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Scaling Laws and Global Dimensions of Disordered Proteins: Single-molecule Data and Polymer Physics Theory (I)

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Sic1 is a disordered kinase inhibitor, which must be phosphorylated on at least six sites to allow its recognition by the WD40 binding domain of the Cdc4 protein in the yeast cell cycle. The highly-cooperative, switch-like dependence on the number of phosphorylated sites on Sic1 cannot be accounted for by traditional thermodynamic models of cooperativity. We used single-molecule fluorescence techniques to study the dimensions and dynamics of Sic1's N-terminal targeting region (residues 1-90, henceforth Sic1) and phosphorylated Sic1 (pSic1). A quantitative relationship between sequence properties and ensemble properties is a prerequisite for understanding IDP phosphorylation and its role in highly cooperative binding.
Single-molecule Förster Resonance Energy Transfer (smFRET) data obtained for dye-labelled Sic1, pSic1, and the pSic1-WD40 complex were used to infer the dimensions of disordered ensembles for different states of Sic1. In a refinement to the conventional approaches for inferring IDP dimensions from smFRET experiments, we use distance distributions from Monte Carlo simulations, which extensively sample coarse-grained protein conformations. The application of polymer physics theory/simulations towards smFRET data interpretation, and towards IDP binding, contributes to the growing toolkit for understanding how IDPs function in the absence of a stable 3D structure.

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