FEBS Letters xxx (2015) xxx–xxx

journal homepage: www.FEBSLetters.org

Review

The multifaceted roles of intrinsic disorder in protein complexes

Vladimir N. Uversky *

Department of Molecular Medicine and USF Health Byrd Alzheimer's Research Institute, Morsani College of Medicine, University of South Florida, Tampa, FL, USA
Institute for Biological Instrumentation, Russian Academy of Sciences, Pushchino, Moscow Region, Russian Federation
Department of Biology, Faculty of Science, King Abdulaziz University, P.O. Box 80203, Jeddah 21589, Saudi Arabia

ARTICLE INFO

Article history:
Received 4 May 2015
Accepted 2 June 2015
Available online xxxx

Edited by Wilhelm Just

Keywords:
Intrinsically disordered protein
Intrinsically disordered protein region
Protein–protein interaction
Protein complex
Scaffold
Regulation
Polyvalent interaction

ABSTRACT

Intrinsically disordered proteins (IDPs) and intrinsically disordered protein regions (IDPRs) are important constituents of many protein complexes, playing various structural, functional, and regulatory roles. In such disorder-based protein complexes, functional disorder is used both internally (for assembly, movement, and functional regulation of the different parts of a given complex) and externally (for interactions of a complex with its external regulators). In complex assembly, IDPs/IDPRs serve as the molecular glue that cements complexes or as highly flexible scaffolds. Disorder defines the order of complex assembly and the ability of a protein to be involved in polyvalent interactions. It is at the heart of various binding mechanisms and interaction modes ascribed to IDPs. Disorder in protein complexes is related to multifarious applications of induced folding and induced functional unfolding, or defines the entropic chain activities, such as stochastic machines and binding rheostats. This review opens a FEBS Letters Special Issue on Dynamics, Flexibility, and Intrinsic Disorder in protein assemblies and represents a brief overview of intricate roles played by IDPs and IDPRs in various aspects of protein complexes.

1. Introduction

Recent years clearly showed that the universe of functional proteins includes ordered, partially ordered, and completely disordered species. The structure-less intrinsically disordered proteins (IDPs) and intrinsically disordered protein regions (IDPRs) are commonly found in various proteomes [1–6], where they functionally complement ordered proteins and domains, typically playing important roles in cell signaling, as well as regulating and controlling various crucial biological processes [7–19]. IDPs/IDPRs are very promiscuous binders that are constantly involved in various interactions with diverse partners [20,21] and are known to play key roles in protein–protein interaction networks [13,22–26]. Since IDPs/IDPRs are structurally heterogeneous [7,27,28], their functions may arise from a specific disordered form, from inter-conversion between disordered forms, and from transitions between disordered to ordered or ordered to disordered states [16,17,29–31]. Furthermore, a template-dependent folding of some IDPs defines their ability to bind to multiple partners, gaining very different structures in the bound state [12,32], and thereby being able to possess unrelated, even opposite functions [33]. The multifaceted disorder defines the multifaceted functionality of IDPs and IDPRs, which can act as *entropic chains* (linkers, clocks, bristles), *display sites* (target sites for post-translational modifications), *effectors* (modulators of the functionality of partners), or *scavengers* (capturers and storages of small ligands) [33]. Furthermore, large multiprotein complexes also take advantage of intrinsic disorder, where IDPs/IDPRs often serve as *assemblers* by assisting assembly [33].

Intrinsic disorder plays a number of important roles in organization, maintenance, and control of protein complexes, ranging from transient signaling complexes to stable oligomers. In relation to protein complexes, there are two different types of functional disorder: *internal*, which is disorder used for assembly, movement, and functional regulation of the different parts a given complex, and *external*, whose major role is in defining the interaction of this complex with external regulators. Irrespective of this internal/external classification, intrinsic disorder has three global functional implications in protein complexes, playing various structural, functional, and regulatory roles. This idea is illustrated by Fig. 1 that represents an oversimplified scheme of the involvement of intrinsic disorder in assembly, function, and regulation of protein complexes (Fig. 1A), while Fig. 1B shows this involvement in more detail. Some of the features shown in this figure are discussed in sections below.

* Address: Department of Molecular Medicine, University of South Florida, 12901 Bruce B. Downs Blvd. MDC07, Tampa, FL 33612, USA.
E-mail address: vuversky@health.usf.edu

http://dx.doi.org/10.1016/j.febslet.2015.06.004
0014-5793/

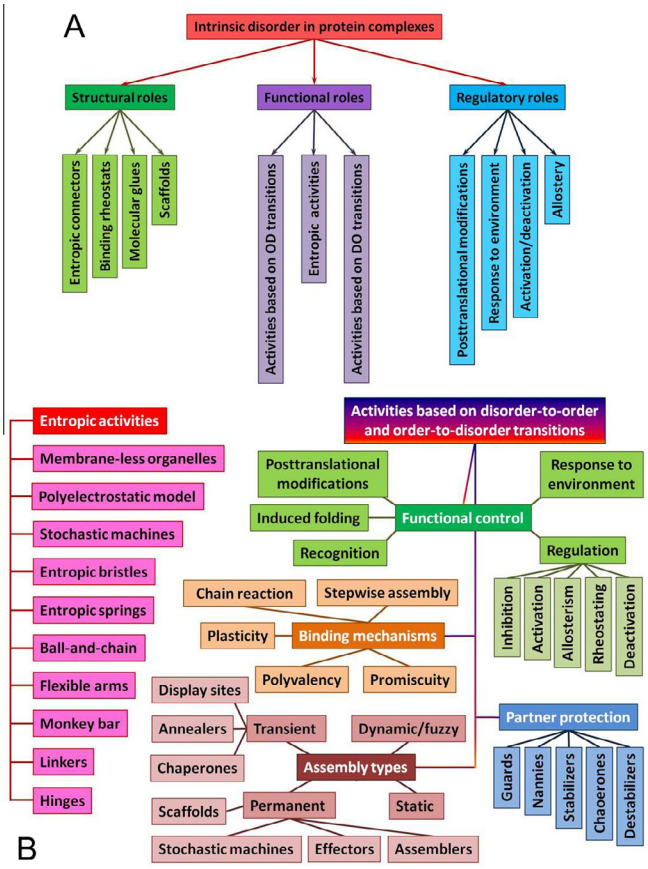

Fig. 1. Various functional structural and regulatory roles of intrinsic disorder in protein complexes. (A) General overview. (B) Illustration of basic entropic activities and roles based on disorder-to-order and order-to-disorder transitions.

2. Roles of intrinsic disorder in assembly of protein complexes

2.1. Binding-induced folding of IDPs/IDPRs as molecular glue cementing protein complexes

It is well-known that protein complexes can be formed following two-state or three-state mechanisms [34–36]. The two-state mode of the protein complex formation is related to the scenario where the protomers are disordered in their unbound forms and fold at the complex formation (see Fig. 2A, right side). In other words, protomers of the protein complexes that are formed *via* a two-state mechanism are intrinsically disordered in their uncomplexed form and clearly undergo the binding-induced folding at the complex formation [37]. On the contrary, in the three-state mechanism, the complex is formed from the independently folded individual chains (see Fig. 2A, left side) [34,35]. Obviously, many complexes cannot be formed by these two mechanisms alone, and in reality some mutual adjustment and co-folding are required for almost any complex formation.

Comparative structural analysis of protein complexes formed via the two-state and three-state mechanisms revealed that their monomers possess very distinctive features, with the per-residue interface and surface areas of protomers that form the three-state oligomers being significantly smaller than those of the protomers that form the two-state complexes [36]. As a result, in the per-residue surface area *versus* the per-residue interface area plot, the two-state and three-state complexes occupy very different areas. Here, the IDPs forming the two-state complexes occupy a broad area in the top-right part of the plot where the protomers with extended shapes and large interface areas are located, whereas the ordered proteins that from complexes in a three-state mechanism are found within the bottom-right corner corresponding to the more globular and compact protomers [36]. These two types of protomers are separated by a boundary line defined by the fact that the maxima of per-residue surface and interface areas for stable monomers lie around 80 Å^2 [36]. Therefore, the per-residue surface area *versus* the per-residue interface area plot can be used for differentiation of two-state and three-state protein complexes with known 3-D structure (see Fig. 2B). The idea of large surface areas serving as identifiers of IDPs that fold at complex formation is further illustrated by Fig. 2C that represents the results of the computational "disassembly" of a eukaryotic ribosome [38]. It is clear that almost all of the individual ribosomal proteins do not have a simple globular structure (i.e., structure that defines the smallest accessible area), but they do possess very unusual shapes [38]. These peculiar mostly non-globular shapes indicate that many ribosomal proteins are involved in the formation of the two-state complexes. Very similar behavior was also emphasized for the nucleosome-forming core histones [39]. It is clear that the ability of IDPs/IDPRs to be involved in the binding-induced formation of the sophisticated highly intertwined structures, where different parts of a given IDP penetrate to binding pockets of different protomers, can be considered as a molecular glue or cement that becomes rigid once the complex forms and thereby serves as a crucial means for stable complex formation.

2.2. Disorder and binding chain reactions

IDP-based complex formation frequently involves at least partial folding of IDPR(s) into specific structures [16,17,29–31,37,40–45], and the disorder-based interactions are characterized by adaptability, promiscuity, and ability of a given IDPR to fold differently upon binding to different targets [12,32]. Also, the ability of an IDP to partially fold at interaction with its binding partner(s) opens a possibility of the "binding chain reaction" mechanism based on the sequential generation of novel binding sites by partial folding of new disordered partners engaged in the consecutive interaction with the existing complex [37]. This model is illustrated by Fig. 3 which shows how interaction between proteins A and B induces structural changes in B or/and A, leading to the creation of new binding site(s) necessary for the additional interactions between A and B that leads to the strengthening of the AB complex. Alternatively, an activated AB* complex is created, where a novel binding site is formed for interaction with a new partner C. At the next stage, some mutual rearrangements take place in the newly formed ABC complex, leading to the creation of new binding sites in the activated ABC* complex that is now ready to interact with a new partner D. Obviously, the stepwise recognition and binding defines the timing and specific order of the assembly of some complexes, e.g., where C cannot interact with A until the AB complex is formed (see Fig. 3) [37]. This model can describe the stepwise directional assembly mechanism of large proteinaceous complexes, such as the Bardet–Biedl syndrome (BBS) protein complex BBSome containing seven BBS proteins (BBS1, BBS2, BBS4, BBS5, BBS7, BBS8, and BBS9) [46], the intraflagellar transport complex [47], the mammalian 20S proteasome [48], and the 60S ribosomal subunit [49]. For example, careful mutational analysis revealed that the BBSome is formed sequentially and directionally, where the BBS7 interacts first with BBS2 and BBS9 to form the BBSome core that serves as an assembly intermediate, to which BBS1, BBS5, BBS8, and finally BBS4 are sequentially added [46].

In line with the stepwise directional assembly model are the observations on the disassembly of protein complexes that always occurs sequentially, in such a way that the least amount of buried

Please cite this article in press as: Uversky, V.N. The multifaceted roles of intrinsic disorder in protein complexes. FEBS Lett. (2015), http://dx.doi.org/10.1016/j.febslet.2015.06.004