine phytoplankton to humans. Chloroplasts harvest light and generate a proton electrochemical gradient (proton motive force) that drives the production of ATP needed for carbon dioxide fixation and plant growth. Mitochondria, bacteria and archaea generate proton motive force to energize growth and other physiologies. Energy transducing membranes are at the heart of proton bioenergetics and are responsible for catalyzing the conversion of energy held in high-energy electrons → electron transport chain → proton motive force → ATP. Whereas the electron transport chain is understood in great detail there are major gaps in understanding mechanisms of proton transfer or circulation during proton bioenergetics. This paper is built on the proposition that phospho- and glycoglycerolipids form proton transport circuitry at the membrane's surface. By this proposition, an emergent membrane property, termed the hyducton, confines active/unbound protons or hydronium ions to a region of low volume close to the membrane surface. In turn, a von Grotthuß mechanism rapidly moves proton substrate in accordance with nano-electrochemical poles on the membrane surface created by powerful proton pumps such as ATP synthase.

Contents

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1. History

The flow of protons through and on cellular membranes is central to bioenergetics, i.e. supply of energy for life. Peter Mitchell, the father of the field of proton bioenergetics, envisioned in 1961 [1] that the thermodynamic potential energy at equilibrium was coupled to a proton gradient across or within energy transducing membranes (i.e. proton motive force, *pmf*). While Mitchell's visionary "chemiosmotic" hypothesis is widely accepted today in its general terms, at that time few structural details of proton pumps or ATP synthase were available; as a consequence, Mitchell's revolutionary new hypothesis was severely debated (reviewed by [2]). Mitchell's concept of delocalized bulk-to-bulk proton gradients was confronted with the idea of a localized, i.e. limited distance of *pmf* coupled to ATP formation, membrane surface-to-surface gradient [3–5]. The latter mechanism was demonstrated in biological systems, where experiments systematically showed that protons do not immediately enter the bulk-water phase, but are in fact retained on membrane surfaces [6,7]. These findings stimulated the first publications suggesting membrane lipids as facilitators of lateral proton transfer [8,9].

Research activity on membrane-water interface proton transport intensified again in the 1990s. Two separate laboratories reported that protons ejected from cells of *Halobacterium salinarum* by archaeal rhodopsin, acting as a proton pump, did not enter immediately the bulk phase or medium [10,11]. Instead, protons effluxed by this light-energized proton pump hugged the membrane surface while traveling a relatively long distance on their journey to ATP synthases. These studies with purple membranes set the stage for several groups from different research areas to establish the importance of membrane surfaces in proton circulation [12–24]. Please note that a complete review of references in the history of this field is beyond the scope of this paper. Furthermore, based on the thermodynamics of ATP synthesis, a membrane-water interface mechanism is apparently required for proton circulation in energy transducing thylakoid, bacterial and mitochondrial membranes [25,26]. Thus, it appears that the proton gradients established at membrane surfaces are in fact essential for proton pumping activity of integral membrane proteins of the respiratory chain complexes, e.g. ATP synthase [27–30].

While numerous lines of evidence confirmed a primary role of lipids in proton circulation along membrane surfaces, a unified model that accounts for the great variety and specificity of lipids in different types of membranes (Fig. 1; Table 1) is still missing. Given their negative charge, anionic lipids have been hypothesized as trap and conduction vehicles (proton wells) for proton transport [8], such that lipid-water interfaces would form a "network" for localized proton sources (pumps) and sinks (ATP synthases) [9,38,39]. A "proton trap" function for oxidative phosphorylation was also attributed to more specific lipids such as cardiolipin (CL) [40–42]. These models, however, do not fully integrate the distinct composition of lipids (e.g. the highly variable proportions of phospho- vs. glycolipids; anionic vs. zwitterionic vs. neutral lipids; as well as the absence of CL in thylakoid and most archaeal membranes) and their possible roles in the bioenergetics of energy transducing membranes. Moreover, the idea of a few lipid classes (e.g. CL) participating in the membrane's interface proton transport is consistent with the localized proton gradients for ATP formation in respiratory supercomplexes [41–49]. The latter concept implies that proton sources and sinks are located nearby, i.e. within a limited distance for proton shuttling. However, this idea has been currently challenged by compelling data. These recent studies have provided evidence for segregated respiratory complexes into microdomains in *E. coli* [50,51], such that protons might have to travel long distances (thousands of Å) between efflux pumps and ATP synthase.

This paper is built on the proposition that lipids are co-catalysts in the bioenergetics of energy transducing membranes. Our challenge is to unify the roles of phospho- and/or glyco-glycerolipids typical of archaeal, bacterial, thylakoid and mitochondrial membranes (Table 1)

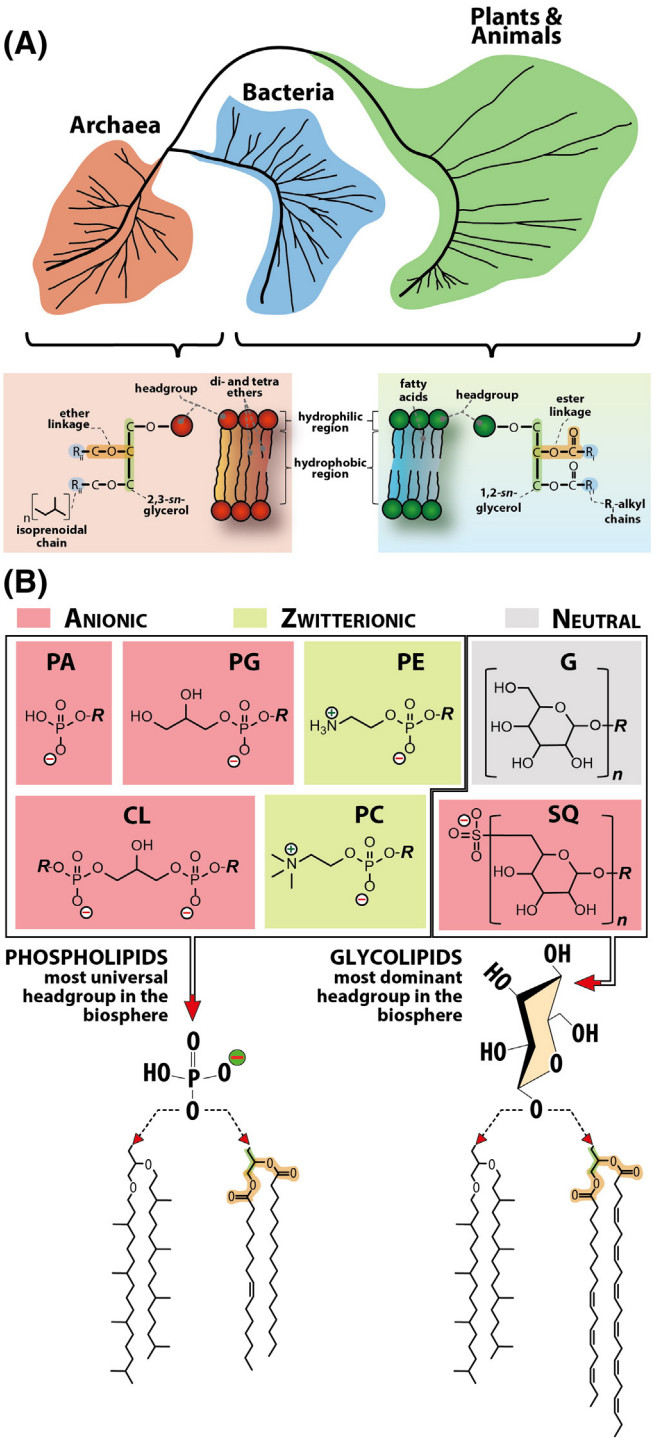

Fig. 1. Structures of phospho- and glyco-glycerolipids in the three domains of life. (A) Major characteristics of archaeal lipids relative to bacterial and eukaryal lipids. Note that archaeal polar lipids are ether-linked to side chains composed of isoprenoids, whereas bacterial and eukaryal polar lipids are ester-linked to side chains most often composed of fatty acids. (B) Phospholipids are intrinsically charged. The attached functional group to the phosphate moiety (e.g. glycerol, ethanolamine) determines the final charge of the phospholipid. These lipids are generally anionic (in red) or zwitterionic (in green). Glycolipids are most often neutral (in gray), but may also display negative charge as the sulfolipids (in red). Sugar moieties can vary greatly in composition (e.g. galactose, glucose) and carry charged functional groups such as the sulfated glycolipids, which are anionic. PA = phosphatidic acid; PG = phosphatidylglycerol; CL = cardiolipin; SQ = sulfoquinovosyl; PE = phosphatidylethanolamine; PC = phosphatidylcholine; G = glycosyl.