Protein-peptide complex structure prediction with NMR driven MELDxMD

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About 40% of the protein-protein interactions are mediated through small peptide epitope. Knowledge of how a peptide or an intrinsically disordered protein fragment interact with a protein would widen of the understanding of gene regulation, transcription and finally drug discovery. However, the folding upon binding nature of majority of the peptide interacting partner, limits the ability of modeling tools to predict structures of such complexes. To address this problem, we show an integrative approach combining cost-effective NMR chemical shift data and physics based molecular simulations to determine structures of protein-peptide complexes. Here in this presentation, we demonstrate our approach for polypeptide complexes formed with the extraterminal (ET) domain of bromo and extraterminal domain (BET) proteins, which exhibit a high degree of binding plasticity. This system is particularly challenging as the binding process includes allosteric changes across the ET receptor upon binding, and the polypeptide binding partners can form different conformations (e.g., helices and hairpins) in the complex. In a blind study, the new approach successfully predicts bound-state structure, using only backbone chemical shift data, in excellent agreement with experimental structure. We show, this approach is successful on not only strongly interacting complexes, but also in the case of weak binder, this method has been successful. MELD+NMR also predicts relative binding affinities of different peptides, consistent with the experimental values. The hybrid MELD+NMR approach provides a powerful new tool for structural analysis of protein-polypeptide complexes involving disorder to order transitions upon complex formation which are not successfully modeled with most other complex predication methods including state of the art docking methods, providing 3D atomistic structures of complexes as well as their relative binding affinities.