Biochemistry and Biophysics Reports 15 (2018) 68

Contents lists available at ScienceDirect

Biochemistry and Biophysics Reports

journal homepage: www.elsevier.com/locate/bbrep

Interactions between the prion protein and nucleic acids

In their recent report [1] concerning interactions between the prion protein (PrP) and nucleic acids, Bera and Biring present a number of RNA secondary structures which are erroneously described as pseudoknots. In the caption of Figure 2 it is stated "Normally, the pseudoknot contains two stems and three loops". An RNA pseudoknot is formed when the bases within a loop undergo Watson-Crick pairing with another otherwise single-stranded region of the same molecule [2]. The structures "MNV" in Figure 1 and "Hm45" and "Cm48" in Figure 2 of the Bera and Biring report [1] do not satisfy that criterion; they are simply multiple stem-loop structures. This in no way invalidates the experimental findings, but it does complicate the interpretation of them.

Many pseudoknots are capable of adopting a variety of alternative conformations, sometimes involving triple-base interactions that are determinative in relation to protein binding, so a proper understanding of protein binding can only be achieved once the three dimensional structure of the RNA in the RNA-protein complex has been identified. The "classic pseudoknot" first postulated by this author [3] has never been verified experimentally, in spite of its *possibility* having been demonstrated across the wide phylogenetic spectrum of PrP mRNA species [4]. However, the binding of the HIV tat protein, among others, to the tandem repeat region of the PrP mRNA [5,6] has been interpreted as indicative of a structure which is very different from the hypothetical pseudoknot, resembling instead the stemloop required for the tat-dependent transactivation of HIV [7].

The finding of Bira and Biring [1] that PrP can bind to the tandem repeat region of its own mRNA is very interesting in relation to hypothetical role of this interaction in the replication of the ætiological agent of transmissible spongiform encephalopathy through ribosomal frameshifting [8,9]. On the other hand extensive experimental investigations (unpublished results) have so far failed to verify the existence of any special structural motifs—particular stemloops [8], pseudoknots [3] or G-quadraplexes [10]—that could facilitate such a process, highlighting the difficulty in progressing from calculated to actual RNA structures.

References

[1] A. Bera, S. Biring, A quantitative characterization of interaction between prion protein with nucleic acids, Biochem. Biophys. Rep. 14 (2018) 114–124.
[2] E. Westhof, L. Jaeger, RNA Pseudoknots, Curr. Opin. Struct. Biol. 2 (1992) 327–333.
[3] P.R. Wills, Potential Pseudoknots in the PrP-encoding mRNA, J. Theor. Biol. 159 (1992) 523–527.
[4] I. Barrette, G. Poisson, P. Gendron, F. Major, Pseudoknots in prion protein mRNAs confirmed by comparative sequence analysis and pattern searching, Nucleic Acids Res. 29 (2001) 753–758.
[5] U. Scheffer, T. Okamoto, J.M.S. Forrest, P.G. Rytik, W.E.G. Müller, H.C. Schröder, Interaction of 68 kDa TAR RNA-binding protein and other cellular proteins with prion protein-RNA stem-loop, J. Neurovirol. 1 (1995) 391–398.
[6] W.E.G. Müller, U. Scheffer, S. Perovica, J. Forrest, H.C. Schröder, Interaction of prion protein mRNA with CBP35 and other cellular proteins. Possible implications for prion replication and age-dependent changes, Arch. Gerontol. Geriatr. 25 (1997) 41–58.
[7] P.R. Wills, A.J. Hughes, Stem loops in HIV and prion protein mRNAs, J. Acquir. Immune Def. Syndr. 3 (1990) 95–97.
[8] P.R. Wills, Induced frameshifting mechanism of replication for an information-carrying scrapie prion, Microb. Pathog. 6 (1989) 235–249.
[9] P.R. Wills, Frameshifted prion proteins as pathological agents: quantitative considerations, J. Theor. Biol. 325 (2013) 52–61.
[10] R.C.L. Olsthoorn, G-quadruplexes within prion mRNA: the missing link in prion disease? Nucl. Acids Res. 42 (2014) 9327–9333.

Peter R. Wills
Department of Physics, University of Auckland, PB 92019, Auckland 1142, New Zealand
E-mail address: p.wills@auckland.ac.nz

https://doi.org/10.1016/j.bbrep.2018.07.004
Received 15 June 2018; Accepted 3 July 2018
Available online 11 July 2018