The First Biological Machines: Exploring Peptides as Precursors to RNA in Life's Origins – A Hypothesis of the Reverse Central Dogma

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Abstract

The RNA world hypothesis, which posits that RNA was the first biomolecule capable of storing genetic information and catalyzing biochemical reactions, has long dominated theories on the origin of life (1). However, RNA's chemical instability under prebiotic conditions raises questions about its viability as the primary molecule in early life (2). This paper proposes that peptides, rather than RNA, may have functioned as the first biological machines. I introduce the hypothesis of the **Reverse Central Dogma**, suggesting a molecular evolution sequence of proteins > RNA > DNA. I hypothesize that simple peptides, particularly those with disulfide bonds, could have formed spontaneously and catalyzed primitive biochemical processes (3). Among potential candidates, the heat-stable toxin (HST) from *Vibrio mimicus* is a compelling model due to its thermal stability, 17-amino-acid length, and specific catalytic activity (4). HST comprises only ten types of amino acids (I, D, C, E, N, P, A, F, G, L), with the sequence "IDCCEICCNPA CFGCLN" (5). This research aims to determine whether peptides formed under prebiotic conditions can exhibit machine-like activity, interact cyclically, and functionally connect with RNA. Testing peptide formation and activity in simulated early Earth conditions may provide insight into the role of peptides as foundational biological machines that set the stage for RNA and DNA evolution.

Introduction

The question of what constituted the first biological machines in early life has intrigued scientists. The dominant **RNA world hypothesis** posits that RNA was the original biomolecule capable of both storing genetic information and catalyzing biochemical reactions, thereby setting the foundation for subsequent evolution of DNA and proteins (1). However, RNA's instability under extreme early Earth conditions—characterized by high temperatures, variable pH, and intense UV radiation—limits the plausibility of RNA as the primary molecule of early life (6). In such an environment, RNA molecules, lacking protective mechanisms, are unlikely to have endured and replicated consistently (7).

Amino acids and peptides, by contrast, are chemically simpler and more stable than RNA, especially under extreme conditions (8). Peptides with **disulfide bonds (S-S bonds)** exhibit notable thermal resilience, allowing them to maintain structural integrity at high temperatures. Additionally, amino acids naturally form peptide bonds under evaporative conditions, a process that could occur on primordial Earth without complex catalysts (10). These features suggest peptides could have acted as the first biological machines, catalyzing early biochemical reactions and establishing biochemical cycles essential for life.

This paper proposes that peptides, rather than RNA, were the initial biological machines on Earth, performing essential catalytic and structural functions (11). The **Reverse Central Dogma**—a hypothetical sequence of molecular evolution from proteins to RNA to DNA—may thus represent an alternative origin pathway (12). Simple peptides with catalytic and machine-like properties could have set the stage for a primitive biochemical system. Among possible candidates, the heat-stable toxin (HST) from *Vibrio mimicus* serves as an example due to its thermal stability, specific amino acid sequence, and catalytic activity in binding GTP to produce cGMP (4). HST's sequence, "IDCCEICCNPA CFGCLN," with only ten amino acids (I, D, C, E, N, P, A, F, G, L), suggests that similarly simple peptides could have performed machine-like roles on early Earth (5, 13).

Main Hypothesis

My hypothesis centers on the notion that simple, heat-stable peptides with disulfide bonds could have served as the first biological machines, based on three main premises:

1. **Chemical Simplicity and Early Formation of Amino Acids**
    - Amino acids, simpler than nucleotides, likely formed first in the prebiotic environment. Experiments such as the Miller-Urey experiment suggest that amino acids can form spontaneously under early Earth conditions (14).
2. **Thermal Stability and Structural Resilience of Peptides**
    - Disulfide-bonded peptides exhibit thermal resilience, allowing them to endure early Earth's extreme conditions better than RNA, potentially maintaining structure and catalyzing reactions (9, 15).
3. **Natural Formation of Peptide Bonds Under Evaporative Conditions**
    - Amino acids can form peptide bonds during cycles of evaporation and rehydration, creating peptide chains without requiring enzymes (10). This could yield peptides with diverse biological activities.

Random amino acid combinations could have formed various peptides with catalytic properties, establishing self-sustaining interactions and biochemical cycles (16). HST's 17-amino-acid structure and GTP-binding activity offer a model of early biological machines, while other peptides could have synergistically contributed to cyclic, self-replicating biochemical systems (4, 12).

Research Objectives

This study aims to:

1. Determine whether random combinations of amino acids can form peptides similar to HST.
2. Assess whether randomly generated peptides display machine-like catalytic properties.
3. Investigate whether these peptides establish self-sustaining biochemical cycles.
4. Explore functional or structural connections between peptides like HST and RNA.

Methodology

The experimental approach includes:

1. **Preparation of Amino Acid Solution**
   - A sterile solution containing HST's amino acids (I, D, C, E, N, P, A, F, G, L) will simulate early Earth conditions (13).
2. **Evaporation and Rehydration Cycles**
   - Repeated heating and cooling cycles will simulate evaporation and rehydration, promoting condensation reactions for peptide bonds (10).
3. **Multiple Reaction Cycles**
   - Several cycles of heating and cooling will optimize peptide yield and complexity (15).
4. **Peptide Isolation and Sequence Analysis**
   - Chromatography and mass spectrometry will isolate and sequence formed peptides, assessing whether HST or similar peptides form (13).

5. **Functional Assays for Machine-like Activity**
    - Peptides will undergo tests for GTP binding or catalysis to evaluate their potential as early biological machines (4).
6. **Cyclic Interaction Potential**
    - Simulations and assays will examine whether peptides can establish recurring biochemical cycles (16).
7. **RNA Interaction Potential**
    - Peptides resembling HST will be tested for interactions with RNA or RNA precursors to explore structural or functional connections (11).

Expected Results and Discussion

This experiment aims to determine whether amino acids can form peptides under prebiotic conditions and if these peptides exhibit machine-like properties. Cyclic heating and cooling should promote condensation reactions, leading to peptide formation (10). Some peptides may demonstrate catalytic activity or structural stability, aligning with their hypothesized role as early biological machines (15). Should HST-like peptides emerge, it would support the Reverse Central Dogma hypothesis, proposing that protein-based biochemical cycles preceded RNA and DNA (12).

If generated peptides display cyclic interactions, it could indicate the initiation of metabolic cycles, suggesting a protein-centric origin of life (16). Cyclic, catalytically active peptides could signify that early biological systems were protein-centered, initiating self-sustaining reactions necessary for RNA's eventual evolution (11). Observed interactions between peptides and RNA would further suggest a functional transition from peptide-based systems to RNA.

Conclusion

This study hypothesizes that simple, thermally stable peptides were Earth's first biological machines, initiating early biochemical cycles. By testing peptide formation and functionality under prebiotic conditions, I aim to determine if these peptides could serve as foundational molecules in life's early evolution. Evidence of machine-like activity and cyclic pathways among peptides would support a Reverse Central Dogma model, where molecular evolution began with proteins, proceeded to RNA, and culminated in DNA. This paradigm offers a protein-first perspective, challenging the RNA World Hypothesis and expanding our understanding of molecular evolution from simple amino acids to complex life.

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