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LETTER TO THE EDITOR

Comment on “Intrinsic protein disorder uncouples affinity from binding specificity”

In a recent issue of *Protein Science*, Lazar et al. published an article entitled “Intrinsic protein disorder uncouples affinity from binding specificity” (Lazar et al., 2022). In this work, the authors challenge the widespread view that intrinsically disordered proteins (IDPs) bind their interaction partners with low affinity but high specificity. In addition, they claim that the concept of specificity is vaguely defined and lacks exact measures. On these points their conclusions are (I) that complexes between IDPs and folded proteins on average are indeed slightly weaker than complexes formed between two folded proteins, and (II) that for IDPs, specificity is uncoupled from affinity.

Concerning their first conclusion, we would like to point out that we have performed and published an almost identical analysis a few years ago (Teilum et al., 2015). This “Perspective Article” was part of the Research Topic “Function and flexibility: friend or foe?” (Pauwels & Tompa, 2016). Given the substantial overlap in ideas, results and conclusions we find it insufficient that our previous work escaped the attention of the authors of the Lazar article and was not cited.

Lazar et al. conclude that the difference in $\Delta G^o$ for binding a disordered or a globular ordered protein to a globular ordered partner is $3.0 \pm 0.4$ (SEM) kcal/mol, essentially identical to the result from our work ($2.5 \pm 0.4$ kcal/mol; see comparison of the data in Figure 1). This difference does not change the conclusion we draw from the data. For a large part of the complexes in our previous work, structural models were available and in our original work we undertook the similar analysis of the interface surface area as Lazar et al. have done and reached the same conclusions. In contrast to Lazar et al., we were able to suggest a thermodynamic explanation for the observed difference in average stability of the two types of complexes. Our analysis suggests that the difference in $\Delta G^o$ is fully accounted for by a difference in the entropic contribution to binding, consistent with the larger loss in conformational entropy associated with binding of a disordered ligand that adopts a fixed conformation in the bound state.

Concerning the second conclusion, we would like to comment on the discussion by Lazar et al. on specificity. We have elaborated on that subject in depth recently (Teilum et al., 2021) and would like to point out that there is a clear physical–chemical definition of specificity (von Hippel & Berg, 1986; Eaton et al., 1995), by which specificity and affinity cannot be uncoupled as otherwise stated in the title of the article by Lazar et al., as well as in their conclusions. Considering this, we would like to invite Lazar et al. to reconsider some of their stronger claims about specificity.

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![FIGURE 1](https://wileyonlinelibrary.com/journal/pro) Density estimates of $\Delta G^o$ of binding for IDP:ordered complexes (ID-OR, red) and for complexes between two globular ordered proteins (OR-OR, blue). The distributions in light colors are from the data compiled by Lazar et al. (2022), whereas the distributions in darker colors are from the data compiled by Teilum et al. (2015). The dashed vertical lines show the average of each distribution.
REFERENCES