Aggregation Dynamics of Misfolded Proteins in Water using Liquid Phase Transmission Electron Microscopy

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Liquid-phase transmission electron microscopy (LPTEM) offers exceptional capabilities for imaging time-resolved structures in their native liquid environment, eliminating artefacts associated with traditional drying or cryogenic treatments. One of the most promising applications of LPTEM is the investigation of molecular structures in cells, such as proteins.[1] The liquid nature of the sample allows access to previously unreachable protein states, as it permits the free movement of soft structures during imaging. This unique feature provides a significant advantage for structural biology research, allowing for real-time exploration of the protein structural landscape.

In our study, we used LPTEM to gain unprecedented insight into the dynamics of misfolded protein aggregation and its structural evolution over time, focusing on amyloid beta peptide (Aβ), which readily aggregates into amyloid fibrils. This process has been intensely studied due to its association with Alzheimer's disease (AD). However, directly observing the microscopic steps in the aggregation reaction and the characterization of intermediate oligomeric assemblies have been highly challenging. We employ LPTEM in combination with all-atom molecular dynamics simulations to enhance our understanding of protein dynamics.

Our findings provide the first visualisation of the dynamics of Aβ oligomers, the formation of Aβ protofibrils, and the interaction of Aβ oligomers with fibril surfaces. [2] This work demonstrates how LPTEM can be utilised to image key molecular events in the Aβ aggregation process, contributing to a deeper understanding of protein aggregation in solution, particularly in the context of Alzheimer's disease.

References

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