Dynamical Ordering of Biomolecular Systems for Creation of Integrated Functions

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Education
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Professional Employment
1991 Assistant Professor, The University of Tokyo
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Awards
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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.

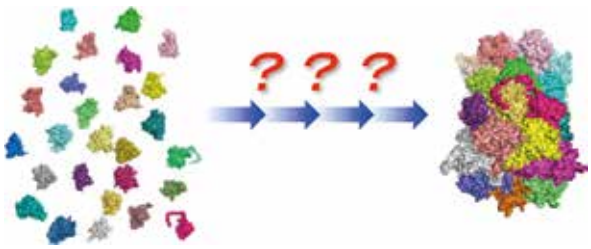

Figure 1. Formation of supramolecular machinery through dynamic assembly and disassembly of biomolecules.

Selected Publications

- K. Kato, H. Yagi and T. Yamaguchi, "NMR Characterization of the Dynamic Conformations of Oligosaccharides," in *Modern Magnetic Resonance, 2nd Edition*, G. A. Webb, Ed., Springer International Publishing, pp. 737–754 (2018).
- T. Yamaguchi and K. Kato, "Molecular Dynamics of Gangliosides," in *Gangliosides*, S. Sonnino and A. Prinetti, Eds., Methods in Molecular Biology, Humana Press; New York, **vol. 1804**, pp. 411–417 (2018).
- K. Kato and T. Satoh, "Structural Insights on the Dynamics of Proteasome Formation," *Biophys. Rev.* **10**, 597–604 (2018).
- K. Kato, S. Yanaka and H. Yagi, "Technical Basis for Nuclear Magnetic Resonance Approach for Glycoproteins," in *Experimental Approaches of NMR Spectroscopy*, The Nuclear Magnetic Resonance Society of Japan, Ed., Springer Nature; Singapore, pp. 415–438 (2018).
- T. Ikeya, D. Ban, D. Lee, Y. Ito, K. Kato and C. Griesinger, "Solution NMR Views of Dynamical Ordering of Biomacromolecules," *Biochim. Biophys. Acta, Gen. Subj.* **1862**, 287–306 (2018).

1. Characterization of Structural Dynamics and Interactions of Immunoglobulin G Glycoprotein

Immunoglobulin G (IgG) is a major serum glycoprotein that exerts antibody functions in the immune system, coupling antigen recognition in the Fab region with a variety of effector functions promoted in the Fc region. Therefore, detailed exploration of the structural dynamics and interactions of IgG is essential to gain deeper insights into their immune functions. We characterized the interaction of IgG-Fc with its cognate receptor (FcγR) using small-angle neutron scattering and molecular dynamics simulation.[1,2] The results revealed conformational deformation of Fc upon the interactions, underscoring the significance of existence of the *N*-glycans of these glycoproteins. In particular, our studies demonstrate that core fucosyaltion of the Fc *N*-glycans disrupts optimum intermolecular interactions mediated by the complex-type *N*-glycan at specific position of FcγRIIIa.[2,3]

We also characterized the antibody interactions using stable-isotope-assisted NMR spectroscopy. We established spectral assignments of FcγRIIIb and IgG-Fc.[4,5] Moreover, we successfully observed methyl-TROSY peaks originating from IgG with a molecular mass of 150 kDa, employing tailored deuteration.[6] On this technical basis, we conducted *in-serum* NMR observation detecting semi-specific antibody interactions in physiologically relevant heterogeneous environments.[4,6]

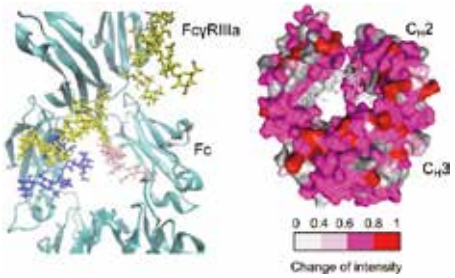

Figure 2. The dynamic view of IgG and its interactions.
Left figure: A snapshot from molecular dynamics simulation of Fc-FcγRIIIa complex. Right: Mapping of the interactions of IgG-Fc and serum components.

2. Dynamical Structures of Biomolecules toward Understanding the Mechanisms Underlying Their Functions

Our group employs multilateral biophysical and biochemical approaches for characterizing dynamical structures of various biomolecular systems that involve proteins, by integrating NMR spectroscopy, X-ray crystallography, high-speed atomic force microscopy, small-angle X-ray scattering, and cryo-electron microscopy. Our data demonstrated a two-step process for the disassembly mechanism of the eukaryotic proteasome, suggesting that scrap-and-build processes are involved in proteasome formation.[7] Based on structural information, we successfully endowed a functionally undefined archaeal protein with proteasome-activating activity by modifying its flexible C-terminal segment.[8] Furthermore, we revealed that an endoplasmic reticulum enzyme UGGT has a flexible modular structure in which the smaller catalytic domain is tethered to the larger folding-sensor region with variable spatial arrangements, offering structural insights into its working mechanism in the glycoprotein quality control system.[9] On the other hand, we created a series of synthetic neoglycolipids displaying functional glycotopes.[10] Surprisingly, the neoglycolipid micelles evoked selective apoptosis in undifferentiated neural stem cells. This serendipitous finding may offer a new strategy for controlling neural cell fates using artificial glycoclusters.

References

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2) Y. Sakae, T. Satoh, H. Yagi, S. Yanaka, T. Yamaguchi, Y. Isoda, S. Iida, Y. Okamoto and K. Kato, *Sci. Rep.* **7**, 13780 (2017).
3) H. Yagi, D. Takakura, L. T. Roumenina, W. H. Fridman, C. Sautès-Fridman, N. Kawasaki and K. Kato, *Sci. Rep.* **8**, 2719 (2018).
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5) R. Yogo, S. Yanaka and K. Kato, *Biomol. NMR Assignments* **12**, 201–204 (2018).
6) S. Yanaka, H. Yagi, R. Yogo, M. Yagi-Utsumi and K. Kato, *J. Biomol. NMR* **71**, 193–202 (2018).
7) T. Kozai, T. Sekiguchi, T. Satoh, H. Yagi, K. Kato and T. Uchihashi, *Sci. Rep.* **7**, 15373 (2017).
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10) H. Yagi, G. Yan, T. Suzuki, S. Tsuge, T. Yamaguchi and K. Kato, *Neurochem. Res.* **43**, 212–218 (2018).

Awards

YOGO, Rina; Poster Presentation Award, The 6th International Symposium on "Dynamical Ordering and Integrated Functions" (2018).
YAGI-UTSUMI, Maho; The Pharmaceutical Society of Japan Award for Young Scientists '18, The Pharmaceutical Society of Japan (2018).
SAITO, Taiki; Poster Presentation Award, ExCELLS Young Scientists Forum 2018 (2018).

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