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Article / Book Information

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論 文 要 旨

THESIS SUMMARY

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要旨（英文 800 語程度）
Thesis Summary（approx.800 English Words ）

This dissertation focuses on suppression of protein aggregation using cyclic and acyclic oligo(ethylene glycol) (OEG) derivatives. Proteins are necessary for wide range of biolological process and maitain cell functionality. After protein formed it adopts a specific 3D structure. However under certain conditions the native form of a protein may misfold, leading to protein aggregation. It is a critical phenomenon associated with neurodegenerative diseases and other pathological conditions. Protein aggregates can be categorized depending on various factors such as size, reversibility, protein secondary, tertiary structure, and morphology. In this study author focus on morphology which is two types: amyloid fibrillation and amorphous aggregation. Amyloid fibrillation is more challenging to detect compared to amorphous aggregation. It is essential to develop complementary technique to confirm the results, especially for amyloid fibrillation. Therefore, Chapter 2, the author explained the complementary chromatography technique to study protein fibrillation. ThT assay is a conventional method to detects amyloid fibrillation. However, this technique has some problems such as competitive binding, which can lead to inaccurate interpretations, particularly in the presence of additives. To overcome these challenges, the author developed a novel method based on Ultra Performance Liquid Chromatography (UPLC). UPLC allows for the analysis of soluble protein components. Using UPLC, the author demonstrated that the disappearance of soluble protein components correlates with the formation of mature fibrils in the presence of additives. This was in contrast to ThT assay results, which occasionally failed to detect fibrils despite their presence. Such variations highlight the importance of using complementary techniques to verify findings. Furthermore, UPLC was able to detect deamidated species, helps to understand the early stages of protein fibril kinetics. In chapter 3 discusses the suppression of protein fibrillation by various OEG derivatives. The results show that molecular structure plays a critical role in inhibiting fibrillation. Acyclic OEG derivatives with naphthalene showed significant efficiency in the suppression of insulin fibrillation. While these compounds also showed some potential in slowing lysozyme fibrillation. Cyclic OEG derivative COEGOCH3 was found to slightly accelerate protein fibrillation, in contrast to acyclic derivatives. Molecules with a suitable hydrophobic-hydrophilic balance can interact favourably with aggregating proteins and disrupt their aggregation pathways. These findings provide a basis for designing more effective inhibitors of protein fibrillation, a key step in the development of therapeutic interventions for diseases such as Alzheimer's and Parkinson's. In Chapter 4, the focus shifts from amyloid fibrillation to amorphous aggregation. Amorphous aggregation typically results in the formation of unordered protein aggregates that lead to loss of protein function. The study used a lysozyme activity assay to monitor the protein aggregation. as the enzymatic activity of lysozyme is a reliable indicator of structural integrity. The results showed that the cyclic OEG derivative COEGOCH3 and a naphthalene-based derivative effectively suppressed lysozyme aggregation. These results contrast with the behaviour of COEGNH, which showed no inhibitory effect on lysozyme aggregation. This suggests that specific structural features of OEG derivatives, such as the nature of the functional groups and the presence of aromatic moieties, significantly influence their ability to prevent aggregation. A key observation was that acyclic molecules were generally more effective in inhibiting protein aggregation than cyclic derivatives. This finding further underscores the importance of molecular design in the development of protein aggregation suppressors. The study highlights the effect of

OEG derivatives on protein aggregation. However, the exact mechanisms underlying the inhibitory effects of these molecules remain unclear. To advance the field, the author suggests that further investigations are required to elucidate the mechanisms by which OEG derivatives interact with aggregating proteins. This could include investigating the thermodynamic and kinetic aspects of these interactions, as well as studying the structural dynamics. In addition, extending this research to proteins associated with neurodegenerative diseases, such as amyloid-beta, could provide valuable insights into the development of effective therapeutics. In conclusion, this dissertation highlights the potential of cyclic and acyclic OEG derivatives as inhibitors of both amyloid fibrillation and amorphous aggregation. By addressing the limitations of traditional analytical techniques such as the ThT assay and introducing complementary methods like UPLC, the research establishes a reliable platform for studying protein aggregation. The findings emphasise the important role of molecular structure in modulating aggregation processes and pave the way for the design of targeted inhibitors. The insights gained from this work have significant implications for the development of therapeutic for prevent protein aggregation. In particular, the results point to the potential of OEG derivatives as promising candidates for further exploration in the context of neurodegenerative disorders. By extending the research to include additional proteins and refining the design of OEG derivatives, this work provide the foundation for future advancements in the field of protein aggregation inhibition.