"Conformations and exchange dynamics of intrinsically disordered proteins in dilute and crowded conditions"

The malleability of intrinsically disordered proteins (IDPs) makes their conformation ensembles highly susceptible to reshaping by nonspecific interactions with bystander macromolecules (or crowders) in cellular environments. Our computational study [1] demonstrated that IDPs are compacted by repulsive crowders, as confirmed by subsequent experimental and computational studies. Computation also suggests that attractive crowders produce more complex effects, and there is urgent need for experimental studies of IDPs under a variety of crowding conditions. Here I report our experimental studies of an IDP called FlgM in the presence of both protein crowders and polymer crowders. Small-angle neutron scattering data showed that, with increasing crowder concentration, the mean radius of gyration of FlgM first decreased but then exhibited an uptick [2]. Moreover, FlgM conformations under crowding segregated into two distinct populations, one compacted and one extended. Coarse-grained simulations showed that compacted conformers fit into an interstitial void, whereas extended conformers snake through interstitial crevices and bind multiple crowder molecules simultaneously. NMR relaxation dispersion further demonstrated exchange between two populations. At 100 g/L dextran, 3 residues in the C-terminal half of FlgM exhibited millisecond exchange. At 150 g/L bovine serum albumin, the number of residues exhibiting conformational exchange increased to 7. With 100 g/L lysozyme, the FlgM residues exhibiting conformational exchange extended to the N-terminal half, although peak broadening, likely due to extensive nonspecific binding with the protein crowder, precluded quantitative analysis of the relaxation dispersion data. Together, these studies suggest that conformational malleability allows IDPs to respond agilely to their crowded cellular environments, including conformational compaction, conformational expansion, persistent disorder, and induced structuring. It is entirely possible that cellular functions of IDPs take advantage of such varied conformational response to crowding.


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Location: Lecture Hall Y44-H-05, UZH Irchel

Contact: Prof. Ben Schuler, Email: schuler@bioc.uzh.ch