Residue-Specific Interactions of Intrinsically Disordered Proteins with Silica Nanoparticles and Their Quantitative Prediction

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Intrinsically disordered proteins (IDPs) play important structural and regulatory roles in biological systems, and their dysfunctions are linked to many diseases, including neurodegeneration such as Alzheimer's and Parkinson's disease. Due to their structural flexibility, IDPs pose immense challenges to be targeted by conventional drug agents such as small molecules or peptides. **The recent advents in nanotechnology provide an alternative strategy for targeting IDPs.** This is because the large surface-to-volume ratio of nanoparticles, especially with tailored surface modification, can selectively accommodate IDP binding via multiple-site contacts, reduce their conformational flexibility, and hence alter their biological functions.

Rational design and successful application of functional nanoparticles calls for a thorough understanding of their integrated effects on biological systems. **However, critical molecular insights of interactions between IDPs and inorganic nanoparticles are still missing**, which hinders the development of IDP-targeting nanomedicines. Conventional analytical techniques often fail to offer high-resolution characterization of such systems. By contrast, solution NMR is routinely used for structural determination and dynamics study of biomolecules at atomic resolution, and recently also gained its popularity in investigating the molecular interactions at bio-nano interfaces. Therefore, we took advantage of powerful solution NMR techniques, along with other analytical methods, to obtain molecular details of IDP-nanoparticle interactions.

We determined the interaction propensities of four different IDPs with anionic silica nanoparticles (SNPs) at residue-level resolution by collecting transverse ^{15}N spin relaxation data in the presence and absence of SNPs (Fig. 1A). From the segmental variations of these interaction profiles, one can learn about the various local binding propensities of different IDPs in response to same type of nanoparticles. Moreover, **such interactions are strongly sequence-dependent, and can be explained based on the SNP-affinities of 20 natural amino acids** that are separately derived using ^{13}Cα relaxation data. To quantitatively understand the contributions of individual residues, we firstly developed an empirical model (Free Residue Interaction Model, or FRIM) that reveals how the interplay of attractive and repulsive Coulomb interactions as well as hydrophobic effects is responsible for the sequence-dependent binding of IDPs to nanoparticles (Fig. 1B,C). We then employed **coarse-grained molecular dynamics (MD) simulation to systematically evaluate such individual contributions**, which agree well with experimental data and FRIM. This represents the very first quantitative study of IDP-nanoparticle interactions from a predictive perspective, which deepens our understanding of the driving forces and binding orientations of biomolecules bound to solid inorganic surfaces, and sheds lights on the potential cause of nanotoxicity.

In conclusion, we combined spectroscopic and computational approaches in a cross-disciplinary study to demonstrate the sequence-dependent interactions of several IDPs and SNPs with residue-level resolution. The resulting FRIM model is transferable to other IDPs with good predictive power, and may guide the design of next-generation nanoproducts for better healthcare.

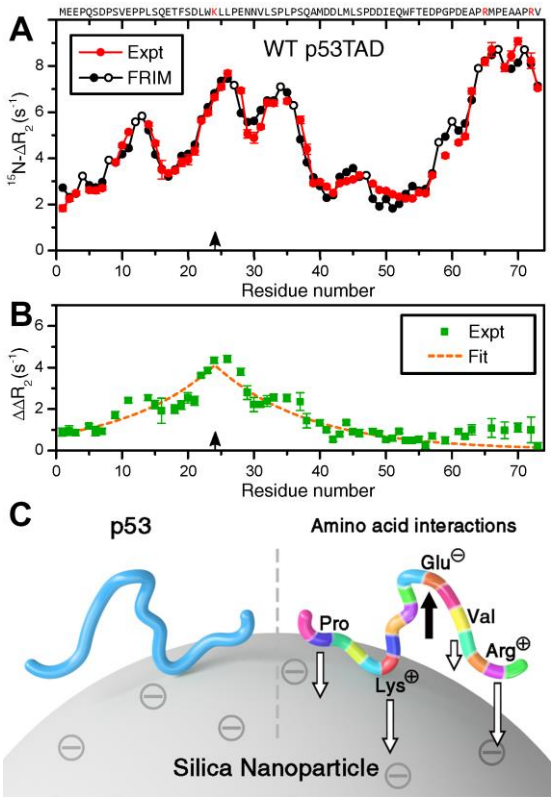

Figure 1. **(A)** The experimental interaction profile (red) of the intrinsically disordered transactivation domain of wild-type human tumor suppressor p53 (p53TAD) with silica nanoparticles (SNPs). The segmental variation can be explained by a collective effect of individual residue contributions. Larger values indicate stronger local binding propensities. Back-calculation by the FRIM model is shown in black. **(B)** The isolated effect of Lysine 24 revealed by mutagenesis (green squares), plotted with a fit using a symmetric exponential decay (orange curve). **(C)** Cartoon illustration of the FRIM model.

Reference

[1] M Xie, AL Hansen, J Yuan, and R Brüschweiler. Residue-specific interactions of an intrinsically disordered protein with silica nanoparticles and their quantitative prediction. *J. Phys. Chem. C* 2016, 120, 24463.