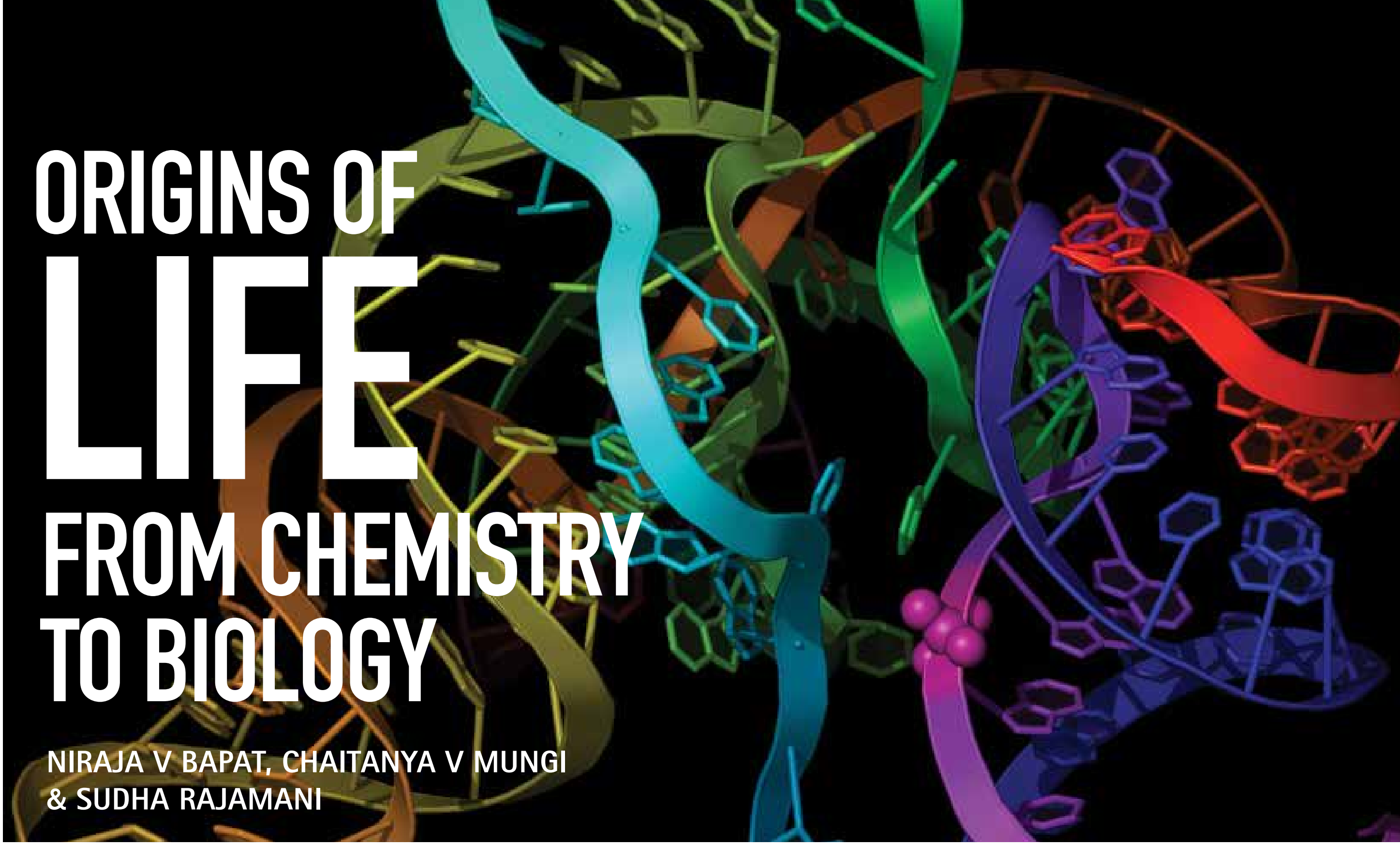

ORIGINS OF LIFE FROM CHEMISTRY TO BIOLOGY

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Understanding how life started on Earth is a long-standing mystery. This article explores the sequence of events that may have led a mixture of simple chemicals to transform into the first living cells; showing how, in recent years, ribonucleic acid (RNA) has emerged as an important clue to this mystery.

Humans have long wondered about the origins of life. The popular view was that a living being could spontaneously arise from non-living matter. Most people believed this to be true, despite their religious beliefs or the lack of it, since they could see life forms, such as fleas and maggots, arise from inanimate matter (dust) or dead animals. Many philosophers tried to explain this phenomenon of spontaneous generation using various hypothetical means, including the "five elements" or "vital heat" etc. However, experiments conducted by Louis Pasteur in the mid-19th century conclusively disproved these unscientific ideas.

Pasteur used meat broth and special type of flasks, called swan-necked flasks, to demonstrate that life could not originate from non-living matter without contamination (see Figure 1). The swan-necked flask has a long downward-

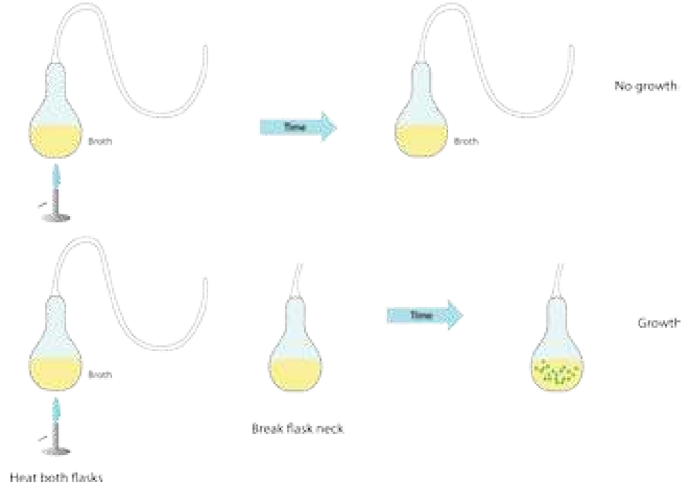

Fig. 1. Pasteur's swan-necked flask experiment. Sterilised meat broth does not show growth if the curved neck of the flask is intact. In contrast, when the neck of the flask is broken, the broth is exposed to dust and air, and shows microbial growth. Adapted from study.com.

curving neck, which prevents particles like dust or spores from falling into the broth. Pasteur boiled meat broth in two flasks, one with its neck intact and the second with its neck removed. Microorganisms were found growing in the flask without the neck whereas the control flask remained sterile. This result demonstrated that complex life arises only from other living organisms. This phenomenon is known as *'Omne vivum ex vivo'* that means "all life (is) from life".

Today, we know this to be true of all life-forms – every living being arises from other beings by means of reproduction. For e.g. the eggs of flies in dead meat give rise to maggots, the spores of microbe and fungi result in their growth in stale food/broth, and complex organisms reproduce by sexual reproduction to give rise to future generations. However, this begs the question of how the very first living being would have come into existence. What chemical mixtures would have allowed life to emerge? What sources of energy did the earliest life-forms use? Finding conclusive answers to a plethora of such questions regarding the origin of life on Earth remains a huge challenge.

To understand the steps that may have led to the origins of life, we need to reduce all living organisms into their most fundamental functional units. A cell is considered to be the basic unit of all life. A cell is fully functional, even on its own, as demonstrated by single-celled organisms such as bacteria, amoeba, paramecium, yeast etc. In fact, each cell can be thought of as a miniature factory – producing energy that is required for living, moving around, absorbing food from its surroundings, and reproducing to form more copies of itself. It achieves this marvellous feat by employing tiny machines called proteins, with each protein doing a specific job in the cell. Proteins are produced by an elaborate process, called translation, of joining amino acids in a sequence dictated by the genetic material of the cell. The genetic material of a cell, in the form of Deoxyribonucleic Acid (DNA), stores all the information required for various cellular processes. In this way, it acts like a blueprint of life! DNA itself is produced by the action of a variety of enzymes, all of which are proteins. In other words, the information stored in DNA is used to synthesize proteins and proteins are required in the process of making DNA. It is the interdependent production of these two important categories of biological molecules that gives rise to the mystery around the origins of life. Similar to the "chicken and egg dilemma", which of these bio-molecules came first – DNA or proteins; information or function (catalysis)?

While there are many different ways in which scientists have tried answering this question, one possible answer is – neither! Instead, Ribonucleic Acid (RNA), a chemical cousin of DNA, may have been the first important biomolecule to emerge. RNA is a unique biomolecule – it can perform functions of both DNA and protein – storing genetic information (as in RNA viruses) as well as catalysing metabolic reactions (in the form of ribozymes, i.e., RNA sequences that act as enzymes). Since RNA alone could acquire both these properties (under exceptionally rare circumstances), it is possible that early life-forms consisted of specific molecules of RNA working together as a network (similar to metabolism). The subsequent evolution of such RNA networks may have led to the complexity of life that we know of today. But, if this is how early life evolved on Earth, how did these RNA molecules come together to form a living organisms? What environmental conditions would have shaped this process?

Several fossil records have shown us that the diversity of life that we see today has evolved from simple unicellular entities giving rise to increasingly complex multi-cellular organisms, over a period of billions of years. This suggests that the first living organisms would have had to be very simple, even simpler than a single cell. In fact, the oldest fossil records of life on Earth, uncovered recently from some rocks in Greenland, are in the form of some simple layered structures called stromatolites. Formed by the activity of microorganisms like cyanobacteria, stromatolites assume different morphological shapes – ranging from the branched to the conical. These structures are about 3.7 billion years old. Cell-like structures from periods pre-dating this would have most likely been much simpler. These older structures are usually referred to as "protocells". National Aeronautics and Space Administration (NASA) defines a protocell as "membrane-encapsulated genetic material capable of growth, replication and Darwinian evolution". To imagine this structure, think of a protocell as consisting of only two basic components *viz.* an outer membrane enclosing some sort of functional molecular machinery, like proteins or nucleic acids. The presence of just these two components would have made the protocell capable of evolving into more complex living forms.

All modern living cells are also bound by membranes. These membranes allow the selective movement of molecules in and out of cells, while also protecting their metabolic networks and genetic material from the external environment. And while the exact composition of this cellular boundary varies with cell types, it mainly consists of complex lipid molecules. In contrast, protocells would not have had the elaborate machinery that modern cells use for the synthesis of complex lipid molecules and their

Box 1. Amphiphiles

Derived from two Greek words, *'amphis'* meaning 'both' and *'philia'* meaning 'love', amphiphiles are compounds that contain both water-loving (polar/hydrophilic) and water-repelling (non-polar/hydrophobic) chemical groups. Thus, in aqueous solutions, amphiphilic molecules assume shapes that allow their non-polar groups to stay away from water. Some examples of amphiphiles that we use in our day-to-day life include soaps, detergents, butter and oils.

maintenance (integrity). Thus, it is likely that their encapsulating membranes would have been composed of some very simple amphiphilic molecules (see Box 1), like fatty acids. Studies show that not only can simple and complex amphiphiles self-assemble to form membrane-like structures; they can also divide under certain conditions to produce more such structures. Other experiments have demonstrated that these interesting molecules are capable of spontaneous encapsulation of entities like nucleic acids and proteins inside compartments called vesicles. The main role of these encapsulating membranes would have been to protect genetic material. However, much like modern cell membranes, membranes composed of fatty acids have also been shown to compete for the selective absorption of resources from the surrounding environment – a property crucial to evolution.

Box 2. Prebiotic chemistry

As the name suggests, prebiotic chemistry is the study of chemical events before the emergence of life on Earth. It explores processes like the formation of biological monomers, the construction of polymers from these monomers, and viable assemblies of polymers that could ultimately gave rise to life. A highly interdisciplinary field, prebiotic chemistry draws insights from a variety of disciplines, including chemistry, geology, computer simulations, astronomy, physics, and biology etc.

On the other hand, primitive genetic material is believed to have been capable of passing on its encoded information to the next generation without the help of proteins. This fact has been clearly demonstrated by several prebiotic chemistry (refer Box 2) experiments in the last several decades. Although the synthesis of organic molecules (*viz.* Urea) from inorganic reactants (*viz.* Ammonium cynate) was first demonstrated by Friedrich Wöhler in the early 19th century, the stage for the field of prebiotic chemistry was truly set by the famous Urey-Miller experiment. In the 1950's, biochemists Stanley Miller and Harold Urey, demonstrated that complex organic compounds like amino acids could be formed spontaneously from very simple chemicals like water, methane, ammonia and hydrogen, under simulated atmospheric conditions of the young Earth.

Over the past several years, many origins of life researchers have begun favouring RNA as the molecule of choice for the earliest genetic material (see Figure 2). This choice is supported by what we are discovering about the functions of RNA within living cells. As we have seen before, RNA can act not only as an information storage molecule, but also as a catalyst for protein synthesis in modern cells. That it performs all core functions in the protein-making factory in modern cells also strengthens the likelihood of a putative 'RNA World' existing during the early stages of evolution on life on Earth. Scientists have shown that ribonucleotides can self-assemble into RNA polymers in an all-chemical environment, without the aid of biological (proteinaceous) enzymes. They have also been successful in showing the evolution of RNA molecules with enzymatic activity (or ribozymes) in the lab. Scientists across the world are now working on simulating the faithful chemical replication of RNA as well as similar nucleic acid molecules. Considering the fact that the replication of nucleic acids in modern cells requires many proteins to work together in a tightly controlled manner, achieving this entirely by chemical means is no small feat!

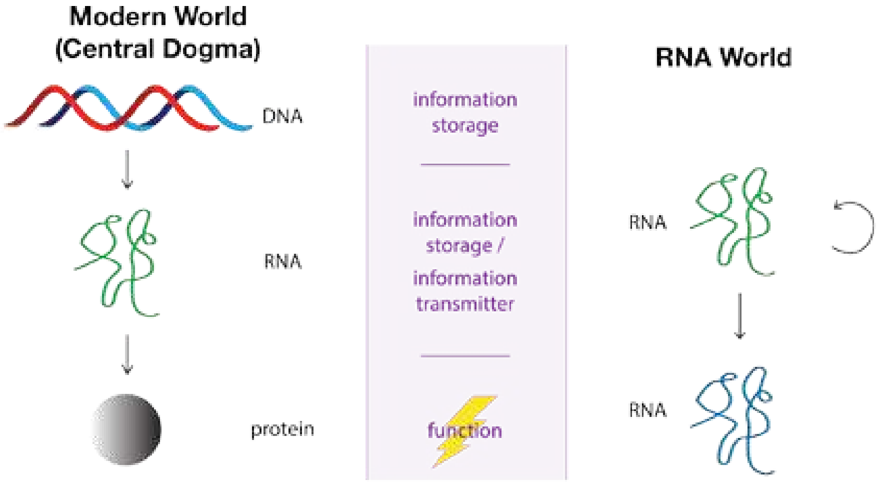

Fig. 2. A putative RNA world may have existed in the early stages of evolution of life on Earth. RNA is believed to have acted both as information-carrying molecules and as catalysts in a putative RNA world. Adapted from www.chemistryworld.com.

The main focus of research in our lab is to understand the basis of the chemical emergence and replication of nucleic acids that can occur in the absence of enzymes under conditions simulating that of early Earth. We seek to understand the process by which RNA polymers are formed from its monomers in the presence of prebiotic molecules like lipids, clay particles etc. We are also working towards understanding the rate and accuracy of enzyme-free copying of information-carrying molecules, especially those from a putative RNA world. These studies are aimed at understanding the emergence and evolution of protocells on early Earth.

In conclusion, it seems likely that the emergence of simple primitive cells marked the transition from complex chemistry to biology during the early history of life on Earth. However, some crucial challenges remain in our understanding of this process. One of which is to demonstrate multiple self-replication cycles of RNA (or similar nucleic acids), a challenge usually referred to as a "Molecular Biologist's Dream". Another challenge has been to demonstrate that self-sustaining protocell-like structures are capable of evolution. Consequently, we still have some way to go to achieve our goal of constructing artificial cells in a test tube. Nevertheless, this is very plausible; and once achieved, will answer some of the most daunting questions about the origins of life on our pale blue dot.

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