Dynamical Ordering of Biomolecular Systems for Creation of Integrated Functions

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Professional Employment
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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 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.

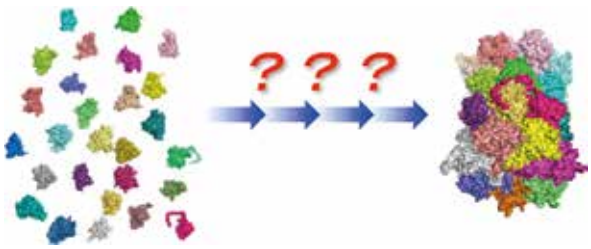

Figure 1. Formation of supramolecular machinery through dynamic assembly and disassembly of biomolecules.

Selected Publications

- 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).
- Y. Kamiya, T. Satoh and K. Kato, "Recent Advances in Glycoprotein Production for Structural Biology: Toward Tailored Design of Glycoforms," *Curr. Opin. Struct. Biol.* **26**, 44–53 (2014).
- Y. Kamiya, T. Satoh and K. Kato, "Molecular and Structural Basis for *N*-Glycan-Dependent Determination of Glycoprotein Fates in Cells," *Biochim. Biophys. Acta, Gen. Subj.* **1820**, 1327–1337 (2012).

1. Exploration of Conformational Spaces of Flexible Oligosaccharides

Conformational dynamics are essential properties of biomacromolecules that are involved in molecular recognition events in living systems. The motional freedom of three-dimensional structures can endow them with adaptability to various interaction partners, occasionally in promiscuous fashions. We employed stable isotope- and lanthanide-assisted NMR approaches in conjunction with replica-exchange molecular dynamics (REMD) simulations to obtain atomic descriptions of the conformational dynamics of high-mannose-type oligosaccharides, which harbor intracellular glycoprotein-fate determinants in their triantennary structures.[1] The experimentally validated REMD simulation provided quantitative views of the dynamic conformational ensembles of the complicated, branched oligosaccharides, and indicated significant expansion of the conformational space upon removal of a terminal mannose residue during the functional glycan-processing pathway (Figure 2).

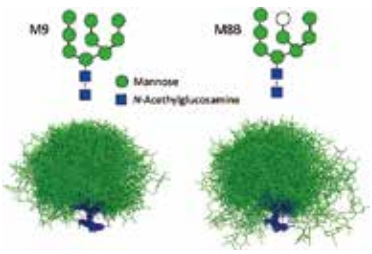

Figure 2. Superimpositions of 240 conformers derived from NMR-validated replica exchange MD simulations of the high-mannose-type M9 (left) and M8B (right) oligosaccharides.

2. Structural Characterization of Biomolecular Interactions Involved in Protein Fate Determination

Using NMR spectroscopy and X-ray crystallography, we characterized structures and interactions of multidomain proteins involved in fate determination of other proteins in living systems. In the endoplasmic reticulum, folding of newly synthetized proteins is facilitated through interaction with various proteins including molecular chaperones. We determined three-dimensional structures of the putative substrate-binding domains of UDP-glucose:glycoprotein glucosyltransferase (UGGT), a folding sensor enzyme, and protein disulfide isomerase (PDI), a folding catalyst, underscoring the importance of conformational changes in substrate recognition.[2,3]

Many of proteins in cells are destroyed primarily by ubiquitin-/proteasome-mediated protein degradation system. We applied a paramagnetic NMR technique to determine the mode of substrate recognition by the Josephin domain of ataxin-3, which has an endo-type deubiquitinase activity.[4] Moreover, our NMR study revealed that Ump1, a proteasome assembly chaperone, is an intrinsically unstructured protein and largely devoid of secondary structural elements.[5]

Our NMR data also contributed to providing structural bases of interactions of amyloidogenic proteins with self-assembled spherical complex displaying a gangliosidic glycan cluster (collaboration with Dr. Sota Sato, Tohoku University and Dr. Makoto Fujita, the University of Tokyo) and with SorLA, a neuronal sorting receptor considered to be a major risk factor for Alzheimer's disease (in collaboration with Dr. Junichi Takagi, Osaka University).[6,7]

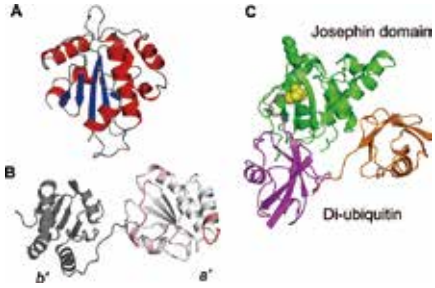

Figure 3. 3D Structures of (A) the Trx3 domain of UGGT, (B) PDI *b'-a'* domains, and (C) the Josephin domain of ataxin-3 complexed with di-ubiquitin.

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3) K. Inagaki, T. Satoh, S. G. Itoh, H. Okumura and K. Kato, *Chem. Phys. Lett.* **618**, 203–207 (2015).
4) T. Satoh, A. Sumiyoshi, M. Yagi-Utsumi, E. Sakata, H. Sasakawa, E. Kurimoto, Y. Yamaguchi, W. Li, C. A. P. Joazeiro, T. Hirokawa and K. Kato, *FEBS Lett.* **588**, 4422–4430 (2014).
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Awards

TONG, Zhu; Young Presentation Award, The 87th Annual Meeting of the Japanese Biochemical Society (2014).
YAGI-UTSUMI, Maho; Poster Presentation Award, The 3rd International Symposium of "Dynamical ordering of biomolecular systems for creation of integrated functions" (2015).
SIKDAR, Arunima; Poster Presentation Award, The Winter School of Sokendai/ Asian CORE Program (2015).

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