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From RNA world to RNA-peptide world: A review

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Abstract. How life starts from small molecules to RNAs and further to modern life is an unanswered question. Cyanosulfitic chemistry established the synthesis of building blocks, including 12 proteinogenic amino acids, 4 ribo- and deoxyribo-nucleosides, and phospholipids, from hydrogen cyanide and hydrogen sulfite under prebiotically plausible conditions. Later on, the non-enzymatic monomer extension of nucleotides provided a plausible pathway from mononucleotides to RNAs giving rise to the RNA world. RNA is one of the key components for the origin of life, firstly, the sequence information can be heritage by template copying reaction. Secondly, RNA is able to fold into a secondary structure which has the capability to catalyze chemical reactions. The RNA world scenario has perfectly overcome the chicken-egg problem, but it still cannot explain why peptides are involved in modern life. Most recently, with the establishment of the reaction between RNA and peptides, the trajectory to the RNA-peptide world theory has opened up a new era of the origin of life research. Here I will discuss the current results relevant to the RNA world to RNA-peptide world theory.

Keywords: RNA world, RNA-peptide world, the non-enzymatic replication of nucleotides.

1. Introduction

The source of life on early Earth is still an uncertain question, with a growing body of literature exploring prebiotic building block synthesis like nucleotides and amino acids. For instance, atmospheric hydrogen cyanide can react with surface water and ferrous ions to form ferrocyanide [1], which can then undergo redox reactions to produce precursors for bio-related molecules. This allows for the simultaneous production of all cellular subsystems through a single type of chemistry, with Cu(I)-Cu (II) photoredox cycling and hydrogen sulfide acting as the reducing reagent to accelerate the process [2]. A concentrated cyanide solution could be created by a stream entering the area or a small amount of rainfall. Calcium cyanamide and magnesium nitride can be produced through thermal transformation of calcium and magnesium cyanoferrates (II). These salts can then generate cyanamide and ammonia upon hydration, which are essential for ribonucleotide and purine synthesis, respectively. Common cyanosulfidic chemistry from hydrogen cyanide can synthesize building blocks for RNA, peptides, and lipids [3]. Molecular cell biology has traditionally been dominated by a protein-centric perspective. However, the discovery of tiny non-coding RNAs suggests that this view may be incomplete. Despite their abundance, these RNAs were initially overlooked but have since been found to have an integral roles in controlling expression of gene at numerous points. As a result, they have become recognized as important contributors to the genetics and evolution of organisms [4].

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2. Noncanonical RNA/DNA copying

The observation of nonenzymatic copying of a number of prebiotically plausible nucleotides has led to the theory that it could have contributed to the formation of RNA as a chemical selection mechanism. If present in the template, nucleotides with changed sugar chemistry, such as arabino-, threo-, and 3'-amino-2'3'-dideoxyribo-nucleotides, can be replicated to generate a canonical RNA strand, although they are less effective than ribonucleotides in nonenzymatic copying. The amino group at the 3'- or 2'-position of the 3'-terminal residue is the primer that is frequently employed for an extension that yields more because of its nucleophilicity, which facilitates the synthesis of phosphoramidate [5]. Primer extension that is Nonenzymatic with triggered arabinonucleotides is significantly less successful than the one with ribonucleotides that are activated. This is according to studies using arabinonucleotides and 2'-deoxyribonucleotides in template-directed primer extension processes. Furthermore, primer extension is strongly hindered by the inclusion of an arabinonucleotide, and primer extension products that have been arabino-terminated cannot be extensively prolonged [6]. These findings support the hypothesis that different copying chemistry's cycles would result in the creation of oligonucleotides consisting numerous ribonucleotides. Further research is needed on the properties and provenance of a potentially primordial form of RNA that contains inosine and 2-thio-pyrimidines [7].

3. Canonical RNA/DNA copying

Although much research has focused on investigating a pre-RNA world, it is important to also consider the possibility of RNA-based RNA replication as a potential hypothesis for the RNA world. The first instances of templated RNA copying were studied by Orgel and his colleagues, who investigated template-directed synthesis on templates with one or more A or T residues within a run of C residues using 32P-labeled hairpin oligonucleotides with oligodeoxynucleotide sequences [8]. More recently, Sosson et al. calculated the rate coefficients for the chemical process of primer extension that involves methylimidazolides or oxyazabenzotriazolides of deoxynucleotides or ribonucleotides. They measured the tie affinity of 15 diverse triggered deoxynucleotides to DNA or RNA templates and provided an explanation for why some primer extensions that are enzyme-free can be copied effectively while others cannot. Effective enzyme-free copying is induced by a grouping of tight binding, quick extension, and slow hydrolysis. They also disclosed the dissociation coefficients for triggered nucleotides binding to their corresponding templates. The rate constants for hydrolysis and the primer extension's chemical process allow for a noble quantifiable alignment between experimentation and theory. This demonstrates that a set of factors, such as the binding coefficients for triggered and inactive nucleotides and the rate coefficients for hydrolysis and the covalent phase of primer extension, is adequate to characterize the reaction of enzyme-free primer extension. To facilitate a more systematic search for RNA primer extensions that provide greater yields, these requirements are best addressed when HOAt esters react with amino-terminal primers [9]. Any of the four ribonucleotides can be incorporated almost quantitatively when an activating reagent (e.g., carbodiimide) and an organocatalyst are combined. In addition to pre-activation chemistry, adenosine 5'-monophosphate was shown to form oligomers in an aqueous solution by in situ activation [10]. Furthermore, the same group evaluated the in-situ activation of all 16 canonical ribonucleotide dimers and two trimers. They discovered that short ribonucleotide oligomers are effective reactants in enzyme-free copying, and that trimers and dimers could be converted to primers on RNA templates using an organocatalyst and optimal condensing agent combination under slightly acidic conditions [11].

Non-enzymatically directed RNA polymerization using activated monomers has been explored for its thermodynamic characteristics since the 1960s. The suggested procedures all start with the template attaching to the activated monomer in a noncovalent reversible fashion. Base stacking that arises from downstream or upstream adjacent mono- or oligonucleotides can facilitate these interactions. The chemical attraction of guanosine 5′-monophosphate (GMP) to the primer-template complex was studied by Tam et al. using isothermal titration calorimetry (ITC) and nuclear magnetic resonance spectroscopy (NMR). Although GMP binding affinity increased by about two orders of magnitude

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when the helper oligonucleotide stabilized the downstream side of the binding monomer [12], the likelihood that GMP binding to the primer-template complex could not pass through the downstream monomer was noticeably increased. In a separate investigation, they showed that using activated helper oligomers did increase rates of nonenzymatic template-directed synthesis. They demonstrate that primer extension can be sped up by employing short 5′-activated oligonucleotides and provide an example of how mixed-sequence RNA templates may be duplicated in a single container. Activated oligomers catalyze the serial addition of activated monomers, producing primer extension products with sufficient fidelity to preserve a genome long enough to form functional ribozymes. Finally, by immobilizing the primer and template on a bead and adding individual monomers in sequence, they successfully produced a large percentage of an active hammerhead ribozyme, creating a bridge between nonenzymatic polymerization and the RNA world.

Using 2-methylimidazole-activated monomers as substrates, Walton et al. explored the impact of varied lengths of downstream auxiliaries. It was shown that downstream oligonucleotides enhance primer extension by creating a high-affinity nucleotide binding site in the 'helper' oligonucleotide's pocket [14]. Using nuclear magnetic resonance (NMR), a unique symmetrical dinucleotide product was identified, which was made possible by a set of activated trimeric oligonucleotides that sped up the successive addition of monomers to primers. Synthetic methods were employed to confirm the presence and catalytic activity of the 2-methylimidazolium-bridged dinucleotide. Non-enzymatic template-directed primer extension with nucleoside 5'-monophosphate imidazolides entails two steps: the formation of the imidazolium-bridged dinucleotide intermediate, and the reaction of the intermediate with the primer on the template to produce the primer extension product. Both the intermediate structure and, in the case of the activated auxiliary oligonucleotide, the additional pre-organization of the RNA duplex structure, affect the rate at which the primer extension process proceeds. The role of the catalytic metal ion in the reaction pathway is currently poorly understood [15].

To better understand the primer extension process, Zhang et al. co-crystallized stable phosphonate analogs with a primer-template duplex [16]. The initial theory proposed that the 3'-hydroxyl group of the primer would react with the incoming phosphate of the activating monomer, altering the leaving group and causing the primer to expand into a nucleotide. They found that when two activated nucleotides interacted, a 5'-5'-imidazolium bridging dinucleotide intermediate was formed. These findings provided evidence for the feasibility of using 2-methylimidazole-activated nucleotides for non-enzymatic primer extension, as demonstrated by Zhang and colleagues. Structural studies of template-bound GpppG (P1, P3-diguanosine-5-triphosphate) have provided evidence in favor of the hypothesis that the imidazolium-bridged intermediate securely binds the template by two Watson-Crick base pairs. In addition, the bound complex is better prepared for in-line nucleophilic assault by the primer 3'-hydroxyl group due to the conformational restriction imposed by the covalent internucleotide bridge [17]. Szostak's group used time-resolved crystallography to identify RNA primer extension that does not require an enzyme. In order to experimentally explain the mechanism of non-enzymatic primer extension, they discovered that the activated ribonucleotide connected to the template produces an imidazolium-bridged dinucleotide intermediate, which may then build a new phosphodiester bond between the primer and nucleotides [18].

Daniel Duzdevich et al. used deep sequencing to investigate RNA primer extension without enzymes. Their approach, NERPE (non-enzymatic RNA primer extension; see Fig. 1), is predicated on a stencil-directed RNA replication technique. To detect mismatches, examine for non-enzymatic ligation, and precisely quantify primer extensions on preset templates, they used a technique they called NERPE-Seq. However, when the single-stranded RNA in the handle is covered by a complementary strand to generate a duplex RNA, their research shows that the primer can successfully extend to the template [19].

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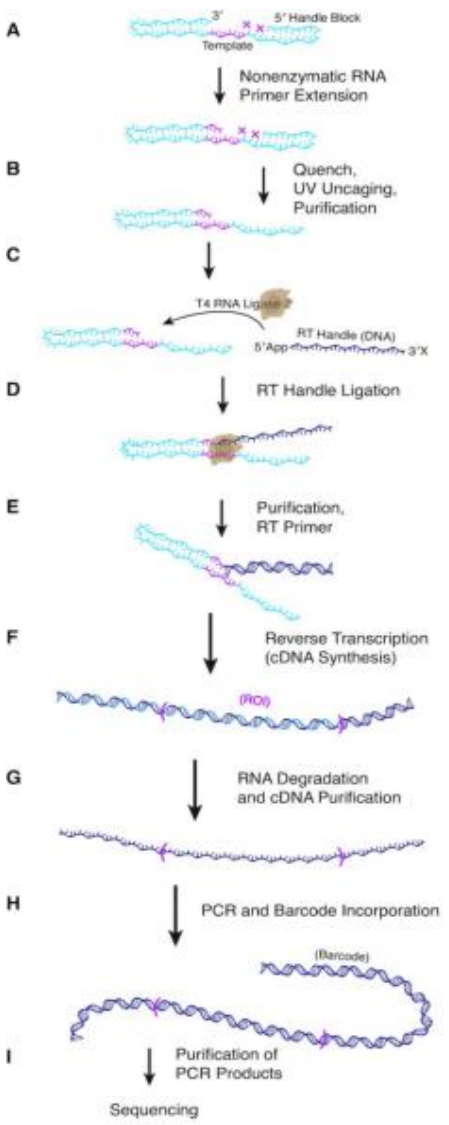

Figure 1. Protocol for preparing RNA hairpin constructs for sequencing:

(A) NERPE-Seq RNA hairpin constructs consist of a hairpin loop connecting the primer and template. This arrangement ensures that the product of non-enzymatic primer extension and the corresponding template are present on a single continuous RNA strand. Two caged bases (represented by magenta Xs) prevent primer extension from encroaching on the downstream 5′ Handle. The 5′ Handle Block, which is complementary to the 5′ Handle, prevents any interference with primer extension.

(B) To quench the primer extension reaction, a desalting size-exclusion spin column is used. The caged bases are then uncaged, and the target RNA is further purified through gel purification.

(C and D) The 3′ end of the RNA hairpin (the site of primer extension) is ligated with the pre-adenylated DNA RT Handle (which is blocked on its 3′ end to prevent self-ligation).

(E) The ligase is removed by digesting it with Proteinase K. The resulting target RNA-DNA complex is extracted using phenol-chloroform. Subsequently, the RT primer is annealed to the RT Handle.

(F and G) Reverse transcription (RT) generates the complementary DNA (cDNA), while degrading the original RNA. The cDNA is isolated using a spin column. The region of interest (ROI) contains the template, hairpin, and any product sequences.

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(H) Polymerase chain reaction (PCR) is employed to add barcodes to the DNA and incorporate flanking sequences. Each barcode uniquely identifies DNA from a specific experiment, allowing the sequencing of samples from multiple experiments simultaneously.

(I) The target PCR products are purified and validated through automated electrophoresis and quantitative PCR before undergoing sequencing [19].

Tracey A. Lincoln and Gerald F. Joyce developed a non-biological system to demonstrate the self-sustaining replication of an RNA enzyme. They conducted two serial transfer studies and found that different reaction conditions and mixtures of enzymes and substrates can produce different outcomes, which may be linked to the nature of the underlying genetic system. They also improved the catalytic properties of the cross-replicating ribozyme [20]. However, the absence of a chemical system that is protocell-compatible and can replicate RNA templates that has all four nucleotides has limited the confirmation of non-enzymatic RNA replication. To bridge the gap between the RNA and non-enzymatic polymerization worlds, the researchers immobilized primers and templates on magnetic beads, added individual nucleotides in sequence, and used short 5' activated oligonucleotides as catalysts to speed up primer extension. By doing so, they successfully created a significant portion of the active hammerhead ribozyme [21].

4. Chimeric phosphoramidate species for RNA copying

Jash et al. discovered that phosphoramidate bonds between the 5'-terminal phosphate of a ribonucleotide and N-terminus of a peptide can form after the interaction between the ribonucleotides and amino in an aqueous condensation buffer. This suggests that spontaneous combination of amino acids and nucleotides can create peptide-RNA hybrid compounds, leading to a peptide-based transfer RNA (tRNA) where the C terminus of the peptide ester-links to the 2',3'- terminus of the oligodeoxynucleotide. The researchers studied how short peptidase RNA interacts with an oligodeoxynucleotide modeled after an RNA strand at its 3′ end. They found that the sequence of the peptide, the dinucleotide's 5'-terminal nucleotides, and the RNA template all affect the speed and efficacy of C-terminal dipeptidyl dinucleotide anchoring to the amino group in their model system. Hybridization close to the primer terminus produced the maximum yield of dinucleotides in all tested cases. The most reactive species, GlyPro-AA, had anchoring yields ranging from 8 to 99% depending on the template. When competing for anchoring at the 3'-UUC-5'-template sequence, LeuLeu-AA, PhePhe-AA, and GlyGly-AA produced a product ratio of 1:2:6, which was independent of the primer's terminal base. These findings suggest that simple double-stranded contexts can control the covalent anchoring of peptidyl RNA at recognized sites of peptidyl tRNA. This process could potentially connect non-template condensation reactions and specialized ribosomal protein synthesis processes [22].

Peptididoyl RNA is the product of ribosome-free single-nucleotide translation and is intriguing from both synthetic and bioorganic perspectives due to its peptide backbone. To stabilize this form of RNA, an amide bond was developed between the C-terminus of a peptide and a 3'-amino-2',3'-dideoxynucleotide in the RNA chain. The preferred synthetic method involved coupling the amino-terminal oligonucleotide to a dipeptido dinucleotide in solution phase using an N-Teoc-protected aminonucleoside support. The resulting hairpin peptide-linked RNA segments (5'-UUGGCGAAAGCdC-LeuLeuAA-3') do not fold cooperatively. This approach enables the creation of doubly RNA-linked peptides on a large scale suitable for investigating their structural and biochemical properties. The presented results demonstrate how a combination of solid-phase chain assembly and template-directed peptide coupling in aqueous solution can prepare RNA-peptide hybrid molecules with the peptide embedded in the RNA backbone. This procedure can create peptidoyl RNAs with different sequences and chain lengths, allowing for the investigation of their chemical and structural characteristics and potential contributions to the prebiotic stage of evolution [23].

Radakovic et al. investigated the role of aminoacylated RNA in templated primer extension and ligation. They found that RNA primer aminoacylation considerably enhanced non-enzymatic replication of RNA templates under certain conditions. Their research also showed that additional

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peptide bonds inside the RNA strand might be created by non-enzymatic ligation using other amino acids. New avenues for ribosome catalysis may open up as a result of these outcomes [24].

The same group was able to assemble a functional ribozyme, which suggests that RNA aminoacylation-encoded peptides may have evolved independently. A key component in translation, aminoacylated RNA can be combined with a template-directed assembly method to create chimeric amino acid-RNA polymers. This chimeric polymer maintains the enzymatic function of all its RNA counterparts, including hammerhead enzymes, RNA ligases, and aminoacyl transferase ribozymes. Previous research by the group showed that short aminoacylated RNAs form amino acid bridges with imidazole-activated oligonucleotides in non-enzymatic ligation processes at a significantly faster rate than unmodified RNAs. By using this approach, the group was able to assemble three chimeric ribozymes, demonstrating that successive ligation processes can produce chimeric amino acid-bridging RNA that is long enough to function as catalytic RNA [25].

5. RNA copying inside vesicles.

In simple living systems, RNAs can serve as both catalysts and genetic information carriers. Encapsulating ribozymes within a lipid-rich environment can enhance their activity and facilitate adaptation. The "rich-get-richer" phenomenon leads to improved RNA catalysts, resulting in greater gains. Protocells can benefit from encapsulated contents, allowing for functional evolution rather than passive containment [26]. According to the stochastic corrector model, population selection among compartments promotes the accumulation of more active ribozymes, reducing errors [27]. Studies by Kevin Leu using various backbone structures (DNA, RNA, etc.) and activated nucleotides show that mismatches significantly slow down non-enzymatic RNA, increasing replication accuracy [28].The process of synthesizing aminoacylated RNA involves phosphorylating amino acids and creating phosphorylated esters before mildly acidolyzing to produce aminoacyl esters. Aminoacyl-tRNAs serve as intermediates in the translation of messenger RNAs into genetically coded protein products, essential for ribosomal peptide synthesis. This process depends on the enzymatic aminoacylation of the 2',3'-diol of tRNAs using aminoacyl-adenylates [29].

6. Homochirality of peptide formation leading by aminoacyl-RNA

The findings of Tamura et. al. suggest that the homochirality of amino acids in proteins may have been produced during aminoacylation and that the RNA may have had a significant role in determining the selectivity (L or D). Prebiotic amino acids that served as asymmetric catalysts for the synthesis of chiral sugars may have also had an impact on RNA chirality [30]. After conducting further research, he discovered that the homologous chirality of contemporary polypeptides is created during aminoacylation and is, in turn, determined by the chirality of RNA that existed prior to aminoacylation. He discovered proof that the aminoacyl transfer step includes a rate-determining phase [31].

7. Evolution view of RNA-peptide world

Bokov et al. developed a hierarchical model to explain the evolution of 23S ribosomal RNA. They identified fifty-nine distinct elements within the 23S RNA molecule, indicating that it did not evolve as a single unit, but rather as distinct components that together maintain the integrity of the ribosome. Through their research, they discovered that an early fragment consisting of approximately 110 nucleotides, which could bind the CCA-3' end of tRNA, was the point at which the evolution of 23S rRNA began. This fragment was replicated and resulted in a molecule capable of binding two CCA-3' termini simultaneously. To enable the transpeptidase process, the two fragments were positioned adjacent to each other in space, allowing the two CCA-3' ends to connect. The ability of these dimers to create oligopeptides with random amino acid sequences likely facilitated their function. In the early stages of evolution, ribosomes were likely little more than RNA molecules. However, the model developed by Bokov et al. does not provide evidence of a complete RNA ribosome [32].

In the early stages of evolution, a steady supply of peptides was essential for the polymerization of activated nucleotides on clay substrates to create primitive RNA molecules. Amino acids could easily

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polymerize to form peptide molecules on the mineral surface, making RNA more stable and easier to produce in the natural environment. RNA and peptides interacted and worked together to broaden their range of function. The current understanding of RNA binding proteins (RBPs) is rapidly expanding, with topics covering techniques for finding RNA binding sites, RBP synthetic design, and the function of RBPs in stress granules and neurodegenerative disorders. A thorough mechanistic comprehension of protein-RNA target interactions is beneficial for all these fields. Intricate molecular structures provide an explanation for RBP's function and binding behavior like the helicase domains preferring to interact with the RNA backbone or particular residues in a YTH m6A reader protein "locking in" a methylated base. The examination of hydrogen bonds that various RNA binding domains create with RNA supports the structural roles of certain domains and illuminates how some domains differ from one another [33]. Peptides played a critical role in the peptide or RNA world hypothesis by reducing the activation energy of chemical reactions, which sped them up. The need for specialized and diverse protein enzymes became crucial for biogenesis in the peptide/RNA world hypothesis. Perhaps the first imperfect translation device was a protein called aminoacylated ribozyme. A key element in the process of translating is the assignment enzymes, like pre-aaRS (aminoacyl-tRNA synthetase), which have changed to bind a particular amino acid to a pre-tRNA molecule. The multilingual enzyme aaRS catalyzes the activation process and connects it with the correct amino acid, according to more studies on tRNA and aaRS. An aminoacyl adenylate is initially produced using an amino acid and ATP. An aminoacyl-tRNA, also known as a charged tRNA, is created when the aminoacyl group is transferred to a particular tRNA molecule. Individual amino acids may be distinguished by the aaRS, which can then activate them with ATP to create their conjugate with AMP [34].

The earliest signs of the proteins transforming to peptide occurred with the creation of the "bridge peptide," which aided the aminoacylation of RNA with particular amino acids. This short peptide binds to a particular RNA molecule and a specific amino acid through stereochemical interactions, encouraging aminoacylation and benefiting the structure of artificial peptides. The hybridization of short aminoacylated RNAs gave rise to bridge peptides, which could then promote interactions between particular RNAs and specific amino acids. Kunnev and Gospodinov suggest that the stabilizing effect of bridge peptides on RNA-peptide complexes would have emerged around the same time as the evolution of the genomic code that is standard. As a result of this RNA-peptide world, ribosomes, ribozymes, and enzyme-directed RNA duplication could have co-evolved during similar era, without the need for RNA-only self-sustaining steps [35]. The hypothesized evolutionary pathway from peptide all the way to aaRS represents an increase in functional complexity and adheres to the continuity rule [34].

The aaRS protozymes suggest that the activation of amino acids catalyzed by peptides originated from a single ancestral gene, allowing the formation of a two-letter coding alphabet in the distant past. This challenges the RNA world hypothesis, which suggests that RNA catalysts came first. The authors propose that the origin of life occurred in an environment where peptides and RNA coexisted and supported each other's early molecular self-organization [36].

The genetic code, which links amino acids to nucleotide triplet codons, serves as the bridge between prebiotic chemistry and biology, as opposed to replication, due to several reasons. Firstly, aaRS enzymes must interact with each other. Secondly, reflexivity intrinsic to the production dynamics of polypeptide aaRS promotes bootstrapping. Thirdly, enzyme seizure of aminoacylation that are RNA-catalyzed will inevitably lead to degraded specificity. Finally, the emergence of the Central Dogma is most likely when duplication and interpretation level of mistakes remain analogous. Catalytic RNA overlooks both the computational nature of translation and the need for catalysts to not only accelerate but also optimize accuracy, leading to an overestimation of the potential catalytic proficiency of ribozymes. Therefore, synchronized evolution of genetic coding was necessary. Protein folding permanently alters genetic information. The Central Dogma guarantees that biological evolution in any RNA world surpasses the simple dynamics of population of natural selection. It is crucial to find experimental evidence supporting the RNA world hypothesis. As the precursors of the first enzymes, aaRS possess three unique functions that grant them special status. Firstly, they

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irreversibly synthesize aminoacyl 5'-AMP by accelerating amino acid activation by a factor of 1014 at the cost of two ATP phosphates. Therefore, the rate of production of prebiotic protein is restricted by the uncatalyzed rates of other protein synthesis reactions, which are orders of magnitude faster than activation. Furthermore, the adenosine functions as an affinity tag that increases the specificity of coding assignment, especially during editing, by a factor of 1000. Finally, they acylate tRNA, where a particular amino acid is attached to a tRNA molecule via a code-cognate anticodon. Code bootstrapping and optimal gene sequences are made possible by the recursive nature of assignment catalysts based on proteins. The search for the optimal code may be substantially accelerated if the protein aaRS tree-like phylogenies offered the possibility of self-organizing quasi species bifurcations. Long polypeptide secondary structures were shown to be structurally complementary to nucleic acids prior to the discovery of catalytic RNA [37].

In today's aaRSs, the conserved modules can be oriented either clockwise or anticlockwise without affecting the enzyme activity. Aminoacyl-tRNA synthetases (aaRS) catalyze two chemical processes essential for complete genetic code translation. Luis Martinez-Rodriguez et al. described 46-residue peptides that contain the ATP-binding sites of Class I and II synthetases, as well as peptides expressed by a gene engineered by Rosetta to make analogous peptides on opposite strands. Saturation can occur for both wild-type and engineered peptides, and the catalysis of both is susceptible to mutations in the active-site residues. The activities of the two peptides show that there are two possible functional interpretations of the information encoded in a gene. These findings lend credence to the theory that the first known peptide catalysts were responsible for the biosynthetic activation of ATP [38].

Class II aaRS must activate all residues required for Class II activity, while Class I aaRS must activate all residues needed for catalysis by Class I active sites. C.W. Carter Jr. and his colleagues have created a model using only bond angles, standard bond lengths, and dihedral angles in which a polypeptide double helix fits precisely into the minor groove of an RNA double helix with the same helix parameters. The model suggests that the two double-helical structures provide some degree of genetic coding and are mutually catalytic for the assembly of one another from activated precursors in the prebiotic soup [39].Two novel modular levels, protozymes and Urzymes, were associated with parallel losses in catalytic proficiency according to parallel experimental deconstructions of Class I and II synthetases. Bidirectional coding supports the essential unification of the proteome. The bidirectional genetic coding of some of the oldest genes in the proteome severely constrains the probability that any RNA World existed before the origins of coded proteins [40].

8. Conclusions

Based on the aforementioned discussions, these suggestions do not guarantee a successful explanation of the origin of life. However, the widely accepted notion of the RNA-peptide world could be crucial in solving this puzzle. Despite having supporters, the RNA-world theory and the RNA-peptide theory are still lacking crucial experimental evidence. Further research into bridge peptides, aminoacylation ribozymes, RNA-binding proteins, and other related topics could provide additional insights into the mystery of life's genesis.

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