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LECTURES

Prebiotic Peptide Bond Formation by the Protoribosome: A Probable Link between the RNA and the Protein Dominated Worlds

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High-resolution structures of ribosomes from various organisms or tissues, determined by us and elsewhere, show that the peptidyl transferase center (PTC) is a semi-symmetrical RNA- made pocket, located in the core of the otherwise asymmetric ribosome. The three-dimensional structure and the nucleotide sequence of this region are highly conserved among all domains of life, hinting at its prebiotic origin, and implying that it could be a remnant of a prebiotic entity, which underwent limited evolution.

These characteristics, in addition to the findings that RNA can create itself and may possess catalytic activities, led to our “protoribosome” concept, which was recently proven experimentally via the successful peptide bond formation (monitored by MALDI and MS) by our representative lab constructs. Hence, it is conceivable that this entity was the origin of the ribosome, therefore the origin of life, which existed in the RNA dominated world. As such it is suggested to be the missing link from the RNA dominating world to the contemporary protein/nucleic acids life. After achieving this feat, we are now attempting determination of the structure of “protoribosomes” to further verify our hypothesis of pocket formation and its role in peptide bond formation.

The following scientists participated in this study: I. Agmon, T. Bose, Disha Gajanan Hiregange, A. André Rivalta, K. Shanmugha Rajan, C. Davidovich, M. Krupkin, G. Fridkin, N. Dinger, Y. Peleg, A. Bashan

On the Origin of Cells, Genomes and Viruses

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Origin of Life is the hardest problem in biology if not in all of science. We might never know what actually happened on Earth some 4 billion years ago that resulted in the emergence of the first cells.

Nevertheless, the only hope to arrive at plausible scenarios of those pivotal events is to seek consilience of (at least) four complementary approaches: 1) theoretical modeling of the first stages of life's evolution, 2) bottom up approach, that is, attempts to recapitulate the events at the origin of life through physico-chemical experimentation, 3) top down approach, that is, attempting to back extrapolate from comparative analysis of extant genomes as well as protein and RNA structures, 4) astrobiology, that is, harnessing data on exoplanets and meteorites for potential insights into the origin of the earthly life, the only one known to us. I will present a mathematical model of the origin of cells via symbiosis between primordial reproducers (protocells) and primordial replicators that gave rise to genomes. I will further resent theoretical arguments for the inevitability of the emergence of parasites in the evolution of replicators and the essential role of host-parasite coevolution in the origin of biological complexity. I will then discuss several attempts on top down reconstruction of the earliest events in biological evolution, in particular, the origin of the translation systems within the primordial RNA-peptide world, the origin of viruses and the concomitant origin of replication and transcription.

A new perspective for Habitability and the Circumstellar Habitable Zone

Amri Wandel

Habitability is linked with the presence of liquid water. The traditional Habitable Zone (HZ) is the circumstellar region where liquid water can exist on a planetary surface. However, this definition of habitability may turn out too strict. Liquid water is present under a relatively thin ice layer on Enceladus and Europa, the moons of Saturn and Jupiter, respectively. Similarly, subglacial liquid water may be expected in exoplanets orbiting their host star outside of the traditional HZ. Combining subglacial water and climate models we extend the conservative HZ, especially for tidally locked planets of Red Dwarf stars. These planets are particularly suitable for biosignature detection using transmission spectra like those recently observed by the James Webb Space Telescope

Early Controversies about the Origin of Life and their Philosophical/Ideological Backgrounds

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Crystals, colloids and (macro) molecules, as well as views on the specificity and constancy of organisms, played major roles in the theoretical concepts and experimental approaches related to the origin and generation of life since mid-19th century. Based on the study of two controversies, (i) between Pasteur and Pouchet on the spontaneous generation of life in the late 19th century, and (ii) between Muller and Oparin on the role of specific genetic material, I argue that researchers' philosophical predilections and political convictions have played important roles in the choice of experiments to solve questions about the origin of life and their interpretation. I show that these controversies have been resolved over time by scientific progress (unless it was prevented for ideological reasons) and that they therefore do not reflect the existence of different, equally valid research styles.

Interior Structures and Potential Habitability of the Super-Earth Exoplanets LHS 1140 b, K2-18 b, TOI-1452 b and TOI-1468 c

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The super-Earth exoplanets LHS 1140 b, K2-18 b, TOI-1452 b, and TOI-1468 c are orbiting M-dwarf stars in the habitable zone. Their relative proximity, within 40 parsecs, makes them prime candidates for follow-up observations and atmospheric and habitability studies. In a recent work we assessed their habitability, considering their internal structure, tidal heating, atmospheric heating, and global transport factors. We model the interior structure of the planets by applying Bayesian inference to an exoplanet's interior model. A constant quality factor model is used to calculate the range of tidal heating, and a one-dimensional analytical model of tidally-locked planets is used to assess their habitability. Assuming no or only thin atmospheres, K2-18 b and TOI-1468 c are likely to be water worlds. However, TOI-1452 b and LHS 1140 b can have rocky surfaces. Considering the atmosphere as a fourth layer reduces the median size of the water ice layer in all four exoplanets. We find that tidal heating is not enough to raise the global mean surface temperature, but atmospheric heating through the greenhouse effect can effectively do so. If the considered planets have retained thick atmospheres, K2-18 b, TOI-1468 c, and TOI-1452 b may, for significant atmospheric heating and heat transport factors, be too hot to sustain life. However, the lower instellation of LHS 1140 b and its significant probability of having a rocky surface give more space for habitable conditions on the planet,
even in the case of a highly transporting atmosphere.

Examination of the Adaptive Habitability Concept in Search for Habitable Exoplanets

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On the search for life on other worlds, the most agreeable observation methods will attempt to find evidence for water or other organic compounds in exoplanetary atmospheres. That is despite theoretical astrobiology holds much more suggestions for life, and even though the ancient life on earth did not even utilize oxygen as we do.

Taking into account that life on earth emerged on different terms than today and then adapted to change, the same can be applied on exoplanetary habitats.

This idea, termed here as "Adaptive Habitability", is demonstrated in this work through a planetary-level ecological-evolutionary model, with a single outer constraint which is the mean surface temperature of the planet.

First only a highly simplistic model is showing the relation between genetic adaptation features and the change in environmental temperature.

Then, certain simplifications are relaxed to include multiple spatial niches, geographical migration, multiple initial species and temperature dependent competition. A simple step function climate change is applied, then periodic change in time, and lastly - a more realistic constraint from a Kozai-Lidov oscillatory solar system.

It is shown that life have an extinction-survival limit on the genetic change rate and environmental tolerance, which is correlative to the external temperature change rate.

Lipid-Hydroxy acids Conjugates as Novel Prebiotic Amphiphiles

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Compartmentalization is one of the essential properties of living systems. The role of compartmentalization in today's biology is exclusively fulfilled by complex lipid amphiphiles. While complex biological lipids such as phospholipids are believed to be a product of prolonged chemical evolution, it is generally accepted that simpler lipids, such as short-chain fatty acids, have exhibited primitive cell-like structures. Early Earth was abundant with molecularly diverse molecules, among them are fatty acids, fatty alcohols, and hydroxy acids (HAs). HAs were reported to catalyze peptide bond formation via ester-amide exchange reactions when mixed with amino acids in dried conditions. Nonetheless, the role of HAs was not studied in the context of primordial amphiphiles.

In this work we tested the hypothesis that HAs can react with simple lipids and form novel functional lipid-HA conjugates. To that end, we studied the formation of HA-lipid conjugates under plausible prebiotic conditions using a set of four hydroxy acids and two lipids. The resulting products were characterized using LC-MS, NMR, light microscopy, DLS, and cryo-TEM. We found that all tested HA-lipid combinations produced modified amphiphiles that contained ester bonds. Prominent results were obtained with lactic acid and phenyllactic acid that formed various products in high yield. Rehydration of the reaction products resulted in the formation of assembled structures including vesicles, micelles, and oil droplets, depending on the solution pH and amphiphile.

Our results suggest that HA-lipid conjugates are plausible prebiotic amphiphiles exhibiting a diverse array of assemblies and unique chemical nature that give rise to promising functionalities.

POSTERS

Oligomerization of Amino acids and Keto Acids under Dried Conditions - Robust Synthesis of Prebiotic Precursors

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Numerous long-standing questions in research of origins of life center on the history of extant biopolymers. While sequences of proteins have been tuned by eons of evolution, it has been proposed that the polypeptide backbone is the product of prior chemical evolution that occurred about four billion years ago. Importantly, metabolism and polymerization of keto acids and amino acids are highly intertwined in extant biology. Due to high abundance of both amino acids and keto acids on the prebiotic Earth, we hypothesized that co-polymerization reactions will occur between those molecules to form heterogenous co-polymers.

To test this hypothesis, we performed simple dry-down reactions for one week between α- and γ- keto acids (pyruvic acid and levulinic acid, respectively) and amino acids (Glycine, Alanine and Valine) under a variety of conditions. Our preliminary results show that reactions between pyruvic acid and various amino acids produced oligomers up to 6-mers. Control reactions involving either keto acid or amino acid alone did not lead to significant product formation. LC-MS analysis indicates that both pyruvic acid and amino acid monomers are heavily consumed in the reactions to form a multitude of heterogenous products. Further examination revealed that oligomers were produced under a wide range of temperatures (25°C-85°C), in both dry and aqueous conditions. These oligomers could have been key players on the path to proto-peptides and proto-metabolism. Our study exemplifies how metabolism-first and polymer-first models can be reconciled via the study of co-polymers composed of keto acids and amino acids under dried conditions.

The sweet origin of glycolipids

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Sugars are integral to the genesis of life and the process of chemical evolution, particularly in their incorporation into the RNA structure and in central metabolism. Lipids, a diverse array of organic compounds encompassing fatty acids, phospholipids, glycolipids, and other molecular constituents, serve as crucial components in the formation of biological membranes. While both sugars and lipids were studied individually in the context of origin of life, the abiotic formation of covalently linked glycolipids and their coevolution into present biology has not been established. In this work, we embarked on exploring the chemical interactions between simple and sugars. To that end, we studied condensation reactions of two lipids, decanol (DOH) and decanoic acid (DA), with three monosaccharides: glucose, fructose, and mannose, under dry conditions. We characterized the obtained products using several analytical techniques, including LC-MS, light- and fluorescent- microscopy. Our results revealed prominent chemical specificity of DOH resulting in several glycolipid products. The products of DOH and sugars self assembled into microdroplets. on the other hand, DA did not react with the various tested sugars. These results signify a preferential reactivity between sugars and fatty alcohols over fatty acids. Notably. contemporary glycolipids such as gangliosides contain ether bonds, similarly to products of DOH and sugars. Our findings may shed light on the chemical roots of this biological selection and delineate new routes. into chemical evolution and the exploration of the chemical origins of life.

Abiotic Phosphorylation Reactions in the Origin of Life

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In current biology, phosphorylation reactions are catalyzed by phosphotransferases and are dependent on the essential supply of inorganic orthophosphate as a fundamental source of phosphorus. Nevertheless, before the emergence of highly evolved enzymes through a prolonged process of chemical evolution, alternative simpler molecules could have been involved in the proto-metabolism of phosphorus. These prebiotic molecules could have acted as phosphate carriers in a proto-metabolic system or as intermediates in the synthesis of phosphate-containing end products. Trimetaphosphate (TMP), a cyclic condensed phosphate that can be produced under volcanic conditions, is a versatile phosphorylating agent of various functional groups, even in the aqueous environment. In the presented study we investigate the potential prebiotic synthesis of simple phosphorylated molecules and their potential role in the origin of life (OoL) in the presence of TMP as an activated phosphorus source. In particular, we investigate N,O-diphosphoserine (N,O-dpSer) as a model of a bis-phosphorylated species containing both phosphate and amidophosphate moieties. As another model system, we investigate the reaction between TMP and different thiol-containing molecules as a route for the formation of direct P-S (thiophosphate) bonds. So far, using ^{1}H- and ^{31}P-NMR spectroscopy, we were able to demonstrate N-phosphorylation and S-phosphorylation of O-phospho-L-serine and thioglycolic acid, respectively, in the presence of TMP under alkaline conditions. Our results imply that in a system containing TMP in the presence of very simple and prebiotic plausible molecules, such as amino acids and mercapto acids, intriguing phosphorylated species that could play a role in the proto-metabolism of phosphorus are formed.

Selective formation of microdroplets in model abiotic depsipeptide reactions

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One of the most fascinating questions in the origin of life field is the driving force that led to the selection of today's 20 universal L-alpha amino acids in biology. An essential aspect of life's emergence involves the formation of compartments, which offers encapsulation for target molecules, provides an isolated unique environment, and thereby can serve as a micro-reactor for catalysis. Assemblies also provide protection from hydrolysis in the aqueous environment. Thus, polymers with the ability to self-assemble could have an evolutionary advantage over polymers lacking this ability. We postulated that primordial peptide assembly could be one of the driving forces that led the chemical selection of alpha amino acids in life today. To test this hypothesis, we used depsipeptides, which are oligomers of amino acids and hydroxy acids that form readily under mild conditions, as model prebiotic peptides. However, it is currently unknown whether depsipeptides form assemblies in an aqueous environment similarly to peptides and proteins. To test the hypothesis that depsipeptides with alpha backbones will form assemblies more readily than beta backbones, we generated depsipeptides using a matrix of eight alpha- and beta- hydroxy acids and six alpha-, beta-, and gamma- amino acids. The reaction products were analyzed by microscopy and DLS to study assembly formation, as well as ATR-FTIR, ESI-MS, and LC-MS for chemical analysis. Preliminary results demonstrate assembly formation in some of the depsipeptide systems, and indicate a strong correlation between the identity of the hydroxy acid and the ability of the resulting depsipeptides to self-assemble.