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Origin of life. Primordial genetics: Information transfer in a pre-RNA world based on self-replicating beta-sheet amyloid conformers

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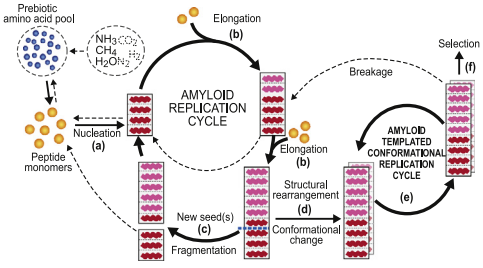
HIGHLIGHTS

- A primordial preRNA information system based on amyloid entities is presented.
- It is characterized by templated conformational self-replication.
- The encoding element is the steric zipper structure of the beta-sheet amyloid fold.
- The information system is stable, environmentally responsive, and evolvable.
- The amyloids are proposed to represent the first indefinite informational replicators.

GRAPHICAL ABSTRACT



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ABSTRACT

The question of the origin of life on Earth can largely be reduced to the question of what was the first molecular replicator system that was able to replicate and evolve under the presumably very harsh conditions on the early Earth. It is unlikely that a functional RNA could have existed under such conditions and it is generally assumed that some other kind of information system preceded the RNA world. Here, I present an informational molecular system that is stable, self-replicative, environmentally responsive, and evolvable under conditions characterized by high temperatures, ultraviolet and cosmic radiation. This postulated pregenetic system is based on the amyloid fold, a functionally unique polypeptide fold characterized by a cross beta-sheet structure in which the beta strands are arranged perpendicular to the fiber axis. Beside an extraordinary structural robustness, the amyloid fold possesses a unique ability to transmit information by a three-dimensional templating mechanism. In amyloidogenesis short peptide monomers are added one by one to the growing end of the fiber. From the same monomeric subunits several structural variants of amyloid may be formed. Then, in a self-replicative mode, a specific amyloid conformer can act as a template and confer its spatially encoded information to daughter molecular entities in a repetitive way. In this process, the specific conformational information, the spatially changed organization, is transmitted; the coding element is the steric zipper structure, and recognition occurs by amino acid side chain complementarity. The amyloid information system fulfills several basic requirements of a primordial evolvable replicator system: (i) it is stable under the presumed primitive Earth conditions, (ii) the monomeric building blocks of the informational polymer can be formed from available prebiotic compounds, (iii) the system is self-assembling and self-replicative and (iv) it is adaptive to changes in the environment and evolvable.

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1. Introduction

One of the greatest challenges in science is to solve the question of how life came into existence on Earth. The question can largely be reduced to the question of what was the first informational system that was able to self-replicate and evolve under the assumedly very harsh early Earth conditions. Of the origin-of-life hypotheses, the RNA world hypothesis (Gilbert, 1986; Orgel, 2004; Robertson and Joyce, 2012) has received most attention. However, RNA with both replicative and catalytic functions is difficult to produce and would probably not have been stable under the harsh prebiotic conditions. It is thus likely that there must have been an informational system preceding the RNA era (Orgel, 2003; Yarus, 2011). Here I present such a system, a stable, environmentally responsive primitive genetic system based on templated conformational self-replication of beta-sheet amyloid entities.

2. Why the amyloid fold?

Accumulating data indicate a unique position of amyloid among the protein folds. It is remarkably stable, withstanding high temperatures, chemicals, ultraviolet and cosmic radiation. It self-assembles and self-replicates (Takahashi and Mihara, 2004; Chiti and Dobson, 2006; Eichner and Radford, 2011), and is able to transmit conformational information (Maury, 2008, 2009a; Wiltzius et al., 2009; Wickner et al., 2014). Of particular interest from a prebiotic point of view is the conformational templating mechanism which, intriguingly, is also a characteristic feature of prions (Prusiner, 1998; Serio et al., 2000; Abid and Soto, 2006). In fact, the structural rearrangement involved with the conversion of the prion protein to the infectious prion state is associated with the generation of a beta-sheet amyloid motif that makes the prion resistant both to proteolysis and high temperatures. Moreover, the transmissibility and strain specificity of the prions, as well as information-transfer by synthetic yeast prions, seem to be dependent of the amyloid motif of the molecule (Legname et al., 2004; Jones and Surewicz, 2005; Ghaemmaghami et al., 2013; Baskakov, 2014; Sano et al., 2014).

There are additional features that make amyloid interesting in the origin-of-life-context: (i) it is polymorphic in nature and environmentally sensitive (Greenwald and Riek, 2010; Eichner and Radford, 2011; Toyama and Weissman, 2011), (ii) it provides a means for short peptides to become functional under harsh conditions (Maury, 2008, 2009a; Bourbo et al., 2011; Rufo et al., 2014), and (iii) experimental evidence shows that a peptide with a prebiotically plausible amino acid composition spontaneously forms amyloid structures (Maury et al., 2012).

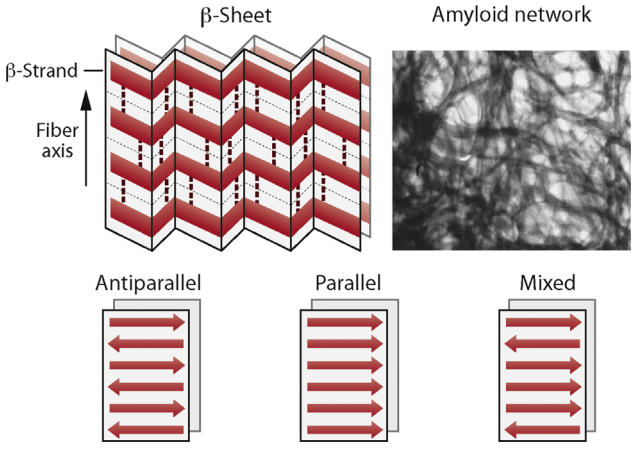

Fig. 1. Structural organization of beta-sheets and amyloid. The amyloid fiber axis runs perpendicular to the beta-strands, which are held together by hydrogen bonds (broken lines). The distance between the beta-strands is about 0.47–0.48 nm and between the beta-sheets 0.8–1.2 nm. Typically, two or more extended beta-sheet structures stack upon one another forming a twisted fibril of about 5–12 nm. The electron micrograph shows a network of amyloid fibrils spontaneously formed in an aqueous solution at 60 °C from a prebiotically plausible nonapeptide. Experimental details were as in Maury et al. (2012).

3. Amyloid and information transfer

A basic requirement for all forms of life is the ability to transmit information, and this step was probably crucial in life's coming into being. The question of what was the first prebiotic informational polymer has been a matter of a number of speculations. In addition to being informational, the putative polymer must be both stable and able to self-replicate, as well as adaptable to environmental signals. I hypothesize that amyloid, being stable, informational, and self-catalytic, is a very likely candidate for being the first informational molecular replicator on the primitive Earth. A significant difference between the amyloid (Maury, 2008, 2009a) and other peptide/protein-based origin-of-life hypotheses (Rode, 1999; Ikehara, 2005; Woolfson, 2000) is that under the harsh early Earth conditions the beta-sheet rich amyloid structure provides a *stable and functional* folding state for short (e.g. 3–12mer) prebiotic peptides; a state that for natively folded peptides/proteins is impossible under such conditions. Moreover, other peptide/protein-first based models lack a clear path for *self-replication and information transfer* under presumed harsh prebiotic conditions. How, then, is the unique functionality of the amyloid fold achieved?

Recent studies have revealed unexpected and surprising properties of the amyloid structure (Fig. 1). It has been shown that the beta sheet amyloid conformers self-assemble by a seeded nucleated growth mechanism characterized by an initial slow kinetic phase followed by a fast, thermodynamically favored phase in which peptide monomers/oligomers are added one by one to the growing end of the protofiber (Fig. 2). The extended beta-sheets stack upon each other with their side chains intermeshed forming a steric zipper forming structure (Greenwald and Riek, 2010). There are no water molecules between the sheets; it is this hydrophobic, dry zipper structure that holds the sheets stably together. Once formed the amyloids are very stable, with the exception that they may break into smaller units forming more growing ends. Importantly, during amyloidogenesis several polymorphic forms of amyloid may be formed from the same monomeric building blocks, i.e. a single amino acid sequence can give rise to distinct amyloid states. Then, in the self-replication phase, a certain amyloid conformer may act as a template and transmit its specific, spatially encoded information to another molecule in a repetitive mode (Figs. 2 and 3). In this molecular imprinting process, it is the *specific conformational information*, the changed three-dimensional architecture, not the constituent building blocks, that is transmitted to daughter molecules.

The basis for the information transfer lies in the zipper structure of amyloid (Wiltzius et al., 2009; Greenwald and Riek, 2010; Eisenberg and Jucker, 2012) that is maintained by hydrogen bonds, van der Waals forces and electrostatic polarization. The strong non-covalent forces hold the informational molecule in an enduring conformational state during the processes of transmission. The steric zippers differ in the architecture of the beta-strands within and between the beta-sheets and in the stacking of the sheets; both packing, segmental and side chain polymorphisms have been identified. The organization reveals a number of structural possibilities even for short homopolymers. The coding element of the system is the steric zipper structure, and recognition occurs by the amino acid side chain complementarity

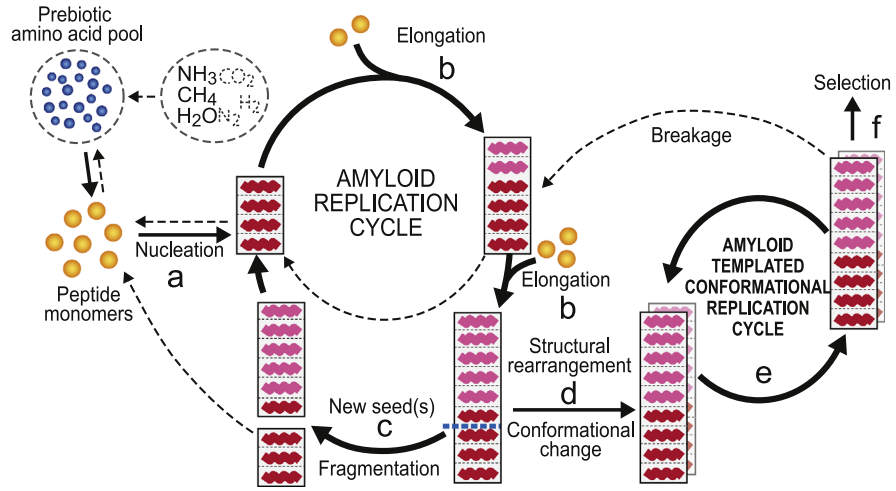

Fig. 2. Schematic representation of the self-replicating cycles of amyloid. The figure outlines the formation and replication of one type of a peptide monomer from a pool of different monomers. An initial slow nucleation phase (a) is followed by a kinetically fast elongation phase (b) where monomers (or oligomers) are added sequentially to the growing end of the protofiber. Breakage of the fiber results in new seeds (c) and repeated replication cycles. Importantly, molecular rearrangements and conformational changes in amyloid may occur (d) that, by a templated *conformational* replication mechanism (e), can faithfully be transmitted to other amyloid conformers. The pool of the environmentally fittest variant(s) then expands (f). The energy required for the prebiotic synthesis of amino acids and peptides probably derives from sources such as cosmic radiation, lightning, hydrothermal vents, and/or meteoritic impacts. The model does not exclude the possibility of an extraterrestrial origin of primordial amino acids or a contribution of extraterrestrial amino acids to terrestrial chemical evolution.

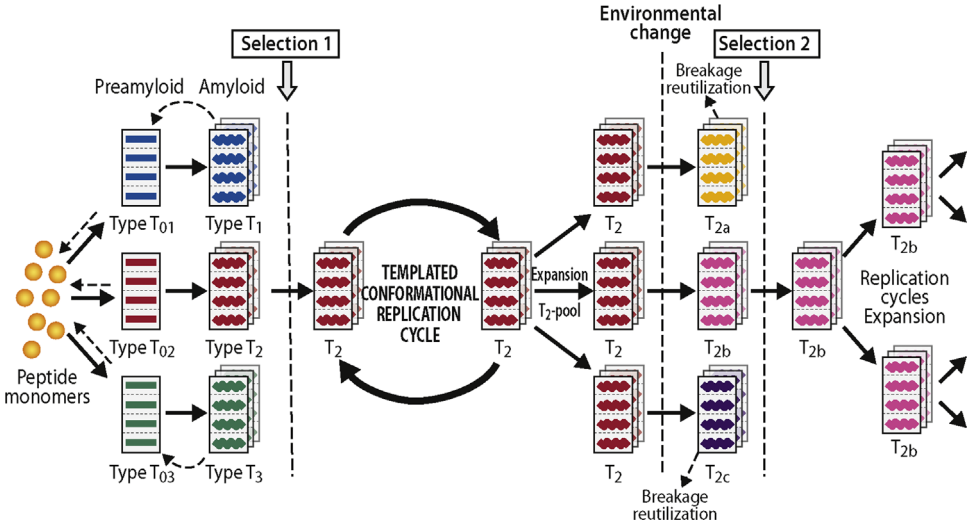

Fig. 3. The amyloid world model. From one type of prebiotic peptide monomer a spectrum of amyloid conformers may be formed (T_1, T_2, T_3). By templated conformational replication, the pool of the environmentally fittest type (T_2, Selection 1) rapidly expands. A change in the environment (e.g., pH, temperature, radiation) induces conformational changes in T_2 (T_{2a}, T_{2b}, T_{2c}). The fittest conformer (T_{2b}) is selected (Selection 2) and undergoes templated conformational replication cycles expanding the (T_{2b}) pool. The environmentally less suitable variants are decomposed and recycled. The environment-induced variations in the amyloid conformations combined with faithful replication of the selected amyloid conformers (variants) and repeated selection cycles allow evolution to occur.

(Wiltzius et al., 2009). From an energetic viewpoint, the amyloid state can be considered to occupy the global free energy minimum and the propensity to form amyloid to be encoded as exitations in the free energy landscape (Zhuravlev et al., 2014).

4. What is an amyloidogenic sequence?

The amino acid sequence is important in determining the propensity to form amyloid; a single amino acid substitution can markedly influence the amyloidogenicity of a polypeptide. In gelsolin, for example, substituting asparagine or tyrosine for aspartic acid at position 187, increases fibril formation by an order of magnitude (Maury and Nurmiaho-Lassila, 1992; Maury, 1994). Although certain short sequence motifs possess a high amyloid-forming tendency per se, and hydrophobicity and clusters of hydrophobic residues, as well as alternating hydrophobic/hydrophilic residues and aromatic moieties are significant determinants of amyloidogenicity (Brack and Orgel, 1975; Brack and Barbier, 1990; Dyson et al., 2006; Galatskaya et al., 2006; Brack, 2007; Gazit, 2007), there is no general consensus sequence for amyloid. Importantly, recent studies have, instead, emphasized the general character of the amyloid fold: most polypeptides can, depending on the conditions (e.g. pH, local protein/peptide concentration, salt concentration, temperature, chaperones, reaction surface, solvent, incubation time) form amyloid. In fact, amyloid formation seems to be an intrinsic propensity of polypeptides in general and the beta-sheet based fold an evolutionary highly conserved structure (Dobson, 2004; Chiti and Dobson, 2006; Goldschmidt et al., 2010).

Several contemporary organisms exploit the amyloid fold for beneficial purposes. This *functional* amyloid, as opposite to the more familiar disease-related amyloid, is involved in a wide range

of biological processes, as diverse as biofilm formation, development of aerial structures, regulation of melanin synthesis, hormone production, epigenetic control of polyamines, and information transfer (Fowler et al., 2007; Maji et al., 2009; Maury, 2009b). In the case of prions, several properties, including transmissibility and species specificity seem to be dependent on the amyloid conformation (Jones and Surewicz, 2005; Toyama and Weissman, 2011; Frederick et al., 2014; Wickner et al., 2014).

Even very short peptides can form stable *and functional* structures when folded as amyloid. This is important with respect to the current model. Under conditions simulating early Earth conditions short peptides are readily produced. Intriguingly, a nonapeptide composed of the six most abundant amino acids produced in experiments simulating prebiotic conditions spontaneously forms amyloid conformers in aqueous conditions at different temperatures (Maury et al., 2012).

5. Homochirality and amyloid

Homochirality is a typical feature of biological macromolecules and has been considered a signature of life (Blackmond, 2010). The origin of the biologic homochirality is not known. Several theories have been suggested; some argue that homochirality preceded life and might have had an extraterrestrial origin and others that it is an artifact of life rather than a precondition. The question arises whether the amyloid model is relevant with respect to the question of homochirality, and, more specific, can the templated, chiroselective conformational self-replication mechanism that characterizes amyloid explain in part the origin of homochirality in nature.

Amyloid is normally found as a homochiral structure; the high enantioselectivity has been explained on the basis of favorable nonbonded contacts between adjacent beta-strands of the homochiral beta-sheets as compared with the poor fit of heterochiral ones (Chung and Nowick, 2004; Wadai et al., 2005). In a prebiotic setting, it is thus likely that homochiral peptides were preferentially incorporated in amyloid. The templated self-replication of amyloid would then result in a rapid expansion of the isotactic amyloid entities. The structural stability of the amyloid conformers, including the thermostability and radiation resistance, would have rendered them an additional advantage in the harsh prebiotic world, whereas the non-recruited peptides – being structurally unstable – would have been degraded. Moreover, the environment-sensitive variations in amyloid structure enable both adaptability and evolvability. Noteworthy, both beta-sheet-induced chirogenesis in the polymerization of oligopeptides (Wagner et al., 2011), and the presence of a chiroselective peptide replicator (Saghatelian et al., 2001) have been reported.

Although the current amyloid model may explain both the chiral amplification step and the chiral transmission step of homochirality, it does not answer the question of the reason for the initial selection of peptides composed of (probably) *levo*rotatory amino acids to be incorporated in the primordial amyloid: was it chance, an initial enantiomeric imbalance (Bada, 1995; Hein and Blackmond, 2012) or both, some other cause, or is there an extraterrestrial (meteorite or meteorite impact) explanation?

6. Prebiotic amyloidogenesis: surface-bound or in solution?

Amyloid formation can experimentally be accomplished in aqueous solutions: pH, temperature and, notably, peptide concentration are important factors. An initially slow rate of synthesis is followed by a kinetically fast phase. The kinetics directly correlates with the formation of amyloid nuclei acting as seeds. By introducing a surface into the reaction mixture, the whole process can be speeded up (Zhu et al., 2002). The surface acts as a platform for amyloid formation: the recruitment of precursor peptides on the surface locally increases the peptide concentration, favors reciprocal interaction, and speeds nucleation (Stefani, 2008). The surface can even act as an autocatalytic layer that initiates the conformational self-replication of amyloid and also function as a reservoir for the amyloid seeds. The seeds may then bud off and spread the replicating entities into the surrounding medium (Hammarström et al., 2011). By lowering the activation energy barrier, interfaces per se are known to promote amyloidogenesis, too (Stefani, 2008). Moreover, oligomers are readily synthesized on certain mineral surfaces (Ferris et al., 1996) and amyloid can spontaneously form fibrillar networks that acts as scaffolds for the amyloid assemblies themselves (Hamley, 2007), as well as for other molecules, such as ribonucleotides (Liu et al., 2008). Amyloid may also enhance the polymerization of ribonucleotides, and nucleic acids may enhance amyloid formation (Braun et al., 2011). Of interest, in the context of the Cairns-Smith's clay-as-genes hypothesis (Cairns-Smith, 1982), is the observation that clay minerals can catalyze the formation of RNA (Huang and Ferris, 2006). Noteworthy, the scaffolding properties of amyloid are exploited by contemporary organisms: microbes are known to utilize amyloid as part of the matrix in biofilm formation (Barnhart and Chapman, 2006), and moths for protecting oocytes from environmental dangers (Iconomidou and Hamodrakas, 2008). It is thus likely that the initial prebiotic amyloid processes occurred on a surface and were surface-catalyzed. This would have met the requirement for a high local precursor concentration and ensured a rapid replication rate.

7. Amyloid: the Urgene?

Although Brack and Orgel already in 1975 suggested a role of the beta-structures in prebiotic chemistry, it was not until the comprehension of the existence a protein conformation-based inheritance mechanism, that a coherent theory of a prebiotic beta-sheet “amyloid world” was envisioned (Maury, 2008, 2009a). Much of the evidence for the “protein-only” mechanism, a key element of the theory, derives from experiments with synthetic amyloids and prions. It has convincingly been shown that recombinant prion amyloid preparations can transmit infectivity and influence strain specificity (Legname et al., 2004; Colby et al., 2009), and that diverse prion amyloid conformers can probe a structural landscape and through intermediate states transform to an optimized conformation (Ghaemmaghami et al., 2013). In yeast, the aggregation propagation domains of prions are composed of short low-complexity sequences suggesting an ancient origin (Chernoff, 2004), and in mesophilic bacteria and eukaryotes, glutamine/asparagine rich motifs display a high propensity to form amyloid (Michelitsch and Weissman, 2000). There exists, moreover, a striking homology between the peptides formed in the salt-induced peptide reaction simulating prebiotic conditions and the sequences of known prions (Rode et al., 1999).

Comprehending the conformation-related information transfer and conformational self-replication mechanisms of amyloid, the beta-sheet-based system seems a very likely candidate for being *the* primordial informational molecular replicator system on the early Earth. The arguments include:

(i) *The resource argument*. To be valid, an evolutionary theory must be able to explain the conversion of resources into building blocks under prevailing early Earth conditions. In contrast to nucleic acids, the building blocks of the self-propagating chiroselective beta-sheet polymers (amino acids and short peptides), are easily synthesized under presumed prebiotic conditions and have also been detected in

meteorites. Importantly, the nano-ordered amyloid assemblies apparently represent a state of an efficient minimal energy arrangement of the peptide chain, and amyloidogenesis may occur even at submicromolar concentrations (Gazit, 2005).

(ii) *The stability argument*. A common problem with the *natively* folded peptide-first and protein-first, as well as the RNA world models, is the stability of the molecules; the natively folded three-dimensional polypeptide/RNA structures are likely to decompose under the harsh prebiotic conditions. In contrast, the amyloid fold is remarkably stable. The basis for the stability is the steric zipper structure: the beta-sheets interdigitate with a remarkable degree of geometric complementarity that excludes water. The robustness is close to the theoretical limit achieved in proteins with maximal density of intermolecular hydrogen bonds (Knowles et al., 2009). Amyloid is resistant to both ultraviolet and ionizing radiation and to high temperatures (Alper, 1993; Meersman and Dobson, 2006; Brack, 2007; Fernie et al., 2007; Mesquida et al., 2007). Germicidal ultraviolet radiation does not inactivate the amyloid-dependent prion activity, nor do 30 to 120 min exposures to temperatures of 100 °C or even higher. In a prebiotic setting the structural stability renders the amyloid conformers a marked selective advantage over natively folded polypeptide and RNA structures.

(iii) *The functionality argument.* Even very short peptides (e.g. 3 to 10 residues long) can achieve well-defined conformations and become functional through the formation of amyloid conformers. In addition to being able catalyze their own formation, the amyloid conformers can catalyze chemical reactions, too (Rufo et al., 2014). Importantly, such short peptides are readily generated in experiments simulating prebiotic conditions. To be functional, *natively folded* peptides, on the other hand, require a sequence of 20 or more amino acids; they are, moreover, difficult to prebiotically synthesize and are easily denaturated. The same argument applies also to RNA, and there is, in addition, a chicken-and-egg problem with the RNA world hypothesis: to be functional, RNA must be relatively long, which requires a metabolic (enzymatic) apparatus, the synthesis of which requires a coding system, which, again, requires genes. The amyloid model, on the other hand, based on the stable beta-sheet amyloid conformers possessing both self-replicative and informational properties is devoid of these problems.

(iv) *The evolvability argument.* The amyloid model fulfills a key necessity of a valid molecular evolution theory, namely, the ability to evolve. And evolution requires variation. Conformational variability is indeed a distinct feature of the amyloid system; the system is responsive to environmental signals (Westergard and True, 2014) and can endurably replicate the fittest, stable variants and allow evolutive forces to act. To explain variability, heredity and evolution on the basis of the peptide/protein-first (Rode, 1999; Ikehara, 2005), clay (Cairns-Smith, 1982) or RNA-world hypotheses (Gilbert, 1986; Robertson and Joyce, 2012), is, on the other hand, more problematic as discussed by several authors (e.g. Maynard Smith and Szathmary, 1999; Barbieri, 2003; Orgel, 2003, 2004; Bullard et al., 2007; Yarus, 2011; Bernhardt, 2012; Robertson and Joyce, 2012).

8. Transition to an RNA world

The information model presented herein is compatible with a coevolving or later evolving RNA world. Amyloid possesses the propensity to form self-propagating stable fibrillar networks that can act as scaffolds for nucleic acids (Nandi and Nicole, 2004; Silva et al., 2008) and other molecules, including lipids (Relini et al., 2008; Domano and Kinnunen, 2008). Moreover, the amyloid surface can promote the polymerization of ribonucleotides, and nucleic acids may also enhance amyloidogenesis (Braun et al., 2011). Importantly, amyloid–nucleic acid complexes enhance nucleic acid hybridization (Braun et al., 2011). Thus, in the transition process towards an RNA world amyloid might have been directly involved in several ways: the beta-sheet structure could provide a scaffold for the nucleic acids, promote their polymerization and protect their inherently labile structure under the harsh external conditions, and, at the same time, amyloid–nucleic acid complexes could promote nucleotide hybridization, a prerequisite for nucleic acid replication.

9. Conclusion

The information transmission model presented herein (Figs. 2 and 3), based on the self-complementary nature of the beta-sheet fold and characterized by self-recognition, self-capturing and conformational self-replication, provides several advantages compared with other current origin of life models: (i) by combining replication (genotype) and metabolism (phenotype) it avoids the chicken-and egg dilemma, (ii) in contrast to the RNA models, or the peptide/protein-first models based on native polypeptide structures, it is both stable *and* functional even under very harsh external conditions, and (iii) it is environmentally responsive and able to produce optimized molecular variants that might undergo Darwinian evolution. The amyloid conformers are postulated to represent the first indefinite informational replicators on the early Earth. Organization and compartmentalization provide means for further evolution; amyloid acts both as a scaffold for itself and for other prebiotic molecules, including nucleobases. The model is compatible with a coevolving or later evolving RNA world.

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