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REVIEW

Origin of ribonucleotide recognition motifs through ligand mimicry at early earth

Deepto Mozumdar[a] and Raktim N. Roy [b]

[a]Department of Immunology & Microbiology, University of California San Francisco, San Francisco, CA, USA; [b]Department of pathology & laboratory medicine, Indiana University School of Medicine, Indianapolis, IN, USA

ABSTRACT

In an RNA world, the emergence of template-specific self-replication and catalysis necessitated the presence of motifs facilitating reliable recognition between RNA molecules. What did these motifs entail, and how did they evolve into the proteinaceous RNA recognition entities observed today? Direct observation of these primordial entities is hindered by rapid degradation over geological time scales. To overcome this challenge, researchers employ diverse approaches, including scrutiny of conserved sequences and structural motifs across extant organisms and employing directed evolution experiments to generate RNA molecules with specific catalytic abilities. In this review, we delve into the theme of ribonucleotide recognition across key periods of early Earth's evolution. We explore scenarios of RNA interacting with small molecules and examine hypotheses regarding the role of minerals and metal ions in enabling structured ribonucleotide recognition and catalysis. Additionally, we highlight instances of RNA-protein mimicry in interactions with other RNA molecules. We propose a hypothesis where RNA initially recognizes small molecules and metal ions/minerals, with subsequent mimicry by proteins leading to the emergence of proteinaceous RNA binding domains.

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1. Introduction

Unravelling the 'Origin of Life' represents one of the most tantalizing quests in science [1,2]. Prior to the advent of the intricate biological machinery observed in the present day, the nascent forms of life had to navigate vastly different landscapes, guided by primitive molecules in a chemical theatre of emergence. Stanley Miller and Harold Urey's landmark experiment in 1953 demonstrated that simple organic compounds, including amino acids and nucleotides, could be formed under conditions mimicking the early Earth's atmosphere [3–5]. This finding laid the groundwork for a whole field of inquiry aiming to recapitulate the origins of life tracing a path from primordial biomolecules. At the heart of this inquiry lies the 'RNA world hypothesis, which suggests RNA molecules emerging as dynamic entities with dual roles as genetic carriers and simple catalysts, served as the cornerstone for the transition from inert chemistry to the vibrant tapestry of life [6–13].

The transition to template-specific self-replication and catalysis would necessitate the emergence (*a priori* and concurrently) of motifs (structured) that recognized ribonucleotides to facilitate reliable and reproducible means of recognition between RNAs. What did these motifs look like? What was the evolutionary path that paved the way for the proteinaceous RNA recognition entities (RNA-Recognition Motifs (RRMs), Zn-finger folds) predominantly observed in the present world [14–20]? Delving into the depths of the RNA world hypothesis to answer such elusive questions poses a formidable challenge. A direct observation of these primordial entities in the fossil record is generally precluded by their rapid degradation over geological time scales. To circumvent this fundamental challenge, researchers have had to employ diverse and ingenious approaches to infer their existence and glean insights into the ancient origins of these motifs.

One strategy in the field involves scrutinizing the evolutionary history of conserved sequences and structural motifs across extant organisms [16,19,21–23]. This approach enables identification of genes encoding critical RNA-binding proteins and the elements they recognize. A more creative approach pioneered by Szostak, Joyce, Orgel employs directed evolution to generate RNA molecules with specific catalytic abilities [24–40]. These experiments reveal the nature of RNA–RNA interactions that could have potentiated such abilities in a primordial RNA world. Both of these approaches are remarkably insightful and elucidate the fundamental principles that may have been required for ribonucleotide recognition.

In this review, we examine the premise of ribonucleotide recognition across several key periods of evolution on early Earth. We start with a simple scenario of RNA interacting with small molecules (Figure 1) and then proceed to further examine existing hypotheses on the role of minerals/metal ions in providing initial scaffolds for RNA to enable structured ribonucleotide recognition and catalysis (Figure 1). Finally, we highlight specific examples of RNA and proteins mimicking each other in the context of their interactions with

CONTACT Deepto Mozumdar deepto.mozumdar@ucsf.edu Department of Immunology & Microbiology, University of California San Francisco, 600 16th Street, S412D, San Francisco, CA 94143, USA; Raktim N. Roy rakroy@iu.edu Department of pathology & laboratory medicine, Indiana University School of Medicine, 950 W Walnut St. E343, Indianapolis, IN 46203, USA

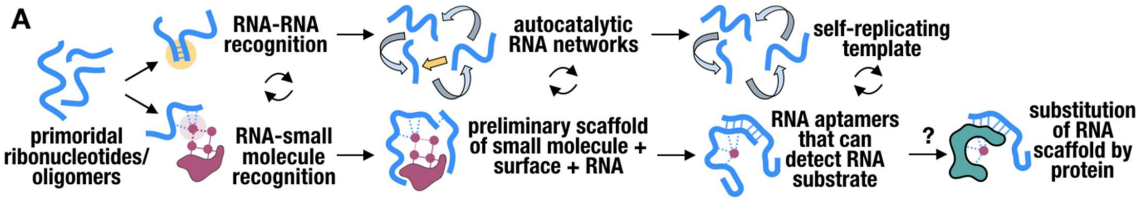

Figure 1. A proposed scenario for the origin of proteinaceous ribonucleotide recognition motifs through substrate mimicry. In early earth, emergent primordial ribonucleotide fragments traverse two chemically interdependent evolutionary paths. In the first trajectory, auto-catalytic networks [41–43] are built through recognition and self-catalytic replication steps that eventually lead to the formation of sustainable propagation of templates below Eigen's error threshold [44]. In the second trajectory, ribonucleotide-metal ion interactions enable initial adsorption to porous rock clusters – such surfaces support further growth of larger ribonucleotide polymers [45–47]. These adsorbed RNAs interact with small molecules/metal ions and provide an initial structured scaffold later used for recognizing other RNA molecules. As RNA-small molecule complexes accrue size and structural complexity they form aptamers that are able to recognize other RNA molecules reliably and reproducibly [48]. Eventually structured proteins/peptide-conjugates replace the RNA recognition scaffolds through molecular mimicry.

other RNA molecules (Figure 1). We provide a plausible hypothesis that recognition of RNA motifs could have started with RNA itself recognizing small molecules and metal ions/ mineral scaffolds. Also, we posit that the mimicry of the structural and functional attributes of RNA molecules (used to recognize ribonucleotide substrates) by proteins, paved the way for the well-conserved proteinaceous RNA binding domains that we know today (Figure 1).

2. Early evolutionary events of small-molecule interaction with RNA

2.1. Small-molecule recognition of RNA

The RNA world hypothesis [6–12] principally concentrates on the advent of RNA-centric life during the subsequent Archaean aeon, spanning from around 3.8 to 2.5 billion years ago. Certain conjectures posit the existence of simpler RNA-driven chemistry or recognition motifs during the earlier Hadean epoch, laying the groundwork for subsequent biological complexity [6,10,12,21,49,50]. The ability of RNA to form complex tertiary structures and interact with small molecules through aptamers [14,15,51–54] emerges as a pivotal aspect in the earliest stages of molecular evolution. It is speculated that such interactions emerged in a prebiotic world on rock clusters [45–47,55], at once acting as geophysical scaffolds for RNA fragments and simultaneously inundated with various small-molecule cofactors. In this scenario, rudimentary RNA recognition motifs may have first developed. Evidence from riboswitches, believed to have evolved early in the history of life, supports this notion [48,56–58]. Riboswitches, which contain multiple-binding sites capable of interacting with apparently distinct molecules [48,56–58], likely played a role in regulating primitive RNA polymerization events in response to environmental cues [48]. Even today, these regulatory RNA elements are found in the untranslated regions (UTRs) of many mRNAs in bacteria and other organisms, orchestrating gene expression in response to specific small molecules or ions [48,56–58]. The aptamer domain from the riboswitch interacts directly with the small molecule or ion (the ligand), to induce conformational changes that modulate the functioning of the expression platform [58–60] (Figure 2A, B). Aptamers could have started as stand-alone, small-molecule recognition motifs that eventually acquired additional regulatory function as the RNA grew in size and cellular structures emerged in the later periods of evolution (Figure 2). It is worth noting that although aptamers are RNAs that bind specific ligands, they need not be catalytic themselves.

For an initial examination of riboswitches, cyanobacteria, a group of photosynthetic bacteria, provide a compelling case study [63,64]. Exploring riboswitches in cyanobacteria offers valuable insights into the small-molecule interactions of the RNA world that may have preceded the emergence of proteins

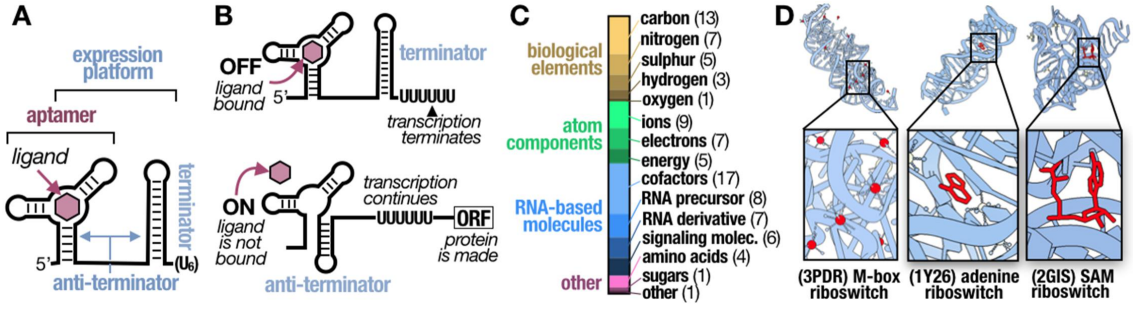

Figure 2. Extant riboswitches illustrate the diversity of small molecules that RNA scaffolds interact with. (A) Riboswitches typically consist of an overlapping RNA aptamer domain (that recognizes and binds a small molecule ligand, red hexagon) and an expression platform (that modulates a specific cellular function). A riboswitch that regulates transcription has been presented as an example [58]. (B) In response to small molecule ligand binding by the aptamer domain, the riboswitch undergoes a structural rearrangement that elicits a specific cellular response (transcription termination in this example) [58]. (C) Riboswitches interact with a plethora of intracellular small molecule ligands. Parentheses indicate the number of known classes of riboswitch that bind a specific category of small molecule ligand. (A-C) adapted from [58]. (D) Example structures of riboswitches that bind metal ions (Mn^{2+}) [61], nucleotide base (adenine) [57] and cofactor (SAM) [62]. Inset – zoomed view of bound ligand (highlighted in red). Parentheses indicate PDB IDs of structures displayed.

and cyanobacteria themselves. Cyanobacteria possess diverse riboswitches crucial for adapting to changing environmental conditions. Examples include flavin mononucleotide (FMN) riboswitches regulating flavin metabolism genes [63,64], cobalamin (vitamin B12) riboswitches controlling cobalamin biosynthesis and uptake [63,64], S-adenosylmethionine (SAM) riboswitches regulating methionine metabolism genes [63–65], and TPP-riboswitches involved in amino acid metabolism regulation [63,64]. These riboswitches regulate precise gene expression in response to nutrient availability, light conditions, and other environmental factors, aiding cyanobacteria in adapting to diverse ecological niches [58,66–68]. More importantly, it lays the groundwork for the idea that mineral-RNA scaffolds could provide a specific recognition mechanism to the other fragment of the RNA, thereby presenting a rudimentary RNA recognition motif.

There are several other examples of RNA-metal complexes that respond uniquely towards other RNA, sometimes purely by the reorganization of tertiary structure. For example, M-box riboswitches, that are prevalent in bacteria, respond with a compaction of tertiary structure in presence of a high concentration of ions [61,69]. Concentrated mixtures of divalent cations, which would be abundant in porous rock clusters of the Hadeanic oceans of early-earth [70], would yield a substructure of the RNA capable of influencing long-range interactions with other RNA motifs. Such rudimentary interactions and cation-dependent recognition of other RNA motifs would pave the way for more complex recognition elements to emerge as evolution took its course.

2.2. Integration of ionic motifs into RNA structure

In the present day, RNA molecules rely ubiquitously on metal ions for a diversity of functions [71–78]. In the case of ribozymes [68,79–82], the proposed pioneer catalysts of the RNA world [6,21,49,50,83–92], Mg^{2+} ions are required to stabilize their folded and catalytically active structures [73,93–96] (e.g. in the group I domain ribozyme or hammerhead ribozyme, Figure 3A) reminiscent of Mg^{2+} s role in extant biology. The functional properties of Mg^{2+} stem from its optimal size, facilitating coordination with oxyanions on phosphate groups [94,95,101–103]. In addition to Mg^{2+} other metal ions also play a crucial role in RNA-dependent processes [77,78,104], including RNA folding and catalysis [100,105–109], self assembly [110] and polymerization [47,111] (Figure 3B). Additionally, metal ions (with similar/distinct identities) can cooperatively bind and influence RNA function [71,112–114]. Collectively, these works highlight the influence of metal ions in providing structural stability to the three-dimensional architecture and function of RNA. In turn, this attribute might have been the impetus during the course of evolution towards conservation of such motifs. Interestingly, metal ions can also induce hydrolysis of RNA molecules by activating a neighbouring 2-OH [115], a process that is exacerbated by stronger Lewis acids (e.g. Pb^{2+}, Cu^{2+}) [116–119] and higher pH [120]. It has been speculated that the RNA may have originated in a low pH environment [120]. With the subsequent increase in environmental pH, evolution (in this case, the heritable propagation of molecular information) may have additionally selected against RNA associations with metal ions that were more likely to drive hydrolysis in these conditions.

In a retrospective analysis of evolution, one could look at the ribozymes from viruses for involvement of ions with RNA catalysis. Studies of the HDV genomic ribozyme reveal that it self-cleaves via a structural Mg^{2+} ion-dependent mechanism and a distinctly different mechanism with combinatory structural and catalytic Mg^{2+} ions [121]. Experiments with various metal ions showed that under conditions favouring the combinatory mechanism, Mg^{2+}, Ca^{2+}, Ba^{2+}, and Sr^{2+} had similar binding affinities, whereas simple structural catalytic modes exhibited tighter binding with smaller ions, indicating two classes of metal ion sites: a structural site with a preference for Mg^{2+} and a weak catalytic site with little ion specificity [121]. This study, further highlights two different kinds of integration of metal ions, within the RNA motif over an evolutionary timescale.

How would these metal ion–RNA interactions have played out in an early earth? It is generally believed that the Hadean ocean of a primordial world was predominantly rich in Fe^{2+}

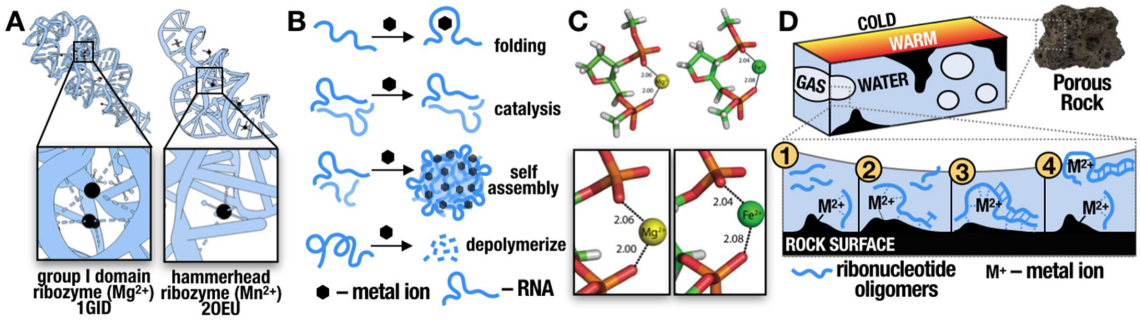

Figure 3. Role of metal ions in extant and primordial biology. Metal ions play extensive roles in extant RNA biology. (A) Structures of ribozymes bound to metal ions [97,98] (indicated in parentheses). Inset shows zoomed-in view. (B) Cartoon illustrating the diverse roles played by metal ions in RNA biology. (C) Quantum mechanical simulation of the RNA-Mg^{2+} clamp from the L1 ribozyme ligase (PDB 2OIU [99] reveal striking similarities in coordination geometry of metal ions Mg^{2+} and Fe^{2+}. Figure adapted from [100]. (D) a proposed model for the growth and evolution of ribonucleotide molecules aided by metal ions on porous rock clusters in a hadeanic ocean. (1) small RNA attaches to porous rock surfaces aided by coordination to exposed metal ions on the surface of the rock cluster. (2) RNA molecules grow in size and complexity on porous rock surfaces. Metal ions and/or small molecules bound to the rock surface get gradually incorporated into the architecture of the growing RNA polymer. (3) structured RNA scaffolds developed on the porous rock surface provide a second layer for other small ribonucleotides/oligomers to attach to. Primordial ribonucleotide recognition motifs emerge. (4) complex molecules with ribonucleotide recognition/catalytic capabilities emerge and the proposed cycle (steps 1-3) occurs to generate a diversity of RNA molecules. Eventually RNA autocatalytic networks emerge.

ions [70,106,122–127]. The plausibility of Fe^{2+} involvement in RNA chemistry is supported by a series of insightful studies [100,106,107,128–130]. One study explores the feasibility of using Fe^{2+} as a substitute for Mg^{2+} in RNA folding and catalysis under conditions lacking free oxygen, reminiscent of plausible early Earth environments [100]. Through a combination of density functional calculations and experiments, it was demonstrated that Fe^{2+} can fulfill the roles of Mg^{2+} in RNA folding and function [100]. Quantum mechanical calculations revealed similarities in the coordination geometry of Fe^{2+} and Mg^{2+} by RNA phosphates [100] (Figure 3C). Chemical footprinting experiments indicated conservation of RNA conformation in the presence of Fe^{2+} or Mg^{2+} [101]. Moreover, the catalytic activities of ribozymes, including the L1 ribozyme ligase and the hammerhead ribozyme, are enhanced in the presence of Fe^{2+} compared to Mg^{2+} [101].

Initially, soluble Fe(II) was abundant in anaerobic conditions; however, with the advent of photosynthesis and an oxygen-rich atmosphere, Fe(II) became less available, and RNA adapted by replacing Fe(II) with Mg^{2+}. Hsiao and colleagues hypothesized that early RNA – Fe(II) interactions were integral to RNA reactivity. Their experiments even show that Fe(II) can catalyse peroxide reduction in structured RNA but not in simple oligonucleotides. Fe(II) supports complex RNA structures and enhances ribozyme catalysis, with studies indicating Fe(II) interactions were more favourable for phosphoryl transfer than Mg^{2+}. Research also shows that Fe(II) and Mg^{2+} support different RNA sequence pools [104,107], suggesting an initial Fe-dominant RNA world later replaced by Mg^{2+}. Additionally, the Iron Responsive Element (IRE) [131–134] in iron metabolism mRNAs illustrates a modern example of functional RNA-Fe(II) interactions, showing how direct RNA-Fe(II) interactions govern regulatory functions in response to iron levels. This indicates that conserved IRE sequences originated early in metazoan evolution, after the Great Oxygenation Event. These findings, coupled with the non-oxidative atmosphere and abundance of Fe^{2+} during the early Archaean Aeon [70,106,122–127], suggest a potential role for Fe^{2+} in an RNA World. In these conditions, RNA and Fe^{2+} could support a more diverse array of RNA structures and catalytic functions than RNA with Mg^{2+} alone.

It is notable here that contrarian studies also exist. Guerrier-Takada et al. [135] highlighted that except for Mn^{2+} no other transition metal could successfully replace the catalytic activity of Mg (Although, Ca^{2+} and Zn^{2+} provide compelling arguments towards potential catalytic involvement [112,136,137]. Nevertheless, it is crucial to recognize that the outcomes might differ significantly under anaerobic and prebiotic conditions that mimic early Earth's environment. The presence of oxygen and the specific metal ions used in contemporary experiments, such as Mg^{2+} and Mn^{2+}, may not reflect the actual conditions of early Earth, where soluble Fe(II) was abundant due to the lack of oxygen [70,106,122–127]. Fe(II) could have played a crucial role in RNA catalysis, influencing the structure and reactivity of RNA differently than Mg^{2+} and Mn^{2+}.

While complexes of metal ions and RNA seem like an obvious feature in today's world, the integration of the two would be the cornerstone for emergence of RNA recognition motifs in the evolutionary cascade. We suggest that cation and cationic clusters, which would be inherently prevalent in porous rocks and mineral clays, would allow for binding of the RNA molecule to the clay/rock itself (Figures 3D, 1). This phase of the binding event could very well be non-specific. But over time, the ions that initially led to the non-specific binding of the RNA would integrate into RNA tertiary structures, in turn regulating the recognition of other RNA moieties (Figures 3D, 2–4). Through their diverse roles in modulating RNA structure, catalysing biochemical reactions, and driving functional changes, metal-RNA complexes provide the first glimpse at the emergence of RNA-recognition motifs.

2.3. Influence of mineral surfaces on building scaffolds for RNA

Previous research has demonstrated the catalytic properties of minerals in various processes crucial to life's emergence, including RNA synthesis, polymerization, and protection from degradation [45,46,138–140]. Mineral surfaces, notably hydroxyapatite, have been proposed (originally by Orgel in 1980[141]) to have the potential to selectively adsorb longer RNAs. Despite this initial observation, this concept has not been extensively explored. However, the selective accumulation of longer RNA molecules on mineral surfaces has significant implications for the RNA world hypothesis. First, it counteracts the bias towards shorter RNAs typically seen in abiotic or ribozyme-mediated synthesis [30,40,46]. Secondly, mineral surfaces protect longer RNAs from loss in self-replicating systems, where shorter sequences replicate more rapidly [46,138,141,142]. Third, the accumulation of long informational RNAs may facilitate cooperative interactions among RNA molecules, promoting complex reactions and collective reproduction within emergent RNA autocatalytic networks [47,143]. This idea underscores the importance of investigating the collaborative effects of minerals and ribozymes in promoting cooperative phenomena, which are often manifested in critical evolutionary steps such as ribonucleotide recognition.

It is important to discuss Montmorillonite in this regard [45,138,140,144]. This clay mineral has been studied since the introduction of the concept by Orgel [145] and represents mineral-based surfaces which could selectively adsorb RNA [46,146]. At a molecular level, ionic motifs from these tangible surfaces bind and stabilize nucleobases, potentially aiding in prebiotic synthesis in favourable environments like hydrothermal vents [45,138,140,144]. These mineral motifs would serve both the functions of elemental catalysts and structural-binding partners to the first few nucleobases, and then quickly transpose themselves into integral motifs of the tertiary structure of these RNA that could stabilize other nucleobases. Hence, there would be the emergence of an RNA recognition from a truly abiological platform of rocks and minerals in early Earth conditions (Figure 3D). Several experiments and

theories reveal that RNA folding is complex, involving parallel pathways and kinetic traps due to a rugged energy landscape [147]. Studies show that slow transitions to RNA's functional state involve misfolded structures serving as kinetic traps, with fast secondary structure formation followed by slower tertiary assembly. Wu and Tinoco's NMR experiments on the Tetrahymena group I intron [148] indicate that Mg^{2+} ions trigger substantial secondary structure rearrangement to achieve the native state. Their findings suggest a nucleation-collapse mechanism for tertiary folding, with implications for similar mechanisms that would have guided the folding and subsequent selection of such RNA in early earth environments. The complex interplay among RNA and minerals sheds light on the conditions and mechanisms underlying life's origin. Investigating these interactions further deepen our understanding of prebiotic chemistry and the pathways that led to the development of RNA recognition.

3. Interactions of RNA aptamers with other RNA

3.1. Rudimentary partners of RNA aptamers

In the exploration of RNA evolution, a pivotal phase arises in the recognition and binding processes, marked by the integration of mineral clusters into RNA's tertiary folds. This integration is followed by the formation of unique folding patterns [48,60] driven by complementary base-pairing interactions and hydrogen bonds among nucleotides within the RNA chain [149–152]. Detailed analyses of RNA structures have unveiled recurring patterns termed conserved motifs [149–152], which act as structural building blocks for more complex architectures. Additionally, longer-range tertiary interactions further contribute to the intricate three-dimensional structures assumed by RNA molecules [149–152].

The focus then shifts to molecular recognition between separate RNAs, where RNA aptamers – short RNA sequences – take centre stage. These aptamers exhibit the capability to selectively bind to target molecules, giving rise to RNA-small molecule complexes [15,51,52,153]. These complexes play a crucial role in assembling complex tertiary structures through non-covalent interactions like hydrogen bonding and base stacking [149–152]. Moreover, the incorporation of small molecules via aptamers introduces new functional capabilities to RNAs. Bound small molecules can act as cofactors for catalytic reactions [154,155], modulate RNA folding dynamics [15], or serve as signalling molecules [156,157]. This expansion of RNA's functional repertoire contributes to the prebiotic world's complexity, setting the stage for the emergence of diverse biological systems. For example, using biophysical and structure mapping techniques, it has been shown [158] that tRNA folding cooperativity increases under physiological conditions with crowding agents like PEG or dextran. Additionally, the presence of low-molecular-weight co-solutes variably affects folding [158], highlighting that crowding agents stabilize tertiary structures to enhance folding cooperativity, paralleling protein folding behaviour. It begs the question if such non-living crowding effects could have been generated in early earth where multiple RNA fragments coming together to induce functional cooperativity while mimicking the crowding effect is well within reason.

Furthermore, the complex tertiary structures formed by RNA-small molecule complexes serve as scaffolds for the binding of additional RNA molecules, leading to the formation of larger RNA networks [42,43,159]. These networks facilitate cooperative interactions between RNA molecules, thereby promoting the emergence of rudimentary cellular processes [160–162]. The integration of RNA-small molecule complexes into complex tertiary structures through aptamers represents a critical step in life's early evolution.

3.2. Evolution of RNA auto-catalytic networks

We cannot discuss the emergence of RNA recognition motifs without the discussion of autocatalytic networks, which would have evolved into the self-sustaining cycle of replication/reproduction [29,33,34,38,41–43,163–165]. Our current day research points to the idea that autocatalytic networks could have emerged only after the advent of RNA-based RNA-recognition motifs. Let us start with a null hypothesis: autocatalytic networks of purely RNA fragments did not require RNA recognition motifs. If true, RNA copying would be random, thereby crossing Eigen's threshold [44] within a few generations and collapsing the system. This mathematical improbability for sustained growth of life suggests that the alternative hypothesis is much more likely to be true.

In the RNA world scenario, autocatalytic networks played a pivotal role in the emergence of self-replicating RNA molecules through the interplay of simple catalysts and far-from-equilibrium phenomena [166]. Autocatalytic networks are dynamic systems where molecules catalyse their own production, leading to exponential growth under prebiotic conditions [166,167]. Through the process of template-directed RNA polymerization, ribozymes could have catalysed the synthesis of complementary RNA strands using simple precursor molecules, such as nucleotides [44,166,167]. This process initiates an autocatalytic cycle where the newly synthesized RNA molecules serve as templates for the production of additional RNA copies, leading to exponential amplification of the RNA population. Far-from-equilibrium conditions are essential for sustaining such autocatalytic networks and promoting the emergence of self-replicating RNA [41,42,159]. These conditions create a thermodynamic driving force that fuels the continuous production of RNAs, overcoming the inherent tendency of chemical reactions to reach equilibrium.

Experimental studies have provided evidence supporting the plausibility of autocatalytic networks in the RNA world [29,33,34,38,40–43,163,165]. For example, *in vitro* selection experiments and extensive computational studies have demonstrated the spontaneous emergence of RNA molecules with self-replicating properties under selective pressure [29,33,34,38,40–43,163,165]. These studies have identified ribozymes capable of catalysing RNA ligation and replication reactions, further supporting the feasibility of autocatalytic networks in prebiotic environments [10,43,159]. Autocatalytic networks, driven by simple catalysts and far-from-equilibrium conditions, provide a plausible mechanism

for the formation of self-replicating RNA in the RNA world. Critically, the intricate dynamics of these networks rely on efficient binding and recognition of partners to enable autocatalytic reactions. In turn, the evolutionary advantage provided by the stability of such autocatalytic networks would provide the impetus for speedy development and sustenance of RNA recognition motifs.

4. Transfiguration of RNA recognition scaffolds into protein scaffolds

Protein-based RNA recognition is widely observed in many fundamental life processes of today's world. Based on the ubiquitous observation of such protein-based RNA recognition motifs in extant organisms, it has been suggested that these motifs are ancient and evolved early on, likely antedating LUCA [168]. How would these primordial RNA-recognition elements gain a foothold in an environment dominated by solely RNA-based recognition? It is possible that in the later stages of this evolution of RNA-recognition, RNA molecules might have collaborated with simple peptides or precursor molecules of proteins [169–171]. Such cooperative interactions could have engendered nascent recognition motifs, serving rudimentary catalytic and binding roles (Figure 4A). What would these motifs look like in transitioning from purely RNA-based recognition to its proteinaceous counterpart that is widely observed today?

Over the course of molecular evolution, nature chose phosphates in RNA (and DNA) backbones for their unique ability to stabilize and retain molecules via negative charges while linking nucleotides and preventing hydrolysis [172]. This stability also applies to their role as energy carriers and metabolites. Phosphates can form reactive intermediates like monomeric metaphosphate ions, making them vital in biochemistry, where enzymatic catalysis drives reactions without the need for highly reactive intermediates [172]. Mutisya et al. [173] investigated the premise if amide linkages could replace phosphodiesters. Although predominantly studied with siRNA, their work in relation to amides as potential substitutes for the phosphate backbone [173] can be conceptually expanded to most RNA. Their research aligns with previous biophysical and NMR data, suggesting that amides exhibit structural characteristics akin to the phosphate backbone, thereby suggesting a possible mechanism of scaffold transfiguration through iterative replacement (Figure 4B). In their work [173], a crystal structure analysis of an amide-modified RNA offered insights into the accommodation of amide linkages within an A-form duplex, shedding light on their structural compatibility. Additionally, the favourable hydration properties of amides along with lesser propensity for lysis further support their feasibility in biological environments. Of particular interest is the observation that amide linkages are well tolerated at internal positions within both guide and passenger strands of siRNAs [173].

A study by the Hlouchova group [174] selected an RNA-binding variant of the ribosomal uL11 C-terminal domain from a library of sequences composed of prebiotically plausible amino acids, which bound RNA with similar affinity but utilized ion bridging (K^+/Mg^{2+}) for stabilization instead of aromatic or basic residues. This suggests early RNA – protein interactions relied on metal ions rather than amino acid. For example, RNA-binding proteins selected from reduced amino acid alphabets show similar binding affinities but differ in their interaction mechanisms compared to their modern counterparts. Additionally, magnesium ions and polyamines were likely crucial in stabilizing early protein structures and facilitating RNA interactions. This study highlights that early RNA – protein interactions could have evolved with metal-ion assistance before the addition of positively charged amino acids to the protein alphabet for enhanced interaction specificity.

Another possible trajectory for the dominance of protein-based RNA recognition involves the emergence of polypeptides through convergent evolution that resemble RNA-based scaffolds. We hypothesize that these polypeptides would eventually replace, *in entirety*, the existing RNA scaffolds (Figure 4C), becoming the primary means of RNA recognition (as observed in the extant world). Was indeed such a trajectory feasible and what were the considerations that determined the preference of protein vs RNA in a recognition scaffold? Herein (section 4 and 5) we examine specific examples of folded proteins that were either incorporated to enhance stability of RNA–RNA interactions, or mimic the structure and/or function of certain RNA molecules providing preliminary support for our hypothesis.

To the former point, the shift from RNA–RNA to RNA–protein interactions not only provided greater catalytic efficiency but also increased the specificity of molecular recognition, thereby promoting the diversification and complexity of early life forms [170,175]. Evidence of such integration is

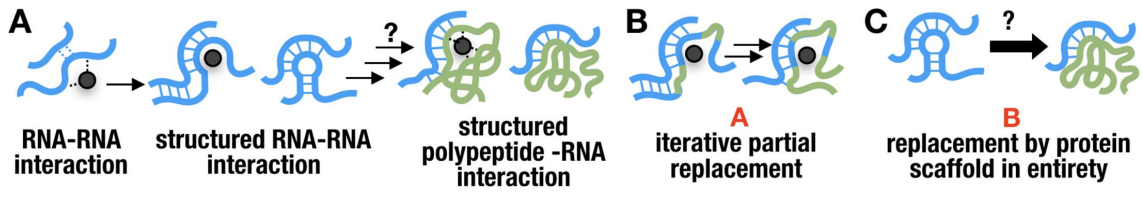

Figure 4. Proposed model for the transfiguration of RNA recognition scaffolds from RNA to protein. (A) In a primordial earth, rudimentary RNA-RNA interactions give way to stable RNA-based recognition motifs as RNA molecules (blue) gain size, structure and complexity. Eventually, through the course of evolution, these RNA-based RNA recognition scaffolds are replaced by the versions that are composed entirely of polypeptides (green) through unknown mechanisms. We speculate that such a transition may have occurred through a combination of two processes. (B) In the first process (A), portions of the recognition RNA scaffold are replaced iteratively by amino acids due to enhanced stability provided by peptide bonds compatible with the RNA structure. Over time, the entire ribonucleotide scaffold is replaced by amino acids. (C) In an alternative process (B), polypeptide sequences that resemble the RNA-based recognition scaffold emerge through convergent evolution, entirely replacing the original RNA-based scaffold.

observed through the analysis of the composition of the ribosome itself. The ribosomal core, composed of ribosomal RNA (rRNA) and ribosomal proteins, catalyses the formation of peptide bonds between amino acids during translation [176–178]. This process occurs in the peptidyl transferase centre (PTC) of the ribosome [179], where the 23S rRNA component plays a central role in catalysis [180]. Bokov and Steinberg in their remarkable finding presented a hierarchical model that hones in on the catalytic motif of the ribosome, which turned out to be an RNA [181]. Their analysis reveals that a critical aspect of 23S rRNA evolution during the post-proto-ribosome era was the stabilization of the proto-ribosome's tertiary structure [181]. Their findings underscore that, despite its apparent complexity, the structure of 23S rRNA adheres to the notion and could have evolved within a relatively short time frame in the context of evolutionary history [181]. Each new addition occurred randomly and was assimilated only if it enhanced the ribosome's stability and efficiency as a transpeptidase [181]. During the early stages of evolution, the ribosome primarily existed as an RNA entity [181]. Subsequently, as ribosomal functioning became sufficiently efficient in protein synthesis, proteins assumed a significant role in the ribosomal structure [181]. They also proposed that the pivotal transition from the RNA world to the protein-based world is punctuated by the critical time point where a proto-ribosome synthesizing peptides and potentially other peptide-like chemical moieties [181], became truly exclusive in the synthesis of peptides. That point in time will also be devoid of the proteinaceous parts of the ribosome and mostly RNA-based.

4.1. First-RNA recognition domains of protein – oldest evolutionary records – RRM motifs

The RRM domain, also known as the RNA-binding domain (RBD) or ribonucleoprotein (RNP) domain, is the most abundant RBD in higher vertebrates and is found across all domains of life, including prokaryotes and viruses [168,182,183]. The RRM domain represents one of the oldest protein motifs, with structural similarities observed between ancient and modern proteins on an evolutionary time scale [168,182,183]. Interestingly, examination of virus hallmark proteins (VHPs), crucial for the genome replication of viruses (infecting all domains of life), reveals a striking commonality – the structural core of these proteins all share the RNA-recognition motif (RRM) domain [168]. Given that viruses infect cells in every domain of life and likely antedate the LUCA, this finding suggests that RRMs emerged in a similar time period. Although RRM motifs are currently found exclusively in proteins, it prompts speculation whether similar structural motifs could also be harboured by RNA itself or small molecule-RNA conjugates [168,184]. Despite its prevalence and importance in modern biology [16,183], research on the origin of the RRM motif has been relatively limited [19,185]. Taking a reductionist approach, examining motifs that recognize ribonucleotides in general provides insights into the origin of such recognition motifs [20]. Moreover, in examining the transition from RNA–RNA to RNA–protein interactions, enthalpy of interaction plays a crucial role. The binding affinities and the stability of RNA-protein complexes are often driven by the favourable enthalpic contributions from hydrogen bonding, van der Waals forces, and ionic interactions (Figure 5B) [20]. These interactions are more specific and stronger compared to RNA–RNA interactions, facilitating the evolution of more complex and efficient biochemical pathways. This shift from RNA–RNA to RNA–protein interactions not only provided greater catalytic efficiency but also increased the specificity of molecular recognition, thereby promoting the diversification and complexity of early life forms.

The RRM domain (Figure 5A), comprising approximately 80 amino acid residues, contains two highly conserved short-sequence motifs known as RNP1 and RNP2 [20,182,183]. These motifs are crucial for RNA recognition and binding, with aromatic amino acid residues in RNP1 and RNP2 likely playing key roles in stacking interactions with RNA bases [20]. In an RNA-only world, aromatic amino acid residues in RNP1 and RNP2 motifs could have originally been composed of other ribonucleotide nitrogenous bases (akin to the amide linkage research [173] we discussed) highlighting the intricate interplay between RNA and protein entities. The formation of stacking interactions and hydrogen bonds between RNA bases and RNP1/RNP2 residues is crucial for sequence-specific recognition of RNA, suggesting that the RRM motif formed from rudimentary RNAs may have played a pivotal role in early RNA–protein interactions and the evolution of RNA-based catalysis (Figure 5).

4.2. Zn-finger domains and 2-metal catalysis (Fig 5A)

Zinc-finger domains are ubiquitous protein motifs [17,18,187–189] characterized by the coordination of zinc ions, which play crucial roles in DNA binding and protein–

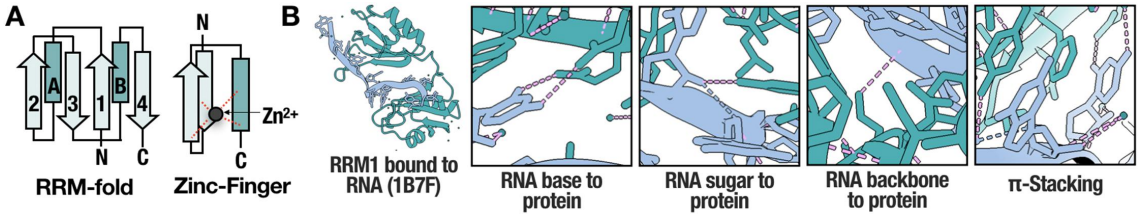

Figure 5. Proteinaceous motifs that recognize RNA molecules are widespread in an extant world. (A) Schematic illustrating the relative arrangement of the secondary structural elements (alpha helices: dark shaded rectangles; arrow: beta strands; zinc ion) in the most common proteinaceous motifs observed in extant organisms, namely RRM (ribonucleotide recognition motif) and zinc finger motif. (B) Structure of the RRM1 domain from the SXL-Lethal protein bound to RNA [186]. Inset illustrates the different modes of interaction between the RNA and protein elements.

protein interactions [17,18,187–191]. These domains often function as transcription factors, regulating gene expression by recognizing specific DNA sequences [17,18,187–189]. Additionally, certain zinc-finger proteins possess enzymatic activities, such as nucleic acid cleavage or RNA processing [192–195], where metal ions are essential cofactors for catalysis. RNA molecules on the other hand, particularly ribozymes [68,79–82], exhibit catalytic activity similar to the world of protein enzymes today. One of the most well-studied catalytic motifs in RNA is the ribonuclease P (RNase P) [135], which utilizes a 2-metal ion mechanism to cleave phosphodiester bonds in RNA-DNA hybrids [71]. In this mechanism, two divalent metal ions, typically Mg^{2+}, coordinate within the active site of the ribozyme, facilitating the nucleophilic attack on the scissile phosphate [71]. Zinc-finger domains and RNA molecules are two distinct biological entities, yet they exhibit remarkable catalytic capabilities, often involving 2-metal ion coordination.

Despite their divergent evolutionary origins and functional differences, zinc-finger domains and RNA share mechanistic similarities in 2-metal ion catalysis [17,18,71,187–189]. Both systems utilize divalent metal ions, such as zinc or magnesium, to facilitate catalytic reactions by stabilizing reactive intermediates and orienting substrates for optimal reactivity [71]. In zinc-finger domains, zinc ions serve as structural scaffolds, promoting protein folding and stabilizing the active site geometry for catalysis [17,18,187–191]. Similarly, in RNA catalysis, magnesium ions (most commonly) play analogous roles, coordinating with RNA functional groups to enhance nucleophilic attack and stabilize transition states [71,73,93–96,102,103]

By overlaying the structural motifs, we observe a striking similarity in the distance between the two cations (Figure 6B). This observation highlights the exciting possibility of shared catalytic motifs or even the possibility that the Zn-finger domains could have emerged through mimicking the similar RNA scaffold, while retaining the position of the catalytically indispensable cations to maintain the chemistry. It is important to mention that this observation, though described as 'mimicry', may simply be a consequence of convergent evolution. The key point here is the apparent interchangeability of protein or RNA scaffolds in precisely positioning two metal ions for catalysis across these diverse macromolecular systems.

5. Functional mimicry in RNA recognition by RNA and proteins

5.1. Functional protein mimics of ribosomal RNA core

The concept that the ribosomal core, responsible for peptide bond synthesis during protein translation, shares functional similarities with the condensation domains (C-domains) found in Non-Ribosomal Peptide Synthetases (NRPS) is an intriguing one [197] (Figure 6D). Both systems are involved in the formation of peptide bonds, albeit through different mechanisms [197]. Similar in function to the ribosomal core for peptide-synthesis, the C-domains are folded protein fragments within NRPS responsible for the condensation of amino acids during the biosynthesis of non-ribosomal peptides [198]. Like the ribosomal core, C-domains catalyse the formation of peptide bonds. Both systems involve the activation of amino acid substrates and their subsequent condensation to form peptide bonds [198]. Structural studies of both the ribosomal core and NRPS C-domains have provided insights into their catalytic mechanisms and substrate recognition properties [196]. While the ribosomal core relies on rRNA for catalysis [176,177,180,181], C-domains utilize protein-based catalytic mechanisms [196] (Figure 6D) involving conserved active site residues. The functional similarities between the ribosomal core and NRPS C-domains raise interesting questions about the evolutionary relationship between

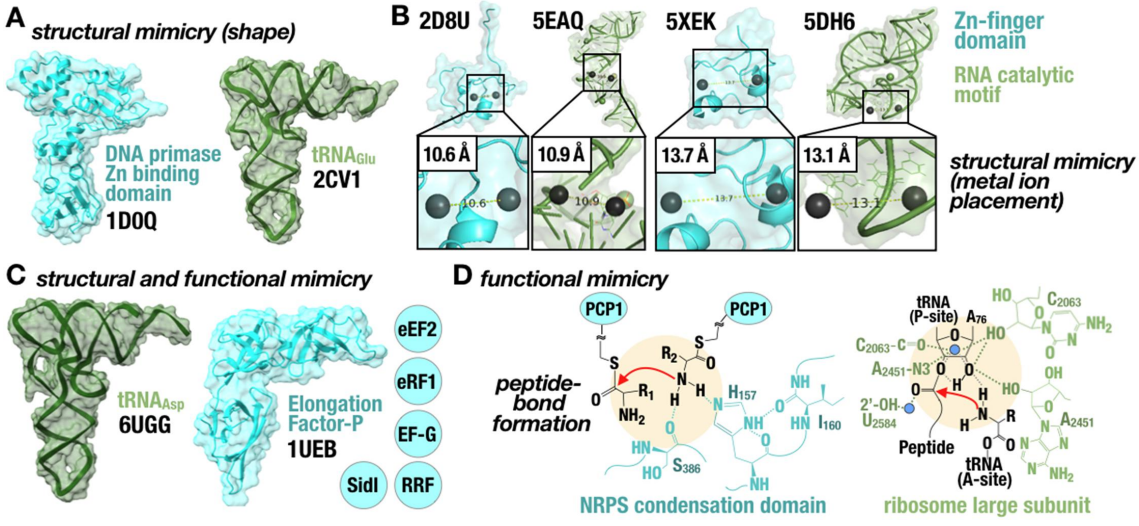

Figure 6. Structural and functional mimicry between protein and DNA molecules. Highlighted examples of protein and DNA molecules exhibiting structural similarity, either in overall shape (A) or in placement of critical metal ions in overall architecture (B). (B) Inset is a zoom in view of the metal ions and the distance between the two-metal ions in each structure is indicated in the top-left. (C) Highlighted examples of proteins that exhibit structural and functional mimicry of tRNA molecules. (D) NRPS condensation domains are an example of a protein [196] that facilitates a function (namely peptide bond formation) canonically enabled by the entirely RNA based catalytic core of the ribosome [176,177,180,181]. The key active site moieties that coordinate the amino acids for peptide bond formation are highlighted in different colors (blue/cyan: amino acid; light green: ribonucleotide). (A-D) color coding: Cyan/Blue: protein/amino acid; green: RNA/ribonucleotide.

ribosomal and non-ribosomal peptide synthesis pathways. It is possible that these systems share a common ancestral origin, with the ribosome representing an ancient ribozyme-based catalyst for peptide bond formation that later evolved into more complex protein-based systems like NRPS. While the ribosomal core and NRPS C-domains operate in distinct cellular contexts and utilize different catalytic mechanisms, their shared function in peptide bond synthesis highlights intriguing parallels between ribosomal and non-ribosomal peptide synthesis pathways.

5.2. Functional mimics of release factors

RNA pseudoknots, formed by base pairing between non-adjacent regions of the RNA sequence, have the potential to mimic the function of translation release factors by adopting conformations that resemble the stop codon–ribosome interaction site. This structural mimicry allows pseudoknots to interfere with the translation termination processes, ultimately affecting protein synthesis. Notable studies by Plant et al. [199] provided evidence for the ability of these intricate RNA structural motifs to stall ribosomes at termination codons, thereby inhibiting translation termination. They demonstrated that intricate RNA structural motifs, such as pseudoknots, can stall ribosomes at termination codons and inhibit translation termination by binding specifically to the ribosome at the stop codon recognition site. High-resolution structural analyses using techniques such as X-ray crystallography and cryo-electron microscopy have revealed the intricate interactions between pseudoknot RNA structures and the ribosome. Another similar study [200] elucidated the detailed molecular interactions between a pseudoknot RNA and the ribosomal decoding centre, providing mechanistic insights into how pseudoknots stall ribosomes during translation termination. These functional pairs are remnants of an evolutionary period when such motifs likely developed through interdependencies and substrate mimicry; a process no longer evident in the present world.

5.3. Viral IRES mimicking translation-initiation complex

Structural studies using techniques such as X-ray crystallography, cryo-electron microscopy, and nuclear magnetic resonance spectroscopy have provided valuable insights into the molecular mechanisms underlying viral IRES-mediated translation initiation [201,202]. Viral IRES RNA elements exploit specific RNA structural motifs to mimic the function of translation initiation complexes, enabling efficient and selective initiation of translation at internal sites within viral mRNAs [201,202]. Unlike canonical translation initiation in eukaryotes, which typically involves the scanning of the 5' untranslated region (UTR) by the ribosome to locate the start codon, viral IRES elements directly recruit ribosomes to initiate translation at internal sites within the mRNA.

Viral IRES elements contain specific structural motifs that interact with ribosomal subunits and initiation factors, facilitating the recruitment of ribosomes to the mRNA. These motifs often mimic the binding sites for initiation factors, such as eIF4G and eIF3, found in canonical translation initiation complexes [201,202]. Similar to its interaction with eIF4G, viral IRES elements contain specific structural motifs that mimic the function of eIF3 in promoting ribosome recruitment and assembly. By mimicking the function of eIF3, viral IRES elements ensure efficient ribosome recruitment and assembly at internal sites within the mRNA, allowing translation initiation to occur independently of the canonical eIF3-mediated pathway [201,202].

5.4. Structural and functional mimics of the tRNA clover-leaf scaffolds

EF-P (Elongation Factor P) and tRNA exhibit structural similarities despite their distinct roles in protein synthesis [203]. EF-P adopts a compact globular structure composed of three domains, with each domain contributing to the overall stability and function of the protein [204]. EF-P's domain III resembles the anticodon stem loop of tRNA, allowing it to interact closely with the ribosome in a manner similar to tRNA. EF-P enhances the translation of proteins by stabilizing the ribosome during the addition of proline-rich sequences, a function that involves recognizing and interacting with the D-arm of the P-site tRNA. This interaction is crucial for accelerating peptide bond formation, highlighting the functional mimicry between EF-P and tRNA in the translation process. Both EF-P and tRNA contain conserved structural motifs critical for ribosome binding and interaction with the mRNA (Figure 6C). The structural similarities between EF-P and tRNA suggest evolutionary conservation of certain features involved in translation elongation. While tRNA molecules would have presented the earliest forms of mRNA recognition motifs, EF-P would have emerged utilizing a substrate-recognition motif by molecular mimicry.

Similar evidence is also seen in primases [205], which share structural similarities with tRNA (Figure 6A). While primases and tRNAs exhibit differences in their overall structures and functional domains, they share certain structural features. Primases often contain conserved domains, such as the zinc finger domain [205] and the catalytic domain, which are involved in nucleic acid binding and RNA primer synthesis [205,206]. Similarly, tRNAs possess conserved structural elements, including the anticodon loop, acceptor stem, and TψC loop, which are critical for amino acid attachment, and mRNA recognition.

A recent study of *Legionella pneumophila* toxin SidI is yet another fascinating example of a protein molecule mimicking an RNA function [207]. Through extensive biochemical and structural characterization, the authors reveal that SidI functions as a tRNA mimic that directly binds to and glycosylates the host ribosome [207]. The N-terminal domain of SidI was observed to adopt an 'inverted L' shape with a surface charge distribution akin to a tRNA molecule enabling direct binding to the host ribosome [207]. Functional interactions are observed in SidI similar to the way tRNAs and translation factors operate. Concomitantly, the C-terminal domain was found to adopt a glycosyltransferase fold that the authors reveal is used by SidI to glycosylate the host ribosome [207]. The synergistic effect of the two domains potently halts protein synthesis that subsequently triggers a ribotoxic stress response within the host [207].

6. Discussion

In this review, we traced the emergence of RNA recognition from a truly abiotic primordial world to the establishment of the proteinaceous RNA-recognition scaffolds of an extant world. We begin our discussion with geophysical scaffolds containing metal ions and cofactors that enable for the first binding events of ribonucleotides (be it in monomeric state or small oligomeric forms). These ionic cofactors on rock clusters allowed for the growth of the RNA and integration of minerals into the tertiary structures. These RNA-metal complexes would allow for binding of other RNAs and provide the first variants of a rudimentary RNA-recognition motif. As amino acids emerged as a more stable replacement of the phosphodiester, several of these RNA-recognition motifs became proteinaceous by simple competitive mimicry of the structural scaffold. Alternatively, small polypeptide sequences, through structural and/or functional mimicry, could gain RNA-recognition and replace original RNA scaffolds.

RNA-binding proteins remain essential components of all forms of life, suggesting that RNA recognition has been a fundamental aspect of biology since early evolutionary stages. In the era after the emergence of proto-recognition motifs, RNA-binding proteins would have evolved into more sophisticated architectures such as RRMs, K-homology (KH) domains, zinc finger domains, and others. As life would continue creating complex RNA-protein complexes, like the ribosome, many of these proto-recognition motifs would integrate into what we know as the translational machinery today, as evident by many ribosomal proteins sharing the same α/β fold also harboured by the most common RNA binding domains (RNP, dsRBD and KH) [208,209]. As life diversified, RNA molecules evolved complex secondary structures, including mRNAs, rRNAs, tRNAs, non-coding RNAs (e.g. miRNAs, lncRNAs), and viral RNAs, the motifs that recognize these elements also grew in complexity.

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Data availability statement

The data that support the findings of this review are openly accessible through PUBMED from the research referenced within the text. Also, upon publication the research references can be openly accessed through the publication.

ORCID

Raktim N. Roy http://orcid.org/0000-0001-8410-5819

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