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Maury, Carl Peter J.

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PERSPECTIVE

Origin of life: β-sheet amyloid conformers as the primordial functional polymers on the early Earth and their role in the emergence of complex dynamic networks

Carl Peter J. Maury

Department of Medicine, University of Helsinki, Finland

Correspondence
C. P. J. Maury, Department of Medicine, University of Helsinki, Helsinki 00290, Finland
Tel: +358 504661050
E-mail: peter.maury@helsinki.fi

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The origin of life has remained a conundrum. Among the origin-of-life hypotheses, the RNA world has gained wide popularity. It has, however, been difficult to explain the emergence of both stable and meaningful RNA under the presumably very harsh early Earth conditions, and it has been assumed that some other replicating system must have preceded the RNA world. The amyloid world hypothesis posits that the first functional polymers on the primitive Earth were structurally stable self-replicating β-sheet-based peptide amyloids. The amyloid hypothesis is examined in this perspective in light of new research results and highlights the role of dynamic interacting networks. The mechanisms of self-amplification and information transfer are discussed, as well as the catalytic, adaptive, and evolutionary properties of the cross-β-sheet ensembles. There is no contradiction between the amyloid and the RNA world hypotheses: In the harsh prebiotic environment, the β-sheet fibrillar networks provide a scaffold and initial protection for nucleobases and other prebiotic compounds, and the cooperative interactions of the β-sheet ensembles with nucleic acids, fatty acids, and natively folded proteins are in concert with the view of an early co-evolving amyloid–RNA–lipid–protein world.

Keywords: abiogenesis; amyloid world; autocatalysis; Darwinian evolution; molecular networks; origin-of-life hypothesis; peptide amyloids; prions; RNA world; β-sheet structures

The origin of life on Earth is a fundamental question in science. Of the origin-of-life hypotheses, the RNA world [1,2] has achieved wide popularity. The demonstration of catalytic activity of some RNA sequences has given additional credibility to the theory [3,4]. However, it has been difficult to explain the emergence of both stable and meaningful RNA sequences under the presumably very harsh early Earth conditions, and it has been generally assumed that some other molecular replicator system must have preceded the RNA world [5–8]. Another popular model, the protein-first hypothesis [9–12], is similarly to the RNA model, problematic with respect to the stability of the molecules: natively folded proteins are rapidly degraded and lose their functionality under the harsh prebiotic conditions. In 2009, a coherent theory on the origin of life based on self-replicating, informational, and catalytic β-sheet amyloids, coined 'amyloid world', was put forward as an alternative model of the origins of life [13]. In this perspective, the amyloid hypothesis, which has gained recent momentum [14–18], is examined in light of new research, and the role of dynamic interacting networks is highlighted. There is no contradiction between the amyloid and RNA worlds: The amyloid model is compatible with an early gradually co-evolving amyloid–RNA–lipid–protein world. The amyloid world hypothesis is an amyloid-first, not an amyloid-only hypothesis.

Requirements of an origin-of-life hypothesis

To be valid, a chemical theory of the origin of life should, at the minimum, be able to explain replication, information processing, proto-metabolism, and molecular evolution under plausible early Earth conditions. This implies that the system possesses a proto-genetic apparatus that can store, replicate, and transmit information, and a proto-metabolic system that can use energy from the environment, acquire prebiotic building blocks, and catalyze simple chemical reactions. The system should also be able to adapt to changes in the external milieu, replicate these changes, and undergo a Darwinian-like evolution. Can the amyloid world hypothesis meet these requirements? As argued herein, the characteristics of the primordial peptide amyloid system make it a likely candidate for the first evolvable molecular replicator system on the early Earth around 4 billion (4×10^9) years ago.

The amyloid fold

According to Anfinsen's principle, a polypeptide is folded into the active native state by descending to the thermodynamically most favorable conformation among thousands of possible conformers [19]. It has, however, become evident that many proteins under native conditions can, in fact, acquire distinct conformations that exist in a dynamic equilibrium [20,21]. The β-sheet-based amyloid fold is one of the conformations that represent an energy minimum in the protein energy landscape [22].

The amyloid structure is evolutionarily highly conserved and the β-sheet amyloid fold has been suggested to represent the first functional protein fold [23]. Given the amyloidogenic potential of most proteins in general and the functional aspects linked to some β-sheet aggregates, the notion that the amyloid fold represents only a misfolded state and a sign of disease has been revised [24]. The concept of functional amyloids was introduced to comprise the beneficial and regulatory roles of the β-structured amyloids in various biological phenomena [25–27]. Functional amyloids have been found in a wide range of organisms from bacteria to mammals, with functions as diverse as biofilm formation, epigenetic inheritance, signal transduction, hormonal storage, and long-term memory consolidation [25–27].

Prebiotic short proto-peptides that spontaneously polymerize into functional fibrillar β-sheet structures constitute the basis of the amyloid world model, a model which proposes a key role for the β-sheet conformers in the initial phase of the chemical processes leading to the emergence of the first living systems on the primitive Earth. This hypothesis emphasizes the early coevolution of the amyloid conformers with ribonucleotides, lipids, and natively folded proteins: The β-sheet amyloid model is an amyloid-first, not an amyloid-only model.

Structural stability

Fibrillar amyloids are extraordinarily stable [28–35]. They withstand high temperatures, various types of radiation, and exhibit protease resistance. Germicidal UV treatment does not abolish the amyloid-dependent infectivity of prions. The basis for the structural stability of amyloids derives from the fibrillar cross-β-sheet conformation characterized by β-strands (peptides of identical or near-identical type with typical lengths of 2–10 amino acids) oriented perpendicular to the long axis of the elongated polymer. The repeating unit usually consists of two tightly packed β-sheet layers in which the side chains form a dry zipper zone with a high degree of geometrical complementarity. Their structural robustness achieves the theoretical limit of proteins with a maximum of intermolecular hydrogen bonds. Tables 1 and 2 summarize the main characteristics of amyloids and various factors influencing the amyloidogenicity of proteins.

Replication and information transfer

A basic requirement for all forms of life is the ability to process and transmit information. This step was probably also crucial in the evolution of life. To understand the amyloid world hypothesis, an insight into the molecular mechanisms of amyloidogenesis and the amyloid structure-related transfer of information is pivotal.

Amyloid fibril formation occurs through a nucleation-growth mechanism [36,37] characterized by seeding, elongation, and equilibrium phases resulting in a sigmoidal kinetic curve (Fig. 1). Elongation takes place *via* proto-peptide monomer (or, in some cases, very short oligomer) addition to the growing end of the protofilament. Fragmentation produces new seeds that initiate repeated replication cycles (Fig. 1). A secondary fibril surface-catalyzed template-driven replication process can follow the primary replication process.

Molecular complementarity has a central role in the replication process [38–41]. The extended β-sheets stack upon each other with their side chains intermeshed, forming a stable hydrophobic interface. Recognition occurs by side chain complementarity. Specific steric information is transferred in the template-driven conformational replication process from the amyloid

Table 1. Characteristics of amyloid[a].

- The defining element of amyloid is a cross-β pleated sheet conformation
- The β-sheet is composed up of short peptide sequences (β-strands) connected laterally by backbone hydrogen bonds.
- Two or more extended β-sheets stack upon each other forming a twisted fibril of about 5 to 12 nm in width[b] and of indeterminate length.
- Amyloid self-propagates by a seeded growth mechanism in which monomers (or short oligomers) are added to the growing end of the protofilament. Secondary nucleation involving a fibril surface-catalyzed step may follow. The replication process can generate new fibrils of the same kind.
- Oligomeric complexes are often intermediates in the polymerization process that can give rise to polymorphic amyloid conformers of which one or more can self-replicate.
- The autocatalytic templated replication process is sequence-, regio- and chiro-selective.
- The catalytic activities of the amyloid fold are fibril-dependent.
- The β-sheet-based amyloid ensembles form scaffolds and fibrillar networks and can interact with nucleic acids, fatty acids and natively folded proteins.
- The amyloid motif is evolutionarily highly conserved.
- The protease resistance, transmissibility, and strain specificity of disease-related prions are dependent on the amyloid β-sheet structure

[a]Both functional and disease-associated amyloids exist. Mutations, overproduction, and aberrant degradation of precursor proteins are common causes of diseases characterized by organ/tissue deposits of amyloid (amyloidoses). The diagnosis of amyloidosis is based on the demonstration of amyloid in tissue biopsies by histochemical, immunohistochemical, and electron microscopy examinations. Congo-red or thioflavin staining combined with polarization microscopy is the most common clinically used histochemical method; [b]Fibril diameters ranging from 2 to 22 nm have also been reported. The fibril morphology varies depending on several factors, including the source of the fibrils (disease-associated/functional/experimental), extraction methods, and experimental conditions.

Table 2. Amyloidogenicity of proteins.

- Certain amino acid sequences are more amyloidogenic than others. Intrinsically disordered proteins, glutamine- and asparagine-rich proteins, clusters of hydrophobic residues, and regions with alternating hydrophobic and hydrophilic residues demonstrate high amyloidogenicity.
- A single amino acid substitution can make a protein, or a fragment of it, amyloidogenic.
- Concentration, pH, temperature, salt, pressure, metal ions, agitation, reaction surface, and reaction time are examples of factors that can influence the kinetics of formation and the morphology of the fibrils.
- Given the right circumstances most proteins can adopt the amyloid conformation.
- Even very short peptides with simple amino acid sequences (e.g., prebiotic proto-peptides) can form functional β-sheet fibrillar networks

conformer to conformers composed of the same constituent peptide monomer as the parent molecule. During the information-transfer process, strong non-covalent forces keep the molecule in an enduring conformational state. Importantly, the process is input sensitive, and changes in the external conditions can induce changes in the three-dimensional structure of the amyloid conformers [42,43]. The molecular system thus sculpts itself and allows for evolutionary forces to act on the conformers formed. Complementarity also drives the co-assembly of amyloid/nucleic acids and provides a self-selection mechanism driving evolution in a non-random way [44,45].

Autocatalytic and catalytic amyloids

The catalytic activity of amyloids is an important aspect of the β-sheet-based hybrid origin-of-life model. Their catalytic activity is not limited to autocatalytic mechanisms generating self-replication loops, but involves activity directed toward the synthesis of simple metabolites. Peptide-based amyloids have been shown to catalyze esterase, redox, and aldolase reactions [46–54]. The catalytic functions are conformation-dependent: The non-aggregated forms of the corresponding constituent peptides are catalytically inactive.

Metal-dependence characterizes many amyloid catalysts: Metal ions shape the ligand geometry, promote fibrillation, and stabilize the fibrillar conformation. Another important factor in amyloid formation is the presence of surfaces [55–61]. Surfaces act as autocatalytic layers initiating conformational self-replication. They also facilitate precursor binding, increase local peptide concentration, affect conformational rearrangements, speed up nucleation, and lower activation energy barriers. The lateral surfaces of the fibrillar assemblies themselves act in the same way. Notably, amyloid entities do not only catalyze their own formation from constituent peptide monomers but are also able to direct the synthesis of the constituent monomers themselves [47].

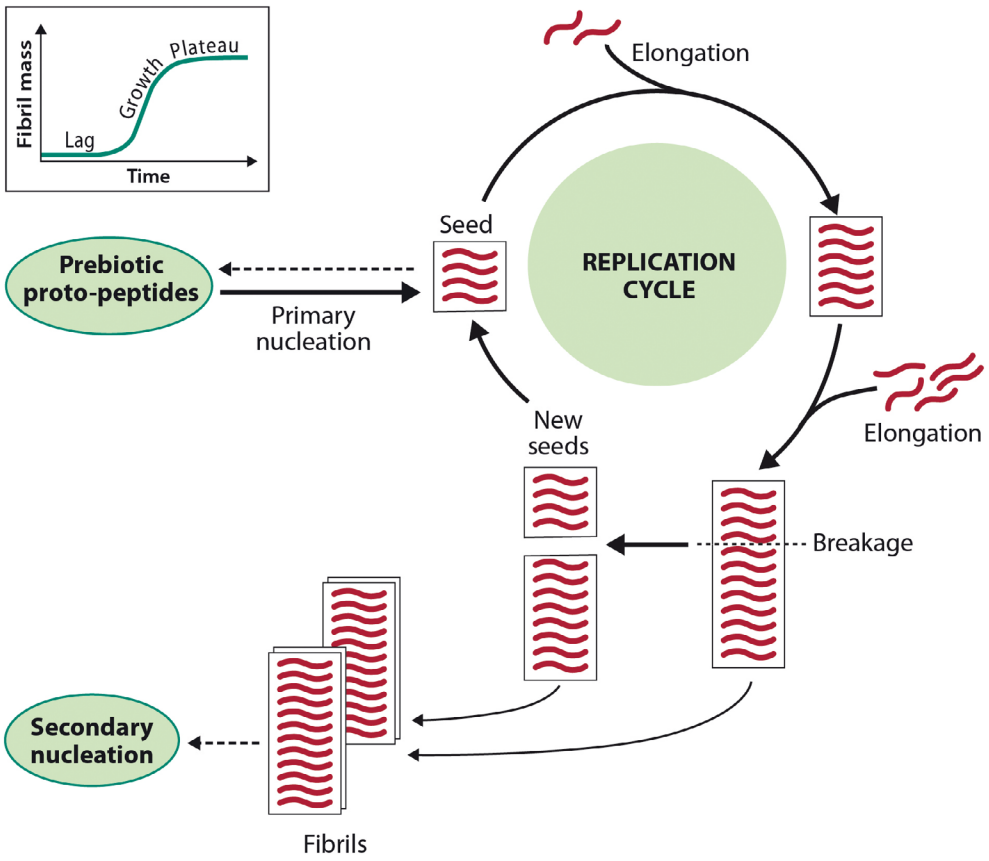

Fig. 1. Schematic representation of the primary nucleation-growth mechanism and a typical kinetic curve of amyloid formation (insert). The replication pathway of one type of a short proto-peptide monomer from a pool of various proto-peptides is outlined.

Prebiotic building blocks

A basic requirement for the amyloid model of the origin-of-life, as well as for any other chemical origin-of-life model, is that the constituent building blocks of the system can be formed by random processes from compounds present on the early Earth. In contrast to nucleotides, the building blocks of amyloids–amino acids and short peptides–are easily produced under assumed prebiotic conditions, and a series of amino acids have been detected in Murchinson's and other meteorites and asteroids [62–69]. Importantly, even very short peptides with simple amino acid sequences can form amyloid structures [70–74]. The energy sources driving chemical processes under prebiotic conditions could have been, for example, ultraviolet light, lightning and/or other types of electromagnetic radiation, hydrothermal vents, and/or meteoritic impacts. The fact that the β-sheet amyloid conformation represents a global minimum of free energy and amyloid formation occurs at (sub)micromolar concentrations [75,76] might have facilitated the prebiotic formation of β-sheet conformers. Importantly, amyloid aggregates have been shown to arise from amino acid condensations under simulated prebiotic conditions [77] and polymorphic amyloid networks are generated from a nonapeptide composed of prebiotic consensus amino acids [74].

In contrast to nucleobases and natively folded proteins, the building blocks of amyloids, short proto-peptides exhibit remarkable structural stability after polymerizing into fibrillar structures: The cross-β-sheet entities withstand even extreme conditions. A study by Rout *et al.* [47] is of particular interest in this context as it shows that under plausible prebiotic conditions, amyloid formed from short peptides can direct a sequence-, regio-, and stereoselective synthesis of its own constituent peptides.

The question of stereoselectivity

Homochirality is a characteristic feature of biological polymers and has even been considered a signature of life [78]. The origin of the chiral symmetry has remained a conundrum [79]. With a few exceptions, all extant

proteins are built up of levorotary (L)-amino acids. Amyloids are, with a few exceptions, homochiral, which has been explained by the more favorable fit between adjacent β-strands of homochiral β-sheets compared to the fit between β-strands of heterochiral β-sheets [80,81]. Due to an initial prebiotic precursor imbalance, the amyloid-related chiro-selective self-amplification cycle could have resulted in an excess of one of the enantiomers, ultimately leading to the eradication of the other enantiomer [82–84]. The cause of such an imbalance, if ever present, remains speculative. Electroweak force interaction, polarized light, lightning, meteoritic impact, or some other external factor could have been important, or it could have been chance alone. An extraterrestrial origin of an imbalance cannot be excluded either: A small enantiomeric excess of L-amino acids has been found in chondritic meteorites [85]. In enantioselective autocatalytic networks, spontaneous mirror symmetry breaking can, under certain conditions, also take place [86]. The isochirality of the biopolymers did not necessarily originate at the very early stages of chemical evolution, but could also have emerged at a later phase of the evolutionary history of life.

The prion relation

The protein-only hypothesis posits that a misfolded form of the prion protein, devoid of any nucleic acid, is responsible for the transmissibility and infectivity of disease-associated prions [87]. The conformational rearrangement of the prion protein that occurs in connection with the transition to the infective form involves the formation of a β-sheet amyloid structure [88–92]. Prions are, however, not only infectious agents causing severe neurodegenerative disorders [93], but may be involved in beneficial and regulatory functions in a wide range of organisms [26,94,95]. The functional element of beneficial prions/prion-like proteins is based on the self-propagating β-sheet amyloid structure.

Prion amyloids are evolutionarily highly conserved [23,96–98] and a striking homology exists between the sequences of contemporary prions and the sequences of peptides formed in the salt-induced synthetic reaction simulating primordial Earth conditions [99]. It is intriguing to speculate that extant prions, with their β-sheet-rich regions, might represent a relic of a pristine amyloid-based information system, as pointed out before [13,40,98–100].

Synergistic networks

Organization and compartmentalization are essential for all living systems. Amyloid aggregates possess an intrinsic propensity to form fibrillar networks which can act as scaffolds and provide protection for nucleobases, natively folded proteins and other molecules [56,101–107]. The cooperative and synergistic interactions between peptide amyloids and ribonucleotides and lipids are of special importance in a prebiotic context. The β-sheet surface promotes the polymerization of polynucleotides, which, in turn, enhances the formation of amyloids [108–112]. Electrostatic complementarity drives the co-assembly of the amyloid/nucleic acid complexes [45], which, in turn, promotes nucleic acid hybridization [113]. Importantly, Rout *et al.* [114] recently demonstrated a sequence-dependent binding of codon-sized RNA:s to peptide amyloids.

For membrane formation, the interplay between lipids and amyloid is of key importance. By lowering the activation barrier, lipid interphases accelerate amyloidogenesis in general, and phospholipids specifically accelerate the nucleation process [59,60,115–117]. Bomba *et al.* [118] reported on a cooperative assembly of amyloidogenic peptides and fatty acids into highly ordered structures, the cooperativity being attributed to the repetitive nature of the fatty acid bilayer and the cross-β-sheet structure mediated by electrostatic interactions. Kwiatkowski *et al.* [119], in turn, reported that chemical gradients in mixtures of amino acids and fatty acids lead to the formation of amyloid-like fibrils localized inside a proto-cellular compartment. Taken together, these interactions are in line with the notion of a gradually co-evolving prebiotic amyloid–RNA–lipid–(protein) world.

The importance of conformation

The amyloid motif highlights the interrelationship between structure and function. The spatial arrangement is key: It is the structure of the cross-β-sheet that is the basis of the extraordinary functional characteristics of the amyloids. The amyloid-related information processing and transfer is dependent on the zipper structure: The zippers differ in the architecture of peptide strands within and between the β-sheets. Recognition occurs *via* complementarity of amino acid side chains [38–41,44,45].

Based on the cross-β-sheet fold of the polymeric peptide structure, the amyloid world model is, in essence, a protein-first model. It differs, however, in important aspects from the protein-first models based on natively folded protein structures: (a) prebiotically plausible short proto-peptides with simple amino acid sequences can spontaneously polymerize into functional fibrillar β-sheet amyloids which, in contrast to natively folded proteins and non-aggregated

peptides, can withstand high temperatures and different types of radiation [28,29,33–35,46–48,120]. (b) The amyloid system is input sensitive and changes in the external conditions and can give rise to structural variants on which evolutionary forces may act. The fittest conformers and those with the fastest overall production rate are preferentially selected and replicated with high fidelity in the autocatalytic sets expanding the pool of selected variants. Environmentally less suitable entities are degraded and reused [15,41–43,121,122]. (c) Amyloid-related template-driven reactions are regio- and chiro-selective, and reportedly error correcting [14,47]. This error correction is intriguing since the risk of an error catastrophe is associated with molecular self-replicating systems [123,124].

The emergence of synergistic networks involving amyloid/polynucleotides/proteins/lipids is an important aspect of the amyloid model: The β-sheet fibrillar networks act as scaffolds for various prebiotic molecules and provide protection for them in the harsh prebiotic milieu. The dynamic and cooperative interplays between RNA and amyloid, between phospholipids and amyloid, between proteins and amyloid, and between lipids and nucleosides have been largely documented [14,45,56,107,111–116,118,121,125–128]. The mutualistic interactions constitute the basis of the envisioned evolutionary path over time toward higher organization, compartmentalization, and membrane formation (Fig. 2).

Toward a more advanced genetic system

The amyloid world hypothesis posits that the first information processing system on the primitive Earth was based on structurally stable self-replicating catalytic amyloid polymers. From a prebiotic pool of random short proto-peptides, template-driven sequence-, regio-, and stereo-specific amplification cycles generated the first 'coded' peptide-based structures that were able to undergo a Darwinian-like evolution [13,15,40,41,47,72,77]. The β-sheet-based system had, however, its limitations, including a relatively low information content [38,41] and further evolution clearly required the emergence of a more advanced genetic system. As envisioned, in the prebiotic soup, interactions between the amyloid conformers and the proto-polynucleotides probably occurred at a very early stage. Several factors are likely to have promoted amyloid/RNA coevolution [13,15]: (a) the protection provided by fibrillar networks [56,101–107], (b) the enhancement of nucleic acid hybridization by amyloid/nucleic acid complexes [113], (c) the selective binding of codon-sized RNA molecules to peptide amyloids [114], and (d) the formation of proto-cellular entities as a result of the interplay between amyloids, fatty acids, and minerals [118]. In the evolutionary path toward a more sophisticated genetic system, the formation of ribozymes and proto-ribosomes was crucial. Over time, along with the evolution of the translation machinery, natively folded proteins took over the role of the main structures performing metabolic activities and as the major drivers of biologic diversity and adaptation.

How the genetic code originally evolved is not known [129]. A key question is how the amino acid–nucleotide associations originated [130]. The close interplay between amyloid and RNA is in line with one of the leading theories, the stereochemical affinity theory [131], which posits that codon assignments were

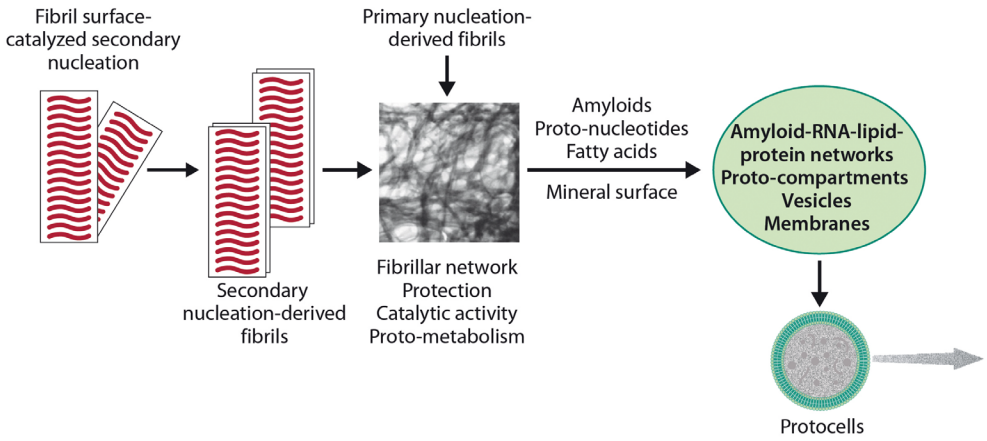

Fig. 2. Schematic representation of secondary nucleation catalyzed by the fibril surface and the formation of functional fibrillar networks and compartments.

influenced by the chemical and physical interactions between amino acids and their corresponding codons (or anti-codons). It is conceivable to assume that before the modern genetic code, simpler forms of the code existed. The GADV-GNC hypothesis is of particular interest in this context [132]. The hypothesis suggests that the universal genetic code evolved from a more primitive GNC code that encoded only the four amino acids Gly, Ala, Asp, and Val. These four amino acids, which represent the most prominent prebiotic amino acids and are found in meteorites too, are also amyloidogenic, giving rise to both β-sheet aggregates [77] and, as constituents of a prebiotically plausible nonapeptide, polymorphic amyloid networks [74]. These viewpoints could be interpreted as an intriguing link between the GADV hypothesis and the amyloid world hypothesis.

What is the evidence for the amyloid world hypothesis?

Arguments in favor of the amyloid world hypothesis are summarized in Table 3. Direct empirical evidence is lacking, but there is an increasing amount of indirect evidence supporting the hypothesis. In experiments performed under plausible prebiotic conditions, the formation of amino acids and short peptides, the building blocks of amyloids, as well as the formation of amyloid networks have been reported [14,47,62,65–67]. A synthetic nonapeptide composed of the six most abundant amino acids formed in experiments simulating prebiotic conditions and also detected in meteorites, spontaneously generates polymorphic networks [74]. Amyloid conformers catalyze their own formation, exhibit emergent catalytic behavior, and replicate in a templated process which is sequence-, regio-, and chiro-selective, and reportedly, error correcting [14,47]. Moreover, fibrillar amyloid assemblies offer protection for both nucleic acids and native proteins, and they can synergistically interact with nucleoproteins to build up complex functional networks. Among these networks, unequal assembly-dependent replication induces a primitive selection for the fittest one, and nucleotide–amyloid interactions selectively bind to codon-sized RNA:s [114,121]. With respect to compartmentalization, the interactions of the peptide amyloids with lipids are crucial: Lipid interphases promote the nucleation and formation of amyloids, and chemical gradients in mixtures of amino acids and fatty acids generate amyloid-like fibrils localizing inside a proto-cellular compartment [118].

However, given the limited knowledge of the conditions on the early Earth and the supposedly extremely long time course of the molecular processes leading to the emergence of living entities [133], the possibilities of creating the actual experimental conditions for obtaining direct evidence for the amyloid-based world hypothesis, or any other chemical origin-of-life hypothesis, are constrained—practically impossible. The power of machine learning can, however, change

Table 3. Arguments for the amyloid world hypothesis.

- *A hybrid model*. The amyloid-based model is a hybrid origin-of-life hypothesis in which the amyloid conformers perform both genetic/replicative and catalytic/metabolic functions. There is no chicken-or-egg dilemma associated with the amyloid model.
- *Resources*. Amino acids and short peptides—the constituents of peptide amyloids—are easily produced under prebiotically plausible conditions. Amino acids have also been detected in meteorites. Even very short peptides with simple amino acid sequences can spontaneously form functional cross-β-sheet amyloid structures.
- *Stability*. The steric zipper structure makes the polymeric amyloid conformers remarkably stable. Amyloid fibrils withstand high temperatures, pressure and different types of radiation.
- *Replication*. Peptide-based amyloids self-replicate and self-organize into functional fibrillar networks with scaffolding and protective properties A template-driven replication process can generate new amyloid fibril copies.
- *Metabolism*. Amyloid possesses autocatalytic and catalytic activity. The catalytic activity is dependent on an intact cross-β-sheet conformation and involves activity directed at the synthesis of its own constituent peptide monomers and the synthesis of simple metabolites.
- *Information transfer*. The amyloid conformers can process and transfer structural information in the templated self-replication cycles.
- *Variation*. One type of a peptide sequence can give rise to several structural variants of which one or more can self-replicate.
- *Evolvability*. The cross-β-sheet conformers are in-put- sensitive and changes in the external milieu can give rise to structural variants on which evolutionary forces may act.
- *Chiro-selectivity*. Homochiral peptides are preferentially incorporated in fibrillar amyloid. The autocatalytic templated replication cycles expand the homochiral conformer pool. The enantioselective replication system is relevant with respect to the discussion on the origins of homochirality.
- *Synergistic interactions and formation of complex networks*. The amyloids form fibrillar networks and interact co-operatively with RNA, lipids, and natively folded proteins setting the stage for the emergence of evolutionary processes toward increased complexity, organization, and compartmentalization.

the picture [134]. Artificial intelligence might, for instance, help analyze and predict processes that occur in complex interacting chemical mixtures over time and assist in determining the biogenicity of organic samples [135]. Machine learning has its limitations, though: The analyses and predictions are input data-dependent, and as long as the input contains unknown or uncertain factors the results are only broadly indicative.

Proteins and the origin-of-life: a historic note

Among the Greek philosophers, Aristotle conjectured on the spontaneous generation of living entities from inanimate material [136]. The idea of a role of protein-like structures in life's molecular origins dates back to the latter half of nineteenth century. In a letter to Joseph Hooker, Darwin wrote (1871) '[But] if, and (oh what a big if) we could conceive some warm little pond with all sorts of ammonia and phosphoric salts, – light, heat, electricity etc present, that a protein compound was chemically formed, ready to undergo still more complex changes'. [137]. Half a century later, Oparin (1924) and Haldane (1929), independently, advanced the view of a 'primordial/hot soup' in which atmospheric gases together with the energy from lightning/ultraviolet radiation could spontaneously give rise to organic compounds [138,139]. In line with this, Miller and Urey, in 1953, demonstrated the synthesis of amino acids (and other organic compounds) under simulated early Earth conditions [62]. In a publication dating back to 1975, Brack and Orgel, in turn, suggested a role for alternating polypeptides in a prebiotic context [140]. Rode's article Peptides in the origin of life [9] in 1999 was followed by several protein-first models [10,11,141]. The studies by Lindquist and colleagues [88,142,143] and by others [38,40,144] on the protein-only mechanism in the first decade of the 21st century, and the observations on the catalytic properties of β-sheet structures [46,54] have been important in the discourse on the role of proteins/peptides in the origin of life. In 2009, this author formulated a coherent theory on the origin of life based on β-sheet peptide amyloids [13]. The model, coined the term amyloid world [13], was put forth as a possible solution to the stability, functionality, and chicken-and-egg problems associated with the origin-of-life hypotheses based on RNA and natively folded proteins. The amyloid model emphasizes the early emergence of dynamic, cooperative networks involving amyloid, RNA, lipids, and natively folded proto-proteins [15,41]. The amyloid hypothesis has gained momentum from several studies, in particular, those by Riek, Greenwald *et al.* [47,114,119], Carny and Gazit [108], and Ashkenasy *et al.* [14,121].

Conclusion

The amyloid world hypothesis of the origin-of-life posits that the first functional polymers on the primitive Earth for about 4 billion (4×10^9) years ago were structurally stable cross-β-sheet-based peptide amyloids that were capable of Darwinian-like evolution. Self-recognition, self-capturing, and self-amplification characterize the amyloid system, which, in addition to the informational and catalytic properties, exhibits chiroselectivity and responds to changes in the external conditions. The protection offered by the amyloid-based fibrillar networks, together with the cooperative and synergistic interactions of the β-sheet aggregates with nucleic acids, nucleoproteins, and lipids generating complex functional networks, is in concert with the envisioned view of an early co-evolving amyloid–-RNA–lipid–protein world.

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Author contributions

CPJM conceptualized, designed, and wrote the perspective.

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