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Review

Intrinsically disordered proteins may escape unwanted interactions via functional misfolding

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ABSTRACT

Intrinsically disordered proteins are highly abundant in nature and play a number of crucial roles in the living cells. They are commonly involved in a wide range of intermolecular interactions, and some of them possess remarkable binding promiscuity, being able to interact specifically with structurally unrelated partners. Although they do not have well-folded structure, some IDPs are known to fold at binding to their specific partners. IDPs are highly pliable and one IDP can form an array of unrelated structures being bound to different partners. It is believed that many IDPs, being mostly disordered, have transient elements of the preformed secondary structure which are highly interaction prone and is used by IDPs for binding to specific partners. The overall disordered nature of IDPs, their high conformational dynamics and flexibility, the presence of sticky preformed binding elements, and their ability to morph into differently-shaped bound configurations raised a very important question about the mechanisms preventing IDPs from unwanted interactions with non-native partners. In this review, a concept of functional misfolding is introduced. Accumulated to date data on the conformational behavior and fine structure of several IDPs suggest that the preformed binding elements might be involved in a set of non-native intramolecular interactions. In other words, there is a chance that a polypeptide chain misfolds to sequester the preformed elements inside the non-interactive or less-interactive cage, therefore preventing these elements from the unnecessary and unwanted interactions with non-native binding partners.

1. Introduction

1.1. Intrinsically disordered proteins and their biological functions

It is becoming increasingly recognized that in addition to transmembrane, globular and fibrous proteins, the protein universe includes intrinsically disordered proteins (IDPs) and proteins with intrinsically disordered regions (IDRs). These IDPs and IDRs are biologically active and yet fail to form specific 3D structure, existing instead as collapsed or extended dynamically mobile conformational ensembles [1–7]. These floppy proteins and regions are known as pliable, rheomorphic [8], flexible [9], mobile [10], partially folded [11], natively denatured [12], natively unfolded [3,13], natively disordered [6], intrinsically unstructured [2,5], intrinsically denatured, [12] intrinsically unfolded [13], intrinsically disordered [4], vulnerable [14], chameleon [15], malleable [16], 4D [17], protein clouds [18], and dancing proteins [19], among several other terms. The variability of terms used to describe such proteins and regions is a simple reflection of their highly dynamic nature and the lack of the unique 3-D structure. Intrinsic disorder in proteins has multiple faces and manifests itself in various forms. IDPs/IDRs could be crudely grouped into two major structural classes, proteins with compact and extended disorder [3,7,20–22]. According to this classification, IDPs can be less or more compact and possess smaller or larger amount of flexible secondary/tertiary structure.

Since these proteins are highly abundant in any given proteome [4,7,23–25] the role of disorder in determining protein functionality can no longer be ignored. Native biologically active proteins were conceptualized as parts of the "protein trinity" [20] or the "protein quartet" [21] models where functional protein might exist in one of the several conformations—ordered, collapsed-disordered (molten globule-like), partially collapsed-disordered (pre-molten globule-like) or extended-disordered (coil-like), and protein function might be derived from any one of these states and/or from the transitions between them. Disordered proteins are typically involved in regulation, signaling and control pathways [26–28], which complement the functional repertoire of ordered proteins, which have evolved mainly to carry out efficient catalysis [29]. IDPs are known to be associated with various human diseases, such as cancer, cardiovascular disease, amyloidosis and neurodegenerative diseases [30].

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1.2. Binding mechanisms and binding promiscuity of IDPs

One of the unique functional features of intrinsically disordered proteins is their binding promiscuity; i.e., the ability of one protein to bind to multiple partners [28]. Such multitasking proteins are known as hub proteins since in protein–protein interaction (PPI) networks they have multiple links. With respect to temporal structure of the PPI networks, some proteins have multiple simultaneous interactions ("party hubs"), while others have multiple sequential interactions ("date hubs") [31]. From a functional perspective, date hubs may connect biological modules to each other [32] whereas party hubs may form scaffolds that enable the assembly of functional modules [31].

Many different IDPs can form highly stable complexes, or be involved in signaling interactions where they undergo constant "bound–unbound" transitions, thus acting as dynamic and sensitive "on–off" switches. The ability of these proteins to return to their highly dynamic and pliable conformations after the completion of a particular function, and their predisposition to gain different conformations depending on the peculiarities of their environment, are unique properties of IDPs which allow them to exert different functions in different cellular contexts according to a specific conformational state [7].

It has been pointed out that the ability to bind to multiple partners involves a mechanism for PPI not contained within the classical molecular recognition mechanisms [33]. In fact, neither the lock-and-key [34] nor the original induced-fit [35] mechanism can readily explain how one protein can bind to multiple partners. On the other hand, several previous studies, both theoretical and experimental, suggested that IDPs are plastic and can adopt different structures upon binding to different partners [1,15,36–40], thereby playing a number of crucial roles in mediating PPIs [1,15,27,36–54]. Based on these observations it has been suggested that molecular recognition via disorder-to-order transitions upon binding would be a reasonable mechanism for binding by hub proteins [27]. Therefore, intrinsic disorder could enable one protein to bind with multiple partners (one-to-many signaling) or to enable multiple partners to bind to one protein (many-to-one signaling) [1]. Several recent bioinformatics publications supported the importance of protein disorder for hubs [41–45]. Disorder appears to be more clearly associated with date hubs [43,45] than with party hubs. However, since some protein complexes clearly use long IDRs as a scaffold for assembling an interacting group of proteins [46–54], the potential importance of disorder for party hubs needs to be examined further. Additional evidence for the importance of disorder for highly connected hub proteins comes from a structure-based study of the yeast protein interaction network [55].

The recognition function of IDPs can be realized via several molecular mechanisms, being frequently associated with the disorder-to-order transition induced by binding to their partners. The binding-coupled folding of IDPs/IRDs may be induced by the template or be selected from the ensemble of conformations. In other words, the IDP structure adopted in the bound form may be enforced by the partner molecule or reflect the inherent conformational preferences of IDPs. One of the models for finding intrinsic disorder-based binders, Molecular Recognition Feature (MoRF) model, involves a short binding region located within a longer disordered region [56–58]. MoRFs were proposed from the study of existing protein complex structures, and application of the MoRF model to proteomes suggests that MoRFs may be a common mediator of PPIs [56–58]. Alternative models of MoRF-like interactions are the Short Linear Motif (SLiM) or Eukaryotic Linear Motif (ELM) based on sequence motifs that are recognized by peptide recognition domains [59]. A different approach is taken by the ANCHOR model, which identifies segments of disordered regions that are likely to fold in conjunction with a globular binding partner [60,61]. In the primary contact site (PCS) model, certain regions within the disordered ensemble are more exposed than others, and thereby may serve as the first sites of contact with the partner [62]. Some IDPs in the unbound state were proposed to have strong conformational preferences for their bound conformations; i.e., they use partially/transiently pre-formed elements for recognition [63].

Very often, IDPs lack the hydrophobic cores typical for ordered proteins and cannot be described as single, rigid structures clearly resembling instead highly dynamic hairballs or diffuse protein clouds. However, even these apparently unordered clouds might have some local preferences for transient secondary structure elements and even for some transient tertiary contacts. Such dynamic pre-organization imposes spatial restrictions on IDPs, therefore exposing some of their potential contact sites. The existence of such pre-formed binding sites enables faster and more effective interactions of IDPs with their targets [7,56,63,64].

2. Functional misfolding

Therefore, IDPs/IDRs are sticky and are readily prepared for interactions. In fact, since they do not have rigid structure, being highly dynamic, pliable, and adjustable, some IDRs clearly possess a chameleon behavior, where a single region of disorder adopts different secondary structures and uses the same amino acids to different extents being bound to different partners [65]. The important question then arose, namely, what is the mechanism of protection of highly promiscuous and potentially sticky IDPs from unwanted interactions. The reasonable hypothesis is that such protection can be done via the functional misfolding (e.g., via the formation of non-native intramolecular interactions). Before talking about the functional misfolding of IDPs, let us briefly consider what is known about non-native interactions in ordered proteins.

2.1. Non-native interactions in globular proteins

In ordered proteins, the roles of non-native interactions are rather well understood. Intramolecular non-native interactions are known to perturb the unfolded state ensemble and affect the equilibrium stability of an ordered protein [66,67]. They also might lead to the accumulation of the on-pathway or off-pathway intermediate states [68–70], perturb the protein folding kinetics and modulate folding landscape by affecting the transition state structure and stability [71–75], and, being a major driving force determining the rapid collapse of an unfolded polypeptide chain during the early stages of the protein folding process, serve as factor preventing proteins from aggregation [76]. Furthermore, for ordered proteins with complex topologies, such as knotted proteins, it was proposed that non-native interactions may be of importance for the correct formation of the knots [77].

Intermolecular non-native interactions were shown to be crucial in binding process of ordered proteins. In fact, they are necessary for the initial formation of the non-specific encounter complexes, where long-range electrostatic interactions increase the diffusion process by the "steering effect", and then short-range hydrophobic interactions facilitate the formation of the final specific complexes by a two-dimensional search on the surface [78–81]. Non-native intermolecular interactions are an obvious cause of protein aggregation and amyloid fibril formation in various human protein deposition diseases [82–87].

2.2. Misbinding: Intermolecular non-native interactions in IDPs

It was proposed recently that the abundance and effects of non-native interactions may be more prominent in IDPs/IDRs [88]. In fact, because of the significant chain flexibility, IDPs are expected to possess more intra- and intermolecular non-native interactions in the folding and binding processes than conventional ordered proteins. The effect of the intermolecular non-native interactions on the binding mechanism of an IDP was recently modeled by introducing the non-native hydrophobic interactions into the Gō-like model of the KIX-pKID complex [88]. This analysis revealed that the non-native