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Are prions related to the emergence of early life? ☆

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Summary DNA and RNA are the modern cellular molecules related to the storage and processing of the genetic information. However, in the Earth primeval environment conditions, these two molecules are far from being the best option for this function due to their great complexity and sensibility to heat. Experiments have been showing that proteins are very stable and reliable molecules even in very extreme conditions and, under certain circumstances, could be related to the transmission of certain phenotypes that are inherited in a non-Mendelian manner.

Prions, infective proteins that are associated to several neurological diseases among mammals by replacing their dominant native state of prion protein by a misfolded one, are remarkably resistant to even the most extreme environments. Furthermore, prions are also associated to the transmission of certain fungal traits in an epigenetical model. These two characteristics support the hypothesis that prions are a possible relic of early stage peptide evolution and may represent the reminiscence of a very ancient analogical code of biological transmission of information rather than the digital one represented by modern nucleic acids.

Introduction

It is now generally accepted that life arose on the Earth early in its history. However, the mechanisms related to the emergence of early life are still associated with many debates. The modern pattern of DNA acting as a reservoir of genetic information is not chemically realistic in the very beginning of

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life in our planet. DNA carries the genetic information required for the synthesis of proteins. The replication and transcription of DNA require a complex set of enzymes and other proteins. Even the shortest DNA strand needs proteins to help it replicate. How then could the first living cells with DNA-based molecular biology have originated by spontaneous chemical processes on the prebiotic Earth? Primordial DNA synthesis would have required the presence of specific enzymes, but how could these enzymes be synthesized without the genetic information in DNA and without RNA for translating that information into the amino acid sequence of the protein enzymes? In other words, proteins are required for DNA synthesis and DNA is required for protein synthesis. Furthermore, DNA's chemical great complexity and sensibility to heat make DNA probably a late sophistication of the cell mechanism of self-replication and transmission of genetic information in a very reliable way.

RNA World

Many scholars consider RNA as a much more suitable molecule to be related to early life. The term ''RNA World'' was first used by Walter Gilbert in 1986 [1]. The RNA World hypothesis is supported by the RNA's ability to store, transmit, and duplicate genetic information, just like DNA does. RNA can also act as a ribozyme, an enzyme made of ribonucleic acid. Because it can reproduce on its own, performing the tasks of both DNA and proteins (enzymes), RNA is believed to have once been capable of independent life and some RNA-viruses may represent a side effect of this capability. Experiments with basic ribozymes, like the viral RNA Q-beta, have shown that simple self-replicating RNA structures can withstand even strong selective pressures [2,3].

Competition between RNA may have favored the emergence of cooperation between different RNA chains, opening the way for the formation of the first proto-cell [2,4]. Eventually, RNA chains randomly developed with catalytic properties that help amino acids bind together (peptide-bonding). These amino acids could then assist with RNA synthesis, giving those RNA chains that could serve as ribozymes the selective advantage. According to this hypothesis, eventually DNA, lipids, carbohydrates, and all sorts of other chemicals were recruited into life [2–4]. Forterre [5] believes that RNA-viruses played a critical role in major evolutionary transitions, such as the invention of DNA and DNA replication mechanisms. This led to the first prokaryotic cells, and eventually to life as we know it.

The ''RNA World'' hypothesis was given a major boost with the deciphering of the three-dimensional structure of the ribosome, which revealed the key catalytic sites of ribosomes to be composed of RNA, with proteins playing only a structural role in holding the ribosomal RNA together [6,7]. Specifically, the formation of the peptide bond, the reaction that binds amino acids together into proteins, is now known to be catalyzed by RNA [6,7]. This finding suggests that RNA molecules were most likely capable of generating the first proteins [8].

However, the ''RNA World'' hypothesis seems implausible because, in today's world, large RNA molecules are inherently fragile and can easily be broken down into their constituent nucleotides with hydrolysis [9]. Even without hydrolysis RNA will eventually break down from background radiation [10,11] and the environmental conditions in prebiotic Earth were very hardy [11]. Many other chemical difficulties, such as the fact that cytosine does not have a plausible prebiotic simulation method because it easily undergoes hydrolysis and the observation that in prebiotic simulations making nucleotides have conditions incompatible with those for making sugars, led many scholars to believe that the ''RNA World'' hypothesis is not chemically realistic [9,12].

A deeper view into the proteins

Proteins constitute the interface between the information of genes and the biological world. They are the universal structural currency of life on Earth and once were considered as the most plausible molecules to be related to the transmission of the genetic information before the milestone description of DNA as the key structure in this function. The structure of proteins determines their function, and a single change to a gene can profoundly influence the higher dimensions of protein structure [13].

Proteins are very sensitive to structural changes. Sequences of amino acids located at key strategic positions are crucially important in giving a protein the unique structure that defines its function. Other amino acid sequences or cluster of amino acids associated in a three-dimensional space form important recognition sites. Proteins are constructed from one-dimensional sequences of amino acids that are specified by the one-dimensional sequence of genes. Although in principle amino acids can orient themselves in a number of different ways, they in fact adopt only two fundamentally different types of basic pattern. These two-dimensional patterns are known as alpha helices and beta

sheets [14,15]. Individual alpha helices and beta sheets are connected to one another by short segments of primary amino acid sequence. The numbers of these two types of structural elements define a protein's secondary structure, and the combinatorial manner in which they are interlinked, its topology [13,14].

The primary sequence contains all the information necessary to specify the higher-dimensional patterns of protein structure. Each amino acid appears to have a general predilection for appearing in certain types of secondary structure. For example, some amino acids such as valine, isoleucine, tryptophan are most frequently found within beta sheets while others, such as alanine, aspartate, glycine and proline are mainly found in alpha helices [13].

Combinations of beta sheets and alpha-helical structural elements may be bent, stapled and folded back upon one another to generate such higher-dimensional patterns. These three-dimensional architectures are known as a protein's tertiary structure. In some cases, amino acids chains exhibit structural heterogeneity and oscillate between two or more alternative tertiary structures. Some proteins, like haemoglobin, are composites of more than one three-dimensionally folded amino acid sequence [13—15].

Some proteins have identical tertiary structure architectures but differ in their topology. The existence of topological variants suggests that proteins have been subjected to a process of topological optimization. While they may have identical distributions in three-dimensional space, different topological organizations of alpha and beta structural elements are likely to influence the efficiency with which the protein can fold and in so doing realize its higher order spatial patterns. Evolution may have selected topological variants on the basis of their relative folding efficiency. The topological plasticity would help ensure that the repertoire of potential folds is kept to a maximum [13].

Chaperonins (or chaperones) are ubiquous proteins characterized by a stacked double-ring structure and are found in prokaryotes, in the cytosol of eukaryotes, and in mitochondria [16]. Chaperones are proteins whose function is to assist other proteins in achieving proper folding. Many chaperones are heat shock proteins (HSP), that is, proteins expressed in response to elevated temperatures or other cellular stresses [17]. The reason for this behaviour is that protein folding is severely affected by heat and, therefore, some chaperones act to repair the potential damage caused by misfolding. Chaperones (or chaperonins) are associated with the target protein during part of its folding process. However, once folding is complete (or even before) the chaperone will leave its current protein molecule and go on to support the folding of another [16—18].

Powerful algorithms now exist which are able to accurately predict the nature of the fold that a primary sequence is likely to generate [13]. These types of algorithms are only partially understood and, in some cases, the assistance of specialized chaperones proteins and foldase enzymes are necessary to facilitate correct folding [19,20]. Others will only fold correctly in the context of proteins with which they form a permanent complex [13,19,20].

''Peptide first'' hypothesis

The hypothesis that suggests that the first life forms were made from collectively autocatalytic peptide networks is called the ''peptide first'' hypothesis [13]. If this was the case, the first rudimentary peptide-based creatures may eventually have been infected by either (1) non-self-replicating RNA molecules, (2) RNA molecules which self-replicated by means of autocatalytic ligation reactions, or (3) autocatalytically self-replicating molecules which utilized a template-based mechanism of replication [13,21,22].

Ferris et al. [23] have shown that peptides of p to 55 amino acids long can be synthesized abiologically on mineral surfaces. It seems reasonable to speculate that under more optimal conditions, it should be possible to synthesize even longer peptides [24]. Folded peptides occur extremely frequently in artificially constructed, random combinatorial libraries which are 80 to100 amino acids long and which are composed of only three different amino acids [13]. Peptides of less than 33 amino acids long are exceptionally stable at high temperatures and are able to fold into discreet structures [13,25].

The first step towards template-based self-replication may have been the infection of pre-existing self-assembling peptide metabolism by abiologically synthesized RNA molecules which were, at this point, incapable of template-based self-replication [13]. Although not initially encoding symbolic information within their digital sequences, these RNA pre-genes may have been able to force and subvert the spontaneous self-organizing dynamics of geneless peptide-based proto-organisms [13,21,22]. They may also have been able to modify the properties of the network components by, for example, chaperoning their folding, increasing their stability, or regulating their activity [21].

However, many proteins are very sensible to heat and degradation by many of the plausible conditions presented on early Earth [9]. Another critical point is that autocatalytic self-construction in macromolecular systems requires the existence of a reflexive relationship between structural components and the functional operations they perform to synthesize themselves [21,26]. The possibility of reflexivity depends on formal, semiotic features of the catalytic structure—function relationship, that is, the embedding of catalytic functions in the space of polymeric structures [21,27]. Reflexivity is a semiotic property of some genetic sequences. Such sequences may serve as the basis for the evolution of coding as a result of autocatalytic self-organization in a population of assignment catalysts. Autocatalytic selection is a mechanism whereby matter becomes differentiated in primitive biochemical systems. In the case of coding self-organization, it corresponds to the creation of symbolic information. According to Wills [21], prions are present-day entities whose replication through autocatalysis reflects aspects of biological semiotics less obvious than genetic coding.

The Prion paradox

In 1982, Prusiner [28] proposed the name ''prion'' for the small *pro*teinaceous *in*fectious particles that were transmitted in spongiform encephalopathies and resisted inactivation by procedures that modify nucleic acids. Prusiner suggested that the transmissible agent might be devoid of nucleic acid (DNA and RNA) and may be composed only of protein. Further research [29,30] supported the prion hypothesis and led to characterization of an aberrantly folded isoform of a host-encoded protein (PrP), that was designated PrP^{Sc}, from scrapie, an endemic prionic disease that naturally occurs among sheep for many centuries. The normal PrP protein fluctuates between a dominant native state (PrP^{C}) and a series of minor conformations, one or a set of which can self-associate in an ordered manner to produce a stable supramolecular structure (PrP^{Sc}). The stable supramolecular structure is composed of misfolded PrP monomers in an autocatalytic formation [30]. Interestingly, the main difference between PrP^{C} and PrP^{Sc} is conformational.

Prions kill animals and humans by replacing their dominant native state of prion protein (PrP^{C}), a transmembrane glycoprotein of unknown function, with the dysfunctional isomer PrP^{Sc} (from scrapie) [31]. PrP^{C} consists primarily of alpha helices, regions in which the protein backbone twists into a specific kind of spiral [29,31]. The PrP^{Sc} form, however, contains beta strands, regions in which the backbone is fully extended. The main difference between PrP^{C} and PrP^{Sc} is conformational [29]. The abnormal and more stable isoform of PrP^{Sc} presents an alternative-folding pathway and accumulates mainly within the neurons and lymphocytes [31]. The mechanism of propagation involves the physical contact between both isoforms [29]. The PrP^{Sc} form propagates itself by contacting PrP^{C} molecules and causing them to unfold and flip from their usual conformation to the scrapie configuration in an autocatalytic reaction [29]. Mutations in the PrP gene render the resulting proteins susceptible to flipping from an alpha-helical to a beta-sheet shape, solving the paradox of a genetic disease that can also be transmissible to previous normal hosts [29,32].

It is important to point out that not all prions are dangerous; in fact, prion-like proteins are found naturally in many plants and animals [32,33]. Because of this, scientists reasoned that such proteins could give some sort of evolutionary advantage to their host. This was suggested to be the case in a species of fungus, *Podospora anserina* [34]. Genetically compatible colonies of this fungus can merge together and share cellular contents such as nutrients and cytoplasm. A natural system of protective ''incompatibility'' proteins exists to prevent promiscuous sharing between unrelated colonies. One such protein, called HET-S, adopts a prion-like form in order to function properly [34]. The prion form of HET-S spreads rapidly throughout the cellular network of a colony and can convert the non-prion form of the protein to a prion state after compatible colonies have merged [33,34]. However, when an incompatible colony tries to merge with a prion-containing colony, the prion causes the ''invader'' cells to die, ensuring that only related colonies obtain the benefit of sharing resources [34,35].

For many decades, a genetic trait termed [PSI+], of the yeast *Saccharomyces cerevisiae* had been described with an unusual pattern of inheritance and any conventional mutation was responsible for the [PSI+] trait [36]. In 1994, Wickner [37] hypothesized that [PSI+] as well as another anomalous heritable trait, [URE3], resulted from prion forms of certain normal cellular proteins. HSP were finely tied to the inheritance and transmission of [PSI+] and many other yeast prions [38]. Since then, researchers have unravelled how the proteins that code for [PSI+] and [URE3] can convert between prion and non-prion forms, as well as the consequences of having intracellular prions [38,39]. When exposed to certain adverse conditions, [PSI+] cells actually fare better than their prion-free siblings; this finding suggests that, in

some proteins, the ability to adopt a prion form may result from positive evolutionary selection [38]. It has been speculated that the ability to convert between prion infected and prion-free forms enables yeast to quickly and reversibly adapt in variable environments [40].

All available evidence suggests that prions epigenetically modulate a wide variety of fundamental biological processes, and many await discovery. They are at the origin of a number of phenotypes that are inherited in a non-Mendelian manner [35,41].

Prions and the emergence of early life

The emergence of early life on the Earth is still under debate. DNA and RNA are not very suitable for this early function for many reasons. Their higher chemical complexity, the existence of many chemical barriers for their synthesis in a abiotic environment and mainly because of the critical sensibility of the modern days nucleic acids to the very hardy conditions of early Earth made many scientists search for other possibilities [9].

According to Chien et al. [42], the prion hypothesis has been extended with the finding that several non-Mendelian traits in fungi are due to heritable changes in protein conformation, which may in some cases be beneficial. Although much remains to be learned about the specific role of cellular cofactors, mechanistic parallels between the mammalian and yeast prion phenomena point to universal features of conformation-based infection and inheritance involving propagation of ordered beta-sheet-rich protein aggregates commonly referred to as amyloid. Wickner et al. [35] believe that prions can be better explained in terms of the physical properties of amyloid-like aggregates. Prion strains, wherein chemically identical infectious particles cause distinct phenotypes and there are barriers that often prohibit prion transmission between different species [29]. There is increasing evidence suggesting that both of these can be manifestations of the same phenomenon: the ability of a protein to misfold into multiple self-propagating conformations [38,40]. Even single mutations can change the spectrum of favored misfolded conformations. In turn, changes in amyloid conformation can shift the specificity of propagation and alter strain phenotypes. This model helps explain many common and otherwise puzzling features of prion inheritance as well as aspects of non-infectious diseases involving toxic misfolded proteins [35].

Chernoff [26] states that prions are self-perpetuating protein isoforms that are both responsible for infectious diseases in mammals and for heritable traits in fungi. Most known prion proteins form amyloids — self-seeded fiber-like aggregates. Prion propagation (''replication'') could be described as a sequence of repetitive cycles of aggregate ''shearing'' into smaller seeds followed by the growth of these seeds into full-size polymers. The ability to form aggregates and to propagate them is controlled by distinct regions of the composite prion domains (PrDs).

Amyloids are self-assembled fibre-like beta-rich protein aggregates [43]. Amyloidogenic prion proteins propagate amyloid state *in vivo* and transmit it via infection or in cell divisions. While amyloid aggregation may occur in the absence of any other proteins, *in vivo* propagation of the amyloid state requires chaperone helpers. Yeast prion proteins contain prion domains which include distinct aggregation and propagation elements, responsible for these functions [36]. Known aggregation and propagation elements are short in length and composed of relatively simple sequences, indicating possible ancient origin. According to Chernoff [43], prion-like self-assembled structures could be involved in the initial steps of biological compartmentalization in early life.

Bousset and Melki [33] considered that they are at the origin of a number of phenotypes that are inherited in a non-Mendelian manner. Prions are very useful to dissect the molecular events at the origin of this structure-based inheritance. The experimental evidence accumulated for the last half of the century clearly suggests that inherited variation is not restricted to the changes in genomic sequences [41]. The prion model, originally based on unusual transmission of certain neurodegenerative diseases in mammals, provides a molecular mechanism for the template-like reproduction of alternative protein conformations. Recent data, that extend this model to protein-based genetic elements in yeast and other fungi, revealed that the reproduction and transmission of yeast protein-based genetic elements is controlled by the ''prion replication'' machinery of the cell, composed of the protein helpers responsible for the processes of assembly and disassembly of protein structures and multiprotein complexes [34—38]. Among these, the stress-related chaperones of HSP100 and HSP70 groups play an important role [36]. Alterations of levels or activity of these proteins result in ''mutator'' or ''antimutator'' affects in regard to protein-based genetic elements [38]. Prion-forming abilities appear to be conserved in evolution, despite the divergence of the corresponding amino acid sequences [41]. Moreover, a wide variety of proteins of different origins

appear to possess the ability to form amyloid-like aggregates, that in certain conditions might potentially result in prion-like switches [40,43].

Rode et al. [8] analyzed the possibility of prions as a relic of an early stage of peptide evolution. Prions are relatively small proteinaceous compounds, highly resistant against UV and ionizing radiation [29]. Based on considerations of chemical stability, geochemical data, and the most likely environmental conditions on the primitive earth, it has to be assumed that peptides and proteins had been produced by chemical evolution much earlier than polynucleotides [9,23,24]. A simple comparison of the most frequently occurring amino acid sequences in known prions with the sequence preferentially formed in the salt-induced peptide formation reaction, the simplest mechanism enabling the formation of peptides under primitive Earth conditions, shows a remarkable coincidence that strongly supports the hypothesis that prions are a relic of early stage peptide evolution [8].

Life may have started mainly on a protein-related basis, before the modern genetic mechanisms of life forms known today started to develop, making DNA/RNA-based evolution more of a final step than the initial step of evolution [8]. However, such a slow and rather inefficient type of life would have been eliminated quickly by the newly emergent RNA/DNA-based mechanism, and its existence would only be recognized nowadays as some weird epigenetically modulation in fungi and among the lethal spongiform encephalopathies in mammals [29,38]. Maybe, prions represent the reminiscence of a very ancient analogical code of biological transmission of information rather that the digital one represent by modern nucleic acids.

Conflict of interest statement

The authors have no conflict of interest to disclose.

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