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ORIGIN OF LIFE. II. FROM PREBIOTIC REPLICATORS TO PROTOCELLS

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ABSTRACT

Origin of life. II. From prebiotic replicators to protocells. - Primitive microvesicles (coacervates, microspheres, marigranules, etc.), *free*-born in aqueous media, are only protometabolic proteinoids surrounded by an amphiphilic protomembrane. In contrast, *surface*-born microvesicles could be initiated in the pores of watered rocks providing primary boundaries coated by amphiphilic compounds and acting as sinks for primitive peptides and their coding nucleobases N-P anchored on polyphosphates. Only presumed replication of these prenucleic infopolymers would qualify the basipetally budded microvesicles as protocells.

Key-words: Evolution; life; prenucleic replicators; protocells.

INTRODUCTION

The first phase of chemical evolution involving the relatively easy formation of biomonomers – amino acids and nucleobases – was followed by the process of prebiotic evolution during which prevailed the organic syntheses which led to the formation of the primal biological polymers. The mechanism of transition from such biopolymers – peptides to protoproteins, prenucleic to nucleic acids – to protocellular structures remains elusive (ORÒ, 1995). According to OPARIN (1938, 1968) and his followers (LYUBAREV & KURGANOV, 1995), the emergence of phase-separated systems (PSSs) was a necessary precondition for the evolution of biologically significant mechanisms. These should counteract an increase in entropy due to spatial separation which permits living cells to interact with the environment selectivity. BERNAL (1967) had the alternative view that the mechanisms of template synthesis of proteins and nucleic acids emerged before the appearance of PSSs. However, as commented by FLEISCHACKER (1990) "Neither approach gives us a standard against which we can identify the *emergence of life* from non-life-historically during the Archaean or experimentally in our laboratories". Consequently, it appears that the shift from prebiology to biology requested the concourse of both models.

The problematic question of the origin and evolution of life cannot be expected to be understood in separate terms of gene-protein alone or of precellular structures also alone but in a parallel consideration of both, i.e. origin of the genetic code and origin of

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chemonanostructures capable to confine macromolecular replicators below a protomembrane and its energy-producing contents (TURIAN, 1998). This problem of confinement of infostructural polymers to a small enough volume was crucial to permit chemical reactions for the development of protocells.

Our survey will therefore sequentially span from protomembranous (1) and precellular (2) models to the only dual systems deserving to be called "protocells" (3) as tentatively modellized (4).

1. Protomembranes

In 1949, BERNAL proposed that "the formation of membranes must be taken into account in all comprehensive pictures of the origin of life". In that process, organic molecules would have been adsorbed on solid mineral particles, particularly clays which better temper them of UV nuisance and favor their condensations (LAHAV & CHANG, 1976). Rather than seeing minerals as assisting in that putative prevital build-up of organic molecules such as amphiphobic lipids, CAIRNS-SMITH (1982) considered clay membranes as much more easily made from weathering solutions which seem to organize themselves fortuitously. Moreover, polyisoprenoid chains of ancient origin matter rather than "modern" polyketides of lipids with hydrophobic proteins have contributed to the assembling of protomembranes while playing a role in energy transduction at this structural level. In 1965, FOX thermally produced proteinoid components of protomembranes that he found to be rich in protective hydrophobic amino acids.

In his theory on the origin of the first cell membrane based upon an autocatalytic surface metabolism, WÄCHTERSHÄUSER (1988) also ascribed a key tole to terpenoids such as phosphorylated isoprenoids which spring from an ancient pathway to form lipid constituents of membrane bilayers. More recently, from their analysis of the organic content of sediments, OURISSON & NAKATANI (1994) have inferred that terpenoids such as hopanoids were plentiful among the constituents of the membranes of extinct cells. As further reported by MADDOX (1994) these authors also proposed a model of a solid surface capable of binding the precursor isopentenol condensed with a phosphate group through the polar head and some means by which further isopentanol units could be condensed at the growing ends of the molecules to form a piece of membrane. For mechanical reasons if no others, such protomembranes would have needed to be re-enforced by other polar molecules such as phospholipids. However, the complex composition of these amphiphilic components of the double layers of "modern" membranes would have delayed their evolutive appearance, even though they could be synthesized in prebiotic simulated conditions (ORÒ, 1995).

2. Precellular vesicular systems

Protomembranes were available from the beginning of prebiotic evolution in order to separate the intraprecellular from the extraprecellular medium. The thereby primitive phase-separated systems (PSSs) produced have been variously described as coacervates, microspheres, "jeewanu", microvesicles, marigranules-marisomes.

OPARIN (1922) pioneered the field of the PSSs with his coa(s)cervated droplets-aggregations of hydrophilic proteinaceous polymers – which could grow at the expense of them and divide, thereby acquiring some superficial characteristics of "life". Later, FOX (1965, 1995) produced his thermal proteinoids swelling in water into microspheres that he saw as models for systems that are on the way to becoming cells. He therefore called them "protocells" on functional criteria of selective diffusion of small molecules and electrical potential across their peptide shell and morphological criteria of their reproductive "budding" (see below). Nevertheless, FERRIS *et al.* (1996) considered a heresy that protein-like microspheric materials, produced with some degree of non randomness by the brutal process of heating and deprived of valid infopolymers, could be considered as true protocells.

Among the other vesicular microstructures artificially produced, self-sustaining coacervates were photochemically formed from formaldehyde mixtures and named "jeewanu" (life particles in Sanskrit) by BAHADUR & RANGANAYAKI (1970) and his Indian school. So-called "marigranules" were later obtained by the Japanese school of YANAGAWA & EGAMI (1980) in sea water enriched in metal cations.

In 1979, WOESE had already supposed that life emerged not in the ocean but in salt water droplets coated with membranes. All these most primitive microspheres would have been made of and surrounded by protein-like polymers necessarily enriched in hydrophobic amino acids. However, their permeability would have been improved if it was conferred by other components among which would be phosphorylated polyisoprenoids before phospholipids (see I.). Aerosol droplets rather covered with a sparse monolayer of lipid might also have been converted to bilayer liposomes on the surface of the primordial sea (TVERDISLOV & YAKOVENKO, 1995).

Following CAIRNS-SMITH's (1982) proposal that a cooperative system can only be gradually constructed if it is built on some support, WÄCHTERSHÄUSER (1988) advanced a hypothesis that metabolism had originated at mineral surface prior to the origin of the first cells, a view shared by CLEGG & WHEATLEY (1991) who supposed that these non-biological surfaces had been subsequently replaced by membranes and nuclear and cytoplasmic matrix proteins.

The role of mineral in the origin of living system was also emphasized by KUHN & WASER (1981) who suggested a model in which early mechanisms of translation could evolve in pores of different sizes in rocks. More recently, and considering the early appearance of liquid water on the Earth surface, NUSSINOV & MARON (1990) and MEKLER (1980) advanced a hypothesis that floating clay-like dust grains called regolith grains or regosomes by analogy with Moon's ground adsorbed lipids located on the water surface.

In the precellular stages, the possibility has been considered by BALTSCHEFFSKY & JURKA (1984) of the simultaneous stepwise emergence of interacting oligopeptides, oligonucleotides and protomembranes. This was recently evidenced by FERRIS *et al.* (1996) who found that longer oligonucleotides and peptides can be obtained if this polycondensation takes place on a mineral surface instead of in free solution. As further concluded by von KIEDROWSKI (1996) "the polymers of life were more likely to have been baked like prebiotic crêpe than cooked in a prebiotic soup".

3. Protocells

Liposome-like microvesicles have then been plausibly constructed in simulated prebiotic conditions, under cycles of hydration and dehydration and they were shown to be capable to enclose, below their bilipid membrane not only polypeptides but also RNA and DNA (HARGREAVES *et al.*, 1977; DEAMER & BARCHFELD, 1982). Only such primitively compartmentalized systems which might have enclosed self-replicating gene-protein alliances should thus deserve to be considered as protocells.

Nevertheless, the problem remains to know how meaningful replicatory competent polymers became enclosed in the original microvesicles. It should be also settled how and what type of primal information (prenucleic polymers?) was first encoded below the partly hydrophobic protomembrane and what was the mechanism of the enclosure and on which substrate (clay?) occurred its anchoring (FERRIS, 1987).

Surface emergent microvesicles proposed by WÄCHTERSHÄUSER (1988) even though possibly containing pyrite (FeS_2) might be passed on when the droplets divided. However, their effects would soon be diluted out because as already stated by CAIRNS-SMITH (1982) "not the good but their means of producton must be inheritable". In other words, evolutively significant reproduction of coacervates should have involved template copying or replication mechanism. Therefore, the major hurdle in the generation of the first protocells was not only concerned with the self-assembly of a minimum number of the necessary coding and catalytic molecules with these nanostructures but the triggering of the duplications process, or autopoiesis (FLEISCHAKER, 1990). Coding infopolymers might have been primally gathered under selection pressure in protogenes (TURIAN, 1998) clothed by the protomembrane. Duplication was then insured by the segregation of their duplicated products into the sister protocellular units formed. Whatever mechanism of compartmentation – budding *versus* binary fission – was "invented" for this primitive division process, it was endowed with the task to distribute the most equally the protogenic infopolymers prealably replicated by the principle of complementarity of nucleobases. Moreover, in such primitive duplicating systems, it could be expected some asymmetric distribution of any sparcely represented polymer into the daughter protocells possibly governed by stochastic differential equations (KAUFFMAN, 1993).

In liposomic protocells could emerge co-ordinated cell-like activities including simple metabolic pathways that would allow the compartments to take up and use energy from the environment. Exergonic and endergonic reactions in coupled protometabolism have been envisaged as possible single ways to push the synthesis of their high molecular-weight compounds by some kind of "osmotic drive" (KAUFFMAN, 1993). Their further bond formation by condensation reaction should release one H_2O molecule diffusing across the semi-permeable lipoidic membrane, leaving inside the larger polymers. Therefore, the osmotic drive for such further syntheses could be provided by the efflux of water from liposomes placed in hypertonic media such as those offered by wet rocky surfaces.

The efficiency of the vectorial processes involved in the reproductive division of protocellular compartments (LYUBAREV & KURGANOV, 1995) would have further been improved with the emergence of the first cellular structures endowed with active transport

systems. Such a gradual transition from the non-living to the living could only have occurred in the early microbial evolution (LAZCANO & ORTEGA, 1995) at the nanosize level in protobacteria born form "inside-out cells" (CAVALIER-SMITH, 1975, 1987).

4. Protocellular morphogenic modelling

The tendency of mixtures of organic and inorganic materials to form structures with phase boundaries has been known since many years (TANFORD, 1978). The thereby formed polymer particles having reached a certain size combine into multimolecular aggregations separating from the solution as microvesicles. Such primitive precelullar microstructures, possibly endowed with autocatalytic protometabolism (WÄCHTERSHÄUSER, 1988, 1992) were still deprived of self-replicating infotemplates and therefore could not be qualified as protocells. Nevertheless, they all shared the common feature of birth by isometric swelling to the limit of their hydrophobic protomembranous boundary.

Some microvesicles could be *freely*-born in the salty water of the primitive ocean or of hot volcanic microlagoons while others could be *surface*-born on rocky surfaces as proposed in 1988 by WÄCHTERSHÄUSER (Fig. 1a). Here, we favor such surface origin which could have provided the boundaries of pores or nanocavities diggered on wet rocky surfaces, not only for translation processes (KUHN & WASER, 1981) but for self-assembly of protomembranes and trapping of the molecular precurssors of the prenucleic polyphosphate system (Fig. 1 in TURIAN, 1998).

As for the process of repetitive budding on a lasting basal zone or stump, it could have confined infopolymers in the midst of its protocytosol (Fig. 1b) as a kind of prenuclear core to maintain a capacity for selective evolution. The stump would not only first provide a birth boundary but also transmit and conserve the informatory materials for further basipetal budding in analogy with the microconidial morphogenesis in Fungi such as *Neurospora crassa* (TURIAN, 1976).

DISCUSSION

To create a living cell needs the symbiotic evolution of a supramolecular community involving genes, catalysts, and membranes (CAVALIER-SMITH, 1987). However, the gap between the simple original macromolecular system of a protocellular "progenote" (POPPER & WÄCHTERSHÄUSER, 1990) and the simplest cell with a built-in bioenergetic system remains immense and largely uncharted.

It has recently be proposed by MAYNARD-SMITH & SZATHMÁRY (1999) that this transition from protocells to cells might thus have occurred by group rather than individual selection which would have required a "stochastic corrector model". This model implies that competition between replicators segregated between new daughter protocells-cells would end by "the survival of cooperators", i.e. only cells inheriting equal numbers of each of the replicative types would survive and "perpetuate". It can then be expected that the first formed protocells would have been submitted to sharp selection for or against on the basis of their integrated performance, i.e. faithful replication, metabolic

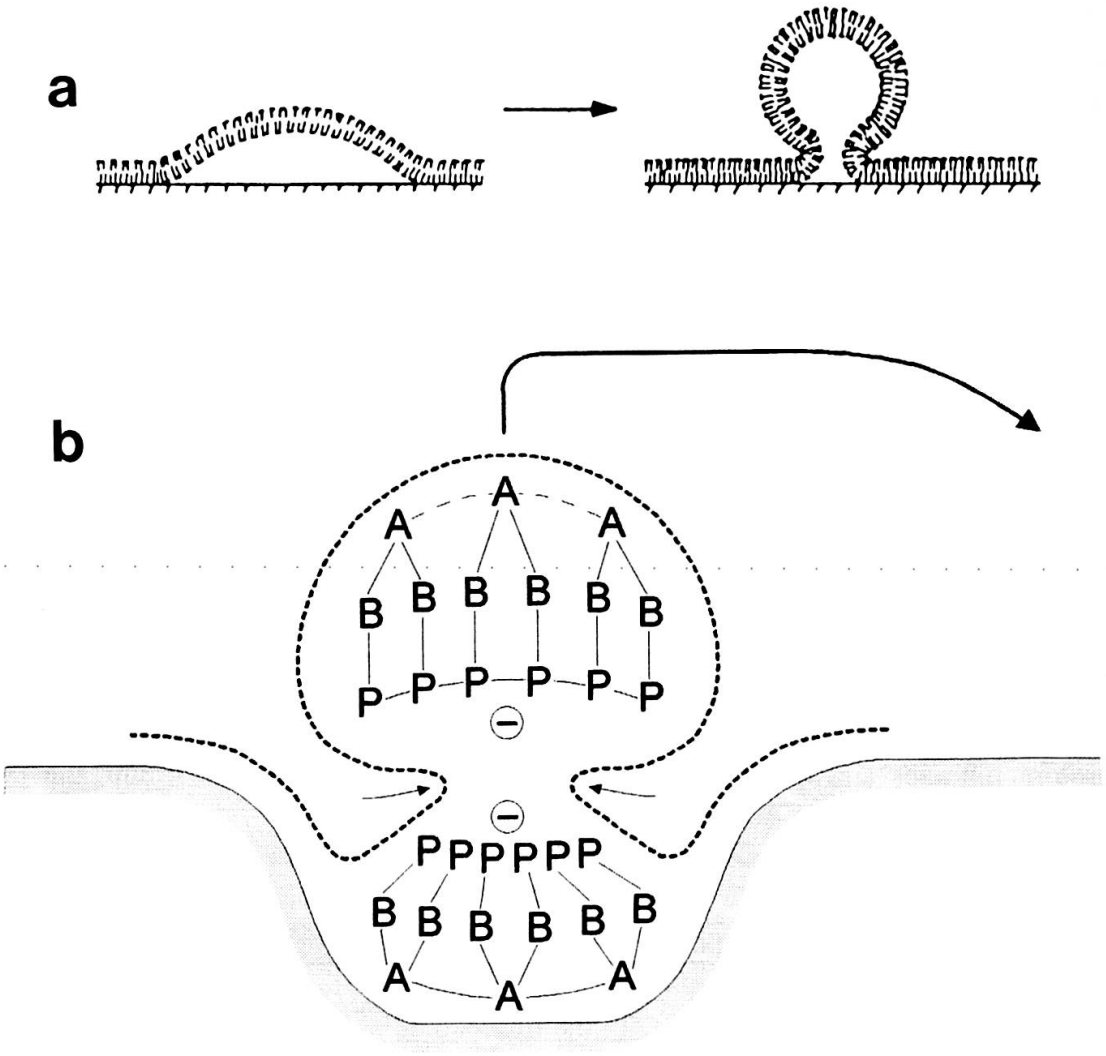

FIG. 1

a) Two-step process of surface arisal of a protocell-like microvesicle as proposed in Fig. 9a by WÄCHTERSHÄUSER (1988).- b) Surface model adapted to pores (nanocavities) of watered rocks emphasizing the morphogenic role of their circular boundary for amphiphilic coating by the protomembrane (---), and their sink effect for the environmentally assembled primordial peptides from amino acids (A) *plus* nucleobases (B) doublets "frozen" on $^-$ charged oligophosphates (P) as infopolymers for initial coding-translation in the prenuclear core of the basal zone. Further generative role of this zone would occur after abstriction and circumdetachment of the 1st protocell (→←) followed by its dispersion (⌐) – "germination" into another nanocavity. The stump will remain informationally competent for further basopetal budding.

efficiency, etc. (see MADDOX, 1998). In initiating fitness, i.e. the capacity to adapt in the environment and to survive, natural selection might thus have been a decisive step in the transition from inanimate to animate matter (LIFSON, 1997).

To SCHRÖDINGER's (1944) Mother of All Questions "What is Life?", biologists can therefore answer today that they do not consider it some magical force that animated lifeless materials, but rather an emergent property based on the behavior of the materials

that make up living things. First of these molecular materials might have been self-catalyzed protein-clothed RNA genes (von KIEDROWSKI, 1986; ORGEL, 1992, also in MADDOX, 1994) energized by chemiosmotically-driven protometabolic processes and preceded by prebiotic replicators, such as prenucleic protogenes (TURIAN, 1998). Further complexifying properties of cellular self-reproduction, mutation-selection and metabolism (EIGEN, 1995) would have endowed the evolutive systems with minimal criteria of living cellular micro-organisms.

Given the conditions on early earth, it may have taken a span of several hundred millions years for the transition from the coordinated activities of such primitively compartimentalized systems – replication, protein synthesis, protometabolism, repair, etc. – to emerge as truly integrated and interdependent biological units, the living cells (POSTLETHWAIT & HOPSON, 1989). This fundamental transition would have involved the reductive reaction from RNA to the more stable DNA which became the informatory component of the genome of the last "common ancestor cell" (cenancestor post-progenote, see LAZCANO & MILLER, 1996; MAUREL, 1997) and of the smallest "modern" cells, the nanobacteria and the Mycoplasmas. From these consideration, it could then be deduced that fully functional life is cellular, having started with the first DNA-containing cells born from the prebiotic, prenucleic-RNA structures of protocells. This conclusion now arises the questions of the minimal quantity of DNA requested to insure life in nanocells and of how small a self-replicating nanocell considered as already living can be? Tentative answers have been provided at a "workshop" recently organized (22-23 October 1998) by the U.S. National Academy of Sciences. There was some consensus for a sphere of about 100 nm in diameter providing space for 250 DNA genes, about the size of oligogenic Mycoplasmas!

RÉSUMÉ

ORIGINE DE LA VIE. II. DES RÉPLICATEURS PRÉBIOTIQUES AUX PROTOCELLULES

Aux divers types de microvésicules (coacervats, microsphères protéinoïdes, marigranules) *libres* en milieu aquatique, sous leur protomembrane amphiphile, nous préférons les microvésicules nées en *surface* sur des rochers humides procurant par leurs pores superficiels un ancrage pour des peptides primitifs et leurs nucléobases codantes N-P liées sur des polyphosphates. Seule la réplication de ces infopolymères prénucléiques pourrait qualifier comme protocellules de telles microvésicules à bourgeonnement basipète.

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