Title:	Conformational Fingerprinting of Phase Separation and Amyloid Formation Through the Lens of Vibrational Raman Spectroscopy
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Abstract:	Conformational Fingerprinting of Phase Separation and Amyloid Formation Through the Lens of Vibrational Raman Spectroscopy Name: Anamika Avni Supervisor's name: Prof. Samrat Mukhopadhyay Intrinsically disordered proteins (IDPs) are a special class of proteins that confronts the classical sequence-structure-function paradigm and exists as a dynamic, heterogeneous ensemble of rapidly interconverting conformations. While IDPs are involved in a myriad of critical physiological functions, their misfolding leads to the formation of amorphous aggregates or amyloids that are linked to various debilitating neurodegenerative disorders. The highly ordered amyloid assemblies share a common core architecture exhibiting a structural diversity in their supramolecular packing arrangement within the backbone. Such an altered packing results in amyloid polymorphism that is often responsible for distinct amyloid strains. We utilized vibrational Raman spectroscopy coupled with hydrogen/deuterium exchange to structurally distinguish distinct amyloid polymorphs displaying altered hydrogen bonding ability and supramolecular packing within the cross-β structural motif. Such structural investigations are crucial to discern the mechanism of amyloid polymorphism and the structure-pathology relationship. Increasing evidence has suggested that in addition to the canonical membrane-bound organelles, cells contain a host of non-canonical membrane-less organelles formed via intracellular phase separation of IDPs along with nucleic acids and other biomolecules. These biomolecular condensates are involved in various cellular functions and human pathologies. We developed and adapted a highly sensitive, single-droplet structural tool involving dispersive laser Raman spectroscopy in a microscopy format that offers a wealth of fundamental molecular information within the condensed phase. Our novel single-droplet surface-enhanced Raman scattering (SERS) technique using plasmonic nanostructures illuminate the inner workings of the protein droplets and captures the crucial interactions, conformational heterogeneity, and structural distribution in a single droplet fashion. Taken together, this thesis elucidates the utility of vibrational Raman spectroscopy as a potent tool to obtain structural insights from a range of protein assemblies formed by amyloidogenic IDPs implicated in physiology and disease.
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