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Nanoplasmonics for Characterization of Protein Assemblies

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Extended Abstract

Proper protein function requires specific structural organization (conformation) of protein molecules. Aberrant conformations or aggregation can lead to severe disorders such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. Despite extensive research, the specific molecular mechanisms driving protein aggregation and misfolding remain poorly understood. A major challenge lies in detecting and characterizing diverse protein assemblies, which can range from β-sheet-rich amyloid fibrils to fluid phase-coacervates. The limited information about the nature and structure of these proteinaceous assemblies has hindered the development of effective anti-misfolding therapies. We employ nanoplasmonics, a technique leveraging optoelectronic effects arising from the excitation of plasmonic waves in metallic nanostructures exposed to light, to enhance the characterization of protein assemblies. Specifically, we utilize hybrid architectures interfacing protein solutions with engineered substrates consisting of nanostructured Au films on dielectric fused silica supports. We combine plasmon-enhanced bright-field confocal microscopy for monitoring protein assemblies in solution with surface-enhanced Raman scattering (SERS) to characterize their vibrational properties. Examples include the characterization of self-assembled fibril networks of recombinant heterokaryon incompatibility protein S (HET-s, 218–289) and phase-coacervates formed through the liquid-liquid phase separation of tubulin-associated unit (tau, 1–441) under varying conditions, such as pH for HET-s and protein concentration for tau. In all cases, plasmonic enhancement of fluorescence enabled the capture of clear confocal micrographs of protein assemblies without staining or contrasting agents. Furthermore, the confocal imaging capability allowed us to focus on specific protein assemblies to collect their SERS spectra. Analysis of these spectra provided dynamic fingerprints of the studied protein aggregates in their respective solutions. The multimodal, plasmon-enhanced characterization technique offers new capabilities for non-invasive and label-free imaging of diverse protein assemblies in solution under ambient conditions, while capturing their vibrational properties within the same experimental setup. This approach has significant potential to address the long-standing challenge of analysing the morphological and dynamic properties of transient protein assemblies.