

## a question of perspective

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Paradigms are meant to be broken. In the 1980s, biology students were taught “the one gene = one protein” dogma which has since stepped down from its pedestal, as we now know that one gene, by way of any number of post-translational modifications on the protein sequence, can actually give rise to more than one protein. Or what would be more correct: to more than one function. In the same way, structural biologists are beginning to realise that proteins are not always stable but that a significant amount exist in particularly unstable forms – which has given them the name “disordered proteins”. Until recently, proteins were thought to fold up into thermodynamically stable forms before getting on with what they had to do. Now we know that it is not necessarily the case. Eukaryotic translation initiation factor 4E-binding protein 2, for instance, is one such disordered protein whose lack of stability gives rise to a new kind of biological regulation.



by Jodee Knowles

Courtesy of the artist

Strangely enough, until the early 1950s, scientists believed that proteins were particularly malleable entities. Then along came the pioneering work on the necessity for two fragments of a ribonuclease to bind tightly for it to be effective, and scientists began to produce the first crystal structures of proteins. Ever since, a stable 3D conformation was considered to be the ideal state for a protein to function. However, in 1986 already, a handful of scientists were beginning to realise that perhaps a few proteins carried out their existence a little differently, and were somewhat unsure as to the stable conformation they wished to adopt. So didn't really adopt any at all.

But it took a further 20 years for such a notion to become popular. This is because of the angle from which structural biologists have been observing proteins. It is not an easy task to predict the kinetics and thermodynamics underlying the conformational states of a protein – not to mention those driving its catalytic reactions and binding properties. So, as is the case in scientific research, biologists set a basis from which they can make powerful correlations. In this case, low energy states and a limited number of combinations of macromolecules which provided links between the 3D conformation of proteins and their functions. However, it is becoming increasingly apparent that proteins carry out their business at higher energy states. Which is beginning to push the initial dogma over the cliff.

This just goes to show how paradigms – though necessary – can impede scientific progress by keeping the understanding of some phenomena within certain limits until other parameters, which researchers cannot ignore anymore, emerge and the paradigm is interrupted and takes a jump forward. The low energy paradigm gave huge insight – and over a long period – into the biological function of proteins, but it slowed the understanding, or acceptance, of highly dynamic states.

Proteins that lead a life in highly dynamic states are what has been coined “intrinsically disordered”, because they do not adopt one sole three-dimensional conformation and stick to it, but rather

they embrace a series of different conformations – although, from a purely thermodynamic point of view, they remain stable. Contrary to expectations, disordered proteins are not a rare event; current predictions estimate that 15% of the proteome is, quote, fully disordered! How do we know, you may ask? Thanks to the field of computational biology and algorithms that are able to predict disorder...

It is hardly surprising that disordered proteins represent a significant challenge to structural biologists. To complicate matters further they are not to be considered only at the level of monomers... Disordered proteins lack perhaps a stable tertiary structure but they are able to carry out numerous biological functions, especially those associated with signalling, transcription regulation, cell division and differentiation. And, as for the more popular stable proteins, post-translational modifications (PTMs) of disordered proteins are a source of additional functions. As an example, disordered protein Eukaryotic translation initiation factor 4E-binding protein 2 (EIF4EBP2) is involved in the suppression of cap-dependent translation initiation, which is brought about by multiple phosphorylation of EIF4EBP2.

EIF4EBP2 is the major neural isoform of a family of proteins that bind to a translation initiation factor eIF4E – so long as another initiation factor known as eIF4G hasn't got there first! Binding or not binding to eIF4E all has to do with the conformation of EIF4EBP2 which depends on its phosphorylation; phosphorylation can occur at multiple sites. When EIF4EBP2 is highly phosphorylated, it is unable to interact with eIF4E, thus leaving the way open for eIF4G. When EIF4EBP2 is weakly phosphorylated or not at all, it

binds to eIF4E very tightly and translation initiation is suppressed.

This is the first time researchers have discovered that translation initiation can actually be regulated via the structural polymorphism of a protein, itself mediated by phosphorylation – a novel mode of biological modulation led by intrinsically disordered proteins. Disorder to order (and vice versa) involves large conformational changes in a protein – as opposed to those which occur when the more “common” ligands bind to their target proteins for instance. EIF4EBP2 is the first protein to have been discovered which undergoes multiple phosphorylation bringing about an important conformational change.

Disordered proteins are shedding light on an entire new domain of biology and concomitantly shattering a long-standing dogma. They are able to carry out multiple functions by way of conformational plasticity, which itself depends on the proteins' state of phosphorylation. What is more, given regions within a disordered protein are – depending on their conformation – able to interact with different target proteins, thus lending the protein multispecificity. Biologists are also beginning to realise that disordered proteins are probably at the heart of evolution since they offer rapid regulatory complexity. This could explain the preponderance of disordered proteins in signalling networks within higher eukaryotes, and scientists expect them to be involved in various pathologies, especially those characterized by loss of biological reaction such as cancer. There is still much to learn about disordered protein PTM-induced folding but there is little doubt that these novel findings will have an important therapeutic impact.

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## Cross-references to UniProt

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