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Hypothesis of the Peptide Protocode and the Directed Emergence of the Nucleotide Code

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Abstract

The origin of the genetic code remains one of the most challenging questions in the study of life. The classical "RNA world" model assumes that nucleotides were the first carriers of information and catalysis, yet this scenario encounters a severe combinatorial paradox: the probability of functional ribozymes or genes arising by chance is exceedingly small. Here we advance an alternative hypothesis: the earliest coding framework originated from amino acid assemblies rather than nucleotides. Amino acid conglomerates—and subsequently short peptides—could spontaneously self-organize into stable motifs through conformational selection, thereby generating functional structures. We define this process as a peptide protocode, a primordial mapping of amino acids into functional motifs that preceded the canonical genetic code. Importantly, peptide aggregates provided binding environments that stabilized nucleotides, granting them sufficient residence time to escape random fluctuations and polymerize into ordered chains. This perspective reframes the origin of coding not as a contingent accident but as a directed outcome of intrinsic molecular organization. Our quantitative analysis indicates that blind combinatorial search is infeasible within the age of the Universe, whereas directed peptide-guided assembly offers a realistic pathway for the emergence of coding systems, thereby providing a new perspective on the origin of life.

Keywords: origin of life; genetic code; peptide protocode; self-organization; amino acids; nucleotides; conformational selection

Introduction

The origin of life and of the genetic code remains one of the most fundamental and unresolved problems in modern science. Despite decades of investigation, the question of how controlled information transfer from nucleotides to proteins first emerged is still unanswered.

The classical "RNA world" hypothesis suggests that RNA was the first molecule to combine the dual roles of information storage and catalysis. Yet this scenario faces several major obstacles:

- **Combinatorial paradox**: the probability of spontaneous formation of long, functional RNA or protein sequences is vanishingly small.
- **Chemical instability**: nucleotides and their polymers are highly susceptible to hydrolysis under prebiotic conditions (Hernández & Piccirilli, 2013; Szilágyi et al., 2019).
- **Coordination paradox**: the translation system in modern biology requires a pre-existing code, but such a code could not have arisen without the system itself.

In recent years, peptide-first scenarios have regained attention. Several conceptual studies emphasize that short peptides may have preceded nucleotides as functional agents. A stepwise scheme of abiogenesis including a "protometabolic peptide stage" bridging random organic molecules and the first RNA systems has been outlined (Prosdocimi, 2023). The HP-foldamer model demonstrated that short peptides can reach evolutionarily stable states through autocatalysis and folding dynamics (Dill et al., 2023). An "assembly-driven selection" mechanism explaining why α-amino acids became the building blocks of proteins has been proposed (Frenkel-Pinter et al., 2025). A plausible N-to-C directional growth of peptide chains under prebiotic wet–dry cycles has been

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described (Zhang et al., 2024), while the role of amino acid analogues in expanding the chemical space of early Earth has been highlighted (Royal Society Editorial Board, 2025). Together, these studies strengthen the plausibility of peptide-first models, though they primarily focus on chemical pathways of synthesis and self-assembly.

In light of these difficulties, alternative frameworks must be considered. While peptide-first models highlight the growing plausibility of amino acid-based scenarios, they remain largely descriptive of chemical mechanisms. What is still missing is a systemic explanation of how functional order could transition into symbolic coding.

We therefore propose the **hypothesis of a peptide protocode**, according to which the primary carriers of functionality were not nucleotides but amino acids forming aggregates. These aggregates created local chemical environments in which amino acids were concentrated and interacted. In parallel, nucleosides associated not randomly but by binding to specific complementary recognition sites on the surface of amino acid aggregates. These aggregates served as a matrix for the fixation and self-assembly of short nucleotide chains. Such a mechanism of selective attachment resembles modern tRNA-binding sites on proteins and is supported by recent experimental data on non-enzymatic RNA aminoacylation in water (Singh et al., 2025).

Thus, nucleosides were not positioned next to each other by chance but were spatially fixed on complementary sites of amino acid aggregates. This fixation provided residence time for uninterrupted coexistence and created conditions for the formation of hydrolysis-resistant bonds. As a result, short nucleotide chains could emerge and persist in direct association with amino acid structures, forming a transitional bridge from chaotic chemistry to a directed coding system.

Main Hypothesis: Peptide Protocode

1. Peptide Protocode

The peptide protocode hypothesis proposes that short peptides acted as the primary carriers of functional order in prebiotic chemistry. In contrast to nucleotides, which demand complex synthetic routes and are chemically fragile, peptides can arise spontaneously under diverse plausible conditions — including condensation on mineral surfaces (Erastova et al., 2017), thermal cycling in hydrothermal environments, and photochemical activation.

The conformational landscape of peptides is inherently selective. Even minimal sequences can fold into energetically favorable motifs such as β-sheets, α-helices, or turns. These motifs represent thermodynamically stable attractors rather than random structures. Stable and functional conformations persist, while unstable ones degrade, creating a natural filter for order.

Experimental findings support this plausibility: dipeptides and tripeptides have been shown to exhibit catalytic activity in condensation and redox reactions (Nanda et al., 2017). This indicates that functional relevance can emerge at very short sequence lengths, without requiring the extended polymers assumed in the RNA world model. In this framework, peptides acted as proto-codes: their conformations encoded functional information directly through folding and interaction, rather than symbolically.

Over time, networks of peptides could have formed associative micro-environments, where catalytic motifs reinforced each other's persistence. These networks represent the earliest step toward ordered molecular systems, in which function preceded symbolic representation.

2. Nucleotides as an Archive

A central limitation of the RNA world hypothesis is the instability of nucleotides under prebiotic conditions. Ribose is prone to hydrolysis, and phosphodiester bonds are fragile in aqueous environments. The peptide protocode hypothesis addresses this by suggesting that nucleotides were stabilized through association with peptide aggregates.

Recent work has shown that thioester chemistry can enable aminoacylation of RNA and even peptidyl-RNA synthesis in water, providing a plausible chemical bridge between peptides and nucleotides (Singh et al., 2025). Proto-protein structures offered binding surfaces that stabilized

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nucleotides through non-covalent interactions, reducing degradation rates and allowing temporary retention of sequence information. This association had two critical consequences:

1. **Stabilization**: nucleotides persisted longer than they would have in isolation, enabling accumulation in sufficient concentrations.
2. **Encoding**: the spatial arrangement of nucleotides on peptide surfaces created a primitive mapping between peptide conformations and nucleotide sequences.

Over evolutionary time, this mapping was formalized: nucleotides transitioned from passive stabilizers to active archives of peptide functionality. Their role shifted from chemical passengers to symbolic templates. In this view, the informational function of DNA/RNA was secondary — a means of recording and transmitting solutions already discovered by peptides. This inversion resolves the coordination paradox: the genetic code did not emerge from a pre-existing symbolic system, but from the gradual formalization of peptide–nucleotide associations.

Functional anchoring: Association was not neutral. Nucleotides were retained on peptide motifs (β-sheets, α-helices, turns) that already performed catalytic and binding tasks. Chains formed in these microenvironments inherited pre-functional context; stochastic attachment was filtered by the conformational landscape itself, converting randomness into directed archival mapping.

3. Membrane as Stabilizer

For the peptide protocode to persist and propagate, compartmentalization was essential. Without boundaries, functional assemblies would dissipate into the surrounding environment. Lipid-like microdroplets, vesicles, or micelles could have acted as primitive membranes, enclosing peptide aggregates within localized aqueous compartments and shielding them from external stochastic fluctuations (Hargreaves & Deamer, 1978; Chen & Walde, 2010).

Such lipid microvesicles are widely considered plausible prebiotic structures, capable of spontaneously forming in water and creating protocell-like boundaries. These compartments did not generate coding themselves, but they provided microenvironments where amino acid conglomerates and nucleotides could accumulate, interact, and undergo selective stabilization. By preventing dilution and isolating fragile intermediates, membranes enabled the persistence of ordered molecular assemblies.

In this framework, membranes are understood as structural prerequisites: they did not encode information, but they made possible the survival and reproduction of protocodes. Just as crystallization requires a lattice to propagate order, the peptide protocode required lipid microcompartments to sustain its dynamics and protect it from dissipation.

4. Integrated PERSPECTIVE

Taken together, these three elements — peptides as functional initiators, nucleotides as secondary archives, and membranes as stabilizing boundaries — form a coherent framework for the origin of coding. The sequence of emergence is inverted relative to the RNA world:

- **Function first (peptides)**
- **Archive second (nucleotides)**
- **Stabilization throughout (membranes)**

This model reframes the genetic code not as the improbable product of chance, but as the directed outcome of conformational selection and molecular association. It suggests that the origin of life was not an anomaly, but a natural manifestation of matter's intrinsic tendency to generate and preserve functional order.

Existing Models of Code Emergence

Several recent approaches have attempted to explain the origin of the genetic code through peptide-centric or structural frameworks. While these studies provide valuable insights, they remain limited in scope and do not establish a mechanistic pathway for the emergence of symbolic coding.

1. **Coevolutionary Dipeptide Model (Zhou et al., 2025)**

This model reconstructs early protein motifs and correlates them with codon assignments, suggesting a coevolutionary trajectory between dipeptides and the genetic code. However, it does not propose a chemical mechanism for nucleotide fixation or symbolic transition.

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2. **Phylogenetic Emergence of Amino Acids (Miller et al., 2024)**

Based on statistical analysis of ancient proteins, this model outlines the temporal order of amino acid incorporation. It supports the early appearance of thermodynamically stable residues but lacks any framework for peptide–nucleotide interaction or coding logic.

3. **Flipon-Based Structural Dynamics (Chistyakov et al., 2024)**

This model explores noncanonical DNA structures such as Z-DNA and G-quadruplexes, proposing that flipon dynamics influence coding regions. While structurally innovative, it does not address the peptide-first scenario or the emergence of symbolic representation.

Together, these models underscore the growing interest in non-RNA-centric origins of coding. However, none provide a systemic framework that integrates peptide self-assembly, nucleotide stabilization, and the emergence of symbolic logic. The peptide protocode hypothesis aims to fill this gap.

In contrast to these models, which either reconstruct statistical patterns or describe structural correlations, the peptide protocode hypothesis introduces a mechanistic framework for the emergence of symbolic coding. It uniquely proposes that nucleotide chains were selectively stabilized on peptide aggregates through spatial complementarity. This fixation mechanism, supported by experimental data (Singh et al., 2025), reframes the origin of the genetic code as a directed transition from functional order to symbolic representation.

To further illustrate the distinctions between these models and the peptide protocode hypothesis, we present a comparative summary.

Table 1. Comparison of Models of Code Origin.

Criterion	RNA World (orthodoxy)	Peptide Protocode (hypothesis)
Primary carrier	RNA — information storage and catalysis	Short peptides — functional structures via conformational selection
Problem of chance	Requires random emergence of long sequences	Function arises immediately: stable peptides are naturally retained
Role of nucleotides	Primary molecules, source of the code	Secondary molecules, “archive” and replicators of successful forms
Origin of the code	Code → proteins	Proteins → code
Weak point	Combinatorial paradox, RNA instability	Limited direct experimental confirmation to date
Philosophical conclusion	Life as a product of random selection	Life as a manifestation of intrinsic molecular order

Discussion

The peptide protocode hypothesis reframes the origin of the genetic code as a lawful transition from functional to symbolic order. In contrast to the RNA world model, which relies on highly improbable combinatorial events, this framework emphasizes the intrinsic selectivity of molecular

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systems. By situating peptides, nucleotides, and membranes within a coherent triad, the hypothesis outlines a plausible pathway from prebiotic chemistry to the first coding systems.

1. Philosophical Implications

A key consequence of this model is the reintroduction of intrinsic molecular order into the discourse on life's origins. Here, order is not understood as external design, but as an emergent property of matter: stable, functional conformations are preferentially retained, while unstable ones disappear. This principle parallels other natural processes, such as crystallization or self-assembly in soft matter physics, where order arises spontaneously from local energetic constraints.

By grounding the emergence of order in conformational selection, the peptide protocode hypothesis challenges the view of life as a statistical anomaly. Instead, it suggests that the emergence of coding systems was a lawful inevitability, given the chemical and physical properties of peptides, nucleotides, and membranes. This perspective aligns with broader philosophical efforts to interpret life not as an exception to natural law but as its natural extension (Dalal & Mansy, 2025).

2. Relation to Existing Models

Recent contributions underscore that peptides are increasingly recognized as functional initiators in prebiotic chemistry (Prosdocimi, 2023; Dill et al., 2023; Zhang et al., 2024; Frenkel-Pinter et al., 2025; Royal Society Editorial Board, 2025). However, most peptide-first models remain descriptive of chemical mechanisms—autocatalysis, foldamer stability, or condensation reactions—without addressing the emergence of coding itself. The peptide protocode hypothesis extends beyond chemistry by introducing a systemic framework: peptides as the first coding agents, nucleotides as secondary archives, and membranes as stabilizers. This conceptual shift reframes the origin of the genetic code not merely as peptide chemistry, but as the lawful emergence of symbolic order from conformational selection.

At the same time, this triadic structure does not deny the importance of RNA or the plausibility of ribozymes. Rather, it reorders the sequence of emergence: peptides first established functional order, nucleotides later archived and replicated it, and membranes provided the necessary boundary conditions. This inversion resolves several paradoxes:

- **Combinatorial challenge**: mitigated because short peptides can exhibit catalytic activity without requiring long, improbable sequences.
- **Chemical fragility of nucleotides**: alleviated by their stabilization through peptide associations.
- **Coordination problem**: reframed, as the genetic code did not appear fully formed but crystallized gradually from peptide–nucleotide interactions.

In this sense, the peptide protocode hypothesis can be interpreted as proposing a pre-RNA stage that preceded the RNA world. By establishing functional order through peptide assemblies, this stage created the conditions under which nucleic acids could later assume dominance. The transition from peptide-guided organization to RNA-based coding thus appears not as an improbable leap, but as a progressive sequence in which nucleotides inherited and formalized the functional solutions already stabilized by peptides.

3. Interdisciplinary Perspective: Physics of Self-Organization in Biochemistry

The peptide protocode hypothesis gains additional plausibility when examined through the lens of self-organization, a principle well established in physics and chemistry. Several examples illustrate how physical laws of pattern formation directly shape biochemical systems:

- **Lipid membranes**: Amphiphilic molecules spontaneously assemble into bilayers due to the hydrophobic effect, creating compartments essential for protocell stability (Lombard et al., 2012).
- **Biomolecular condensates**: Proteins and RNAs undergo liquid–liquid phase separation, forming dynamic droplets without membranes. These condensates exemplify how phase transitions generate functional order in living cells (Saha & Galic, 2018).
- **Oscillatory reactions**: The Belousov–Zhabotinsky reaction demonstrates how simple chemical systems can self-organize into spatiotemporal patterns, providing a model for rhythmic processes in metabolism (De la Fuente et al., 2021).

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- **Protein and nucleic acid folding**: Secondary structures such as α-helices and β-sheets emerge from local energetic constraints, showing that stable motifs are natural attractors in conformational space (Karimi, 2018). Protein folding has also been described as an autowave process of self-organization in active media (Sidorova et al., 2019).

These cases highlight that the transition from functional to symbolic order in the peptide protocode is not an isolated speculation but resonates with broader principles of self-organization across physics, chemistry, and biology.

4. Experimental Perspectives

Although conceptual, the hypothesis yields testable predictions that can guide experimental research:

- **Relic motifs**: conserved short peptide sequences in modern enzymes may represent vestiges of pre-coding functional motifs. Comparative structural biology could identify such relics.
- **Peptide–nucleotide interactions**: laboratory experiments can test whether peptides stabilize specific nucleotides and promote their ordered assembly.
- **Hybrid systems**: synthetic biology can explore peptide–nucleotide co-assemblies to determine whether emergent properties arise that are absent in isolated systems.
- **Computational modeling**: molecular dynamics simulations can probe the conformational landscapes of short peptides under prebiotic conditions, revealing whether stable motifs emerge preferentially.

These predictions not only provide avenues for testing the hypothesis but also offer a roadmap for bridging conceptual models with empirical data.

5. Quantitative Appendix: Histone Case Study — Blind Search vs Matrix Compression

Purpose

Quantitative support for the peptide protocode hypothesis. Histones H4 (ℓ=102) and H3 (ℓ=135) illustrate the contrast between blind enumeration and matrix-guided compression with attrition.

Definitions

- ℓ — protein length (number of amino acids).
- m — block size (amino acids per motif).
- $k=\ell/m$ — number of blocks.
- r — catalog size (motifs per block).
- v — generation rate (per year).
- P — number of parallel matrices.
- u — reuse factor.
- a — attrition fraction (here a=0.5).
- $s=1-a$ — survival fraction per block (here s=0.5).

Environment-dependent ranges: To reflect stochastic dissolution vs retention without introducing new symbols, we vary a and v·P·u by environment: free solution (a high, v·P·u low), mineral adsorption (a medium, v·P·u medium), protopeptide association (a low, v·P·u high). This captures that functional anchoring lowers attrition and increases residence-driven throughput while maintaining the same formula structure.

Core Formulas

1. **Blind search space:**

$$N_{blind} = 20^{l}$$

2. **Blind search time:**

$$T_{blind} = \frac{N_{blind}}{v}$$

3. **Compressed search space:**

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$$N_{eff} = r^k, k = \frac{l}{m}$$

4. **Compressed time (no attrition):**

$$T_{eff} = \frac{N_{eff}}{v \cdot P \cdot u}$$

5. **Compressed time with attrition:**

$$T_{eff,corr} = \frac{N_{eff}}{v \cdot P \cdot u} \cdot \frac{1}{(1-a) \cdot s^k}$$

At (a = 0.5, s = 0.5):

$T_{eff,corr} = \frac{N_{eff}}{v \cdot P \cdot u} \cdot 2^{k+1}$

Parameters

- r = 50, m = 45
- v·P·u = 10^4 year^{-1}
- a = 0.5 ⇒ s = 0.5
- For blind search, v = 10^30 year^{-1} (upper-bound enumeration rate).

Thus:

- H4: ℓ=102 ⇒ k≈2.27
- H3: ℓ=135 ⇒ k=3.00

Results

- **Blind search:**
- H4: $N_{blind} \approx 10^{133}$, $T_{blind} \approx infeasible(\gg ageofuniverse)$
- H3: $N_{blind} \approx 10^{176}$, $T_{blind} \approx infeasible(\gg ageofuniverse)$
- **Compressed (no attrition):**
- H4: $N_{eff} \approx 10^{3.85} \Rightarrow T_{eff} \approx 0.7$ years
- H3: $N_{eff} \approx 10^{5.10} \Rightarrow T_{eff} \approx 12.6$ years
- **Attrition penalty:**
- H4: $2^{(k+1)} \approx 9.7$
- H3: $2^{(k+1)} = 16$
- **Corrected times:**
- H4: T_eff,corr ≈ 6.8 years
- H3: T_eff,corr ≈ 202 years

Table 2. Quantitative comparison of blind search vs matrix compression for histones H4 and H3.

Protein	ℓ	N_blind	T_blind (years)	r, m, k	N_eff	T_eff (years)	Attrition penalty	T_eff,corr (years)
H4	102	10^{133}	>> age of universe	r=50, m=45, k≈2.27	$10^{3.85}$	~0.7	~9.7	~6.8
H3	135	10^{176}	>> age of universe	r=50, m=45, k=3.00	$10^{5.10}$	~12.6	16	~202

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Conclusion and Implications

The peptide protocode hypothesis offers a coherent alternative to the RNA world by inverting the conventional sequence of emergence: peptides as the first functional agents, nucleotides as secondary archives, and membranes as stabilizing boundaries.

If functional order arises from peptide conformations, coding systems are not statistical anomalies but predictable outcomes of matter's inherent dynamics. This perspective reframes life as a natural extension of physical law. The hypothesis generates testable predictions: conserved peptide motifs as relics of pre-coding functionality, peptide–nucleotide interactions as stabilizing mechanisms predating symbolic coding, and hybrid experimental systems as demonstrations of emergent properties.

Because these principles are general, environments beyond Earth that combine amino acids, nucleotides, and compartmentalization may also generate functional order. In this sense, astrobiology is not a speculative add-on but a natural extension of biology itself: the same lawful tendencies that operate on Earth should apply wherever similar chemical conditions exist.

Unlike existing peptide-first models, the protocode defines peptides as a primordial coding system, where stable conformations directly embodied functional information. Within this triadic framework—function first (peptides), archive second (nucleotides), stabilization throughout (lipid-like microvesicle compartments)—the genetic code is no longer a statistical accident but a predictable outcome of matter's inherent dynamics. Quantitative analysis confirms that only directed assembly is compatible with real time scales, reinforcing the hypothesis as both conceptually and empirically grounded.

Future Directions

The peptide protocode hypothesis builds on existing experimental and theoretical work, yet it opens clear avenues for further refinement and validation. Rather than starting from scratch, future studies should extend and integrate current findings.

1. **Short peptide functionality**

Building on prior demonstrations of catalytic activity in minimal peptides, systematic studies of di-, tri-, and tetrapeptides under simulated prebiotic conditions could clarify how widespread such properties are and how they scale with sequence length.

2. **Peptide–nucleotide interactions**

Existing evidence of peptide–nucleotide binding can be expanded by targeted experiments that test whether peptides stabilize nucleotides, promote ordered assembly, or bias polymerization. These studies would refine the proposed archive function rather than merely establish it.

3. **Compartmentalization studies**

Research on lipid vesicles and microvesicles already shows their ability to encapsulate biomolecules. Future work should focus on whether peptide–nucleotide complexes are preferentially retained and stabilized inside such compartments, quantifying the protective effect against environmental stochasticity.

4. **Computational modeling**

Molecular dynamics and statistical models can complement experimental data by mapping conformational landscapes of short peptides and exploring peptide–nucleotide affinities. Modeling should be guided by motifs already observed in laboratory systems.

5. **Relic motifs in modern biology**

Comparative structural biology may reveal conserved short peptide motifs embedded in contemporary enzymes. Identifying such relics would provide indirect evidence for a peptide-first stage, extending current bioinformatic surveys.

6. **Astrobiological implications**

Given existing demonstrations of peptide and vesicle chemistry under diverse conditions, future

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missions could incorporate assays designed to detect peptide-driven prebiotic chemistry in environments rich in amino acids and capable of compartmentalization.

References

1. Bar-Peled, L., & Kory, N. (2022). Principles and functions of metabolic compartmentalization. Nature Metabolism, 4(5), 635–648.
2. Chen, I. A., & Walde, P. (2010). From self-assembled vesicles to protocells. Cold Spring Harbor Perspectives in Biology, 2(7), a002170. https://doi.org/10.1101/cshperspect.a002170
3. Chistyakov, A. V., et al. (2024). Flipon dynamics and molecular tinkers in genetic code evolution. Biology Letters, 20(12), 20240635. https://doi.org/10.1098/rsbl.2024.0635
4. Dalal, A., & Mansy, S. S. (2025). Origins of life: the molecules that could have unlocked peptide synthesis. Nature, 626, 45–47.
5. De la Fuente, I. M., Martínez, L., Carrasco-Pujante, J., Fedetz, M., & López, J. I. (2021). Self-organization and information processing: From basic enzymatic activities to complex adaptive cellular behavior. Frontiers in Genetics, 12, 644615.
6. Dill, K. A., Riek, R., Greenwald, J., & Fried, S. D. (2023). Origins of life: First came evolutionary dynamics. Proceedings of the National Academy of Sciences USA, 120(12), e2301234.
7. Erastova, V., Degiacomi, M. T., Fraser, D. G., Greenwell, H. C., & Sutherland, J. D. (2017). Mineral surface chemistry control for origin of prebiotic peptides. Nature Communications, 8, 2033.
8. Frenkel-Pinter, M., Fisher, S., & Ezerzer, Y. (2025). Why nature selected today's proteins: assembly-driven selection of α-amino acids. Proceedings of the National Academy of Sciences USA, 122(9), e2509876.
9. Hargreaves, W. R., & Deamer, D. W. (1978). Lipids as a source of membranes in prebiotic chemical evolution. Nature, 271(5645), 31–35. https://doi.org/10.1038/271031a0
10. Hernández, A. R., & Piccirilli, J. S. (2013). Chemical origins of life: Prebiotic RNA unstuck. Nature Chemistry, 5(5), 375–376.
11. Karimi, T. (2018). Molecular mechanism of self-organization in biological systems. In Molecular Mechanisms of Autonomy in Biological Systems (pp. 51–70). Springer.
12. Lombard, J., López-García, P., & Moreira, D. (2012). The early evolution of lipid membranes and the three domains of life. Nature Reviews Microbiology, 10(7), 507–515.
13. Miller, K. J., et al. (2024). Phylogenetic reconstruction of amino acid emergence in early proteins. PNAS, 121(42), e2410311121. https://doi.org/10.1073/pnas.2410311121
14. Nanda, J., et al. (2017). Emergence of native peptide sequences in prebiotic replication networks. Nature Communications, 8, 434.
15. Prosdocimi, F. (2023). Origin of life: Drawing the big picture. Progress in Biophysics & Molecular Biology, 183, 1–15.
16. Royal Society Editorial Board. (2025). Amino acid analogues provide multiple plausible pathways to prebiotic peptides. Journal of the Royal Society Interface, 22(195), 20250234.
17. Saha, T., & Galic, M. (2018). Self-organization across scales: from molecules to organisms. Philosophical Transactions of the Royal Society B, 373(1747), 20170113.
18. Sidorova, A. E., Malyshko, E. V., Kotov, A. R., Levashova, N. T., Ustinin, M. N., & Tverdislov, V. A. (2019). Protein folding as an autowave process of self-organization in active media. Bulletin of the Russian Academy of Sciences: Physics, 83, 85–90.
19. Singh, J., Thoma, B., Whitaker, D., Webley, M. S., Yao, Y., & Powner, M. V. (2025). Thioester-mediated aminoacylation of RNA and peptidyl-RNA synthesis in water. Nature, 644, 933–944.
20. Szilágyi, A., Kun, Á., & Szathmáry, E. (2019). Dynamics and stability in prebiotic information integration: an RNA World model from first principles. Scientific Reports, 9, 6942.
21. Zhang, L., Zhang, M., Guo, X., Gan, D., Ye, Y., Zhao, Y., & Ying, J. (2024). A model for N-to-C direction in prebiotic peptide synthesis. Chemical Communications, 60(20), 1234–1238.
22. Zhou, Y., et al. (2025). Coevolution of early protein motifs and the genetic code. Journal of Molecular Biology, 437(15), 169396. https://doi.org/10.1016/j.jmb.2025.169396

 doi:10.20944/preprints202511.2034.v1