Summary: protein is an intelligent micelle

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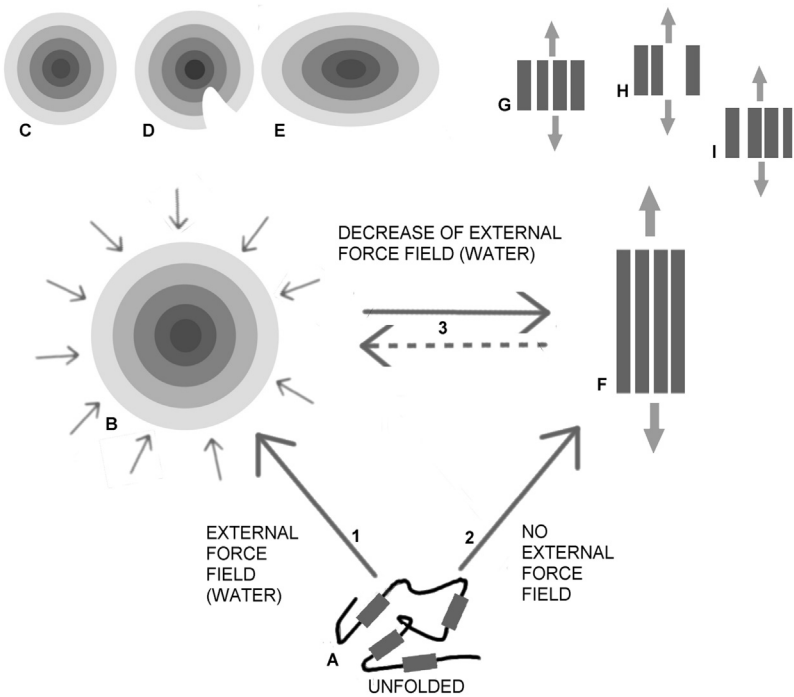

Folding or misfolding. A – unfolded form of polypeptide B – spherical micelle as the result of water environment influence (path 1), C,D,E – different forms of locally

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discordant spherical micelle, F — amyloid form with linear propagation of bands of different hydrophobicity level (low influence of water environment — path 2). Path 3 — possible transformation of globular form to amyloid form. Dashed line — path not observed however the search of reverse transformation highly expected for therapy.

Schematic depiction of alternative folding pathways, depending on the influence of the aqueous environment.

Path 1: transition between the unfolded structure (A) and an ordered form conditioned by the influence of water (micelle-like structure; B)

Path 2: weak influence of the external force field results in the folding process being dominated by the intrinsic properties of each residue, and — consequently — in linear propagation of bands characterized by variable hydrophobicity (F)

Path 3: amyloid transformation resulting from a decrease in the influence of the aqueous environment.

Path 3 (dashed line): hypothetical reverse transformation of an amyloid form into a globular form.

C, D, E — various local deformations in the structure of a micellar hydrophobic core.

G, H, I — various linear patterns depending on the sequence of the polypeptide.

This chapter discusses the potential for structural transformation represented by the dashed line (reverse path 3).

Summarizing all the collected results, we can state that the spontaneous process caused by the influence of the aqueous environment upon molecules characterized by variable hydrophobicity produces a concentration of hydrophobic residues at the center of the protein body, along with the corresponding exposure of hydrophilic residues on its surface (Chapters 1 and 2). Using antifreeze and fast-folding proteins as examples, we provide evidence of protein structures which resemble near-perfect spherical micelles. The role of a prominent hydrophobic core is particularly evident in the case of fast-folding proteins, which — when unfolded — are capable of near-instantaneous reversion to their native form. It appears that this process is driven mainly by hydrophobic interactions. The information content of such proteins may be regarded as low, given their highly ordered, symmetrical structure (Chapters 3 and 4.). Recreating such a structure following disruptions should be relatively easy — this determinism is therefore important for the proteins' functional properties (Chapter 5).

Our analysis of lysozymes, ribonuclease and other proteins shows that a hydrophilic sheath encapsulating a hydrophobic core is consistent with the theoretical distribution of hydrophobicity, and also with the structure of a spherical micelle. We may conclude that the sheath forms naturally, as a

result of interaction between the polypeptide chain and the aqueous environment. With regard to single-chain enzymes, we note that they also resemble spherical micelles — at least to a substantial degree. The discussed examples show that some polypeptide chain of certain amino acid sequence are not able to generate the spherical micelle. This disability coded in amino acids sequence appears to be responsible for specific discordance. This specific discordance appears to carry information determining the biological activity of discussed protein (Chapter 6).

In the case of local deviations from the theoretical distribution of hydrophobicity, these may manifest either as deficiencies — typically corresponding to binding cavities (e.g. in the case of enzymes, as discussed above) — or local excess, which is particularly noteworthy if it occurs on the surface. Both types of deviations encode information required to attract a bind a specific ligand (in the former case) or form a complex with another protein (in the latter case).

The discordance appears to be coded in amino acid sequence.

Influence of protein on water environment

Encoding of information is also required in order to send signals out to the environment. Variable properties of the protein surface — particularly relation between polar and non-polar areas - may affect the structure of the surrounding solvent, which differs (in subtle ways) depending on what type of surface it remains in contact with. This effect can be observed on the example of antifreeze proteins, which possess a wide range of signaling capabilities — from a near-perfect micelle all the way to complex structures which include solenoid fragments, representing ordered deviations from the Gaussian distribution of hydrophobicity. The essential purpose of antifreeze proteins is to dispatch signals to the environment in such a way as to prevent formation of ice crystals. If the solenoid is capable of sending signals, why wouldn't other structures be able to do the same? (Chapter 7). Advantage coming from fuzzy oil drop model is the possibility to measure all these effects in quantitative way.

The degree of complexity increases further when we consider proteins which contain multiple discordant fragments (local excess or local deficiencies). Many large proteins deviate from the monocentric distribution of hydrophobicity because they consist of multiple domains. In such cases, however, each domain, when analyzed on its own, is typically found to adhere to the theoretical model, i.e. it resembles a spherical micelle with a

prominent hydrophobic core. Assembling several domains produces a structure which — in its entirety — does not follow a Gaussian distribution of hydrophobicity. This effect is also a means of encoding information since the placement of each component domain is precisely determined (Chapter 8).

One interesting example is provided by lyase, whose complex structure appears to fulfill many conditions required for biological activity. In order to support its mechanism of action, the protein generates an internal force field. Which, when confronted with the surrounding environment, creates specific conditions facilitating the process of catalysis. The structure of this protein includes a fragment which guarantees solubility (parts of molecule accordant with assumed model), despite the presence of fragments which significantly deviate from the micelle-like conformation promoted by the surrounding water (Chapter 8). The discordance versus the idealized 3D Gauss distribution on the other hand influences the surrounded water directing the water molecules ordering in a specific form. This influence appears to be quite complicated and differentiated in lyases (Chapter 7). The force field present in protein molecule is not only influencing the water environment. It is delivering the specific force field for catalytic reaction. Solenoid with linear order of hydrophobicity distribution in lyeases is isolated from the water contact. Is seems to generate the specific local force field which probably is necessary for catalytic reaction.

Information — regardless of quantity — encoded in each protein causes fragments of the structure to deviate from the theoretical model while other fragments remain consistent with the Gaussian distribution (and therefore produce a micellar structure). It therefore seems more interesting to speculate about the structural properties of discordant fragments rather than of fragments which conform to the model. The question of how a protein chain reaches a conformation which includes discordant fragment may be addressed in two ways: either the specific sequence of amino acids directly encodes areas of discordance, or the discordance emerges as a result of information coming from an external source. In either case, we may conclude that no single, uniform and general method may be applied to all possible protein structures to produce specialized, targeted biological activity. One uniform procedure of optimization (energy minimization) seems not to be sufficient to generate the order accordant with energy minimization on one hand and local discordance on the other. The final structure seems to be the result of specific consensus between internal force field (interatomic interaction) with external force field (influence of environment) (Chapter 2).

The presented scale of structural complexity also includes molecular robots (Chapter 4). While no specific example is presented here, an analysis of the GroEl chaperonin [1] is a very big construction with highly complex structure may be found in Ref. [2]. The big amount of information necessary in such case comes from — multi-chain (21 chains) and multi-domain (14 chains — 3 domains each) construction. This "robot" is expected to act as folding chamber. The structure of GroEl — highly symmetrical in relaxed form — during performing its job looses its symmetry completely [1]. The symmetry is necessary to find the way to return to the initial relaxed form.

Some proteins — as shown in the Chapter 9 — require permanent presence of a complementary molecule which modulates the external force field. In the absence of this chaperone (which provides additional external information) the base structure reverts to an information-free state, i.e. to a ribbonlike micelle. Ribbon-like structures may, in principle, be generated for any sequence of amino acids in which strong fluctuations of hydrophobicity are confined to short fragments. Amyloid transformation may therefore be viewed as a process by which a structure which encodes information converts to an information-free form. Analysis of amyloid structures listed in PDB helps us establish specific criteria for identification of amyloids, as explained in Chapter 10.

Solenoids, where bands of high and low hydrophobicity propagate in a manner similar to amyloids, are found in biologically active proteins. In such proteins, solenoids are typically equipped with additional structural elements which counteract unchecked complexation and ensure solubility — these "stop" fragments may be analyzed in order to devise new methods of preventing formation of amyloid fibrils, as suggested in Chapter 11.

On the basis of the fuzzy oil drop model, we propose a set of criteria for identifying amyloid structures — these include the presence of a linear arrangement of alternating bands of high and low hydrophobicity, stretching along the axis of the fibril. In terms of fuzzy oil drop model parameters, amyloid structures are characterized by high values of RD (for both: T-O-R as well as for T-O-H) along with low (even negative) HvT and TvO correlation coefficients and high HvO correlation coefficients. Altogether, these values represent a specific type of discordance versus T, which may be regarded as systemic — instead of the tendency to generate a hydrophobic core, the polypeptide chain adopts an entirely different structural pattern.

If the above observations are correct, it becomes possible to identify fragments which may promote amyloid transformation in properly folded

proteins. In this publication, we focus on transthyretin, which is a known amyloid precursor. Of course, the structure of transthyretin supplied by PDB is not an amyloid — in order to become an amyloid, it must undergo conformational rearrangement, which is a speculative process — however, our point is that such rearrangement is not ruled out solely by the protein's structural properties (Chapter 12.).

In the authors' opinion the presented model meshes well with the observed properties of protein folding, as well as with pathological changes which lead to misfolded proteins. Further studies of amyloidosis should, first and foremost, acknowledge the structural properties of the surrounding medium (i.e. water), which determines the properties of the external force field and provides a ubiquitous background for processes occurring in living organisms.

Influence of water environment on amyloid transformation

The view expressed in this work is that amyloidogenesis, which — as it turns out — does not always require chemical changes in the protein, results from abnormalities in protein-water interactions. The aqueous solvent enables the protein to achieve the correct fold and therefore become biologically active. Thus, analyses of misfolding phenomena should focus on the structural properties of the solvent and the external force field generated by it.

Specific facets of the problem which, in our view, merit attention include:

1. Structural properties of pure water — lack of universal water force field definition
2. Structural effects caused by addition of 0.9% of NaCl
3. Causative link between increasing concentrations of NaCl and reversible denaturation of proteins
4. Phase boundary effects — structural properties of water surfaces and their interaction with ambient air — this is related to the widely used technique of producing amyloids by shaking (which increases the phase boundary surface area)
5. Effect of SDS on the structural properties of water (as opposed to its effect on proteins)
6. Effect of DMSO on the structural properties of water (as opposed to its effect on proteins)

7. Effects caused by exposure of hydrophobic surfaces — this research is ongoing, and the presented work cites some available results [3–6].

The notion of "structural properties" refers to specific arrangement of water molecules which gives rise to a continuous force field. It would be useful to investigate potential intermolecular communication channels which rely on enforcing a certain structural order (or disorder) in the aqueous medium. This has already been attempted in the so-called iceberg model [7–9], however, in the Authors' view, a more comprehensive approach is required.

If the presented model is based on correct assumptions, it can be applied to design structures capable of arresting unrestricted propagation of amyloid fibrils. By analyzing fragments which appear to perform this function in certain active proteins, we can propose artificial "caps" — amphipathic helices — capable of binding to the tip of the fibril (with the required specificity) and exposing a hydrophilic surface, thus preventing unchecked growth [10,11], (Chapter 11). The amphipatic character of stoppers is not limited to helical forms. Any structure which satisfy the compatibility to elongated fibril on one site and introducing hydrophilic part on the opposite site may play a role of stoppers.

Regarding theoretical research (computerized simulations), the authors are interested in simulating the folding process under variable external force fields which can be modeled as dynamic changes in the structure of the encapsulating 3D Gaussian. It seems that this process may produce conditions which favor the production of spherical and/or ribbonlike micelles devoid of biological information. The experiment would also enable us to quantify the role of the environment in ensuring that proteins attain their native forms. The presented research should be therefore considered prospective in character (Chapter 9).

The influence of chemical and physical factors widely discussed in Refs. [12,13]. The results of these experiment shall be consumed not only as factors influencing structural changes in protein. They should be consumed in form of water force field construction treated as continuous medium sensitive to environmental factors (pH, presence of ions, temperature etc).

Protein is an intelligent micelle

In summary one shall conclude, that controlled local discordance (in respect to spherical micelle hydrophobicity concentration in central part

of protein molecule) is aim-oriented. The degree of his discordance is highly differentiated. It encodes the specific biological activity of proteins. This local doscordance is carrying information determining the biological activity. It seems to be reached as the effect of the consensus between external force field (influence of environment) and internal force field (interatomic interaction).

Bi-polar molecules – as all amino acids – in water environment tend to minimize the disadvantageous entropic hydrophobic/hydrophilic effects. As long as idealized spherical micelle can be generated it appears as the native final structure. The determined neighborhood (peptide bonds) of differentiated hydrophobicity/hydrophilicity obligates to generate more or less ordered micellar forms.

In case when the idealized spherical micelle is impossible to be generated other form minimizing the unfavourable hydrophobicity-water contact the ribbon-like micelle is constructed.

The molecules which undergo the amyloid transformation appearing are acting in vivo in form of complex (called here permanent chaperones – Chapter 9). Deprivation of the permanent target with disability to generate the spherical micelle directs these proteins to generate the only possible structure minimizing the exposure of hydrophobic regions which is the ribbon-like micelle.

Despite the larger than usual size of the publication it is impossible to discuss other models of amyloidogenesis interpretation what has been the subject of many publications over the years. Readers can familiarize themselves with progress in this field by referring to comprehensive reviews such as Chiti and Dobson [14–16] and two books edited by Prusiner [17,18]. It is, however, difficult to compare the presented work with other published studies given that other authors do not acknowledge the effect of hydrophobic interactions upon amyloid transformation. The influence of water environment is widely discussed [3–6,19–39] as well as amyloids are the objects of many papers which may be recognized as complementary to the model presented in this work [40–64].

We hope that presented here discussion may introduce interpretation of amyloidogenesis from the point of view of environment influence on protein structure and misfolding in particular.

We hope also that the interpretation of proteins as intelligent (spherical) micelles and amyloids as ribbon-like micelles deprived of any form of information carried appears legimited.

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