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The neglected functions of intrinsically disordered proteins and the origin of life

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ABSTRACT

The example of gelatine shows that extended proteins behave quite differently than globular ones: with water they form a gel. Historically the colloid view of protoplasm was discredited in favour of membrane-(pump)-theory (MPT), but unjustified. In his association-induction hypothesis Ling demonstrates that MPT is full of contradictions and that the colloid view has to be re-considered. In that case IDP's play a crucial role in this. What Ling calls the 'living state' consists of the unitary protoplasmic structure from which it was experimentally demonstrated that it can survive and keep Na^+ and K^+ concentrations without a delineating membrane. It consists of unfolded polypeptide chains whereby the repetitive backbone peptide groups orient and polarise many layers of water, in which Na^+ and other solutes have reduced solubility and whereby the polypeptide β- and ϒ-carboxyl-groups adsorb K^+. This 'associated' state is the resting state: a coherent high-energy low-entropy meta-stable state. It can be kept by adsorbed ATP (NTP) eventually for years without consumption of ATP as demonstrated by Clegg on Artemia embryo's. Stimuli can transform this state into a lower-energy higher-entropy action state with dissociation of ADP and P_i and newly synthesised ATP can reinstall it. Rest-to-action and action-to-rest were shown to be real phase-shifts. Ling's theory is a complete quantitative theory with corroborated equations for solute distribution, transport, cell potentials and osmotic behaviour and describing the cell's energy cycle. IDP's are involved in all this. The new view on IDP's leads to new insights on the origin of life.

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Abbreviations: MPT, membrane-pump-theory; AIH, association-induction hypothesis; RRM, resonant recognition model; IDP, intrinsically disordered protein; IDPR, intrinsically disordered protein region; EMOC, effectively membrane-pump-less open-ended cell; HDW, high density water; LDW, low density water; QED, quantum electrodynamics.

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1. Introduction

First crystallographic studies of proteins were made on stable proteins, which could be easily isolated and purified in sufficient quantities, and this may have resulted in an effect of bias as to the 3D-structure of proteins insofar that all the one studied were of a rather compact nature. For several decades this trend went on. Although the existence of short regions with higher flexibility was known at that time, the idea that the living cell harbours a large number of proteins exhibiting very extended regions with an unfolded conformation had to wait until about the onset of the new millennium (Wright and Dyson, 1999; Dunker et al., 2001; Uversky, 2002). This type of proteins are now generally known as 'intrinsically disordered proteins' (IDP's). IDP's and intrinsically disordered protein regions (IDPR's) are defined as functional proteins or protein regions that do not have unique 3D structures under functional conditions. Despite not being folded their functionality is encoded in an often quite conserved and specific amino-acid sequence with low overall hydrophobicity and high net charge and exhibiting distinctive conformational behaviour. IDP's can participate in one-to-many and many-to-one interactions giving rise to complex combinatorial situations (Uversky, 2013a, 2013b, 2015). Functions of IDP's are tuned via alternative splicing and posttranslational modifications (Uversky et al., 2008; Niklas et al., 2015). When getting out of control these proteins are often implicated in the pathogenesis of several diseases including cancer (Uversky, 2013a; Yakoucheva et al., 2002), cardiovascular diseases, amyloidoses, neurodegenerative diseases and diabetes (Uversky et al., 2008).

2. Kinds of IDP's and agreed functions

In the presently accepted view unfolded parts of IDP's are thought to exert the following general functions.

1 In numerous complex proteins, which are particularly abundant in Eukaryotes, unfolded parts often link more globular regions. Interactions of these globular parts with one another and with other bio-molecules often necessitate large spatial flexibility, for which the conformational freedom of unfolded regions is very suitable. This flexibility allows many different conformational combinations for the binding of receptors, effectors and modifying enzymes. This is particularly useful in complex regulatory processes such as those associated with cell signalling, transcription control and chromatin remodelling (Yakoucheva et al., 2002; Collins et al., 2008; Sandhu, 2009). So called 'linkers' are usually rather long and are rich in polar uncharged amino-acids. Some have a role in the assembly of macromolecular arrays (Dyson and Wright, 2005).
2. 'Linear motifs' are usually short and sometimes they are not classified as IDP's properly, for which an artificial criterion of a minimal length of 30 consecutive amino-acids in the unfolded state has been agreed. But on a functional basis they belong to this group. They too possess unfolded stretches and they too regulate functional interactions with proteins, RNA, DNA and complex sugars, and are often involved in regulatory processes such as cell shape control, subcellular localisation of proteins and control of protein turnover.
3. Several IDP's possess unfolded regions able to transform into a helical conformation and vice versa. These '*dynamic helices*' are characterised by the absence of hydrophobic residues. Such transitions are initiated by the binding of ligands including nucleic acids. (Sandhu and Dash, 2007). These authors suggest that they act as '*molecular switches*' in the regulation of certain biological processes.
4. Some other IDP's are highly unfolded and remain so after ligand-binding, which in most cases is DNA (Fuxreiter et al., 2011; Fuxreiter, 2012). Specificity of DNA binding is to some extent correlated with the length of the fuzzy regions, which can be altered by alternative splicing.
5. Some IDP's assist as chaperones in the folding process of other proteins and are involved in quality control (Kovacs et al., 2013).

In general, changes in the primary structure of the unfolded parts of IDP's are often implicated in disturbance and decrease of cellular order, which may lead to a number of diseases associated with disorder as for instance cancer (Uversky et al., 2008). This is not so unexpected given the cellular functions listed above. In this context the presence of only a few percent of IDP's in the genotype of Archaea and Eubacteria, and the widespread presence in Eukaryote genotypes (Ward et al., 2004; Uversky and Dunker, 2010) appears to parallel the degree of regulatory control.

3. Ignored functions are due to a wrong understanding of cell physiology

IDP(R)'s may have additional important general functions, which for historical reasons are ignored today. All these ignored functions have to do with the physical state of water and K^+ in cytoplasm, both of which change when a cell or part of a cell changes from an inactive (resting) state into an active one or the reverse. The physico-chemistry of these changes are real phase transitions and unfolded protein (regions) are the actors. Insofar IDP(R)'s have decisive important functions in controlling both the local and the overall physico-chemistry of the cell in a deeply penetrating but yet ignored way.

The existence of some unstructured proteins or protein regions was noticed occasionally by separate authors over the last 75 years, but almost unanimous considered as an anomaly (Uversky, 2014). Almost complete ignorance also existed and still exists as to the proposal of Ling (1965) that quite large amounts of unfolded proteins should exist in living cells, if not the physico-chemistry of the