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Self-reproducing catalytic micelles as nanoscopic protocell precursors

Amit Kahana and Doron Lancet

Abstract | Protocells at life's origin are often conceived as bilayer-enclosed precursors of life, whose self-reproduction rests on the early advent of replicating catalytic biopolymers. This Perspective describes an alternative scenario, wherein reproducing nanoscopic lipid micelles with catalytic capabilities were forerunners of biopolymer-containing protocells. This postulate gains considerable support from experiments describing micellar catalysis and autocatalytic proliferation, and, more recently, from reports on cross-catalysis in mixed micelles that lead to life-like steady-state dynamics. Such results, along with evidence for micellar prebiotic compatibility, synergize with predictions of our chemically stringent computer-simulated model, illustrating how mutually catalytic lipid networks may enable micellar compositional reproduction that could underlie primal selection and evolution. Finally, we highlight studies on how endogenously catalysed lipid modifications could guide further protocellular complexification, including micelle to vesicle transition and monomer to biopolymer progression. These portrayals substantiate the possibility that protocellular evolution could have been seeded by pre-RNA lipid assemblies.

A key question in the study of life's origin is how an abiotically formed mixture of non-living chemicals gave rise to the first reproducing and evolving protocells — prebiotic precursors of living cells. This Perspective suggests that such an early transition was made possible by the emergence of micellar protocell precursors, much simpler than the widely explored vesicle-based protocells[1,2]. This is based on a growing body of evidence that lipid micelles are capable of harbouring catalysis, forming catalytic networks undergoing self-reproduction and passing compositional information from one generation to the next[3,4]. We, thus, propose that micelles composed of molecularly diverse amphiphiles could be evolutionary precursors to more elaborate protocellular entities, en route to life as we know it.

Protocells are typically described as self-reproducing, membrane-enclosed assemblies of mutually interacting compounds[1,5]. Crucial to the function of a protocell is the capacity of its molecular constituents to self-copy, a requirement for subsequent Darwinian selection and evolution. In one origin of life scenario, the protocell includes vesicle-enclosed ribozymes that control their own replication[1,6]. In another scheme, the reproducing chemical entity is a population of small molecules, such as oligopeptides, that form a self-copying collectively autocatalytic set (CAS)[4,7–11], contained within a lipid vesicle[12].

However, for an entire protocell to breed true, the internal content has to synchronize kinetically with amphiphiles that make up the container[13]. This may happen by internally catalysed amphiphile production[14,15] or accretion[2,3], and, in parallel, through lipid-assisted polymerization of nucleotides[16,17]. More generally, a requirement for successful protocellular reproduction is kinetic coupling between the inner molecular network and the membrane components[12] through specific, mutually catalytic interactions. Therefore, it is important to examine the capacity of lipids and their assemblies to manifest catalytic properties, a notion that is rarely invoked in both the origin of life and the biochemistry literature.

In this Perspective, we explore the widespread experimental evidence for lipid micelle catalysis, including emerging recent accounts on life-like dynamic attributes of mixed micellar assemblies. In addition, we highlight the agreement between these experimental observations and results from our well-documented chemical kinetics model, wherein we regard the capacity of lipid assemblies to compositionally reproduce and pass on information to progeny. Taken together, such published accounts support the premise that lipid assemblies may well have played a central role in protocellular emergence and function, both in the traditional role of compartmentalization and in the unorthodox capacity for catalytic self-copying of chemical information[18]. In this case, information is composition-based, akin to non-genetic (epigenetic) information, such as the spectrum of lipids, proteins and RNAs, which are passed on by present-day cells[19]. We, thus, put forward the idea that lipid micelles are strong candidates for initiating evolutionary processes that subsequently enabled the advent of biologically relevant biopolymers.

Protocellular lipids

In accounts of present-day life, lipid-mediated catalysis is largely non-existent — once high-fidelity protein and RNA catalysts emerged, lipids gradually specialized in chemistries that underlie effective containment, including barrier formation, material transport and signal transduction. However, primordial lipids appear to have been much more structurally and functionally diverse[20,21]. This likely encompassed head groups with catalytic moieties, allowing a broad spectrum of chemical characteristics, including selective enhancement of reaction rates[22], as portrayed in the next section. Thus, protocellular lipids could harbour both catalysis and compartment-forming features, justifying the term 'lipozymes' for early lipid assemblies in a 'lipid world' scenario[23].

Terrestrial infall as well as energized synthesis appear to have led to a tremendous primordial chemical diversity or 'messy chemistry'[24], inhabiting various water bodies, sometimes referred to as the

prebiotic soup[24]. This likely included a considerable assortment of amphiphilic molecules as found in carbonaceous meteorites[25–27] and, as recently reported, in computationally derived networks of prebiotic chemical reactions[10]. It is, therefore, appropriate to consider simple lipid molecules as prebiotically prevalent and chemically diverse, essential for their proposed significance at the dawn of life.

The biological repertoire of lipids has certainly changed since the prebiotic origin, so it is important to note the inherent differences occurring along the timeline. Thus, while contemporary membranes contain mainly diacyl lipids, protocellular model membranes, as well as early micelles, likely comprised simpler amphiphiles and lipophiles. These could include single-chain fatty acids, along with isoprenoids and polycyclic aromatic hydrocarbons[26,28]. Thus, amphiphiles may have undergone differential accretion in aquo to form micelles or vesicles based on their chemical structure[29] and concentration[30], as well as environmental temperature, pH, ionic strength and concentrations of divalent metal cations[31,32]. Therefore, it stands to reason that, in various niches on the ancient Earth, there would have been varying mixtures of mutually interacting vesicles and micelles.

Micellar protocell precursors

A widely accepted protocell model consists of a microscopic vesicular structure with a lipid bilayer enclosing a watery core. Vesicular protocells have two advantages when compared with micelles: first, vesicles have a much larger surface area that enables a greater number of functional molecules to attach. Second, their enclosed aqueous core may contain a variety of protocellular molecules, affording their mutual interactions. Though micellar protocell precursors do not possess both characteristics, they have several advantageous attributes for early evolution. Herein, we explore the unconventional hypothesis that very early protocellular precursors were nanoscopic lipid micelles and address their eventual necessary transit to vesicular form.

In terms of proliferation, micelles are similar to vesicles — both can undergo assembly growth and fission[33–35] (FIG. 1). In parallel, micelles have numerous properties that are advantageous when compared with vesicles in an early prebiotic context (FIG. 2). A key micellar advantage is nanoscopic size (FIG. 2a). While a micellar protocell precursor would typically be composed of several hundred amphiphiles, a 1-μm vesicular protocell would require several orders of magnitude more. In addition, the large size of vesicles could compromise the collision capacity needed to establish effective mutual interactions[36], whereas the nanoscopic micellar dimensions have the potential to better support all-against-all mutual catalysis, critical for reproduction[3]. Small dimensions could also enable novel network states through only a few compositional mutations[4]. Finally, small assemblies formed in a highly heterogeneous chemical environment would each statistically acquire different lipid blends, resulting in a combinatorial library, which could constitute a basis for selection processes[3,19].

Other micellar advantages include an augmented surface to volume ratio (FIG. 2c) and very high reactant concentrations (FIG. 2d), as well as facile formation due to substantial chemical promiscuity regarding lipid size, geometry and functionality (FIG. 2b). The latter renders micelles compatible with the chemically diverse planetary prebiotic environment[3]. Although the micellar scenario entails the loss of an aqueous core, with its payload of life-related polar compounds, lipid micelles can adsorb and/or enclose diverse molecules with a wide range of polarities. This is mediated by a gradient between the polar surface Stern layer, the more apolar palisade layer and the lipophilic micellar internal core[37] (FIG. 2f).

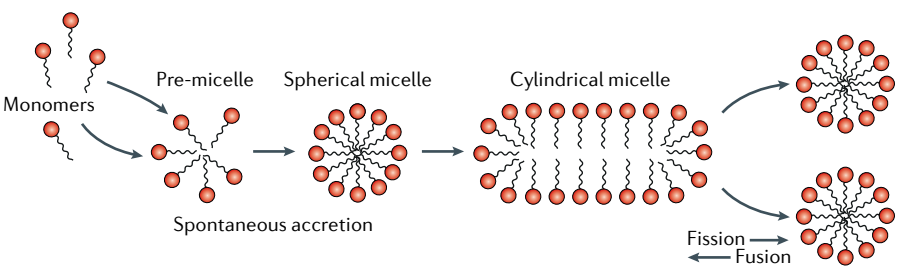


Fig. 1 | **Dynamics of micellar proliferation.** Micelle growth and fission: the progression includes (from left to right) spontaneous monomers accretion, pre-micelle nucleation towards a spherical micelle, the emergence of unstable states exemplified by elongation and fission[33–35]. In high aggregate concentrations, fusion between micellar assemblies can also occur.

As stated above, protocellular reproduction necessitates the involvement of catalysis. Rewardingly, there is remarkable literature on micellar lipid catalysis[38,39], which has accumulated over several decades, as summarized in many monographs and reviews[37,40,41]. Numerous studies provide detailed information on the catalytic roles of diverse amphiphilic lipid molecules in a variety of micellar entities (FIG. 3). In parallel, there is also ample evidence of lipid-mediated catalysis in vesicular bilayers[42]. However, although some of these papers[16,43] report that lipid catalysis takes place due to encapsulation within the vesicular aqueous core, the majority[15,17,38,39] present evidence that lipid catalysis occurs within the bilayer or in direct interaction with it, showing an analogy to the underpinnings of micellar catalysis, as described below.

Micellar catalysis is sometimes attributed to physicochemical properties such as surface augmentation, reduced dimensionality[3], enhanced concentrations and effective lateral diffusion[44] (FIG. 2c–e). In these aspects, it may resemble catalytic, prebiotically invoked[45] mineral surfaces (FIG. 2g). However, there is considerable evidence for the involvement of specific lipid chemical moieties, such as an amino acid[46] (FIG. 3a), a peptide[47], a metal chelator[48] and mixed-domain head groups with molecular recognition traits[35,49] (FIG. 3b). Such specific catalytic groupings are conceptually more analogous to the pivotal residues of protein enzymes (FIG. 2h). Indeed, many accounts of micellar catalysis highlight remarkable points of similarity between micelles and globular protein enzymes, including exceptional rate accelerations[50] and the involvement of dynamic aptamers[51], including catalytic dyads and triads[42,52] (FIG. 3c). In this vein, micelles can impart specific catalytic selectivity, stabilizing the relevant transition state by precise lipid interactions, and affording reaction stereospecificity[37,47,53] and substrate selectivity[54] (FIG. 3d). An extreme example of macromolecular similarity are micelles that form conformationally stable non-covalent structures[55], highly resembling folded proteins. Some of the above catalytic attributes provide compatibility with aqueous prebiotic scenarios, eliminating the need for organic solvents, which are replaced by mixed-polarity lipid constituents. Similarly, prebiotic environmental heterogeneity challenges are addressed by micellar catalytic flexibility and micellar intake of dilute reactants promotes the

generation of augmented concentrations (FIG. 2d), which supports mutually catalytic interactions.

Reproducing catalytic micelles

The proposed role of lipid micelles as early nanoscopic, life-like protocell precursors receives a strong backing from studies of catalysis-mediated micellar growth and proliferation. This relates to cases in which micelles catalyse the metabolism-like modification or production of micelle-joining amphiphiles. In pioneering studies by Luisi and colleagues, fatty acid micelles were found to catalyse the hydrolysis of a precursor, leading to autocatalytic micellar reproduction[44,56]. Evidence is also demonstrated for the covalent synthesis of micelle-forming amphiphiles from separate head and tail compounds[57,58]. This process is proposed to be catalysed by reactants' proximity within the micelles (physical autocatalysis)[57]. In parallel, there is evidence for the involvement of more specific molecular recognition paths[58], including a resemblance to template-based self-replication[35] (FIG. 3b). Such findings may suggest similar overall principles in the chemical dynamics of micelles and in living cells, including absorption of environmental compounds, metabolism-like processing, growth and proliferation[59] (FIG. 1).

From these examples, the realism of life-mimicking autocatalytic growth and self-reproduction is demonstrated. However, such single-amphiphile systems fall short of capturing the molecular diversity of living cells and the consequential emergence of multicomponent catalytic networks. Furthermore, single-component micelles transfer trivial information from one generation to another, whereas mixed micelles harbour significant compositional chemical information, which may be transmitted to the next generation and mediate elementary selection[60]. Finally, with the immense chemical heterogeneity of the prebiotic milieu[24], multicomponent micelles could form with a much higher probability than single-component ones. These arguments point to the relevance of recent studies focusing on heterogeneous catalytic micelles.

Life-like catalytic mixed micelles

An important step towards catalytic mixed micelles has been recently reported[58], whereby, in addition to the catalytic lipid and its building block reactants, several secondary catalysts were also tested for their capacity to further enhance the rate of lipid formation. The most hydrophobic catalyst was most effective, reflecting its propensity to join the micelle and exert its rate enhancement within the same compartment. However, these experiments still involve only a single lipid product.

In a later paper[61], a more complex case of catalytic mixed micelles was examined, using one head group and three different tail group precursors (FIG. 4a). In a flow reactor under kinetic control, the three produced lipids assumed different dynamic steady-state concentrations. Such asymmetry was attributed to autocatalytic and cross-catalytic effects prevailing among the employed micellar components. These results, observed in a reproducing multimolecular assembly, whereby a predominant lipid can emerge from the pool of equimolar competing precursors, are described as exhibiting life-like selection[61]. Significantly, when this system is allowed to progress towards equilibrium by stopping the reactor flow, a side product, which has a higher thermodynamic stability, assumes dominance in the reactor. This highlights the unique stationary non-equilibrium state prevailing while the flow is activated. A recent continuation paper[62] provides further evidence for life-like properties of self-assembling, self-reproducing protocell models. A competition among amphiphilic compounds is presented, governing the structural features of the formed assemblies, as well as revealing dissipative self-assembly dynamics. Overall, the experiments described above show that even a simple mixed amphiphile system can display more complex life-like behaviour, including reproduction, selection and potential evolution.

Another revealing case of catalytic mixed micelles is embodied in a system in which the self-reproduction of micellar aggregates results in a spontaneous amplification of chiral excess[53]. The system includes two

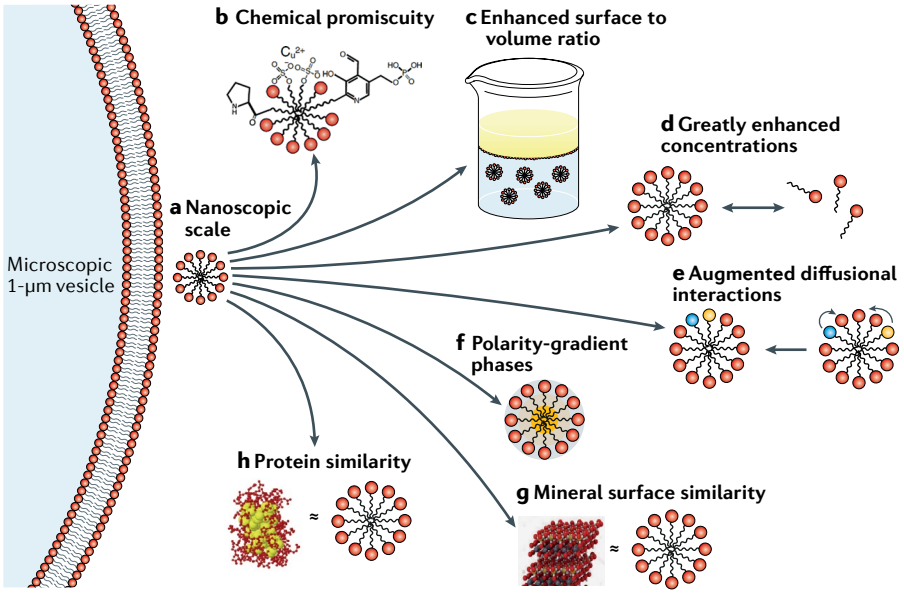
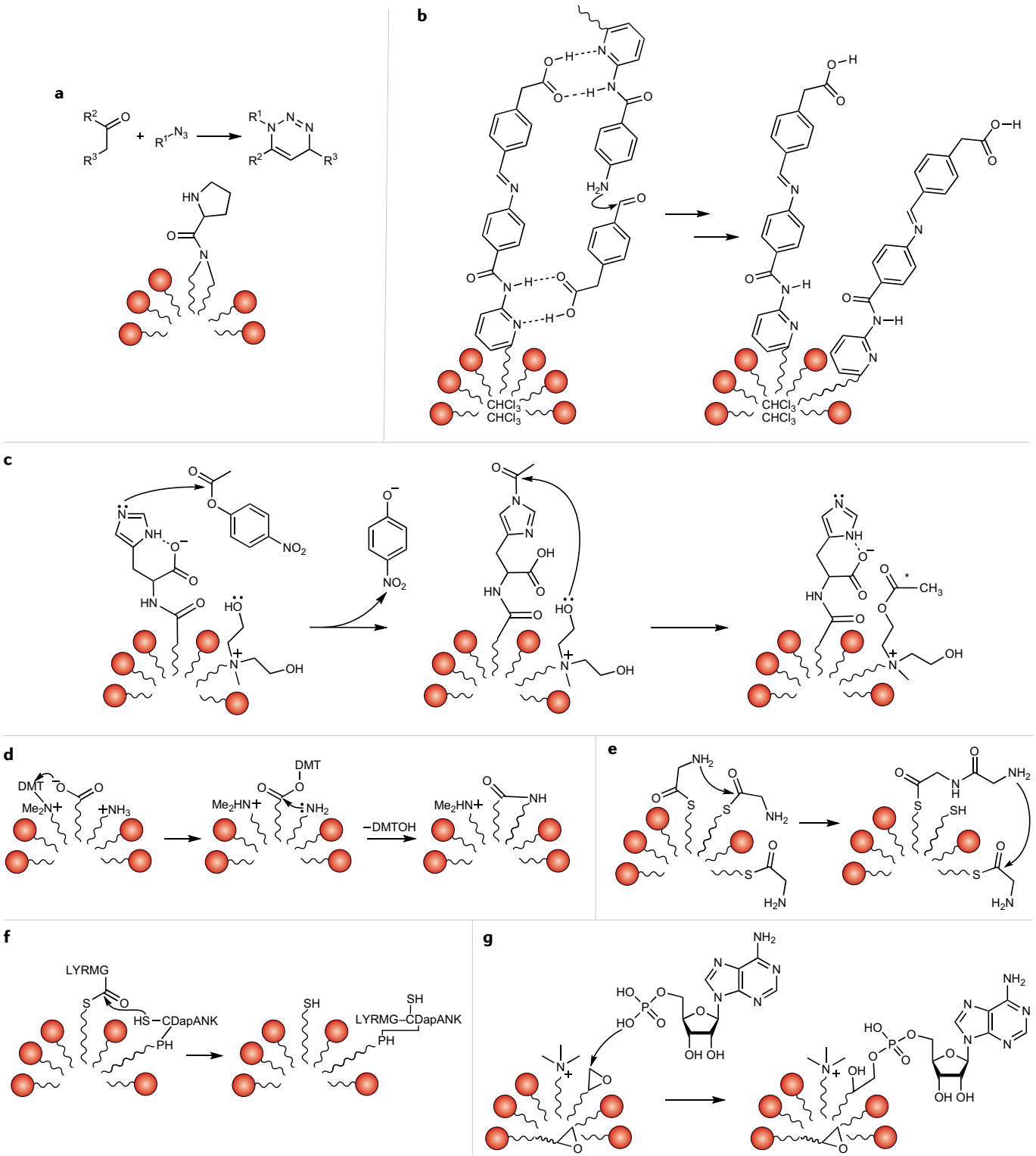


Fig. 2 | **Advantages of micellar systems for priming early life. a** | Nanoscopic scale: micelles that typically contain 100 amphiphiles are superior to vesicles with millions of monomers, as they are much more sensitive to compositional changes and allow more effective all-against-all mutually catalytic network interactions. **b** | Chemical promiscuity: micelle formation is compatible with a broad spectrum of chemical moieties of different sizes, geometries and functional groups[42]. Therefore, micelle formation is more probable in comparison with vesicles, under prebiotic environmental conditions. **c** | Enhanced surface to volume ratio: this allows much higher activity for surface catalysis[61]. **d** | Greatly enhanced molecular concentrations: in pure amphiphilic bulk, molecular concentrations could reach one molar, which is several orders of magnitude larger than in a vesicular core or the external environment. **e** | Augmented diffusional interactions: this results in reduced dimensionality, which leads to an enhancement of binding and rate parameters, accompanied by fast lateral diffusion[104]. **f** | Polarity-gradient phases: micelles can accommodate diverse compounds with contrasting polarities, distributed at the Stern layer, the intermediate palisade layer and the hydrophobic core, which generates a polarity gradient conducive to enhanced catalytic interactions[37,126]. **g** | Mineral surface similarity: micellar catalysis bears a strong resemblance to heterogeneous catalysis on mineral surfaces, a phenomenon widely invoked in prebiotic catalysis reports[45]. **h** | Protein similarity: micelles and globular proteins share similar dimensions (5–20 nm in diameter); structure, with a hydrophobic core and a polar surface; and diverse catalytic capacities[42].



asymmetric head group enantiomers and a single symmetric apolar tail. When partially enantioenriched head precursors are used, strong enantioselection is observed in the lipid-catalysed micellar lipid production (FIG. 4b). This is another noticeable case in which one possible micellar product is kinetically selected over another. The authors point out that being capable of self-assembly, catalysis and cross-generation, compositional information transfer presents a plausible model for pre-polynucleotide lipid world scenarios.

A highly related case of lipid-catalysed covalent synthesis, realized in lipid vesicles with direct relevance to micellar assemblies, provides similar insights[38]. In this multicomponent system, a lipid-chelated Cu^{I} catalyst promotes the formation of another lipid, as well as itself, from head and tail reactants. This system is shown to formally constitute a lipid-embodied, mutually catalytic network[3]. Significantly, this experimental setup also

◀ Fig. 3 | **Representative cases of micellar catalysis.** Catalytic chemistry can be enacted by lipid-attached functional moieties on a micellar surface. The substrate and/or product may be lipid attached (*cis*) or, alternatively, reside in the external environment (*trans*). **a** | Ketone-azide cycloaddition, which forms a triazole, directly catalysed by a proline-derivatized lipid (*trans*)[46]. **b** | Autocatalytic stereospecific synthesis of amphiphilic imines (*cis*) from head and tail precursors directed by molecular recognition. The resultant lipid flips to join the micelle, leading to micellar proliferation[35]. **c** | Esterolysis of p-nitrophenyl acetate by a histidine-derivatized lipid, which turns over by a second lipid (*trans* with *cis* intermediates). The reaction mechanism mimics that of the chymotrypsin catalytic triad, with rates comparable with those of the enzyme[52,127]. Hydrolysis occurs to yield an acetic acid leaving group, thus, the micelle returns to its original state (indicated by an asterisk). **d** | Multistep selective formation of peptide-like amide bonds via dehydrocondensation of amphiphile head groups (*cis*), kinetically facilitated by a lipid-attached dimethoxytriazine (DMT)[54]. **e** | Catalysed synthesis of a lipid-attached oligoglycine (2–7 units) from S-alkyl ester lipids (*cis*)[102]. **f** | Concatenation of thiol-linked lipopeptides to form a longer, biologically relevant peptide by native chemical ligation (*cis*)[103]. **g** | Synthesis of an adenosine monophosphate (AMP) nucleolipid with an active epoxydodecane apolar precursor, catalysed by the cetyltrimethylammonium bromide (CTAB) lipid salt (*cis*). This reaction type shows regioselectivity for the AMP–UMP admixture, potentially stemming from nucleotide base pairing[110]. Dap, non-encoded amino acid 2,3-diaminopropionic acid; PH, photocleavable linker.

portrays selection, whereby longer tails are catalytically incorporated at higher propensity into the three-tailed lipid catalyst. Furthermore, on serial transfers, the inert carrier lipid is diluted, and the catalytically synthesized ones become dominant through a selection-like process. The results are described as relevant to modelled lipid-based prebiotic systems, which may propagate their chemical composition and exhibit homeostasis.

While in the above study covalent bond formation was attained by somewhat elaborate Cu^{I}-catalysed click chemistry, similar results have been reported, whereby diacylphospholipid was catalytically synthesized within micelles, using a prebiotically compatible fatty thioester[63]. In the same vein of prebiotic compatibility, we remark that insights on micellar reproduction are typically obtained with uncomplicated experimental setups. Only a few studies have employed a more complex apparatus, such as a flow reactor mentioned in this section, a technology used to specifically obtain guiding concepts regarding early non-equilibrium steady states.

The studies described above focus on micellar growth processes mediated by catalysed covalent synthesis or hydrolysis. Analogous phenomenology has been described for assembly growth that takes place through lipid catalysed non-covalent accretion of environmental lipid monomers[64]. In one relevant study, small concentrations of long-chain fatty acids augment the rate of incorporation of short-chain ones into vesicles[65]. An apolar membrane-joined peptide was also reported that can enhance fatty acid uptake into vesicles[2]. Similarly, selective non-covalent anchoring of functionalized lipids in vesicles[66], and the capacity of specific lipid compositions to promote the stereospecific partitioning of organic compounds into mixed inverse micelles[67] and mixed liposomes[68], have been observed. Along similar lines, the local[69] or global[70] composition of vesicular membranes may affect the kinetics of micelle–vesicle fusion. Such studies further support the notion that catalysis-mediated growth of mixed lipid micelles, whether involving covalent or non-covalent reactions, may have played an essential role in life's emergence.

Modelling micellar reproduction

The accounts above involve experiments with rather limited molecular repertoires. The next step should tackle more complex molecular networks and examine their capacity to reveal more elaborate life-like properties, such as dissipative non-equilibrium dynamics[62,71], more intricate selection properties and primitive evolution. This constitutes a major challenge to present-day experimental technologies, suggesting a need to pursue certain advanced computational analyses in parallel[10,72]. Such an approach is embodied in the increasing success of systems chemistry in addressing prebiotic evolution[73], along with the advent of systems protobiology[3,4] to help guide future protocell experimentation[5,74,75].

In this vein, in the past two decades, computer-based methodologies have been applied to fathom the dynamics of growth and fission of mixed lipid assemblies, addressing both catalysed lipid accretion[18,76] and synthesis[77]. This was done in the context of a prebiotic lipid world scenario[23], based on the graded autocatalysis replication domain (GARD) chemical kinetics model. GARD is affiliated with the concept of membrane heredity, which points out that cell inheritance depends on the direct genetic continuity of membranes[19,20,78], mediated by molecular complementarity of membrane proteins, and by membrane lipid composition[79,80]. Furthermore, GARD is based on away-from-equilibrium, free-energy-dependent formalism, general enough to be consistent with any set of amphiphilic chemical compounds. For GARD modelling, chemically realistic differential equations were employed with experiment-based parameters that address lipid diversity[18]. Based on this model, Monte Carlo computer simulations of catalytic micelles were performed, with an exterior lipid repertoire of 30–300 types[3]. We note that such computational methodologies are known to faithfully mimic experimental results in realms such as surface diffusion, crystal growth and heterogeneous catalysis[81,82], all of which are relevant to micellar dynamics.

Importantly, GARD simulations of mutually catalytic networks provide strong support for the validity of the CAS concept[7,83]. Specifically, such simulations, performed in a mixed micelles framework, have shown self-copying[84] and catalytic closure[3], two centrepieces of the CAS literature[7]. Furthermore, the simulations also demonstrated that only rare catalytically closed sets, those with privileged chemical compositions (composomes), are capable of homeostatic growth, in line with similar suggestions[85]. Such monomer accretion behaviour enabled these unique molecular assemblies to transmit compositional information along growth-split cycles, a process synonymous with self-reproduction[3,4,85,86]. This key evidence was obtained by using widely acclaimed kinetic methodologies in the realm of dynamic chemical reaction networks[87–89].

Notably, these simulations present dynamics that highly resemble the operational principles of present-day living cells, in which metabolic networks allow homeostatic growth, manifested in the doubling of all molecular counts prior to cell division[90] or in lipid composition stability during organelle proliferation[91]. It is also akin to the above-mentioned experiments with mixed micellar steady states along continuous growth and split dynamics[61], which demonstrate kinetically controlled micellar compositions consistent with compositional homeostasis. The authors point out that these findings may have implications for the evolution of amphiphile-based prebiotic chemical systems[61], a view strengthened by a connection between self-sustainability and heredity[92].

It is legitimate to ask whether self-reproducing micelles could supplant

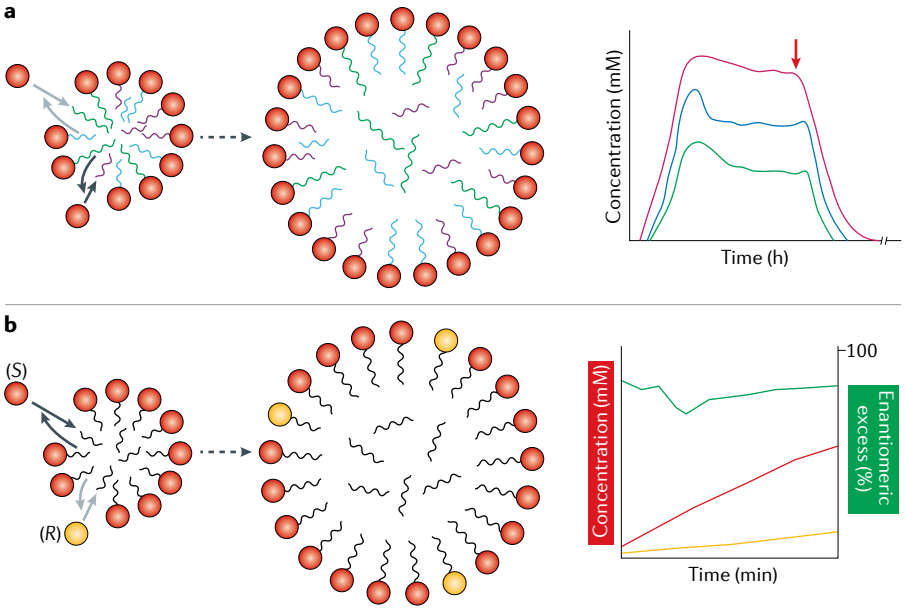


Fig. 4 | **Selection in heterogeneous catalytic micelles. a** | An experimental system based on micellar synthesis of lipids from one head and three tail precursors of different lengths, which shows non-equilibrium compositional selection among the three different catalytically synthesized lipids (different colours)[61]. A flow reactor is fed with heads and tails, which initially get synthesized slowly at a macroscopic phase interface, and then reveals exponentially increasing formation rates as more micelles form and proliferate. Different kinetically controlled steady states are attained (right), based on unequal values of micellar autocatalytic and cross-catalytic effects acting on different precursor substrates (left). One explanatory scenario for the system steady state is that different tail concentrations prevail within growing individual micelles (centre). When flow is stopped (red arrow), a competing lipid decomposition process leads to a non-lipid product that is more stable at equilibrium. **b** | A mixed micellar system portraying attributes of self-reproduction and selection[53]. Amphiphiles are synthesized from a hydrophobic tail and one of the two enantiomers of a chiral, water-soluble head group. Micelles form by a process as invoked in panel **a**, leading to catalytic formation of more amphiphiles and micelles. As in panel **a**, unequal mutual catalytic values are at work (left), hence, differential rates of production for the two lipidic enantiomers. In this particular case, autocatalysis is strong: on seeding a racemic reaction mixture with micelles enriched with the (*S*) enantiomeric lipid, an (*S*) enantiomeric excess is preserved along micellar growth (centre), shown in the graph (right, colour code representing the enantiomers).

the evolutionary feats of replicating polynucleotides[93]. Indeed, it has been contended that digital information in RNA may be stored and propagated more accurately than compositional information in lipid assemblies. However, detailed scrutiny shows that the self-copying capacities of micelles, despite being imprecise, result in evolution-supporting behaviour, with low sensitivity to lipid repertoire size[3,94]. In one example, non-equilibrium simulations of reactors with a large number of micelles[76] demonstrate how several micellar populations, each with its typical lipid composition, compete with each other and portray variable reproductive success, as assessed by micelle copy numbers. Crucial support for this phenomenology is provided by the non-equilibrium multi-assembly reactor experiments[53,61,62]. These simulations[76] also show differential uptake of individual lipid molecule types — a crucial facet of such survival of the fittest behaviour. Yet, natural selection happens at a supramolecular (systems) level, with the composition of multi-lipid assemblies playing a role akin to that of the sequence of RNA. Notably, micellar populations portray dynamic behaviour[95] analogous to that of RNA quasispecies[96], including compositional mutations showing error catastrophes[95]. In parallel, another simulation study[94] showed that the reproductive fitness of different micelles is dependent on the environmental presence/absence of individual lipid types. All these reports support a similarity in evolutionary functional outlines between the two systems: reproducing lipid micelles and replicating polynucleotides.

Evolutionary prospects

The above-mentioned portrayals demonstrate a potential for catalytic micellar protocell precursors to store and transmit chemical information to the next generation, and to undergo compositional reproduction and selection, a basis for primal evolutionary attributes. As such, micellar protocell precursors constitute an appropriate departure point for a gradual evolutionary progression towards more complex protocells (FIG. 5). In this realm, it is obligatory to delineate how the supramolecular complexity of micelles composed of simple molecules leads to increasing molecular complexity, as embodied in sequence-based biopolymers[97]. We envisage that the first steps relevant to such progression would be instances in which bio-monomers and bio-oligomers serve as functional lipid head groups[22] (FIGS 3a,c,e–g,5c). Such modified lipids have recently shown to be generated by prebiotic chemical activation[98] and through wet–dry cycles[99]. Additional reports show micelle-catalysed oligopeptide synthesis and elongation[100–103] (FIG. 3d,e). Potentially, these condensation reactions could have been mediated by reduced hydrolysis in a partially non-aqueous lipid environment[104]. Similar outcome is secured by wet–dry cycling[16,105,106], where a ratcheted kinetic trap mechanism is at work[107].

In the realm of nucleic acids, several studies report micellar nucleolipid chemistries (FIG. 5d). These include a lipid-attached ribozyme that catalyses oligonucleotide elongation[108]; lipids with nucleobase head groups that catalyse an aromatic dephosphorylation reaction[109]; a role for complementary base pairing in modulating micellar nucleolipid synthesis[110] (FIG. 3f); and the observation of sustained Watson–Crick base pairing between nucleolipids at a micellar surface[111]. Having lipid-attached amino acids and nucleobases on the same micellar surface could, thus, promote the co-evolutionary synthesis of peptides, oligonucleotides and other biomolecules, embodying even more life-like mutual interactions[98,112,113]. The prebiotic sources of free energy and catalysis for oligomer elongation reactions have been described in considerable detail[114–116].

In another realm of expected evolutionary complexification, it is necessary to seek plausible chemical paths from micellar to vesicular lipid assemblies (FIG. 5e). Rewardingly, such transitions are well documented[117], based on changes in the lipid admixtures, hence, varying the packing geometry of the assembly constituents[29]. In one case, micellar composition was altered by the in situ catalytic synthesis of a two-chain lipid from simpler precursors[118]. In another case[119], reductive disulfide cleavage of a micelle-compatible gemini lipid

induces a transformation to vesicles. In a more life-like case, a recent report[63] shows that micellar-enzyme-free synthesis of natural two-chain phospholipids is accelerated by synergy between charge interactions and intramicellar proximity. This allows gradual compositional alterations, resulting in a structural transition towards vesicles. Finally, we note that micelle to vesicle transitions may be induced by environmental changes, such as varying ion concentrations, which translate to chemical modifications of micellar components[21,28]. In the framework of lipid assemblies capable of compositional inheritance, the ensuing lipid aggregation states would be passed along composition-preserving reproduction trajectories[62]. Once vesicles become dominant, their membrane catalytic components[120] and core content have to be jointly reproduced[13] (FIG. 5), as addressed under the title 'metabolic GARD'[3] and elsewhere[85].

The orderly serial progression we describe is a simplified process (FIG. 5). In a more realistic evolutionary scenario, lipid assemblies will form haphazardly, generating mixtures of vesicles and micelles, depending on lipid types and environmental ionic compositions. In this scenario, micelles and vesicles would readily interact with each other, including feeding of micellar lipids into coexisting vesicles[69,70,121], which may drive assembly proliferation and support micelle to vesicle progression. As part of the expected compositional variability, hybrid vesicular membranes could form, which involve both micelle-promoting and vesicle-promoting monomers[122], with stabilizing effects[123]. We note that, in some cases, changes in lipid concentrations[30] or admixtures[119] could also lead to reverse transitions from vesicles to micelles.

A major challenge for further experimental progress is to attain self-reproduction at a much higher chemical heterogeneity than employed so far, as befits life processes. Some suggestive tips for future experimentation in this realm may be derived from predictions of the GARD model. These relate to the tendency of GARD assemblies to undergo selection for replication[124], explainable by prevailing attractor dynamics[3,95]. This behaviour is similarly observed in other computational analyses of chemical networks[125], as well as by experiments with mixed micelles, which attain the same compositional target state, irrespective of initial conditions[61]. If realized, such attractor behaviour would narrow the experimental search space for heterogeneous micellar protocell precursors.

Conclusions

Life arose from chemical entities that could harbour both catalysis and reproduction. An acknowledged embodiment for such duality is polyribonucleotides, widely considered crucial for life's origin. This Perspective provides evidence that lipid micelles may be endowed with a similar chemical duality. On the one hand, we present extensive literature supporting catalytic properties of lipid micellar aggregates, thus, bearing similarity to globular proteins in structure, size and underlying chemical functionalities. On the other hand, we reveal strong evidence that mixed lipid micelles can generate their own copies by growth and fission, mediated by collectively catalytic interactions. Such observations lend credence to the proposition that nanoscopic micellar protocell precursors could serve as evolutionary forerunners for more complex protocells.

Furthermore, micelles offer a considerably more parsimonious origin path than the competing models. First, these reproducing non-covalent nanoscopic assemblages form spontaneously in environments of high molecular heterogeneity and extreme physical conditions. This is in contrast to the unlikely covalent stringing of selected monomers in an orderly sequence necessary for biopolymer replication.

Second, for micelles, the same molecular assemblies that mediate collective catalysis and reproduction also delineate spatial containment. This contrasts with a process in which, en route to protocells, biopolymers have to join forces with a separately formed, chemically orthogonal lipid container. In other words, micellar aggregates made of appropriately functionalized lipids appear to be the only chemical entities that possess the three pillar attributes of life-like function in one go — catalysis, reproduction and containment.

The recently published pioneering results on non-equilibrium reproduction in heterogeneous lipid micelles via endogenous, mutually catalytic interactions have strengthened previous studies on the reproduction of autocatalytic single-component micelles. Importantly, when the new experiments were performed in a flow reactor setting, the participating compounds showed a kinetically controlled steady state, such that they preserved their relative amounts over time. Such homeostatic behaviour echoes the chemical kinetic simulations, in which homeostatic growth followed by random fission is shown to be equivalent to compositional information transfer across generations, a life-like process that can support natural selection.

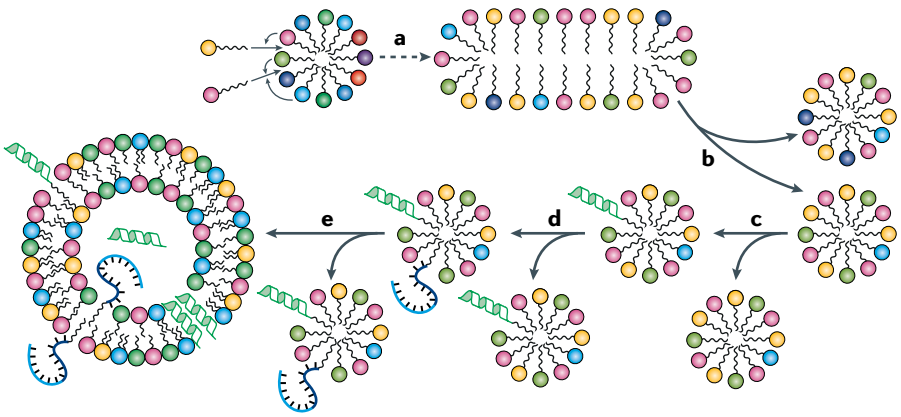


Fig. 5 | **Micellar reproduction and evolution. a** | According to the graded autocatalysis replication domain model, mutually catalytic interactions between micellar lipids and free lipidic monomers in solution influence the rates of entry (and exit) of monomers into (and from) the micellar assembly[3,18]. On catalysed growth, micelles are shown to eventually assume specific lipid compositions (composomes) with narrower lipid repertoire. Graded autocatalysis replication domain simulations show that such kinetically instructed compositions exhibit homeostatic growth. **b** | The grown micelle splits while transmitting its compositional information to the next generation, in other words, it is reproducing[3,18,76]. **c**,**d** | On growth and splitting, homeostatic compositional reproduction (curved arrows) with mutations (straight arrows) may involve both non-covalent accretion depicted in panel **a** and covalent lipid modifications, as occurring in certain catalytically reproducing heterogeneous micelles[61]. These reactions could, among others, involve catalysed oligomerization of micelle-attached amino acids and nucleotides (green, α-helical peptide; blue, short folded RNA). **e** | Some lipid modifications, such as a conversion of single-chain to double-chain lipids, could result in a micelle to vesicle transition, including the addition of core content and transmembrane molecules. The sequence of events depicted here portrays a gradual progression from micelles that undergo purely compositional inheritance to more elaborate vesicular protocells that embody sequence-based replication and core metabolism[3].

Glossary

Accretion
Gradual growth in size by external addition.

Breed true
Producing offspring of a similar breed or variety.

Catalytic closure
A state of a molecular network where the formation of each molecule in the set is catalysed by at least one set member.

Fission
A splitting or breaking up into parts.

Gemini lipid
A class of lipids containing two head groups and two aliphatic tails linked by a spacer.

Palisade layer
The border region between the polar head groups and the hydrophobic core.

Parsimonious
Related to the simplest explanation of a phenomenon.

Prebiotic
Occurring or existing before the emergence of life.

Primordial
Ancient, existing from the beginning.

Quasispecies
A group of highly similar molecules or organisms.

Reduced dimensionality
A phenomenon in which reactions are speeded up by reactants adsorbing to a 2D surface.

Stern layer
The immediate proximity of the micellar surface.

Terrestrial infall
Incoming extraterrestrial material that falls on Earth.

As expected from a proposed simple origin scenario, we describe specific paths that would enable micellar entities to heighten their complexity towards more chemically elaborate protocells. Such paths are supported by documented experimentation, and additional progress along these lines could be reinforced by computer modelling and simulations. Among others, such simulations reveal that, since in the GARD model genotype-like and phenotype-like attributes are joined in one micellar entity, the door is open for pre-evolutionary selection for reproduction, making the emergence of protocellular self-copying more plausible than previously thought.

In summary, this Perspective offers, perhaps for the first time, a detailed, well-based biopolymer-independent origin scenario, based on the amalgamation of experiments and modelling. Such a scenario affords spontaneous appearance of nanoscopic, highly simple reproducers from messy chemistry, avoiding an unlikely leap from prebiotic mixtures to complex polyribonucleotides and polypeptides. This should eventually help to outline a path in which templating biopolymers and encoded proteins would be the result of evolution, rather than a prerequisite for it.

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