



Bridging prebiotic chemistry and protocellular systems: a critical perspective on RNA-centered and alternative models

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Abstract. The origin of life continues to represent one of the most complex and unresolved questions in modern science, necessitating the convergence of geochemistry, prebiotic chemistry, molecular biology, and evolutionary theory. This work explores the transformation from non-living chemical systems to the first biological forms, placing particular emphasis on the RNA world hypothesis and its connections to alternative models such as metabolism-first and lipid world scenarios. Available evidence supports the feasibility of RNA as an early biomolecule capable of fulfilling both informational and catalytic roles. Nonetheless, significant obstacles remain, including the prebiotic formation of nucleotides, the development of self-replicating ribozymes, and the achievement of high-fidelity replication under plausible environmental conditions. An increasing body of experimental and theoretical research points toward hybrid or co-evolutionary frameworks in which RNA, peptides, lipids, and protometabolic systems interacted from early stages and collectively facilitated the emergence of protocells. Comparative analyses of these competing models suggest that they are more appropriately interpreted as complementary elements within a multistage process, rather than as strictly competing hypotheses. Ongoing unresolved questions—such as the origin of the genetic code, the shift toward DNA–protein systems, and the coordination of replication with metabolism and compartmentalization—highlight the necessity for integrative, experimentally validated, system-level approaches. This study seeks to elucidate the current state of knowledge, identify major conceptual and experimental constraints, and underscore the critical role of integrative frameworks in advancing our understanding of the emergence of life.

Keywords: RNA world, metabolism-first hypothesis, protocells, ribozymes, LUCA, autocatalytic networks.

Introduction. Research into the origin of life constitutes an intrinsically interdisciplinary field, combining geochemistry, prebiotic chemistry, molecular biology, and evolutionary theory to reconstruct the progression from non-living matter to the earliest biological systems. Instead of being viewed as a singular event, this transition is now increasingly interpreted as a continuous series of physicochemical processes that gradually produced molecular complexity, functional organization, and evolutionary capacity, ultimately culminating in the emergence of the last universal common ancestor (LUCA) (Schwander et al 2023; Bora & Kovacs 2023; Prosdocimi & de Farias 2023; Petrescu-Mag & Proorocu 2022; Malaterre et al 2022; Moody et al 2024).

Fundamentally, the origin-of-life question seeks to clarify how simple inorganic and organic molecules present on the early Earth developed into systems capable of information storage, catalysis, compartmentalization, and Darwinian evolution. Addressing this issue entails not only identifying credible prebiotic synthetic pathways, but also explaining how these pathways became functionally integrated into self-maintaining and evolving networks. Accordingly, contemporary research increasingly considers prebiotic chemistry, protometabolism, and early evolutionary processes as interconnected phases of a unified and continuous trajectory.

Within this conceptual framework, the RNA world hypothesis continues to occupy a central position, particularly regarding its relationship with alternative or complementary models. It offers an elegant resolution to the “chicken-and-egg” dilemma of genes versus enzymes by suggesting that RNA originally performed both informational and catalytic functions. Nevertheless, growing evidence indicates that RNA most likely did not function independently, but rather interacted from early stages with peptides, lipids, and small-molecule metabolic systems. Consequently, current perspectives emphasize hybrid or co-evolutionary models in which multiple molecular systems arose and stabilized concurrently (Schwander et al 2023; Prosdocimi & de Farias 2023; Malaterre et al 2022; Moody et al 2024).

Simultaneously, significant attention is devoted to assessing the physicochemical plausibility of early Earth environments, including hydrothermal systems, mineral substrates, and geochemical gradients, which could have supplied the energy fluxes, catalytic surfaces, and compartmentalization necessary for prebiotic evolution. These environmental constraints play a crucial role in bridging the divide between laboratory-based models and realistic planetary conditions.

Scope and Objectives. The objective of this work is to synthesize and critically assess the current understanding of the transition from prebiotic chemistry to early biological systems, with particular emphasis on the role and inherent limitations of the RNA world hypothesis. More specifically, this study aims to: (i) describe the principal stages proposed in the emergence of RNA-based systems and their evolutionary trajectory toward LUCA; (ii) analyze the major experimental and theoretical challenges related to RNA synthesis, replication, and catalytic activity; (iii) compare RNA-centered models with metabolism-first and lipid world frameworks, emphasizing their potential complementarities; and (iv) examine integrative scenarios in which RNA, peptides, lipids, and protometabolic networks co-evolve into progressively more complex protocellular systems.

By preserving a balance between empirical evidence and conceptual limitations, this analysis seeks to differentiate well-supported components of existing models from more speculative aspects, while also identifying promising directions for future research.

Current Status of the RNA World Hypothesis. Fine and Pearlman compile evidence indicating that RNA predates both encoded proteins and DNA, proposing that life developed through a succession of stages—pre-RNA, early RNA, late RNA, and near-LUCA—ultimately leading to the canonical DNA→RNA→protein flow of genetic information (Fine & Pearlman 2023). A range of studies demonstrate that ribozymes can catalyze diverse reactions, that prebiotic nucleotide formation and non-enzymatic RNA replication have received partial experimental validation, and that the ribozyme-mediated mechanism of peptide synthesis within the ribosome provides strong support for an RNA-dominated phase in early evolution (Pressman et al 2015; Penny 2005; Zorc & Roy 2024; Orgel 2004).

Despite these developments, several key issues remain unresolved (Table 1, Figure 1). Among these are the emergence of RNA from chemically complex prebiotic mixtures, the origin of the first self-replicating ribozyme, and the realization of efficient, high-fidelity RNA replication under plausible environmental conditions (Robertson & Joyce 2012; Zorc & Roy 2024; Kun et al 2015; Orgel 2004; Szilágyi et al 2017).

Goldman and Kacar point to modern nucleotide-containing cofactors as possible remnants of an earlier RNA-centered biochemistry (Goldman & Kacar 2021), whereas Zorc and Roy underline the significance of autocatalytic RNA networks as precellular evolutionary systems (Zorc & Roy 2024). Concurrently, an expanding body of research indicates that RNA likely coexisted and coevolved with peptides and other molecular components, rather than operating independently (Pressman et al 2015; Ligrone 2021; Preiner et al 2020; Tagami & Li 2023; Higgs & Lehman 2014; Kocher & Dill 2024; Müller et al 2022).

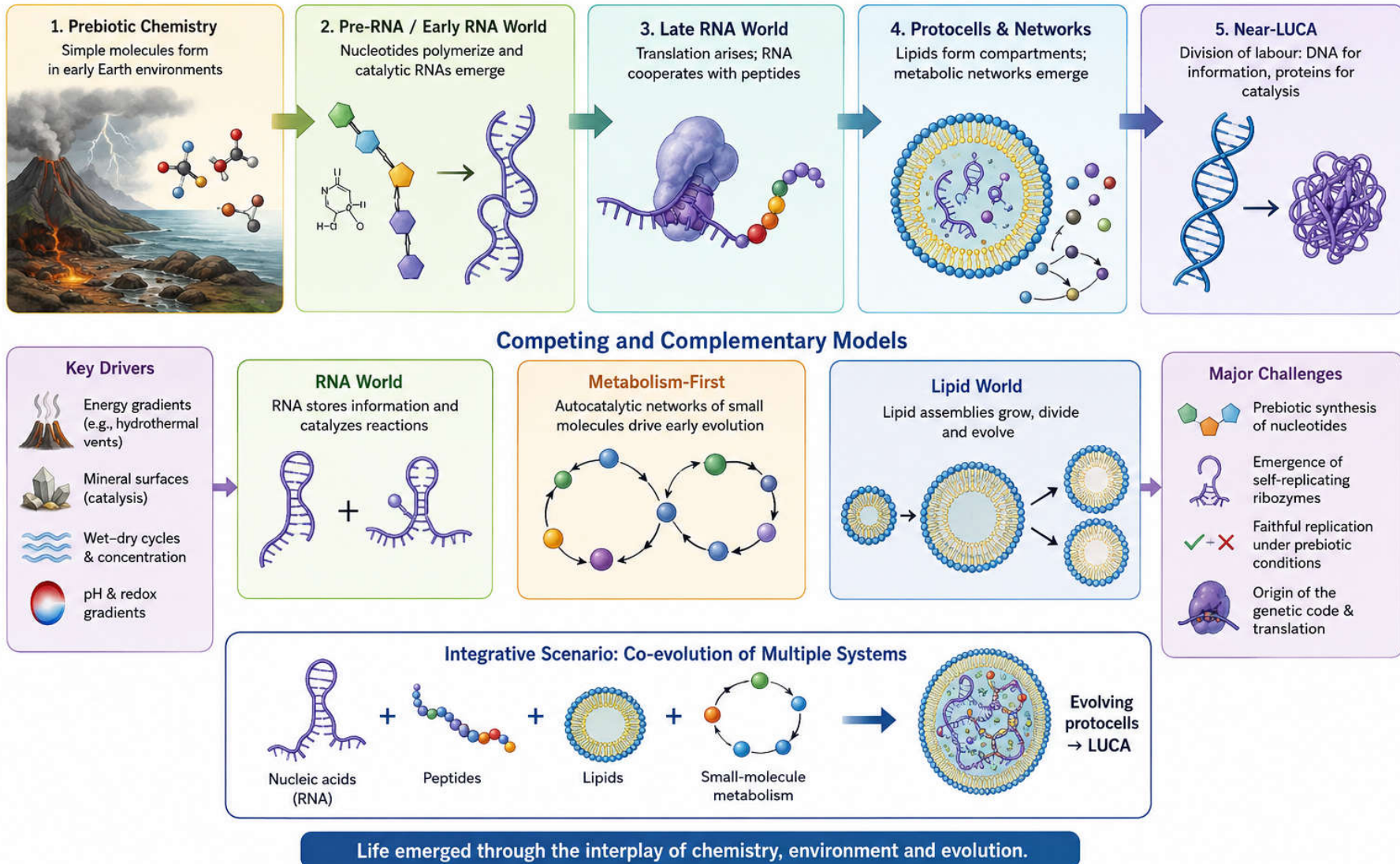


Figure 1. From prebiotic chemistry to life: an integrative perspective (this outline was conceived by Ioan Valentin Petrescu-Mag and generously provided to the authors).

Table 1

Stages and bottlenecks in the RNA World

<i>Stage</i>	<i>Main ideas and challenges</i>	<i>Literature</i>
Pre-RNA / prebiotic	Nucleotide synthesis, non-enzymatic polymerization and copying in realistic geochemical settings; avoiding intractable product mixtures	Penny 2005; Robertson & Joyce 2012; Zorc & Roy 2024; Orgel 2004
Early RNA world	Emergence of catalytic ribozymes, rudimentary replication, autocatalytic sets, ecological stability of replicator systems	Fine & Pearlman 2023; Pressman et al 2015; Zorc & Roy 2024; Kun et al 2015; Szilágyi et al 2017
Late RNA world	Origin of translation, involvement of proto-ribosomes, coevolution with peptides, early genetic code	Fine & Pearlman 2023; Penny 2005; Ligrone 2021; Tagami & Li 2023; Higgs & Lehman 2014; Agmon 2024; Kondratyeva et al 2022; Müller et al 2022
Near-LUCA / DNA–protein world	Division of labour (DNA information, protein catalysis), replacement of RNA scaffolds by proteins, fixation of modern cofactors	Fine & Pearlman 2023; Penny 2005; Ligrone 2021; Goldman & Kacar 2021; Agmon 2024; Kondratyeva et al 2022.

Comparing RNA World, Metabolism-First, and Lipid World Models. Conventional dichotomies—such as RNA world versus metabolism-first—are increasingly considered artificial constructs, with numerous authors arguing that these frameworks should be interpreted as complementary rather than mutually exclusive (Ligrone 2021). RNA-centered approaches emphasize the dual informational and catalytic functions of biopolymers (Fine & Pearlman 2023; Pressman et al 2015; Penny 2005; Robertson & Joyce 2012; Higgs & Lehman 2014; Zorc & Roy 2024; Kun et al 2015; Orgel 2004; Szilágyi et al 2017).

By contrast, metabolism-first and systems protobiology models propose that networks of mutually catalytic small molecules or lipids—capable of growth and compositional inheritance—preceded the emergence of sequence-based genetic systems (Penny 2005; Lancet et al 2018; Szilágyi et al 2017). The GARD model introduced by Lancet and collaborators describes heterogeneous assemblies of amphiphiles (“composomes”) that can grow, divide, and undergo evolutionary processes, displaying homeostasis, selection, and adaptive properties (Lancet et al 2018).

In a similar vein, hydrothermal vent and flow-reactor scenarios highlight the role of geochemical gradients and autocatalytic cycles, which may have simultaneously facilitated energy transduction and compartmentalization (Penny 2005).

Integrative viewpoints are increasingly prevalent within the field. Preiner et al. and Ligrone contend that realistic models for the origin of cells must incorporate RNA, peptides, lipids, and protometabolic networks within a unified framework, ultimately converging toward the emergence of evolving protocells (Ligrone 2021). Lipid-world hypotheses, in particular, stress the importance of self-assembled amphiphilic compartments, compositional inheritance, and lipid-driven catalysis as a pre-RNA evolutionary stage that remains compatible with subsequent RNA integration (Penny 2005; Lancet et al 2018).

System-Level Constraints and the Physics of Prebiotic Organization. Most origin-of-life models are traditionally formulated in terms of distinct molecular systems—such as RNA, peptides, lipids, or metabolic networks. However, an equally critical dimension concerns the system-level constraints imposed by the physical and chemical environment in which these systems arose (Avanzini et al., 2024; Walde, 2010). Rather than serving merely as a passive

background, early Earth conditions actively influenced the pathways and likelihoods of prebiotic organization (Siddique et al., 2026; Dzieciol & Mann, 2012).

One of the primary constraints is the availability of energy flux. The transition from simple chemical reactions to organized, evolving systems requires a continuous input and dissipation of energy (Barge & Price, 2022; Chin et al., 2020; Martin & Douliez, 2021). Environments characterized by persistent disequilibria—such as hydrothermal systems, redox gradients, or UV-driven surface settings—not only provide the energy necessary for synthesis but also impose selective pressures that sustain non-equilibrium structures (Barge & Price, 2022; Werlang et al., 2022; Erastova et al., 2017; Siddique et al., 2026; Dzieciol & Mann, 2012). In this framework, prebiotic evolution may be interpreted as a process of optimizing energy dissipation, in which increasingly complex molecular assemblies arise as more effective mediators of energy flow (Avanzini et al., 2024; Chin et al., 2020; Walde, 2010).

A further essential constraint involves spatial and temporal heterogeneity. Prebiotic reactions do not occur in homogeneous, well-mixed systems, but rather within highly structured environments characterized by mineral surfaces, pores, interfaces, and dynamic conditions (Zeng et al., 2021; Sangma, 2025; Werlang et al., 2022; Campbell et al., 2019; Siddique et al., 2026; Pulselli et al., 2009). These microenvironments facilitate concentration, compartmentalization, and the selective stabilization of intermediates that would otherwise remain too dilute or unstable (Zeng et al., 2021; Sangma, 2025; Barge et al., 2017; Campbell et al., 2019; Pulselli et al., 2009). Cyclical processes—such as wet-dry cycles, thermal gradients, or tidal fluctuations—introduce temporal structuring capable of driving polymerization, selection, and error correction in ways not reproduced by static laboratory systems (Zeng et al., 2021; Sangma, 2025; Barge et al., 2017; Campbell et al., 2019; Vázquez-Salazar, 2026; Hassenkam & Deamer, 2022; Walde, 2010).

Diffusion and dilution constitute additional limiting factors. In open systems, molecular assemblies are continually subjected to dispersal, counteracting the accumulation of complexity. This creates a requirement for either physical confinement (e.g., lipid vesicles or mineral pores) or dynamic self-maintaining mechanisms capable of preserving localized organization (Singh et al., 2024; Truong et al., 2025; England, 2015; Dujardin et al., 2022; Vázquez-Salazar, 2026; Pulselli et al., 2009). Consequently, the emergence of protocells can be interpreted not only as a biological innovation but also as a physical necessity for overcoming diffusion-driven loss of information and function (Singh et al., 2024; Truong et al., 2025; England, 2015; Dujardin et al., 2022; Vázquez-Salazar, 2026; Pulselli et al., 2009).

Importantly, these constraints act simultaneously and interact with one another. Energy availability affects reaction kinetics and stability, spatial structuring influences diffusion and concentration, and temporal variability modulates both synthesis and degradation pathways (Avanzini et al., 2024; Barge & Price, 2022; Werlang et al., 2022; Chin et al., 2020; Siddique et al., 2026; Walde, 2010). As such, the origin of life is more accurately understood not as a sequence of isolated molecular innovations, but as the progressive stabilization of systems that satisfy multiple, often competing, constraints (Avanzini et al., 2024; Barge & Price, 2022; Chin et al., 2020; Siddique et al., 2026; Walde, 2010).

Incorporating these system-level considerations offers a unifying framework that complements molecule-centered models (Avanzini et al., 2024; Walde, 2010). It implies that the plausibility of any given scenario—whether RNA-based, metabolism-first, or lipid-driven—depends not only on chemical feasibility but also on its compatibility with the physical context of the early Earth (Barge & Price, 2022; Sangma, 2025; Werlang et al., 2022; Siddique et al., 2026; Pulselli et al., 2009; Dzieciol & Mann, 2012). This perspective shifts the emphasis from identifying a single dominant pathway toward delineating the constrained space of viable trajectories leading to biological organization (Avanzini et al., 2024; Chin et al., 2020; Siddique et al., 2026; Walde, 2010).

Unresolved Problems: Faithful Replication and the Transition to DNA/Proteins. A key unresolved problem concerns the emergence of accurate replication under prebiotic conditions. Current studies consistently indicate that no ribozyme exhibiting fully processive RNA polymerase activity from monomers has yet been discovered, and that the origin of the first self-replicating RNA system remains uncertain (Pressman et al 2015; Penny 2005; Tagami & Li 2023; Robertson & Joyce 2012; Zorc & Roy 2024; Kun et al 2015; Orgel 2004; Kondratyeva et al 2022; Szilágyi et al 2017).

Theoretical analyses further emphasize constraints such as competitive exclusion among replicators, error thresholds that lead to informational instability, and the difficulty of integrating multiple genetic components into coherent protocellular systems (Kun et al 2015; Szilágyi et al 2017).

The transition from an RNA-based system to an RNA–protein world and ultimately to a DNA–RNA–protein system introduces additional conceptual difficulties. Several researchers question the plausibility of a strictly RNA-only stage and highlight the absence of clear evidence for a systematic replacement of ribozymes by protein enzymes, particularly within the ribosome (Preiner et al 2020; Goldman & Kacar 2021; Higgs & Lehman 2014; Agmon 2024; Bowman et al 2015; Kondratyeva et al 2022). Bowman, Hud, and Williams suggest that ribosomal peptidyl transfer chemistry may reflect a unique, potentially pre-Darwinian context that complicates standard RNA-world interpretations (Bowman et al 2015).

Co-evolutionary frameworks offer a possible resolution to these challenges by proposing an early mutual dependence between RNA and peptides. Experimental findings by Tagami and Li show that simple peptides can enhance ribozyme activity and may resemble structural motifs present in modern polymerases (Tagami & Li 2023). Agmon’s “three biopolymers” model similarly supports an early RNA–protein system involving interacting proto-ribosomes, proto-tRNAs, and proto-polymerases (Agmon 2024).

Müller et al. propose a chemically plausible RNA–peptide world in which RNA directly facilitates peptide formation, generating hybrid RNA–peptide complexes that could have progressively diverged into contemporary nucleic acid and protein systems (Müller et al 2022). The origin of the genetic code and translation remains one of the most challenging problems, with no current model offering a fully coherent and gap-free explanation (Kondratyeva et al 2022).

Epistemological and Experimental Limits in Origin-of-Life Research. Despite substantial progress in both experimental and theoretical domains, the origin of life remains fundamentally limited by epistemological and methodological constraints (Nogal et al., 2023; Müller et al., 2022; Camprubi et al., 2017). In contrast to most areas of biology, this field lacks direct empirical access to its primary object of study: no physical traces of the earliest prebiotic systems have been preserved, and all reconstructions depend on indirect evidence, contemporary analogues, and laboratory-based simulations (Muchowska et al., 2020; Pressman et al., 2015).

A major limitation stems from the intrinsic incompleteness of the geological record. Conditions on the early Earth are only partially constrained, and key variables—such as atmospheric composition, ocean chemistry, and the distribution of specific microenvironments—remain highly uncertain (Ranjan et al., 2018; Saha et al., 2022; Bizzarri et al., 2021; Pressman et al., 2015). Consequently, experimental models frequently rely on simplified or idealized scenarios that may not accurately capture the complexity of natural environments (White & Rimmer, 2024; Barge & White, 2017; Kitadai et al., 2019).

A second challenge involves the discrepancy between laboratory feasibility and prebiotic plausibility. Many reactions demonstrated under controlled experimental conditions require highly specific reagents, purification procedures, or externally imposed sequences of steps (Sasselov et al., 2020; Rodriguez et al., 2024; Jenewein et al., 2024; Barge & White, 2017). Although such experiments are essential for establishing chemical feasibility, they do not necessarily demonstrate that the same processes could occur spontaneously under realistic

prebiotic conditions (Nogal et al., 2023; Müller et al., 2022; Camprubi et al., 2017). This distinction between what “can occur” and what “likely occurred” remains a central issue in the evaluation of competing hypotheses (Muchowska et al., 2020; Ranjan et al., 2018; Lopez & Fiore, 2019).

Temporal scaling introduces an additional level of complexity. Prebiotic evolution likely unfolded over extensive timescales, involving numerous concurrent and interacting processes (Rodriguez et al., 2024; Müller et al., 2022; Camprubi et al., 2017). In contrast, laboratory experiments are conducted over limited timeframes and typically isolate individual mechanisms. While this reductionist strategy is methodologically necessary, it may fail to capture emergent properties that arise only within large, interacting systems operating over extended periods (Müller et al., 2022; Barge & White, 2017; Fine & Pearlman, 2023; Kitadai et al., 2019) (Table 2).

Table 2

Examples of experimental vs. natural conditions:
how experimental setups simplify early Earth complexity

<i>Theme</i>	<i>Typical lab feature</i>	<i>Prebiotic concern</i>	<i>References</i>
Atmosphere/oceans	Defined gas and ion mixtures	Real early Earth composition uncertain	White & Rimmer, 2024; Ranjan et al., 2018; Saha et al., 2022; Lopez & Fiore, 2019; Pressman et al., 2015
“Do-nothing” chemistry	Active human intervention	Need chemistry that proceeds autonomously	Nogal et al., 2023; Müller et al., 2022; Bizzarri et al., 2021; Kitadai et al., 2019
Hydrothermal systems	Simplified flow cells	Natural gradients, minerals more complex	Jenewein et al., 2024; Sojo et al., 2016; Kitadai et al., 2019; Goldman & Kacar, 2021.

Dependence on specific models further complicates interpretation. Distinct theoretical frameworks—such as RNA-centered, metabolism-first, or systems chemistry approaches—tend to prioritize different criteria for plausibility and explanatory success (Rodriguez et al., 2024; Sossi et al., 2020; Müller et al., 2022; Barge & White, 2017; Fine & Pearlman, 2023; Camprubi et al., 2017). As a consequence, identical experimental findings may be interpreted in divergent ways depending on the underlying conceptual framework. This plurality of perspectives reflects both the complexity of the field and the absence of a single, unified explanatory model (Muchowska et al., 2020; Yoshida et al., 2024; Camprubi et al., 2017).

Finally, an inherent issue is that of historical contingency. Even when a plausible pathway to the emergence of life can be demonstrated, it remains uncertain whether it corresponds to the actual pathway realized on the early Earth (Muchowska et al., 2020; Rodriguez et al., 2024; Müller et al., 2022; Yoshida et al., 2024). Multiple alternative trajectories may have been viable, and the origin of life may have depended on rare or stochastic events that are difficult to reproduce or even to identify (Nogal et al., 2023; Jenewein et al., 2024; Sojo et al., 2016; Goldman & Kacar, 2021).

Acknowledging these limitations does not diminish the advances achieved in origin-of-life research; rather, it provides a more realistic framework for interpreting current findings (Muchowska et al., 2020; Nogal et al., 2023; Müller et al., 2022; Camprubi et al., 2017). It highlights the importance of integrative strategies that combine experimental data with geochemical constraints, system-level modeling, and comparative evaluation of alternative scenarios (Muchowska et al., 2020; Ranjan et al., 2018; Bizzarri et al., 2021; Camprubi et al., 2017; Pressman et al., 2015). Ultimately, progress in the field will depend not only on the acquisition of new data, but also on a critical understanding of the interpretative limits within which such data can be assessed (Nogal et al., 2023; Müller et al., 2022; Barge & White, 2017; Kitadai et al., 2019).

Conclusions. The origin of life is most appropriately interpreted as a progressive, multistage transition from geochemical processes to biologically organized systems. The RNA world hypothesis continues to serve as a central conceptual framework, supported by the dual informational and catalytic functions of RNA and its essential role in contemporary biology. Nevertheless, its limitations—especially those related to prebiotic plausibility and the emergence of efficient self-replication—suggest that RNA alone is unlikely to constitute a complete explanatory model.

Comparative evaluation of RNA-centered, metabolism-first, and lipid world frameworks reveals a clear shift toward integrative approaches. Current evidence indicates that early life most likely arose through the interaction of multiple molecular systems, including nucleic acids, peptides, lipids, and small-molecule metabolic networks, rather than from a single dominant component. Such co-evolutionary models offer more plausible solutions to fundamental challenges, including the coupling of information storage with catalysis, the stabilization of replicating systems, and the development of compartmentalization.

Despite substantial advances, several key issues remain unresolved, including the origin of reliable replication mechanisms, the emergence of the genetic code and translation machinery, and the transition to the modern DNA–RNA–protein world. Bridging the gap between controlled laboratory experiments and the complex, heterogeneous conditions of the early Earth remains a major obstacle.

Future research should therefore emphasize experimentally testable, system-level models that integrate chemical, physical, and biological constraints. Greater focus on realistic environmental conditions, autocatalytic networks, and protocellular organization will be crucial for further progress. Ultimately, a comprehensive understanding of the origin of life will likely require the integration of multiple complementary approaches, reflecting the inherent complexity of the problem.

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