Do Moonlighting Proteins Belong to the Intrinsically Disordered Protein Class?

Sergio Hernández1, Isaac Amela1, Juan Cedano2, Jaume Piñol1, JosepAntoni Perez-Pons1, Angel Mozo-Villarias3 and Enrique Querol4*

1Institute of Biotechnology and Biomedicine, Department of Biochemistry and Molecular Biology, Universitat Autònoma de Barcelona, 08193 Bellaterra, Barcelona, Spain
2Immunology Laboratory, University of North Regional Republic Salto, Rivera 1350, CP 50000 Salto, Uruguay
3Biomedical Research Institute and Department of Experimental Medicine, University of Lleida, 25198 Lleida, Spain

Abstract

Moonlighting is the capability of some proteins to execute two or more biological functions. According to some authors, there is a relationship between protein conformational fluctuations and promiscuous functions of proteins. This promiscuity would be due to the conformational properties of the structurally disordered regions. To check if moonlighting proteins belong to the Intrinsically Disordered Protein (IDP) class, we have predicted IDP/IDR (Intrinsically Disordered Regions) for a number of moonlighting proteins. Our results suggest that most moonlighting proteins do not belong to the IDP class.

Keywords: Moonlighting proteins; Multitasking proteins; Intrinsically disordered proteins; Intrinsically disordered regions

Moonlighting proteins refer to those proteins presenting two or more functions performed by a single polypeptide chain. They were initially reported by Wistow and Piatigorsky in the late 1980s when lens crystallins turned out to be previously known metabolic enzymes [1,2]. Moonlighting proteins present alternative functions which are mostly related to cellular localization, cell type, oligomeric state, cellular concentration of ligands, substrates, cofactors, products or post-translational modifications [3-11]. In many cases, a protein uses a combination of these mechanisms to switch between functions. Although some findings suggest involvement of a protein in extra functions, i.e., they can be found in different cellular locations or in amounts exceeding those required for their canonical function. Usually, moonlighting proteins are experimentally revealed by serendipity. Therefore, any alternative method to identify these proteins would be very valuable. In previous works, we have explored the possibility of identifying moonlighting proteins by bioinformatics [12] and protein interactomics-database mining [13].

Some authors have pointed out that there is a relationship between protein conformational fluctuations and promiscuous functions of proteins. This promiscuity would be possible due to the conformational properties of the structurally disordered regions. In solution, proteins exist in a range of conformations, and structurally disordered regions can alter their secondary-structure propensities as well as their conformational flexibility in response to different environments or to interacting partners [14-19].

To check if moonlighting proteins belong to the Intrinsically Disordered Protein (IDP) class, we have predicted IDP from their amino acid sequences for a number of well-known moonlighting proteins. This promiscuity would be due to the conformational properties of the structurally disordered regions. To check if moonlighting proteins belong to the Intrinsically Disordered Protein (IDP) class, we have predicted IDP/IDR (Intrinsically Disordered Regions) for a number of moonlighting proteins. Our results suggest that most moonlighting proteins do not belong to the IDP class.

*Corresponding author: Dr. Enrique Querol, Institute of Biotechnology and Biomedicine, Department of Biochemistry and Molecular Biology, Universitat Autònoma de Barcelona, 08193 Bellaterra, Barcelona, Spain, Tel: 34-93-5811429; Fax: 34-93-5812011; E-mail: enric.querol@uab.cat

Received October 05, 2012; Accepted November 08, 2012; Published November 15, 2012

Citation: Hernández S, Amela I, Cedano J, Piñol J, Perez-Pons JA, et al. (2012) Do Moonlighting Proteins Belong to the Intrinsically Disordered Protein Class? J Proteomics Bioinform 5: 262-264. doi:10.4172/jpb.1000247

Copyright: © 2012 Hernández S, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
consider that belonging to this class requires stretches of at least 40 amino acids in disordered regions [24], the number would be smaller, since the disordered amino acid stretches are quite short. In many cases, these structures are located in the N- and C-terminal regions of the polypeptide, which are known to be quite mobile regions. Indeed, many of the IDRs match loops and coil regions and, in fact, the IDP/IDR prediction program DisEMBL, which predicts both IDP and loop regions, shows that they usually coincide.

Alternative local conformations can be achieved without a great change in the structure of the protein. The analysis and mapping of X-ray structures of four moonlighting proteins indicate that they use different regions for each activity and that these regions correspond to quite complex domains or motifs, not to disordered amino acid stretches [6]. Of course, there are some examples of moonlighting proteins that are IDPs, such as the human chemokine lymphotactin [11,16,18,25], but we suggest that most moonlighting proteins do not belong to the IDP class. Indeed, a moonlighting protein, Ribosomal Protein S10, which was once considered an IDP, has recently been
shown to adopt the same global fold in complex with NusB and in the ribosome. This fact excludes the possibility that its structure is extensively remodelled. Therefore, S10 binds to RNA and to NusB at different regions of the protein. RNA-binding is accomplished by a long loop, which is the only unfolded region [26].

The above results suggest that moonlighting proteins might not specially require fully disordered regions. Loops are flexible enough to allow for the adaptation to different interactions. And the capability to interact with new partners is probably the first step to achieve a new function. There are examples of multispecific proteins that interact with many partners through the same binding interface without being a disordered region [27]. Moreover, interactomics has shown that proteins – both IDPs or permanently structured - have the ability to interact with many partners, most of them other proteins. In fact, the cell has to solve the problem of choosing a specific partner by means of subcellular compartmentalization, expression phase, oligomeric state, etc. New functions could be related more to establishing additional interactions using existing sequences rather than incorporating new amino acid stretches or changing the local structure. This is suggested by the following analysis. We have multialigned, by CLUSTALW [28], the sequences corresponding to different bacterial species of a number of the proteins used in this work in search of major differences in domains (shown as differences in length or even in amino acid sequence). The alignment shows that they are highly conserved (results not shown), thus new functions are not likely related to incorporating new amino acid stretches/conformations, but rather to new interactions. For example, a highly conserved group of moonlighting enzymes, those of glycolysis, interact with different host partners in different bacterial pathogens [29].

Acknowledgements

This research was supported by Grants BIO2007-67904-C02-01 and BFU2010-22209-C02-01 from the MCYT (Ministerio de Ciencia y Tecnología, Spain), from the Centre de Referència de R+D de Biotecnologia de la Generalitat de Catalunya (Spain) and by Comisión Coordinadora del Interior (Uruguay). IA acknowledges a postdoctoral fellowship from La Marató de TV3. The English and has been revised and corrected by Mr. Charles J. Simmons, a native English-speaking Instructor of English of the UAB.

References

1. Wistow G, Platigorsky J (1987) Recruitment of enzymes as lens structural proteins. Science 236: 1554-1556.
2. Platigorsky J, Wistow GJ (1989) Enzyme/crystallins: gene sharing as an evolutionary strategy. Cell 57: 197-199.
3. Wool IG (1996) Extraribosomal functions of ribosomal proteins. Trends Biochem Sci 21: 164-165.
4. Jeffery CJ (1999) Moonlighting proteins. Trends Biochem Sci 24: 8-11.
5. Jeffery CJ (2003) Moonlighting proteins: old proteins learning new tricks. Trends Genet 19: 415-417.
6. Jeffery CJ (2004) Molecular mechanisms for multitasking: recent crystal structures of moonlighting proteins. Curr Opin Struct Biol 14: 663-668.
7. Jeffery CJ (2009) Moonlighting proteins—an update. Mol Biosyst 5: 345-350.
8. Platigorsky J, Platigorsky J (2007) Gene Sharing and Evolution: The Diversity of Protein Functions. Harvard University Press.
9. Gancedo C, Flores CL (2008) Moonlighting proteins in yeasts. Microbiol Mol Biol Rev 72: 197-210, table of contents.
10. Nobeli I, Favia AD, Thornton JM (2009) Protein promiscuity and its implications for biotechnology. Nat Biotechnol 27: 157-167.
11. Copley SD (2012) Moonlighting is mainstream: paradigm adjustment required. Bioessays 34: 576-588.
12. Gómez A, Domedel N, Cedano J, Piñol J, Querol E (2003) Do current sequence analysis algorithms disclose multifunctional (moonlighting) proteins? Bioinformatics 19: 895-896.
13. Gómez A, Hernández S, Amela I, Piñol J, Cedano J, et al. (2011) Do protein-protein interaction databases identify moonlighting proteins? Mol Biosyst 7: 2379-2382.
14. Tsai CJ, Ma B, Nussinov R (1999) Folding and binding cascades: shifts in energy landscapes. Proc Natl Acad Sci U S A 96: 9970-9972.
15. Tsai CJ, Ma B, Sham YY, Kumar S, Nussinov R (2001) Structured disorder and conformational selection. Proteins 44: 418-427.
16. Tsai CJ, Ma B, Nussinov R (2009) Protein-protein interaction networks: how can a hub protein bind so many different partners? Trends Biochem Sci 34: 594-600.
17. Ma B, Kumar S, Tsai CJ, Nussinov R (1999) Folding funnels and binding mechanisms. Protein Eng 12: 713-720.
18. Tompa P, Szász C, Buday L (2005) Structural disorder throws new light on moonlighting. Trends Biochem Sci 30: 484-489.
19. Amitai G, Gupta RD, Tawfik DS (2007) Latent evolutionary potentials under the neutral mutational drift of an enzyme. HFSP J 1: 67-78.
20. Ishida T, Kinohashi K (2007) PfDoS: prediction of disordered protein regions from amino acid sequence. Nucleic Acids Res 35: W460-464.
21. Linding R, Jensen LJ, Diella F, Bork P, Gibson TJ, et al. (2003) Protein disorder prediction: implications for structural proteomics. Structure 11: 1453-1459.
22. Ward JJ, Sodhi JS, McGuffin LJ, Buxton BF, Jones DT (2004) Prediction and functional analysis of native disorder in proteins from the three kingdoms of life. J Mol Biol 337: 635-645.
23. Dosztányi Z, Csizmok V, Tompa P, Simon I (2005) IUPred: web server for the prediction of intrinsically unstructured regions of proteins based on estimated energy content. Bioinformatics 21: 3433-3434.
24. Dyson HJ (2011) Expanding the proteome: disordered and alternatively folded proteins. Q Rev Biophys 44: 467-518.
25. Tuniistra RL, Peterson FC, Kutlesa S, Elgin ES, Kron MA, et al. (2008) Interconversion between two unrelated protein folds in the lympectinatocytin native state. Proc Natl Acad Sci U S A 105: 5057-5062.
26. Luo X, Hsiao HH, Bubunenko M, Weber G, Court DL, et al. (2008) Structural and functional analysis of the E. coli NusB-S10 transcription antitermination complex. Mol Cell 32: 791-802.
27. Erijman A, Aizner Y, Shifman JM (2011) Multispecific recognition: mechanism, evolution, and design. Biochemistry 50: 602-611.
28. Larkin MA, Blackshields G, Brown NP, Chenna R, Mcggettigan PA, et al. (2007) Clustal W and Clustal X version 2.0. Bioinformatics 23: 2947-2948.
29. Henderson B, Martin A (2011) Bacterial virulence in the moonlight: multitasking bacterial moonlighting proteins are virulence determinants in infectious disease. Infect Immun 79: 3476-3491.

Submit your next manuscript and get advantages of OMICS

Group submissions

Unique features:
- User-friendly/feasible website-translation of your paper to 50 world’s leading languages
- Audio Version of published paper
- Digital articles to share and explore

Special features:
- 200 Open Access Journals
- 15,000 editorial team
- 31 days rapid review process
- Quality and quick editorial, review and publication processing
- Indexing at PubMed (portal), Scopus, DOAJ, BIBSCO, Index Copernicus and Google Scholar etc
- Sharing Option: Social Networking Enabled
- Authors, Reviewers and Editors rewarded with online Scientific Credits
- Better discount for your subsequent articles

Submit your manuscript at: http://www.editorialmanager.com/proteomics