Solid-State NMR for Molecular Science

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2001 Assistant Professor, Yokohama National University
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Keywords Solid State NMR, Biomolecules, Developments

In order to elucidate functions of molecules, characterization of the molecule is the first step. There is a variety of important molecules, which are insoluble in any solvents and functional at amorphous state. Solid-state NMR enables us to obtain a variety of information at atomic resolution without damage to molecules and significant restrictions. Thus, solid-state NMR is one of the essential tools for the characterizations of those molecules.

We have been working on methodology and hardware developments of solid-state NMR and their application to structural biology and materials science. We study characterizations of membrane proteins and peptides, organic materials, natural products and synthetic polymers. Characterization of those molecules based on solid-state NMR is underway through collaborations with several research groups.

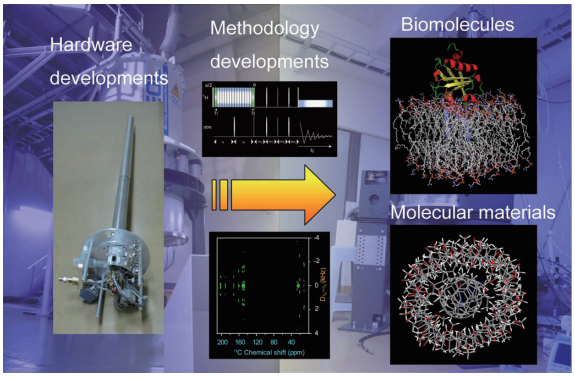

Figure 1. Outline of our studies.

Selected Publications

- M. Tanio and K. Nishimura, "Intramolecular Allosteric Interaction in the Phospholipase C-δ1 Pleckstrin Homology Domain," *Biochim. Biophys. Acta, Proteins Proteomics* **1834**, 1034–1043 (2013).
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- M. Yagi-Utsumi, K. Kato and K. Nishimura, "Membrane-Induced Dichotomous Conformation of Amyloid β with the Disordered N-Terminal Segment Followed by the Stable C-Terminal β Structure," *PLoS One* **11**, 0146405 (10 pages) (2016).
- N. Huang, L. Zhai, D. E. Coupry, M. A. Addicoat, K. Okushita, K. Nishimura, T. Heine and D. Jiang, "Multi-Component Covalent Organic Frameworks," *Nat. Comm.* **7**, 12325 (12 pages) (2016).
- N. Ousaka, F. Mamiya, Y. Iwata, K. Nishimura and E. Yashima, "'Helix-in-Helix' Superstructure Formation through Encapsulation of Fullerene-Bound Helical Peptides within a Helical Poly(methyl methacrylate) Cavity," *Angew. Chem., Int. Ed.* **56**, 791–795 (2017).
- M. Yagi-Utsumi, S. G. Itoh, H. Okumura, K. Yanagisawa, K. Kato and K. Nishimura, "The Double-Layered Structure of Amyloid-β Assemblage on GM1-Containing Membranes Catalytically Promotes Fibrillization," *ACS Chem. Neurosci.* **14**, 2648–2657 (2023).

1. Structural Determination of Amyloid-β Protein Oligomer Promoted on Model Neuronal Cell Membranes Using State NMR[1)]

Amyloid β (Aβ) protein is disordered in solutions under diluted conditions, however it conforms insoluble amyloid fibrils, which are found in senile plaque as a hallmark of Alzheimer's disease. Although molecular structures of amyloid fibrils have been determined, its molecular process for fibrillation in vivo has not been clarified yet. However, accumulated evidences suggest that the fibrillation process may be promoted on neuronal cell membrane. Especially, it has been reported that Aβ specifically interacts with ganglioside GM1 which is one of the key lipids in lipid raft. Therefore, GM1 embedded into lipid bilayers composed of neutral lipid DMPC may be considered to be the most simplified model neuronal cell membrane. In order to clarify the role of GM1 in the fibrillation process, first, we have successfully determined the oligomeric structure of Aβ(1-40) induced on DMPC bilayers based on solid-state NMR.[2)] We have been collaborated with Prof. Kato group and Prof. Okumura group for those Aβ studies.

In the current study, the molecular structure of Aβ(1-40) oligomer induced on model neuronal cell membranes consisting of GM1 and DMPC have been determined together with their intermolecular packing using solid-state NMR. Based on information of intra- and intermolecular distances and torsion angles of backborn obtained from solid-state NMR analyses, precise molecular structure of Aβ oligomer was determined from restrained molecular dynamics simulations. In addition, the location of C-terminal segment of Aβ(1-40) on the lipid bilayers has been clarified by solid-state NMR experiment in addition to biochemical experiments.

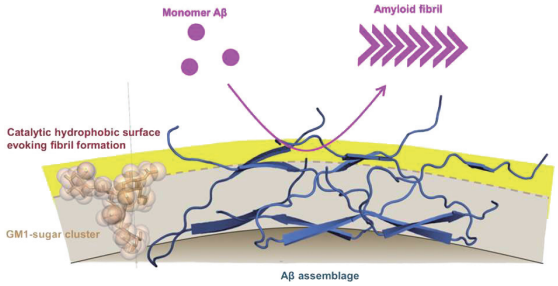

Figure 2. Schematic drawing of Aβ assemblage on GM1-containing membrane which catalytically promotes amyloid fibrillization.

The determined Aβ structure conforms disordered N-terminus followed by center and C-terminus β-sheets. Aβ takes intermolecular configuration of antiparallel β-sheet among adjacent molecules, in which different from Aβ fibrils prepared in solution and also Aβ oligomer induced on DMPC bilayers.[2)] Those suggest specific roles of GM1 for the formation of Aβ oligomers. Based on those experimental evidences, finally we have proposed the model process that Aβ assemblage on GM1-containing membrane catalytically promotes amyloid fibrillization as shown in Figure 1. We expect the significant contribution of our determined Aβ oligomer structure to reveal the molecular mechanism of Aβ fibrils on neuronal cell membranes, and thus understanding of Alzheimer's disease.

2. Developments of Core Technologies for Solid-State NMR Probes

We have been working on developments of totally original solid-state NMR probes during a couple of years. The probe has been built using originally designed parts except for spinning module. Then, we have been working on developments of original sample spinning modules for magic angle spinning (MAS) solid-state NMR probes which are fully compatible with currently using Bruker spectrometer and commercial sample tubes. We started the design of a spinning module for standard 4.0 mm sample tube for Bruker. After 3 times of version up, our original spinning module over the spinning performance of commercial one from Bruker. In order to improve spinning performance further for our original spinning module, the development of original sample tube may be essential due to the lack of strength of commercial sample tube.

Currently, final version of the spinning module is under development in order to realize installation of the module to a narrow bore solid-state NMR probe with outer sleeve diameter of 38 mm.

References

1) M. Yagi-Utsumi, S. G. Itoh, H. Okumura, K. Yanagisawa, K. Kato and K. Nishimura, *ACS Chem. Neurosci.* **14**, 2648–2657 (2023).
2) M. Yagi-Utsumi, K. Kato and K. Nishimura, *PLos One* **11**, 0146405 (10 pages) (2016).