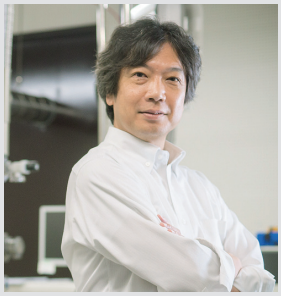
Dynamical Ordering of Biomolecular Systems for Creation of Integrated Functions

Department of Life and Coordination-Complex Molecular Science
Division of Biomolecular Functions



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Living systems are characterized as dynamic processes of assembly and disassembly of various biomolecules that are self-organized, interacting with the external environment. The omics-based approaches developed in recent decades have provided comprehensive information regarding biomolecules as parts of living organisms. However, fundamental questions still remain unsolved as to how these biomolecules are ordered autonomously to form flexible and robust systems (Figure 1). Biomolecules with complicated, flexible structures are self-organized through weak interactions giving rise to supramolecular complexes that adopt their own dynamic, asymmetric architectures. These processes are coupled with expression of integrated functions in the biomolecular systems.

Toward an integrative understanding of the principles behind the biomolecular ordering processes, we conduct multidisciplinary approaches based on detailed analyses of dynamic structures and interactions of biomolecules at atomic level, in conjunction with the methodologies of molecular and cellular biology along with synthetic and computational technique.

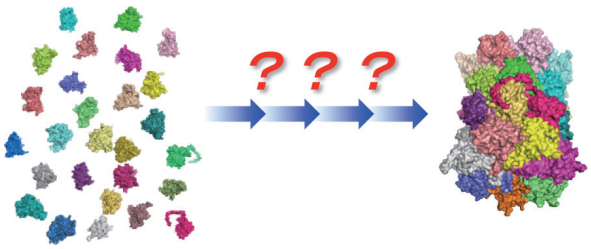

Figure 1. Formation of supramolecular machinery through dynamic assembly and disassembly of biomolecules.

Selected Publications

- K. Kato and H. Yagi, "Current Status and Challenges in Structural Glycobiology," *Trends Carbohydr. Res.* **15**, 38–46 (2023).
- K. Kato, H. Yagi and S. Yanaka, "Four-Dimensional Structures and Molecular Designs of Glycans," *Trends Glycosci. Glycotechnol.* **34**, E85–E90 (2022).
- M. Yagi-Utsumi and K. Kato, "Conformational Variability of Amyloid-β and the Morphological Diversity of Its Aggregates," *Molecules* **27**, 4787 (2022).
- K. Kato, T. Yamaguchi and M. Yagi-Utsumi, "Experimental and Computational Characterization of Dynamic Biomolecular Interaction Systems Involving Glycolipid Glycans," *Glycoconjugate J.* **39**, 219–228 (2022).
- H. Yagi, S. Yanaka and K. Kato, "Structural and Functional Roles of the *N*-Glycans in Therapeutic Antibodies," in *Comprehensive Glycoscience, 2nd edition*, J. Barchi, Ed., Elsevier; Oxford, **vol. 5**, pp. 534–542 (2021).
- S. Yanaka, R. Yogo and K. Kato, "Biophysical Characterization of Dynamic Structures of Immunoglobulin G," *Biophys. Rev.* **12**, 637–645 (2020).

1. Exploring Dynamic Biomolecular Organization: Insights from Amyloid β Assembly and Protein Folding Analyses

Utilizing our structural analysis techniques, we enhanced and developed our collaborative research network both within and outside IMS to investigate the mechanisms governing the dynamic organization of biomolecules. Specifically, our focus was on exploring the dimerization process during the early stages of amyloid β (Aβ) protein oligomerization, a process implicated in the onset of Alzheimer's disease. Through molecular dynamics (MD) simulations and in vitro assays, we uncovered that intramolecular electrostatic interactions between the Arg5 side chain and the carboxyl terminal play a pivotal role in the dimerization of Aβ42 (in partnership with the Okumura group).[1] The Aβ protein is recognized for its interaction with GM1 ganglioside, a glycolipid abundant in neuronal cell membranes, and its role in promoting the formation of amyloid fibrils. Our investigation encompassed a comprehensive three-dimensional structural analysis of the GM1-Aβ complex using solid-state NMR and MD simulations, revealing a distinctive assembly characterized by a double-layered antiparallel β structure.[2] Furthermore, our findings indicate that this specific Aβ assembly does not undergo a transition into amyloid fibrils directly. Instead, it facilitates the conversion of Aβ monomers into amyloid fibrils by presenting a hydrophobic surface composed of β sheets on the GM1 glycan (in collaboration with the Nishimura and Okumura groups).

We also pursued an analysis of protein folding processes using NMR techniques. Using hydrogen/deuterium exchange NMR spectroscopy, we captured residual structural information in proteins denatured by 6 M guanidinium chloride (in collaboration with Dr. Kunihiro Kuwajima of the University of Tokyo),[3] and by capturing proteins within the cavity of spherical self-assembling complexes, we were able to observe hysteresis behavior in the folding and refolding processes of proteins (in collaboration with Dr. Makoto Fujita of the University of Tokyo and IMS).[4]

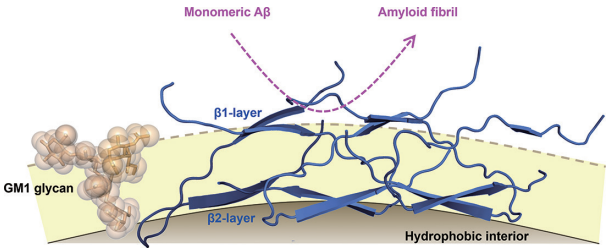

Figure 2. Schematic drawing of Aβ assemblage on GM1-containing membrane which catalytically promotes amyloid fibrillization. The distance between β1- and β2-layers of the assemblage is almost the same as the GM1 glycan dimension. The β1-layer provides a catalytic hydrophobic surface evoking fibril formation in GM1-sugar clusters.

2. Exploration, Design, and Control of Higher-Order Functions Arising from Multidomain Proteins

Multidomain proteins can manifest intricate functions through cooperative interactions and allosteric regulation, achieved by spatial rearrangements of their constituent domains. Our study delved into the potential of utilizing multidomain proteins as a foundation for Förster resonance energy transfer (FRET) biosensors, with a specific focus on protein disulfide isomerase (PDI) and Lys48-linked ubiquitin (Ub) chains as model cases.

The substrate-recognition domains of PDI undergoes redox-dependent conformational changes. Both experimental and computational approaches were employed to characterize FRET efficiency across various redox states of these domains fused with fluorescent proteins as the FRET acceptor and donor. In vitro and in vivo assessments revealed heightened FRET efficiency of this biosensor in the oxidized form of PDI, underscoring domain reorganization and its responsiveness to intracellular redox environments.[5]

On a different note, the conformational flexibility of Lys48-linked diUb presented a distinctive framework for engineering Ub-based biosensors, enabling the detection of environmental conditions like temperature and pH, as well as the recognition of binding molecules. The present findings emphasized the sensitivity of the open-closed conformational equilibrium of diUb to modifications at position 48 of the distal Ub unit, offering a means to manipulate its conformational distribution.[6]

Furthermore, our investigation into the impact of serum proteins on the functionality of therapeutic antibodies revealed that the human serum albumin (HSA) and the Fab region of serum immunoglobulin G (IgG) non-competitively inhibit antibody-dependent cellular cytotoxicity mediated by the interaction of Fcγ receptor III (FcγRIII) with rituximab, an anti-CD20 mouse/human-chimeric IgG1.[7] Stable-isotope- assisted NMR data demonstrated the interaction of HSA with the Fab and Fc regions of rituximab, as well as the extracellular domain of FcγRIII. These findings suggest the significance of considering interactions with serum proteins in the design and application of therapeutic antibodies.

References

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6) M. Hiranyakorn *et al.*, *Int. J. Mol. Sci.* **24**, 6075 (2023).
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