The Origin of Life

The Emergence of Cells During the Origin of Life

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Modern living organisms are organized into cells. Fundamentally, a cell consists of a genome, which carries information, and a membrane, which separates the genome from the external environment. By segregating individual genomes from one another, cellular organization is thought to be critical to the evolution of replicating systems (1, 2). Some of the oldest known rocks on Earth (~3.5 billion years old) contain biochemical signatures of life and also contain tantalizing suggestions of cellular fossils (3). But how did early self-replicating chemicals give rise to the “cell” as a unified entity? The combination of a genome and membrane does not constitute a unified cell unless interactions between the components result in mutual benefit. Was it a lucky accident that genomes and membranes began to cooperate with each other (e.g., evolution of an enzyme to synthesize membrane lipids)? Or are there simple physicochemical mechanisms that promote interactions between any genome and membrane, leading to the emergence of cellular behaviors? We explored such mechanisms experimentally, using model protocells.

A protocell could be constructed by encapsulating a self-replicating genome inside a chemically simple, self-replicating membrane (1). This minimalist, forward-engineering approach is akin to early evolution, which must have also used a minimal set of components. RNA is a particularly elegant genomic material, because it can act as both information carrier and enzyme [e.g., as an RNA polymerase (4)]. The discovery that the ribosome contains a catalytic ribozyme core lends considerable weight to the theory that an RNA world preceded the modern DNA-RNA-protein world (5–7). For the membrane, fatty acids are simple amphiphilic molecules that self-assemble into bilayer vesicles. These vesicles have interesting self-reproducing properties, including the ability to undergo multiple cycles of growth and division (8). Fatty acids have been synthesized under a variety of prebiotic conditions and have been found on meteorites (9–11). To validate this experimental model, we showed that the hammerhead ribozyme, which catalyzes a self-cleavage (or ligation) reaction, is active when encapsulated in vesicles composed of fatty acid (myristoleic acid) and its cognate glycerol monoester (12).

During the origin of life, what behavior would demonstrate the emergence of the cell as a new level of biological organization? A defining behavior of living systems is Darwinian evolution, which may act at any level, including that of the gene and the cell. Using model protocells, we observed a competition between vesicles encapsulating RNA and empty vesicles (13). Vesicles encapsulating high concentrations of RNA experienced substantial osmotic stress, driving the uptake of fatty acid from unstressed membranes. This resulted in the transfer of ~25% of the membrane from empty vesicles to vesicles containing RNA, relieving the membrane tension caused by the osmotic gradient. The growth of the osmotically stressed vesicles and the reduction of the unstressed vesicles were measured by the fluorescence resonance energy transfer (FRET) between fluorescent dyes incorporated into the membrane.

We suggest that a similar process took place during early evolution—vesicles encapsulating highly active genomic replicators would generate osmotic pressure, causing them to “steal” membrane from other vesicles containing less active sequences. Genomic fitness (i.e., replicative ability) would be translated into cellular fitness as the genome and membrane increased together, moving the evolutionary unit from the replicating molecule to the whole cell. As soon as replicators became encapsulated, a primitive form of competition could emerge between cells (see the figure). Remarkably, this process does not require a chance increase in complexity (e.g., addition of a new enzyme), but instead relies only on the physical properties of a semipermeable membrane encapsulating solute.

In a complementary experiment, we also demonstrated how membrane fitness (i.e., growth) might contribute to cellular fitness. Fatty acid vesicles can grow spontaneously by incorporation of a feedstock, such as fatty acid micelles (14). We found that membrane growth generated a transmembrane pH gradi-
uptake of amines to aid RNA folding. Again, no additional enzymes need to be evolved for this basic form of energy capture and storage, which is only a consequence of the physical properties of the vesicles.

These results demonstrate that simple physicochemical properties of elementary protocells can give rise to essential cellular behaviors, including primitive forms of Darwinian competition and energy storage. Such pre-existing, cooperative interactions between the membrane and encapsulated contents could greatly simplify the transition from replicating molecules to true cells. They also suggest intriguing possibilities for further investigation. For example, a corollary of vesicle competition is that a charged genetic polymer, such as nucleic acid, would be much more effective at driving membrane uptake than an electrically neutral polymer, because most of the osmotic pressure is due to counterions associated with the charged polymer. Could this influence the natural selection of the genetic material itself? Furthermore, competition for membrane molecules would favor stabilized membranes, suggesting a selective advantage for the evolution of cross-linked fatty acids (e.g., di- and triglycerides) and even the phospholipids of today. Greater membrane stability leads to decreased dynamics, however, and the evolutionary solutions to this problem (e.g., permeases, synthetic enzymes) could cause a “snowball” effect on the complexity of early life (16). Exploration of these minimal systems promises to lead to more exciting insights into the origins of biological complexity.

References