Case for an RNA–prion world: a hypothesis based on conformational diversity

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Received: 11 December 2010 / Accepted: 13 January 2011 /
Published online: 8 February 2011
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Abstract Prions and other misfolded proteins can impart their structure and functions to normal molecules. Based upon a thorough structural assessment of RNA, prions and misfolded proteins, especially from the perspective of conformational diversity, we propose a case for co-existence of these in the pre-biotic world. Analyzing the evolution of physical aspects of biochemical structures, we put forward a case for an RNA–prion pre-biotic world, instead of, merely, the “RNA World”.

Keywords Drawbacks of “RNA world” · Prions · Conformational diversity · Coexistence of RNA–prion-misfolded proteins

A recent article [1] devotes much discussion to the capability of prions and many other misfolded proteins to impart their (faulty) structures to normal cellular counterparts. The purpose of the present proposal is to explore the facets of this assertion, especially with regard to pre-biotic life.

It is believed by a large section of the scientific fraternity that ribonucleic acids (RNA), with their ability to catalyze, self-replicate, and store genetic information, were the key players in early evolutionary times. Many think that the pre-cellular world was essentially (the so-called) “RNA World”. The “RNA world” [2] hypothesis proposed that a world with life based on RNA predated the current world of life based on deoxyribonucleic acid (DNA) and proteins. The rRNA (RNA in the ribosome which catalyzes protein production), according to many, is an evolutionary remnant of the “RNA world”.

It is not for nothing that the “RNA world” hypothesis is popular. RNA can store, transmit, and duplicate genetic information;—all the functions that we associate with DNA. However, any freshman of structural biochemistry knows that the theoretical plausibility of the last

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sentence should be taken with, probably, a tablespoon of salt, because of the conspicuous presence of hydroxyl group at the 2'-position of the ribose sugar in RNA, which makes the latter a bit unstable. In fact, this hydroxyl group compels the ribose into a C3'-endo sugar conformation unlike the C2'-endo conformation of the deoxyribose sugar in DNA. As a result of all these (details of which can be found in any standard biochemistry textbook), the RNA double helix resembles A-DNA more than the (common) B-DNA. Likewise, one can gather several little pieces and figure out the reasons for inherent instability of large RNA molecules. (In fact, the level of fragility of RNAs can be appreciated if one observes the ease with which RNA breaks upon hydrolysis.) It therefore seems somewhat unreasonable to think that RNA could have been used for storing bulk information.

But what other options did nature have in those pre-biotic days?

Although the catalytic abilities of proteins are far more diverse than that of RNA, the major limitation is that proteins cannot direct synthesis of self-similar molecules. RNAs can perform this, since they can break and join phosphodiester bonds, provide a template for synthesis of identical molecules, and perform many other catalytic activities. But RNAs have their fair share of well-known problems too (apart from the ones already discussed). For example, the aromatic bases of RNA absorb strongly in the ultraviolet region, which makes them more susceptible to damage by background radiation [3]. Thus, while one can view RNAs as information storage systems, they are rather inefficient ones owing to their being more mutation prone and energy intensive (nature would need a consistent and ever-present machinery to perform repair and replacement of damaged RNAs).

So we have a conundrum. Although RNAs can have a case put forward for them, the possibility that they can perform the necessary functions critical to life all by themselves seems a bit remote. Why can we not think that some other tools, capable of performing at least some of these functions better, aided them? It is here, that one might find the reports from the aforementioned recent article [1] to be helpful.

Let us think of prion proteins (PrP): proteins that exist in several alternative but functionally distinct conformations, at least one of which is self-templating [4]. To start with, let us pick up the (apparently unconnected) pieces one by one. What do we have?

1. We know that intrinsically disordered or naturally unfolded proteins and protein domains are more common than rare exceptions [5]. They demonstrate that structural differences between isomers of the same protein sequence can vary dramatically; and furthermore, can be so global as to affect the entire structure of the protein (that is, one conformation being fully ordered, the other, absolutely disordered). The magnitude of this conformational diversity in proteins ranges from fluctuation of side chains, to the movement of loops and secondary structures, and even, to global tertiary structure rearrangements. Continuing further, it seems reasonable that a protein that adopts several different conformations could, in principle, exert several different functions [6].
2. Looking at the same set of facts discussed in the last paragraph from the perspective of evolution, we discover another facet. From an evolutionary point of view, intrinsically disordered proteins provide a powerful demonstration of the fact that a defined 3D structure is not a prerequisite for function [7]. Hence, as has been observed in a recent work [8], probably it will not be unfair to view critically the logic that folds have evolved before function. (What selective advantage can be achieved with a fold to which no particular function can be assigned?). Rather, it makes more sense, probably, to think of the scenario where, to achieve certain biological goals, categorical functions were planned; and subsequently, particular structural specifications (viz., the

- folds) have been laid down [9]. Or else, perhaps equally plausibly, one might think of co-evolution of functions with the folds [8].
3. Persisting with evolution, we note that prion replication has been shown to be subject to mutation and natural selection, just like other forms of replication [10]. This, perhaps, points to the existence of a definite strategy of nature to handle the “misfolded” ones. To concentrate on prions further, we notice that prion proteins are found throughout the bodies of healthy individuals and animals, implying perhaps that nature did not consider them to be some liability. Global conformational changes are more commonly found in prions than with any other biological macromolecule. In fact, prion proteins interconvert between all α -helix, PrP^c and all β -sheet, and PrP^{Sc} conformations [11, 12]. While PrP^c (‘C’ indicates commonly found cellular prion proteins) is structurally well-defined, PrP^{Sc} (Sc refers to ‘scrapie’, a prion disease occurring in sheep) is polydisperse and defined at a rather poor level. Would it be too illogical to associate such wide-scale conformational changes with protein promiscuity? The fact that nature evolves new functions by recruiting existing promiscuous activities and gradually improving them over time is not new. It has long been suggested [13] that, under changing circumstances, promiscuous activity in an existing protein (originally called “substrate ambiguity” [14]) might endow the organism with a selective advantage and thereby enable its survival and further evolution.

Added to these are some other findings. Although no particular nucleic acid could consistently be associated with preparations of PrP^{Sc} [14], reports of presence of small amounts of nucleic acids in infectious samples are not uncommon [15, 16]. Reports tell us (quite unambiguously) that PrP^{Sc}’s interaction with RNA is marked with high affinity to the former [17]. It does not end there; findings from another study suggest clearly that RNA may help to catalyze the conversion of PrP^c to PrP^{Sc} in vitro [18].

Based on the body of presented evidence, we can argue that the pre-biotic world was not merely RNA-world, but one of RNA and prion proteins. The ability of prions and other “misfolded” proteins to impart their “structure” and “function” to similar “normal” molecules, as has been reported in the aforementioned recent article [1], presents the template for a definitive scheme for proteins to pass information from one to another. It does not stretch our imagination much to make out that in absence of an efficient machine like the ribosome, a population of misfolded proteins will significantly increase. Such high population of misfolded and prion proteins, quite reasonably [1], could have accounted for the relay of vital structure and function information between ancient proteins. The inherently high level of conformational diversity of PrP^{Sc} was surely recognized by nature as extremely helpful for this purpose. A protein, possibly misfolded, but endowed with a particular catalytic function, could impart its functionalities to other proteins. One finds strong support to this assertion from two previous works [19, 20], where it was shown that inherent conformational diversity of prion proteins, along with their ability to self-sustain the autocatalytic propagation of possible alternative conformations, might form the basis of their cellular functioning.

Nature, as one can easily imagine, needed a consistent protocol to sample huge vistas of conformational space for macromolecules, before selecting a few that are most efficient to perform certain specific functions. The prion proteins connect foldable proteins with a single low-energy conformation and nonfoldable polypeptides that possess a practically unlimited number of 3D structures of comparable energies [20]. Hence, nature found PrP^{Sc} (with its conspicuous absence of well-defined structural features) and the other misfolded avatars, to be the most useful agents that can work alongside RNA and

efficiently take care of various aspects of catalysis. Furthermore, since RNA is known to help the conversion from PrP^c to PrP^{Sc} [18], it hardly seems difficult to detect the presence of a directional and well-defined blueprint for the aforementioned protocol. Reports of PrP^{Sc}'s high affinity for RNA [17] and the presence of nucleotides during the preparation of PrP^{Sc} [15, 16], only strengthens the plausibility of this scheme. In fact, the entire body of evidence can be elegantly described by considering a co-existence of RNA, prions and other misfolded proteins because it seems logical that RNAs were aided by some other devices, capable of performing efficient catalytic activities, which RNA molecules, alone, must have had difficulty to perform (owing to their narrow range of catalytic features). The prions and other “misfolded” proteins, precisely because of their peculiar structural features, may well be considered as the ideal choice for the aforementioned aids, in those pre-cellular days.

Acknowledgement One of the authors, Anirban, acknowledges the support from COE-DBT scheme (Government of India).

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