Intrinsically disordered nucleoporin domains show inter-chain interactions which affect their supramolecular assembly

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Abstract

Nuclear pore complexes (NPCs) are the gates that mediate the exchange of all proteins and nucleic acids between the cytoplasm and the nucleus. They are highly selective: inert proteins bigger than 30 kDa cannot diffuse through NPCs unless they are bound to nuclear transport receptors (NTRs). This selectivity arises from a supramolecular assembly of natively unfolded nucleoporin domains containing phenylalanine-glycine (FG)-rich repeats, so called FG-repeat domains (FGRDs).1

Different models for the size and species selectivity of the permeability barrier have been suggested that build on different putative supramolecular assemblies of FGRDs. The "selective phase" model predicts the formation of a selective, gel-like phase of FGRDs driven by inter-FG repeat interactions.2 On the other hand, the "virtual gating"3 and "reversible collapse"4 models seek to explain the selectivity by the formation of repulsive bristles by the FGRD, where inter-FG repeat interactions are not considered. The strength and functional relevance of inter-FG repeat interactions remain hence controversial.

Recently, we reported the design of end-grafted FG-repeat domain monolayers as a model system of the nuclear pore permeability barrier.5 In the present study, we use this model system and a toolbox of biophysical characterization techniques to characterize the supramolecular assembly of FGRDs. We investigated the mobility of FGRDs within the films, phase separation, and the mechanical properties and thickness of the FGRD films. We show that the strength of inter-chain interactions varies between different FGRD species, and that these interactions have a profound impact on the morphology of the supramolecular FGRD assembly. We propose that the strength of inter-chain interactions has evolved to promote the formation of a homogeneous meshwork with a small mesh size. The results highlight the importance of inter-FG repeat interactions for NPC functionality, and hence contribute important information to refine the model of transport across the permeability barrier.

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