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Mechanistic roles of protein disorder within transcription

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Understanding the interactions of proteins involved in transcriptional regulation is critical to describing biological systems because they control the expression profile of the cell. Yet sadly they belong to a less well biophysically characterized subset of proteins; they frequently contain long disordered regions that are highly dynamic. A key question therefore is, why? What functional roles does protein disorder play in transcriptional regulation? Experimental data exemplifying these roles are starting to emerge, with common themes being enabling complexity within networks and quick responses. Most recently a role for disorder in mediating phase transitions of membrane-less organelles has been proposed.

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Introduction

A third of eukaryotic proteins contain long disordered regions, that is, they do not have a well-defined tertiary structure, but can have varying degrees of fluctuating secondary structure and tertiary contacts. This prevalence of protein disorder, and the observation from bioinformatics studies that it can be evolutionarily conserved, have led to the suggestion that it plays important biological (functional) roles. But what are these roles? Early bioinformatic studies provided clues through cataloging proteins that are predicted to be intrinsically disordered (IDPs) or contain long intrinsically disordered regions (IDRs) [1]. It elapsed that IDPs and IDRs are over-represented in signaling processes such as transcription [1]. In fact, over half of eukaryotic transcription factors are predicted to be mostly disordered, as a result of their depletion in 'order-promoting' residues (such as bulky hydrophobic amino acids) and enrichment in 'disorder-promoting' residues (such as polar and charged residues, glycine and proline) [2]. Protein disorder is not restricted to long 'linker' regions, but often includes identified interacting domains. Activation domains, which act to recruit the transcriptional machinery, are particularly disordered [2]. And whilst most DNA binding domains are ordered, many others are disordered. For example the second largest category of transcription factors (and the largest that operates solely within eukaryotes) is the bZIP family, whose basic disordered DNA binding domains fold into helices only upon DNA binding [3,4]. AT-hooks, which bind in the minor groove of AT-rich sequences, are also predicted to be nearly totally disordered [2]. Furthermore the regions directly flanking structured DNA binding domains exhibit significant disorder [5].

IDRs are extremely dynamic, adopting a myriad of highly heterogenous conformations that rapidly interconvert over a range of timescales [6,7]. They may have varying levels of fluctuating secondary structure, and even tertiary contacts. In some cases transient helical content can be quite high, for example, ~70% in a segment of cMyb transactivation domain [8]. In others IDRs are fairly well described by random coil models, or as more 'structured' molten globules, for example, the NCBD domain of the transcription co-activator CBP [9]. Describing the structural heterogeneity of IDPs is challenging but over the last few years methods for combining multiple experimental measurement types, to generate representative ensembles have emerged [10]. A database of structural ensembles, pE-DB (http://pedb.vib.be/), is accessible online and currently holds 24 entries, none of which are transcription factors or coactivators [11].

IDRs frequently make specific interactions with macromolecular binding partners, that is, other proteins, or nucleic acids. These reactions can be associated with folding of the disordered region, which is known as coupled folding and binding [12,13,14•]. The structures of thousands of such complexes are already deposited in the PDB including many disordered transactivation domains of transcription factors folded into simple topologies. However in other cases the disordered region remains disordered upon binding, forming what is termed a 'fuzzy' complex. Reviewed recently [15•], some examples of this behavior may be found catalogued within the new database FuzDB [16] (http://protdyn-database.org/).

In reality all of these bound proteins are probably best viewed as lying at some point along a spectrum of disorder, just as is the case for the unbound state (Figure 1).

Clearly regions that are disordered in the free and/or bound states of transcription factors play important biological roles. Removing these regions is expected to, and has been shown in many cases to, alter key parameters such as binding affinity and 'switch-like' properties. This is slightly distinct to uncovering a functional role of the biophysical property of protein disorder itself. It is the current evidence for some of these potential biological advantages of disorder within transcription factors that are reviewed here. Many of the principles discussed can apply equally to proteins with other cellular roles, especially for those involved in signalling. Finally, it is worth noting that although we concentrate here on the potential mechanistic roles of disorder, disorder may also present genetic advantages through improved possibilities for alternative splicing and enhanced evolutionary rates.

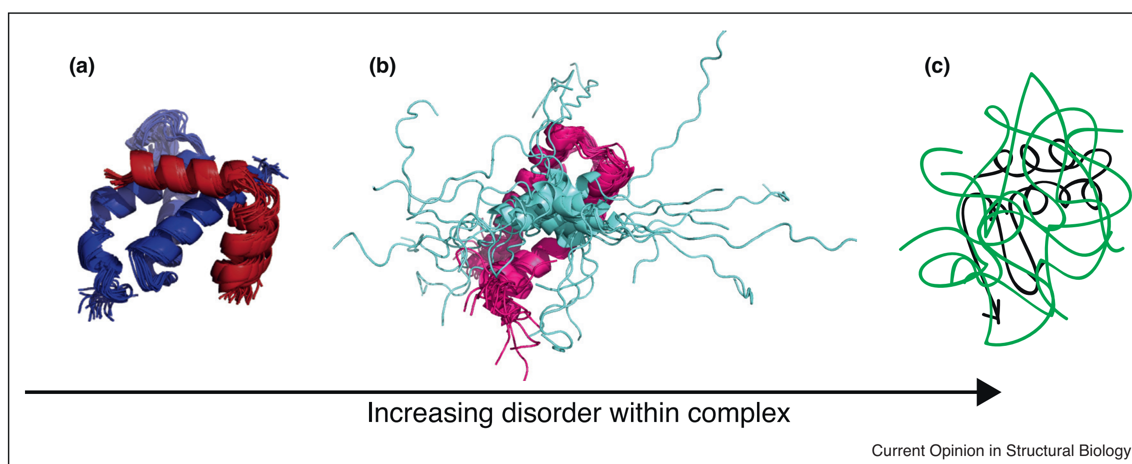
Fast binding

Transcriptional processes must respond quickly to potential changes in conditions, despite potentially low concentrations of the proteins involved. Consequently, one might assume that reactions will be characterized by high association rate constants. The limited kinetic evidence assembled so far indicates this may be the case. Examples of fast binding reactions are found with peptides of the disordered transcription factors that bind to the structured KIX domain of the co-activator CBP [17•]. Indeed, if electrostatic enhancements are neglected, cMyb.KIX is the fastest reported reaction for formation of a structured complex [18]. Kinetic experiments using more ordered versions of cMyb have revealed similar binding rates, suggesting that the process follows an induced fit mechanism [17•,19]. In pure induced fit mechanisms all proteins within the structural ensemble are able to bind to the partner protein, and subsequently fold (Figure 2). Similar behavior was observed this year in simulations of cMyb-KIX binding [20]. This contrasts with a pure conformational selection mechanism where only pre-folded proteins within the ensemble are binding-competent (Figure 2), and binding rates are decreased accordingly [12]. Since both induced fit mechanisms and fuzzy complexes remove this obstacle these may later elapse to be favored within transcription. Both mechanisms actually have the potential to modestly increase association rates over that of folded proteins by increasing the capture radius of the disordered protein and/or increasing the reactive surface of the target [21,22,23••]. Whether this represents a functional advantage for disorder is less clear since pronounced enhancements in rates could anyway be achieved by altering charge interactions. So far there is currently little evidence that disordered proteins in general are characterized by different binding rates to those of folded proteins [18,24].

Weak binding

For proteins which undergo coupled folding and binding, binding affinities will be lowered by the disordered nature of the binder due to the energetic cost of folding it. On

Figure 1



Disordered regions may exhibit a range of structural heterogeneity and transient structures, both in their free-state and when bound to partner macromolecules. Even canonical examples of coupled folding and binding reaction, such as **(a)** pKID domain of CREB (red) forming a simple helix upon binding to CBP-KIX (blue), have an aspect of "fuzziness" since the folded region in the complex remains flanked by disordered sequence. PDB code 1KDX. **(b)** the central activation domain of GCN4 (cyan) has been observed to form additional α-helical structure upon binding the Mediator subunit Gal11 (pink), but not to bind in a defined orientation [59]. Structural ensemble was generated by combining NOE and spin-labelling data. PDB code 2LPB. **(c)** cartoon picture of a domain (green) that remains highly disordered whilst interacting with its partner (black) e.g. glutamine-rich domains of transcriptional activator Sp1 and TAF4 (component of TFIID) [60].

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