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Solid-State NMR Studies of Misfolding and Cross-Seeding for 42-Residue β-Amyloid

（42 残基 β アミロイドの凝集とクロスシーディングによる凝集についての固体 NMR 解析）

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As the aging of society progresses in many developed countries, including Japan, understanding of age-related disorders, such as Alzheimer's disease (AD), is critical. AD is associated with misfolding of β-amyloid (Aβ) peptides into long filaments, called fibrils. Recent studies, however, indicate the significance of Aβ oligomers in AD as more toxic species than fibrils.

This thesis is composed of three chapters. Chapter 1 presents introduction of AD and Aβ. Two major hypotheses describing the relationship between Aβ and the pathology of AD are discussed. This chapter also discusses the basic structural motifs of Aβ fibrils and oligomers.

Chapter 2 presents structural studies of an oligomeric species of 42-residue Aβ (Aβ42), called spherical amyloid assembly (SPA). Structural study of oligomers has been difficult due to their instability in the oligomeric states. In this research, we prepared SPA as a possible model for a pathologically relevant oligomer, called amylospheroid (ASPD). We characterized its site-specific structure and its transition to the fibril using solid-state NMR (SSNMR) spectroscopy. The TEM results showed the spherical morphology with the average diameter of 15.6 ± 2.1 nm. The SSNMR and immunological results showed that SPA is structurally similar to ASPD, having a unique off-register parallel β-sheet arrangement. SPA undergoes a large conformational change to form the fibril, which structurally differed from the previously reported Aβ42 fibril. The study provides an insight in the misfolding pathway of Aβ42.

Chapter 3 presents the interaction of Aβ42 with the fibril of its isoform, 40-residue Aβ (Aβ40), on the misfolding of Aβ42 monomer to investigate the prion-like behavior between isoforms of Aβs in AD. The TEM results showed that mature fibrils were formed when Aβ42 monomer was coincubated with seed Aβ40 fibril. The kinetic and SSNMR results showed that the misfolding of Aβ42 depended on the amount of added seed Aβ40 fibril and that the formed fibril contained structure of Aβ40 fibril (U-shaped) in addition to that of Aβ42 fibril (S-shaped). Our previous results indicated that the misfolding of Aβ40 was unaffected by the addition of seed Aβ42 fibril. This asymmetric prion-like behavior presents the association between the tertiary structure of the seed fibril and compatibility of monomers to the fibril structure in the development of AD and possibly other amyloid diseases.