Trends in Biochemical Sciences
An official publication of the INTERNATIONAL UNION OF BIOCHEMISTRY AND MOLECULAR BIOLOGY

Cell Press
REVIEWS

Review

Mineral–Lipid Interactions in the Origins of Life

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Protocells, the first life-like entities, likely contained three molecular components: a membrane, an information-carrying molecule, and catalytic molecules. Minerals have a wide range of properties that might have contributed to the synthesis and self-assembly of these molecular components. Minerals could have mediated the formation and concentration of prebiotic organic monomers, catalyzed their polymerization into biomolecules, and catalyzed protometabolic pathways, leading to protocell self-assembly. This review considers the following major aspects of protocell membrane-mineral interactions: (i) the effect of dissolved cations on the stability of mixed fatty acid and phospholipid vesicles; (ii) the rate of lipid self-assembly to vesicles; and (iii) the role of photocatalytic minerals in harvesting light energy to drive electron transfer reactions across membranes in the development of protometabolism.

Lipid Membranes – Compartments

The appearance of life around 4 billion years ago was a result of a series of geochemical events involving the interaction of a primitive atmosphere, water, and minerals with simple molecules leading to the formation of biopolymers, such as peptides, nucleic acid oligomers, and lipids [1–4]. The encapsulation of these biomolecules in a membranous structure is considered an important feature during the emergence of protocells, the first life-like entities. On modern Earth, prokaryotic cells live in association with minerals and water in **biofilm** (see Glossary) communities because of the many benefits conferred by the mineral–water interface. Therefore, it is reasonable to assume that the earliest life forms may also have appeared in proximity to the mineral–water interface [2,4–8].

Minerals may have influenced the formation and stability of protocell membranes [9–15], polymerized monomers into polymers of the biomolecules [7,16–19], as well as catalyzed transmembrane redox reactions in the early stages of the development of metabolism [20–22]. Mineral surfaces have long been recognized as having the potential for chiral selectivity of amino acids and sugars potentially contributing to the origins of **homochirality** [3,23]. Pores in rocks may have also have served the function of microreactors and protected biomolecules from hydrolysis, and thermal and UV degradation on the early Earth [5,19,24]. Minerals have a wide range of physical and chemical properties, such as their specific chemical composition, crystal structure, dielectric constant, Hamaker constant, band gap, particle size, and surface roughness, which might have influenced any of these interactions with organic and inorganic molecules.

Modern cell membranes are composed of **phospholipids** (PLs). It was initially believed that the prebiotic synthesis of PLs was difficult. Hence, protocell membranes are believed to have been composed of single chain amphiphiles (SCAs), such as **fatty acids**, (FAs), for example, decanoic acid, (DA), fatty amines (e.g., decylamine, DN), and fatty alcohols (e.g., decanol,

Highlights

Mixed FA and PL vesicle systems exhibit greater stability to divalent cations than pure FA membranes.

Dissolved magnesium and other divalent cations act as an environmental selection pressure for the transition of mixed FA–PL membranes to PL-enriched membranes

Minerals increase the initial rate of vesicle formation depending on the surface charge and particle size of the mineral.

Minerals play a key role as a catalyst to drive energetics in a model protocell or across its membrane.

The structure–activity relationship between mineral properties and organics under different environmental conditions are crucial for extrapolating probabilities of the origin of life on other solid worlds.

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https://doi.org/10.1016/j.tibs.2018.11.009
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DOH). These SCAs would have been prebiotically available through endogenous and exogenous sources [25–30]. More recently, several studies have achieved the synthesis of PLs and related compounds, such as acylglycerol and glycerol phosphates, suggesting that such molecules may have been present on the young Earth in trace quantities [31–36]. In addition to SCAs and PLs, alternative protocell boundaries, such as a proteolipid (protein–lipid complex) membrane supported on mesoporous silica particles [37], 'mineral membranes' [38–42], and the spaces between mica sheets [42] have also been proposed. The self-assembly and stability of protocell membranes would have depended on geochemical environmental factors, including the type and concentration of dissolved ions present, the mineral surfaces that the membranes encountered, and the temperature of the system [43]. In this review, we focus on recent advances in the area of lipid–mineral interactions, relate these interactions to mineral properties, thus, identifying structure–activity relationships, which are critical to assessing the probability of the origin of life on other solid worlds beyond Earth. We also highlight gaps that could be addressed in future studies of relevance to the origins of life.

Effect of Dissolved Ions on Membrane Stability

The dissolution of minerals from primitive oceanic (komatiite) and continental-type (tonalite) crust and the precipitation of secondary (sedimentary) minerals would have primarily controlled the dissolved ion (e.g., Mg^{2+}, Ca^{2+}, Fe^{2+}, CO_3^{2-}, S^{2-}, PO_4^{3-}, etc.) inventory on early Earth [2,44]. The Hadean ocean is estimated to have been mildly acidic to near-neutral pH [45]. Modern ocean water is mildly alkaline (pH ~8.5) and has an ionic strength of 0.5 M (mainly, Na^+, Mg^{2+}, Cl^- and SO_4^{2-}), whereas freshwater has a near-neutral pH and ionic strength of only about 0.1–1 mM (mainly, Ca^{2+}, HCO_3^-, and soluble silica).

Model protocell membranes composed of FAs are stable only within a narrow pH range and low ionic strengths [46,47]. They tend to form aggregates/precipitates by the binding of divalent cations with the negatively-charged carboxylic acid head group of the FA. Various studies have shown that the introduction of cosurfactants, such as fatty alcohols, fatty amines, and fatty glycerol monoesters to FAs can significantly increase vesicle stability against dissolved ions, extreme temperature, and a wide range of pH [48–52]. This effect is due to hydrogen bonding between the cosurfactant and deprotonated carboxylate head group of the FA. Phosphate amphiphile vesicles are also stable at low pHs [35].

Recently, Dalai *et al*. [52] have demonstrated the transition of mixed FA–PL membranes to more PL-enriched membranes in the presence of Mg^{2+}, where the cation acts as an environmental selection pressure (Figure 1). The FA–PL system consisted of oleic acid (OA) and 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC). It was shown that the immunity of mixed FA–PL vesicles to Mg^{2+} increases as the OA/POPC ratio decreases. Thus, the 'fatal Mg^{2+} concentration' at which vesicles are destabilized increased from ~5 mM for pure FA vesicles to 20 mM for OA/POPC = 10:1 and up to 50 mM of $MgCl_2$ for OA/POPC = 1:1 [52]. These results were confirmed by another group [53]. Among various ions, Mg^{2+} is one of the most important as it is required at high concentrations (~75 mM) for both nonenzymatic, templated, and montmorillonite clay-catalyzed polymerization of RNA nucleotides [16,54–56].

The increased immunity of OA–POPC vesicles against Mg^{2+} was explained as a selective binding of Mg^{2+} to negatively charged OA and abstracting it from the mixed OA–POPC vesicle, thus enriching the vesicles in POPC (Figure 1) [52]. POPC is a neutrally charged (zwitterionic) lipid, hence, it is more tolerant to cations. Thus, the resulting vesicles evolved from mixed FA–PL towards more stable PL membranes. A similar effect of selective abstraction of the FA from mixed DA–DOH (1:1 and 2:1) vesicles was shown for Mg^{2+} and Ca^{2+}. It was found that Ca^{2+}

Glossary

Biofilm: an assemblage of microbial cells embedded in an EPS matrix made of polysaccharides, proteins, lipids, and nucleic acid.

Critical vesicle concentration (CVC): the minimum lipid concentration at which stable vesicles are formed.

Fatty acid (FA): an amphiphilic molecule consisting of a hydrophilic carboxylic acid head group and a hydrophobic hydrocarbon chain.

Homochirality: having a single handedness or chirality.

Micelle: an aggregate of surfactant molecules (e.g., FAs) dispersed in solvent with the head group in contact with solvent and tails in the micelle center. Micelles are usually formed by single-chain amphiphiles, since it is difficult to fit two chains into a micellar structure. Micelles lack a bilayer and interior volume.

Phospholipid (PL): a class of lipids that are an integral component of all cell membranes. A PL molecule is made up of two hydrophobic FA tails and a hydrophilic head consisting of a phosphate group. The two components are connected by a glycerol molecule. The phosphate groups can be modified with simple organic molecules such as choline. PL molecules are arranged as a bilayer in water with the head groups facing towards water and tails away from the water.

Polyprenols: are long-chain isoprenoid lipids found in plants. A prenol (3-methyl-2-buten-1-ol) with more than four isoprene units is a polyprenol.

Quorum-sensing: is the phenomenon of altering gene expression by detecting and responding to changes in cell population density.

Reactive oxygen species (ROS): chemically reactive oxygen species, including hydroxyl radicals (OH^*), peroxides (H_2O_2), and superoxides (O_2^{-*}), formed by UV or ionizing radiation. An increase of ROS concentration in cells may cause damage to DNA, RNA, proteins, and lipids, and may cause cell death.

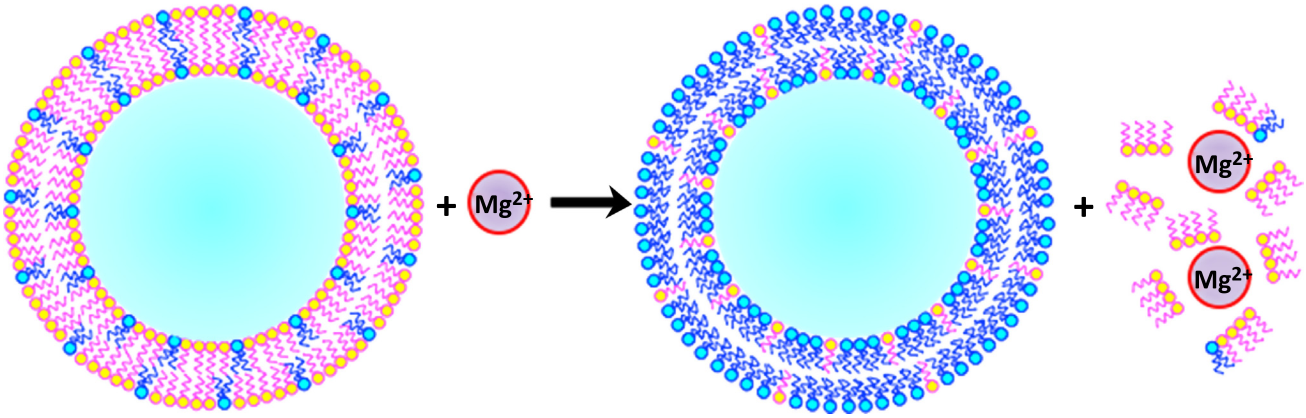

Figure 1. Schematic of Fatty Acid-Phospholipid Mixed Vesicle Interaction with Divalent Cation (Mg^{2+}). The resulting vesicles are enriched with phospholipid, as Mg^{2+} preferentially binds to and removes fatty acid molecules. Yellow spheres with magenta tails = fatty acid; cyan spheres with blue tails = phospholipid. Adapted from [52].

has lower fatal concentrations than Mg^{2+}. This is because Mg^{2+} is more strongly hydrated than Ca^{2+}, and forms a larger hydration sphere, so that the interaction with the negatively charged FA headgroup is weaker.

The retention of an enclosed molecule is important for the survival of a protocell while still allowing some mass exchange with the extravesicular environment for maintenance of the protocell. Model protocell membranes composed of SCAs are generally highly permeable to solutes, in contrast to PL membranes, that are effectively impermeable to ions and need specialized machineries such as ion channels for mass transport across the membrane. It was observed that mixed FA–PL (OA–POPC) vesicles were semipermeable to Mg^{2+} and permeability decreased as the ratio of OA/POPC decreased [52]. Thus, the transition of pure FA to PL membranes induced by divalent cations could be considered an advantageous evolutionary step to compensate for the permeability limitations associated with either pure FA or pure PL systems.

In an alternative approach, the toxic effects of Mg^{2+} on FA vesicles were mitigated by complexing the Mg^{2+} with 200 mM citrate [56,57]; however, the prebiotic availability of such high concentration of citrate is an open question. Finally, it was shown that cationic peptides derived from the ribosomal core can promote RNA polymerase ribozyme activity at low Mg^{2+} concentrations [58]. This represents a more evolved system than the mineral–lipid system.

Lipid Adsorption and Vesicle Formation on Mineral Surfaces

Prebiotic simulation experiments involving minerals and biomolecules such as amino acids, sugars, and nucleic acids have been widely studied, however literature on the influence of minerals on lipid and their self-assembly is scarce. Recently, SCA and PL adsorption and vesicle stability in the presence of minerals was investigated by various analytical and theoretical modeling approaches [9–13,59]. Studies demonstrated that minerals could enhance the initial rate of vesicle formation from **micelles** [13–15] as well as the rate of vesicle formation by rehydration of a dried lipid thin film [13]. DA–DOH vesicle formation was found to be enhanced up to 1000-fold in the presence of minerals compared with the rate in solution [13]. The rate enhancement was observed even in the vicinity of the particle surface without the necessity for direct contact between vesicles and particles [15]. Sahai *et al*. [13] further found that the rate of vesicle formation is dependent on the isoelectric point (IEP) and reactive surface area of the mineral. The IEP is described as the pH when the electric potential at the mineral surface is zero. The IEP is related to surface acidity, crystal structure, and chemical composition [60]. The enhancing effect of the mineral surfaces was explained as a result of instantaneous lipid adsorption on the mineral surface. These adsorbed lipid islands that served as a 'template' or 'matrix' for additional lipid molecules to be adsorbed from the solution and autocatalyzed further vesicle formation (Figure 2) [13].

The relationship between the rate of vesicle formation and the IEP of the mineral was explained based on electrostatic forces and Derjaguin–Landau–Verwey–Overbeek (DLVO) theory of colloidal stability [10,11,13]. The SCA vesicles used in the studies have a net negative charge and, hence, more lipid could be adsorbed on the positively charged mineral surfaces (e.g., γ-alumina, goethite, and zincite), resulting in increased rate of vesicle self-assembly compared with that on negatively charged mineral surfaces (e.g., silica, anatase, montmorillonite, and pyrite). Nonetheless, negatively charged surfaces were still able to adsorb lipid and catalyze vesicle formation because of hydrogen bonding between the lipid head groups and the neutrally charged (zero charge) surface sites, which comprise the majority of total surface sites [61]. Furthermore, DLVO theory suggested that van der Waals

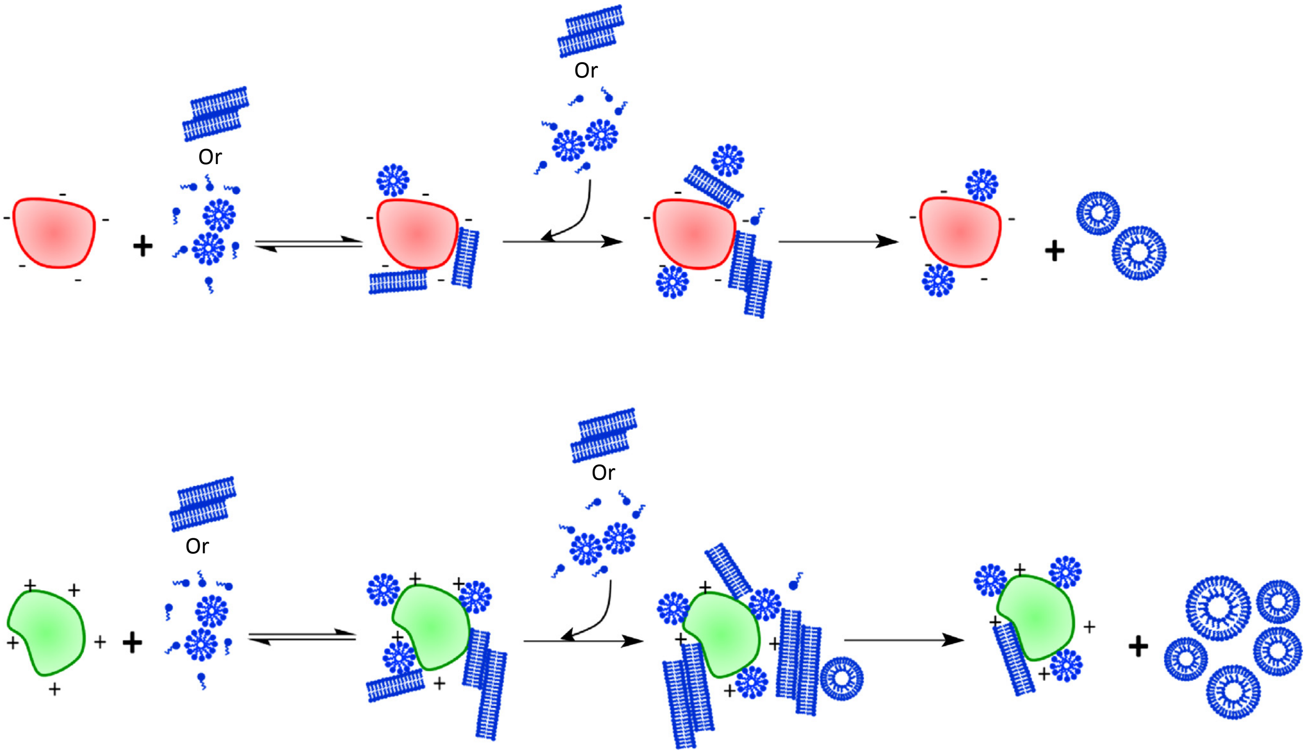

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Figure 2. Schematic Model for Mineral Surface Enhanced Vesicle Formation Rate. Upper and lower panels represent negatively and positively charged mineral surfaces respectively. First, lipid (blue) micelles or bilayers adsorb rapidly on mineral surfaces to form the partially lipid-coated mineral template. A greater amount of adsorption of negatively charged lipids occurs on the positively charged mineral surfaces (green) than on the negatively charged mineral surfaces (red). The adsorbed lipid islands provide templates for further lipid attachment from solution, which autocatalyze self-assembly into vesicles. A greater amount of initial adsorption on positively charged minerals compared to negatively charged minerals is responsible for the dependence of rate enhancement on mineral isoelectric point (surface charge). Adapted from [13].

forces between the lipid and the mineral could also lead to lipid adsorption on the particle surface.

Multiple bilayers of lipid could be adsorbed on the mineral surfaces because of van der Waals interactions between the lipids and mineral surfaces and between adjacent lipid bilayers [10,11,13]. The physical presence of the lipid bilayers excluded solvent and counterions from the vicinity of the mineral surface, thus, effectively extending the electric double layer to a distance of several nanometers (7–8 nm for negatively charged and 13–15 nm for positively charged minerals) away from the surface (Figure 3). Hence, even though direct contact of subsequent

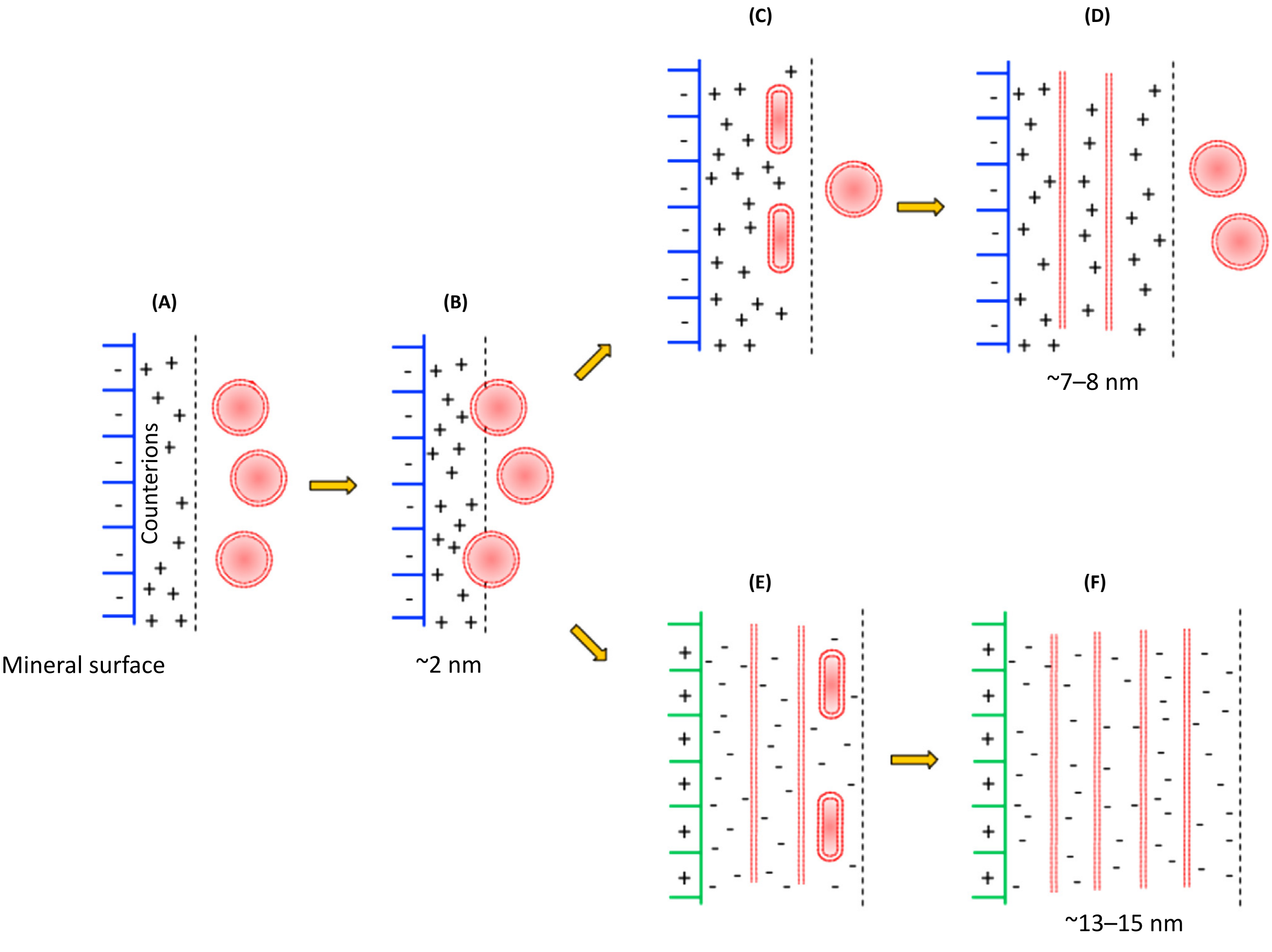

Figure 3. Schematic Model Explaining How Mineral-Promoted Vesicle Formation Rate Enhancement Can Operate Even without Direct Contact with the Mineral Surface. Panels A and B apply to both positively charged (green line) and negatively charged (blue line) mineral surfaces with lipid vesicles (red spheres). Panels C and D are for negatively charged surfaces while panels E and F apply only to systems with positively charged mineral surfaces. The distance of closest approach of the diffuse electric double-layer is shown by the dashed line. Adsorption of vesicles within the diffuse layer leads to formation of up to two planar lipid bilayers (red vertical lines) mainly due to van der Waals forces in the case of the negatively charged mineral surface, whereas formation of multiple bilayers occurs due to both van der Waals and attractive electrostatic interactions on positively charged surfaces. This results in greater expulsion of the solvent and counterions from the vicinity of the positively charged mineral surface and a greater thickening of the electric double layer compared with the negatively charged surface, so that electrostatic forces are felt even at large distances (13–15 nm) from the mineral surface. Thus, the autocatalytic process for vesicle formation can occur even without directly contacting the mineral surface. Adapted from [11].

lipid molecules did not occur with the mineral surfaces [15], the surface electrostatic charge could still be ‘felt’ away from the surface [13]. In summary, a combination of electrostatic interactions, hydrogen bonding, and van der Waals forces contributed to lipid adsorption on the mineral surfaces with greater adsorption on positively charged mineral surfaces.

The adsorption and self-assembly of zwitterionic PL on metal oxides was also examined by adsorption affinity and atomic force microscopy studies [59]. Ditridecanoylphosphocholine (DTPC) was found to have oxide-dependent adsorption affinity at 40 °C and neutral pH. The adsorption of DTPC was higher on rutile (α-TiO_2) than on quartz (α-SiO_2), and corundum (α-Al_2O_3) at low lipid concentration (0.65 mM), consistent with a trend of decreasing Hamakar constants (a measure of van der Waals forces) for the above-mentioned oxide minerals. Thus, adsorption at lower lipid concentration was driven primarily by van der Waals forces. However, at high lipid concentration (1 mM), adsorption was highest on corundum followed by rutile and quartz, consistent with decreasing mineral IEP. This indicated greater contribution from electrostatic effects at higher lipid concentrations. Furthermore, at high lipid concentration, the formation of multiple lipid bilayers (up to three) on corundum was observed compared with single bilayers on the negatively charged rutile or quartz. The physical phenomenon of solvent and counterion exclusion from the mineral vicinity, thus, effectively thickening the electric double layer, was responsible for this charge-dependent formation of multiple bilayers at high concentration on positively charged corundum versus a single bilayer or negatively charged minerals (Figure 3) [10,11,59].

The thermodynamics of SCA self-assembly, i.e., the **critical vesicle concentration** (CVC) is also related to the mineral IEP and to the amount of mineral present in suspension [13]. The CVC is defined as the minimum concentration at which stable vesicles are formed. The CVC increased from 1 to 5–7 mM for DA/DOH (2:1) in the presence of positively charged nanoparticulate minerals, e.g., γ-alumina, goethite at 1 mg/ml mineral loading compared with negatively charged mineral surfaces. Adsorption of the negatively charged FA on the positively charged mineral surfaces and settling of the lipid–mineral aggregate caused lipid removal from the solution, thus apparently increasing the CVC. At particles loading less than 1 mg/ml, settling of particle–lipid aggregates was limited and no effect of minerals on CVC was observed. Thus, the apparent CVC of the lipid was affected by surface charge but only under higher mineral loading conditions.

Simple amphiphiles derived from **polyprenols**, the polyprenyl phosphates (C_{15} or more) have been shown to self-assemble into vesicles [62–65] and might also have formed primitive membranes. Montmorillonite clay was found to catalyze the formation of polyprenols [66]. In the reaction, geraniol (C_{10}) and its isomers were synthesized from monoprenols (C_5) in the presence of catalytic montmorillonite. Further, condensation of geraniol with isopentenol resulted in the formation of farnesol (C_{15}) and isomers. The same research group [67] have also shown several addition reactions catalyzed by iron(III) sulfide mineral, which lead to the conversion of farnesol to squalene (C_{30}), a terpenoid. Terpenoids are present in the cells of all living organisms and are involved in stabilizing membranes [63].

Mineral Surface Toxicity – Reactive Oxygen Species

As mentioned earlier, minerals may have facilitated prebiotic chemistry by protecting organic molecules from UV radiation and thermal decomposition, concentrating them through adsorption and, finally, catalyzing polymerization reactions [16,19,68,69]. However, certain transition metal bearing minerals (e.g., pyrite, anatase, rutile, olivine, and pyroxene) could also cause nucleic acid and lipid membrane degradation by the generation of **reactive oxygen species** (ROS), such as (OH^* and H_2O_2), at the mineral surfaces by UV radiation [70–72]. This may have affected the organic inventory on the prebiotic Earth. For instance, titania (TiO_2) phases exhibit bactericidal effect toward *Escherichia coli* and *Pseudomonas aeruginosa* cells by breaking the cell wall through surface-bound hydroxyl OH* radicals [71,73,74]. The generation of specific ROS is dependent on mineral properties (electronic structure, particle size, and IEP), UV wavelength, solution pH, and presence or absence of molecular oxygen [72]. Xu *et al*. [72] identified anatase and rutile as more active ROS generators compared with hematite and other minerals. These authors identified different pathways for ROS generation at the TiO_2 versus α-Fe_2O_3 surfaces, which could be related to their band gaps. In TiO_2 suspensions, OH* radicals were generated mainly through the oxidation of OH^- by holes and H_2O_2 was formed by the combination of an OH* radical with an OH^- and a hole. Thus, ROS generation on TiO_2 could proceed in the absence of molecular oxygen. These results show that even under the anoxic conditions on primitive Earth, such ROS could have caused decomposition of organic molecules. In contrast, the formation of H_2O_2 and OH* in hematite suspensions required the reduction of molecular O_2, and ROS formation was inhibited under anaerobic conditions.

The survival of microorganisms in the mineral–water interface is mainly credited to their ability to form biofilms. Xu *et al*. [71] studied the role of extracellular polymeric substances (EPSs) from biofilms in protecting cells against mineral nanoparticle toxicity. It was observed that wild-type EPS-producing strains of *P. aeruginosa*, PAO1, have greater viability against mineral cytotoxicity as compared with their isogenic (same genotype) mutant, Δ^-*psl*, which has limited biofilm forming capacity. The PAO1 cells were unaffected by the mineral nanoparticles (amorphous silica, anatase, and γ-alumina) as they produced abundant EPSs and eventually biofilm. In contrast, Δ^-*psl* cells demonstrated reduced viability in the presence of minerals. Thus, the EPS provided a physical barrier separating the minerals from the cell.

The highest cytotoxicity was observed in the presence of alumina followed by anatase, and amorphous silica showed minimal or no effect [71]. This trend follows the IEP of the minerals from highest to lowest. High-resolution transmission electron microscopy showed that the alumina nanoparticles entered the EPS-limited Δ^-*psl* cells, while titania nanoparticles remained close to the cell wall without entering the cells, and silica nanoparticles did not come in contact with the cells. The distance of approach of the particles to the cell correlates with the electrostatic forces between the negatively charged cell and the mineral particle with alumina being positively charged, titania having a small negative charge, and amorphous silica carrying a larger negative charge. Alumina killed the Δ^-*psl* cells by intracellular toxicity, while anatase was able to kill bacteria extracellularly because of the presence of surface ROS. Removal of surface ROS by an enzyme abrogated the cytotoxicity of titania.

Furthermore, if the EPS of wild-type PAO1 was removed by gentle washing, the viability of the cells was reduced in the presence of alumina and titania, but the population recovered with time due to the formation of EPS in response to the presence of the minerals [71]. Thus, it was shown that EPS is not just a passive physical barrier but that minerals can induce active formation of EPS in response to their toxicity. These results suggest that the evolution of EPS might have been an adaptation to shield against mineral nanoparticle toxicity and, simultaneously, provided a mode of attachment to mineral surfaces, in addition to providing a protected environment for cells from UV radiation and a viscous medium for passing metabolites, lateral gene transfer, and **quorum-sensing**.

Membrane Energetics with Minerals – Energy Harvesting Systems

A cell membrane is unique in its properties as it separates the cellular components from its environment while providing the barrier to create the chemiosmotic gradient required to drive various metabolic reactions, including the generation of ATP. The walls of pores between mineral grains at 'white smoker' hydrothermal vent chimneys have been proposed to comprise the earliest cell membranes rather than organic molecules [38,40,75,76]. It was further proposed that these mineral membranes could maintain a proton gradient across the membrane originating from the difference in pH between the mildly acidic seawater (pH 5–6) with alkaline vent fluid (pH ~12). In simulated hydrothermal experimental scenarios, 'chemical gardens' analogous to hydrothermal vent chimneys were formed by mixing dissolved Fe^{2+} with sulfides producing inorganic membranes that maintained a transmembrane electrochemical gradient [39,77]. The generated electrochemical gradient may have provided energy for abiotic synthesis of organics. In accordance with this proposal for the origin of life at white smoker chimneys, a chemoautotrophic metabolism, the Wood–Ljungdahl pathway, also known as the reductive acetyl-coenzyme A pathway that operates in some acetogens, has been proposed as the earliest metabolism [38,78,79]. In this metabolism, organisms use molecular hydrogen as an electron donor and carbon dioxide for generating acetate as an end product of anaerobic respiration with Fe–S clusters as cofactors for enzymatic activity. Furthermore, these mineral membranes may have advantages over organic membranes as they remain relatively unaffected by environmental factors such as dissolved ions and temperature. However, it is not clear how protocells with mineral walls would have grown and reproduced.

In a different scenario for the origins of life, some attempts have been made to explore the role of photocatalytic minerals to mimic a photoheterotrophic protometabolism for a hypothesized scenario where life originated at the surface of the Earth [20–22,80]. Photoheterotrophic organisms (e.g., heliobacteria, and purple and green nonsulfur bacteria) use light as their energy source and organic compounds such as carbohydrates and alcohols as the carbon source instead of carbon dioxide. Depending on their band gaps, photocatalytic minerals may have contributed to the development of photoheterotrophic protometabolisms. An artificial photoheterotrophic energy-transducing system is generally composed of: (i) a reductant/terminal electron donor (e.g., ethanol, EDTA, serine, or ascorbic acid) analogous to water in natural photosynthesis; (ii) photosensitizer organic compound or photocatalytic mineral comparable to the Ca–Mn complex in chlorophyll (e.g., ruthenium bypyridinium, TiO_2, CdS, and CdSe); and (iii) an oxidant or terminal electron acceptor comparable to O_2 (ferricyanide ($Fe(CN)_6^{3-}$), NAD, or flavin mononucleotide (FMN).

In a transmembrane electron transfer reaction (TMETR), separation of the terminal oxidant and terminal reductant is achieved by the vesicle membrane. Transmembrane electron transport is a key step in the simulation of a photoheterotrotrophic metabolism. In general, photocatalytic minerals generate an electron-hole pair when irradiated with UV. The electrons are subsequently passed to various electron donors in ETRs. A single step TMETR was demonstrated with dihexadecyl phosphate (DHP) vesicles in the presence of CdS as a photocatalytic mineral, benzylalcohol as a sacrificial electron donor and cetylmethylviologen ($C_{16}MV^{2+}$) as the electron acceptor [20] (Figure 4). In the experimental set up, CdS particles were confined to the inner leaflet of the DHP bilayer and $C_{16}MV^{2+}$ was present both in their inner and outer leaflet of the vesicle bilayer. In the process, $C_{16}MV^{2+}$ was reduced. In a separate study, TMETR was also reported across a DA membrane using only an intramembrane polyaromatic hydrocarbon, that played the role of both photosensitizer and transmembrane electron shuttle, and no photocatalytic minerals were used [81]. As a result of the ETR, ferricyanide ($Fe(CN)_6^{3-}$), an anionic hydrophilic species, encapsulated within the vesicle was reduced to ferrocyanide ($Fe(CN)_6^{4-}$) with extravesicular EDTA as the sacrificial electron donor.

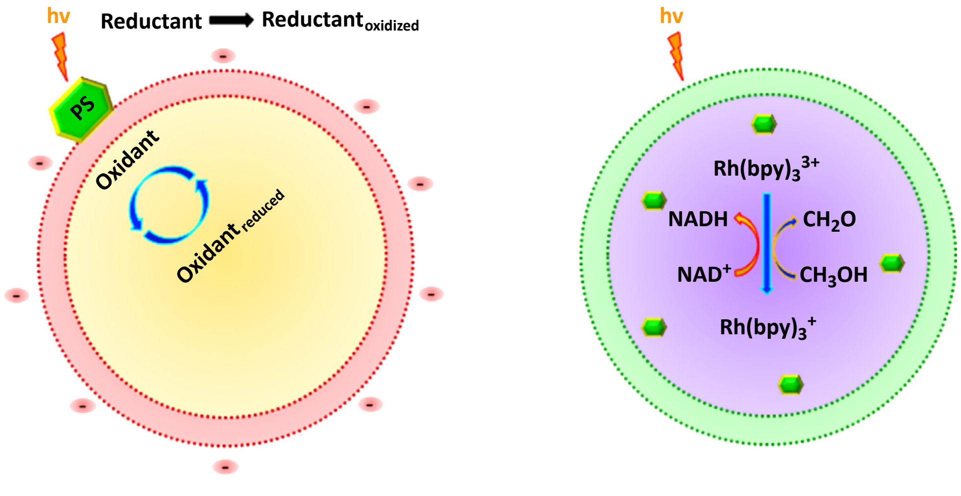

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Figure 4. Schematic Representation of Model Photoheterotrophic Protometabolisms in Lipid Vesicle Systems. Modern metabolism may be characterized as a network of reactions involving coupled, transmembrane electron transfer reactions. Simple protometabolisms have been shown to occur across (left) or within (right) fatty acid or phospholipid vesicle membranes. Green hexagons represent a PS compound or a photocatalyst mineral. In the transmembrane system (left), a PS or photocatalytic mineral promotes electron transfer across the membrane such that the intravesicular oxidant is reduced and the extravesicular reductant is oxidized. This is a single-step transmembrane electron transfer reaction. In the system contained within a vesicle (right), the photocatalytic mineral reduces the oxidant (rhodium trisbypridine, $Rh(bpy)_3^{3+}$) to $Rh(bpy)_3^+$ and the $Rh(bpy)_3^+$ further reduces cofactor, NAD, to NADH. This is a two-step electron transfer reaction, however, there is no transmembrane electron transfer in this system. Thus, each system represents a part of a metabolic system but does not completely show a series of coupled, transmembrane electron transfers. Abbreviation: PS, photosensitizer.

Photo-oxidation of simple molecules (e.g., amino acids and alcohols) is an attractive way of trapping redox energy for one-electron photochemistry; however, driving net two-electron chemistry is a complex process. A two-electron transfer reaction with the photocatalyst, oxidant, and reductant all encapsulated within the volume of a PL or FA membrane has been shown [22] but the experimental set up does not represent a transmembrane reaction (Figure 4). In summary, despite some research conducted on artificial protometabolism, a multistep electron transfer reaction network across a protocellular transmembrane remains a grand challenge in the field.

Fe–S clusters are considered ancient cofactors that may have played important functions in Fe–S-bearing protoenzymes to support a heterotrophic protometabolism on the prebiotic Earth. Fe–S clusters complexed by peptides may have played a transition role between pure Fe–S mineral nanoclusters and enzymes with Fe–S clusters at their active cores. Recently, it was shown that *in-situ* Fe–S clusters (Fe_2S_2 and Fe_4S_4) can be formed by UV illumination of ferrous ions and photolysis of organic thiols inside model protocells composed of FAs. These Fe–S clusters were stabilized by cysteine-containing peptides such as glutathione [82].

Concluding Remarks

Mineral surfaces could have played various roles in prebiotic chemistry with impact not only on the formation and self-assembly of biopolymers but also on their degradation, thus influencing the total organic inventory and its evolution on early Earth. Even after the emergence of life, the evolution of cell membranes and biofilm could have been impacted by interactions with minerals. Chemical and physical characteristics of a mineral such as its chemical composition,

Outstanding Questions

There are many key questions that remain prime research targets with respect to mineral–organic interactions in origins of life studies. Which minerals were dominant on early Earth and other solid planetary bodies and how did their presence influence the aqueous speciation of inorganic ions under the corresponding atmospheric conditions? For example, what were the sources of phosphate on early Earth and what were the mechanisms for concentrating it sufficiently to allow the prebiotic synthesis of nucleotides and phosphate-based lipids?

How did the mineralogical composition and atmospheric composition of the early Earth and other solid planetary bodies influence the pH of surface water and ocean water? In turn, which surfactant molecules could form stable membranes at acidic pHs, which was more likely for the ocean on early Earth and for icy worlds like Europa?

How did the presence of mineral surface ROS affect the chemical inventory on the prebiotic Earth? Can comprehensive studies of mineral reactivity under different environmental conditions help develop predictive relationships about the probability for the emergence of life on other planetary bodies? For example, under which environmental conditions can UV radiation in the presence of minerals promote prebiotic organic molecule formation versus promote their degradation by the generation of ROS?

Can developing structure–activity relationships between mineral properties and specific prebiotic reactions help to develop predictive relationships about the probability for the emergence life on other planetary bodies? For instance, conducting comprehensive studies of the physicochemical properties of minerals, such as their chemical composition, crystal structure, dielectric constant, Hamaker constant, band-gap, particle size, and surface roughness, with, say, the ability of minerals to promote ribonucleotide polymerization or TMETRs.

Are there certain minerals that should be preferred for a targeted study? That is, should the more commonly crystal structure, dielectric constant, Hamaker constant, band-gap, particle size, and surface roughness of the mineral all contribute to interactions of the minerals with organic molecules, water, and inorganic dissolved ions. Finding mechanistic correlations between such properties of minerals and specific interactions with organic molecules and cells allows us to extend our understanding of prebiotic evolution and early evolution of life to other solid environments beyond the Earth. Many research questions regarding the potential role of minerals in the origins of life remain to be explored (see Outstanding Questions).

occurring primary and secondary minerals be examined in greater detail in origins of life studies rather than ad hoc minerals that simply work for a specific prebiotic reaction?

Are minerals necessary for the origin of life, i.e., can life originate on planets that do not have a rocky surface?

Acknowledgments

We acknowledge financial support provided by NSF-EAR grant (EAR-1251479), Simons Foundation Origins of Life Initiative award (290359) and start-up funds from the University of Akron, USA.

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