4t Protein Aggregation in the Pathogenesis of Amyloid Diseases

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Approximately 20 neurodegenerative diseases, including Alzheimer's disease (AD) and Parkinson's disease, have been linked to the aggregation and deposition of normally soluble protein to form insoluble fibrillar assemblies. To date, none of these disorders can be successfully treated. Recent advances in the field implicate that fibril formation may be an intrinsic property of proteins and that even non-disease related protein aggregates are cytotoxic. These findings imply a common mechanism for amyloid diseases, suggesting that a common therapy for these diverse disorders might be possible. So far, the mechanism and driving forces of protein fibril formation and the pathway by which protein aggregates result in neurotoxicity are still unclear. We have shown that protein aggregation proceeds through the formation of a structurally perturbed intermediate and followed by the assembly of these intermediates to form aggregates. These two steps are fundamentally controlled by the stability of the protein's native structure and the nature of protein-protein interactions in solution. Factors that disrupt the native structure, stabilize the aggregated state, or induce favorable protein-protein interactions have been found to drive aggregation. The cell membrane has been implicated to play an important role in AD pathogenesis by mediating amyloid-β protein (Aβ) fibril formation and neurotoxicity. We show that lipid membranes promote Aβ fibril formation by providing an interface to which Aβ peptides adsorb or insert, undergo conformational changes which lead to higher aggregation propensity, and finally assemble into fibrils. Furthermore, Aβ insertion and disruption of lipid monolayers have been directly visualized, hinting that disruption of cell membrane integrity may serve as a pathway by which Aβ exerts neurotoxicity. To further test this hypothesis, factors that impact AD pathogenesis, namely, Aβ assembly state, membrane lipid composition, cholesterol, and metal ions on Aβ-membrane interaction and fibril formation are being investigated. Findings from these studies will significantly advance our understanding of the molecular mechanism of the pathogenesis of AD and other amyloid diseases, including Parkinson's disease, Huntington's disease, and transmissible spongiform encephalopathies.