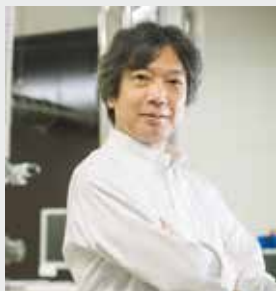


Dynamical Ordering of Biomolecular Systems for Creation of Integrated Functions

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1986 B.S. The University of Tokyo
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Professional Employment

1991 Assistant Professor, The University of Tokyo
1997 Lecturer, The University of Tokyo
2000 Professor, Nagoya City University
2008 Professor, Institute for Molecular Science
Professor, Okazaki Institute for Integrative Bioscience
Professor, The Graduate University for Advanced Studies
2006 Visiting Professor, Ochanomizu University
2013 Project Leader, JSPS Grant in Aid for Scientific Research on Innovative Areas "Dynamical Ordering of Biomolecular Systems for Creation of Integrated Functions"

Awards

2000 The Pharmaceutical Society of Japan Award for Young Scientists
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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



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

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.

Selected Publications

- M. Yagi-Utsumi, T. Yamaguchi, R. Kitahara and K. Kato, "NMR Explorations of Biomolecular Systems with Rapid Conformational Exchanges," in *Molecular Science of Fluctuations Toward Biological Functions*, M. Terazima, M. Kataoka, R. Ueoka and Y. Okamoto, Eds., Springer; Japan, pp. 87–103 (2016).
- M. Yagi-Utsumi and K. Kato, "Structural and Dynamic Views of GM1 Ganglioside," *Glycoconjugate J.* **32**, 105–112 (2015).
- T. Satoh, T. Yamaguchi and K. Kato, "Emerging Structural Insights into Glycoprotein Quality Control Coupled with *N*-Glycan Processing in the Endoplasmic Reticulum," *Molecules* **20**, 2475–2491 (2015).
- Y. Zhang, T. Yamaguchi, M. Yagi-Utsumi, Y. Kamiya, Y. Sakae, Y. Okamoto and K. Kato, "Conformational Dynamics of Oligosaccharides Characterized by Paramagnetism-Assisted NMR Spectroscopy in Conjunction with Molecular Dynamics Simulation," in *Advances in Experimental Medicine and Biology*, Springer; Switzerland, **842**, pp. 217–230 (2015).
- T. Yamaguchi and K. Kato, "Paramagnetism-Assisted Nuclear Magnetic Resonance Analysis of Dynamic Conformations and Interactions of Oligosaccharides," in *Glycoscience: Biology and Medicine*, Springer; Japan, **1**, pp. 137–145 (2014).

1. Characterization of Dynamic Process of Protein Assembly and Disassembly

In our group, various physicochemical and biochemical approaches are integrated to characterize assembly and disassembly of proteins exemplified by formation of proteasomes and cargo receptor complexes. The core part of the eukaryotic proteasome contains heteroheptameric rings composed of α 1-7 subunits. Among these homologous subunits, α 7 is spontaneously assembled into a homotetramer having a double ring structure as shown by our crystallographic analysis. Intriguingly, our native mass spectrometric (MS) data indicate that this double ring is disrupted upon addition of α 6, suggesting that proteasome formation involves the disassembly of non-native oligomers, which are assembly intermediates.¹⁾ Furthermore, we characterized the pH-dependent coiled-coil interactions of yeast putative cargo receptors (Emp46p and Emp47p), identifying the key residue that controls this interaction.²⁾ These results contribute toward understanding the molecular mechanisms underlying the dynamic cargo receptor assembly in the yeast secretory pathway. Our findings will provide a framework for designing molecular assembly and disassembly systems mediated by intermolecular interactions.

2. Structural Basis of Drug-Induced Conformational Change of HIV-1 Reverse Transcriptase

Human immunodeficiency virus type 1 reverse transcriptase (HIV-1 RT) is an important target for antiviral therapy against acquired immunodeficiency syndrome. Using NMR and native MS methods, we characterized the interactions between the heterodimeric HIV-1 RT enzyme and non-nucleoside reverse transcriptase inhibitors with different inhibitory activities.^{3,4)} We also applied a paramagnetism-assisted NMR technique for detecting the inhibitor-induced conformational change of HIV-1 RT, offering a strategy to identify allosteric inhibitors.⁵⁾ Our approaches thus provide useful tools in protein-based drug screening in developing anti-HIV drugs.

3. Interactions of Amyloidogenic Proteins with Membranes and Molecular Chaperones

Lipid membranes provide active platform for dynamic interactions of a variety of biomolecules on cell surfaces. Our

solid-state NMR data of amyloid β (A β) employing 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC) vesicle as model membrane have elucidated the membrane-induced dichotomous conformation of A β , in which the disordered N-terminal segment is followed by the stable C-terminal β strand, providing an insight into the molecular processes of the conformational transition of A β coupled with its assembly into parallel β structures (Figure 2).⁶⁾

It has been proposed that molecular chaperones actively contribute to the suppression of toxic aggregate formation of various neurodegenerative disordered proteins. We identified a *chaperone-philic* binding motif of α -synuclein on the basis of NMR data and determined the crystal structure of its complex with the substrate-binding domains of protein disulfide isomerase (PDI) (Figure 2).⁷⁾ Our findings provided a structural basis for the mechanism underlying the redox-dependent substrate binding of PDI.

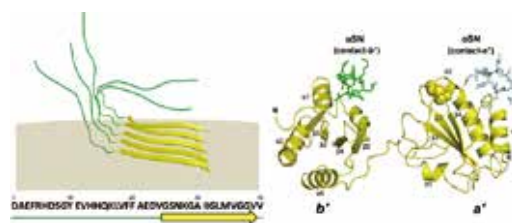


Figure 2. Structural model of A β (1–40) bound to DMPC bilayers characterized by solid-state NMR analyses (left). Crystal structure of the oxidized PDI *b'*–*a'* domains complexed with the α SN peptide (right).

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- 2) K. Ishii, H. Enda, M. Noda, M. Kajino, A. Kim, E. Kurimoto, K. Sato, A. Nakano, Y. Kobayashi, H. Yagi, S. Uchiyama and K. Kato, *PLoS One* **10**, e0140287 (2015).
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- 4) R. Thammaphorn, K. Ishii, M. Yagi-Utsumi, S. Uchiyama, S. Hannongbua and K. Kato, *Biol. Pharm. Bull.* **39**, 450–454 (2016).
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- 6) M. Yagi-Utsumi, K. Kato and K. Nishimura, *PLoS One* **11**, e0146405 (2016).
- 7) M. Yagi-Utsumi, T. Satoh and K. Kato, *Sci. Rep.* **5**, 13909 (2015).

Awards

YOGO, Rina; Best Presentation Award, The Tokai Branch Meeting of the Pharmaceutical Society of Japan (2015).

TONG, Zhu; Poster Presentation Award, The 4th International Symposium of “Dynamical ordering of biomolecular systems for creation of integrated functions” (2015).

TONG, Zhu; Young Scientist Award, The 12th Forum of the Glycoscience base for Chubu (2015).

YANAKA, Saeko; The 32nd Inoue Research Award for Young Scientists (2016).

YANAKA, Saeko; Poster Award, The 80th Annual Meeting of Chubu Branch, the Japanese Biochemical Society (2016).

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