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Note

Letter to the Editor: A still unresolved mystery in the interaction between intrinsically disordered proteins: How do they recognize multiple target proteins? A commentary on "No folding upon binding of intrinsically disordered proteins: Still interesting but not unique and novel. by Sigalov, A. B., Biophysics and Physicobiology 17, 156–158 (2020). DOI: 10.2142/biophysico.BSJ-2020025"

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A considerable number of proteins without well-organized secondary or tertiary structures have been found to be present in cells. These proteins, or parts of proteins, have been called "intrinsically disordered proteins/regions (IDPs/IDRs)" [1]. Their structural feature is to form a well-ordered three-dimensional structure upon binding to their partner molecules. This has been called "coupled binding and folding" mechanism. However, an exceptional case has been first found by Sigalov *et al.* [2], in which "no folding upon binding" is observed during the interaction between IDPs/IDRs. In addition, this unusual phenomenon has been clearly evidenced by the careful comparison of monomeric and dimeric forms of cytoplasmic domain of the T cell receptor ζ subunit using heteronuclear NMR [3]. Although a growing number of examples of "no folding upon binding" has been found as listed in a recent publication by Sigalov [4], we consider that this is still rare and unusual mode of interaction that is not categorized within the well-accepted "coupled binding and folding" mechanism. In this context, we found several novel aspects in the interaction between two different IDPs/IDRs.

First, we should mention that the review article we published recently in Biophysics and Physicobiology [5] corresponds to a summary of our series of works on homo-oligomerization of Sp1-QB domains and hetero-molecular interaction between Sp1-QB and TAF4-Q-rich domains [6–8]. By carefully comparing these series of studies, a novel and prominent nature of the interaction has clearly emerged. The concepts that we would like to emphasize in our review are:

- Both Sp1-QB and TAF4-Q-domains are intrinsically disordered even after the formation of homo- or hetero-oligomers.
- The same region of Sp1-QB domain is responsible for both homo-oligomerization and heteromolecular interaction with TAF4-Q-domains.

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As found in Table 1 in the commentary by Sigalov [4], the interaction between Sp1-QB and TAF4-Q-domains is the first example that showed two different IDPs/IDRs bind to form a hetero-oligomer without any detectable conformational changes. In addition, Sp1-QB has been demonstrated to use the same region (from the center to C-terminus: residue numbers 420–490) for the binding to TAF4-Q-domains as that used in homo-oligomerization among themselves (Compare Figs 2 and 4 in Hibino & Hoshino [5]). These findings are described in the abstract as "One of the IDRs in Sp1 exhibited homo-oligomer formation. In addition, the same region was used for the interaction with another IDR found in the TAF4 molecule. In both cases, we have not detected any significant conformational change in that region, suggesting a prominent and novel binding mode for IDPs/IDRs". In addition, we also describe in the last paragraph as, "This novel mode of interaction might be common for the interaction between an IDP and another IDP, that is, it might be the result of two flexible IDPs mutually fitting each other."

Evidently, the above sentences indicate that the main concept and originality in the review by Hibino and Hoshino [5] is not the finding of "no folding upon binding" phenomenon, but the fact that the same region of Sp1-QB domain was specifically used for both homo- and hetero-oligomer formation between two IDPs/IDRs. We consider that this finding is very important, because it brings us further to an unresolved question, that is, how does Sp1-QB domain use the same region for different (homo- and hetero-) molecular recognition? This interaction is quite mysterious if we keep in mind that these proteins remain disordered even after complex formation.

Nevertheless, we recognize that the title and abstract of the review by Hibino and Hoshino [5] may have been misleading for the readers, and appreciate the valuable commentary by Sigalov [4]. We hope these commentary notes bring about further attention to this interesting and still unresolved topic concerning the interaction mode of IDPs/IDRs.

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