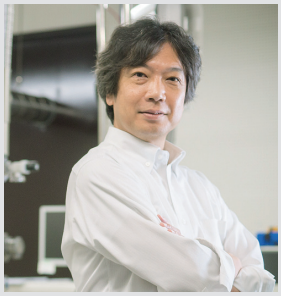
Dynamical Ordering of Biomolecular Systems for Creation of Integrated Functions

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



KATO, Koichi
Professor
[kkatonmr@ims.ac.jp]

Education
1986 B.S. The University of Tokyo
1991 Ph.D. The University of Tokyo

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 (–2018)
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"
2018 Professor, Exploratory Research Center on Life and Living Systems (ExCELLS)

Awards
2000 The Pharmaceutical Society of Japan Award for Young Scientists
2011 The Pharmaceutical Society of Japan Award for Divisional Scientific Promotions
2011 The 48th Baelz Prize

Member
Associate Professor
YAGI-UTSUMI, Maho*
YANAKA, Saeko†
Assistant Professor
KANDA, Tomoya
Post-Doctoral Fellow
IWASAKI, Miyuki
SAITO, Taiki
TATEO, Seigo
HAYASHI, Seiichiro
Graduate Student
SEKI, Takehito
NAKANO, Rio‡
HOSHINA, Mei‡
TAKAGI, Katsuki‡
NISHIZAKI, Ryuhei‡
Technical Support Staff
NISHIO, Miho
KAMIJO, Masahiro
NIIMI, Shiori
Secretary
FUKUTOMI, Yukiyo

Keywords Biomolecule Organization, NMR

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.

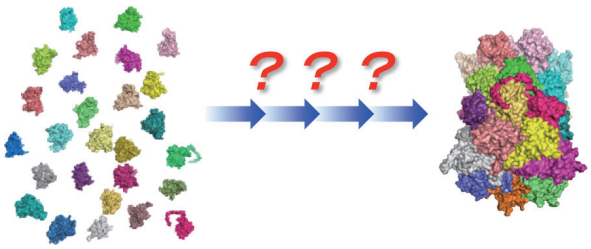


Figure 1. Formation of supramolecular machinery through dynamic assembly and disassembly of biomolecules.

Selected Publications

- H. Yagi, K. Takagi and K. Kato, "Exploring Domain Architectures of Human Glycosyltransferases: Highlighting the Functional Diversity of Non-Catalytic Add-On Domains," *Biochim. Biophys. Acta, Gen. Subj.* **1868**, 130687 (2024).
- 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. Comprehensive Multi-Scale Analysis of Protein Glycosylation: Structural, Functional, and Evolutionary Insights

Glycosylation, a diverse post-translational modification, is ubiquitous among proteins in nature. Our research group employs a multi-scale approach, from molecular to cellular levels, to elucidate the intricate mechanisms of protein glycosylation. In the Human Glycome Atlas Project, we are conducting research to obtain comprehensive and systematic information about human glycosylation.[1)] In humans, approximately 200 glycosyltransferases orchestrate the complex process of glycosylation. To gain insights into their molecular architecture, we analyzed the domain architecture of these enzymes using the AlphaFold Protein Structure Database.[2)] Our investigation particularly focused on non-catalytic add-on domains, systematically categorizing their structures and potential functions.

Concurrently, we examined the Golgi apparatus, the primary organelle of glycosylation, to unravel its spatiotemporal dynamics and glycoprotein transport pathways. We established a technical foundation for the localization analysis of glycosyltransferases within the Golgi apparatus using super-resolution microscopy.[3)] Our study of sub-Golgi distribution patterns of N-glycan diversifying enzymes revealed subtle localization differences even among enzymes presumed to coexist within the same Golgi compartment (Figure 2). Importantly, we revealed molecular codes within CTS regions as crucial determinants of their sub-Golgi localization.

We also conducted structural and functional analyses of molecular systems involved in glycoprotein folding and degradation.[4,5)] These analyses provided novel insights into the fate determination of glycoproteins within the cell through glycan recognition.

Furthermore, through collaborative research with the Deep-Sea and Deep Subsurface Life Research Group at ExCELLS, we performed glycoproteomic analysis of archaea, yielding important findings that enhance our understanding of the evolutionary dynamics of glycosylation and the molecular basis of microbial interactions in extreme environments.[6,7)]

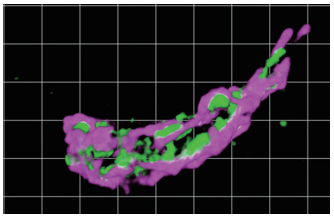


Figure 2. 3D images of two glycosyltransferases. Dual-color 3D super-resolution microscopy image of the Golgi ribbon area of an Expi293F cell expressing B3GALT6-mScarlet (magenta) and FUT9-mNeonGreen (green).

2. Biophysical Characterizations of Antibody Functions and Protein Dynamics

We also worked to elucidate the mechanisms of higher-order functional expression through the dynamics of biological molecular systems, utilizing various biophysical methods. In particular, we conducted collaborative research with the Biomolecular Dynamics Observation Group at ExCELLS, using high-speed atomic force microscopy (HS-AFM) to study interaction systems between antibodies and effector molecules central to immune defense.

While immunoglobulin G (IgG) bound to antigens forms hexamers to recruit the complement component C1q, we previously reported that a mouse IgG mutant lacking the Cγ1 domain binds to C1q and activates the complement pathway regardless of antigen presence. In this study, using HS-AFM, NMR spectroscopy, and mutation experiments, we revealed that the deletion of the Cγ1 domain enhances binding between the C_L domain and C1q through electrostatic interactions, enabling a monomeric IgG molecule to activate the complement system without forming hexamers (Figure 3).[8)]

Furthermore, quantitative analysis of the interaction between therapeutic antibodies and Fcγ receptors using HS-AFM revealed that the dwell times of antibodies on effector molecules are robust indicators of therapeutic antibody efficacy.[9)]

These studies highlight previously unknown potential binding sites for effector molecules within IgG molecules, paving the way for developing more refined therapeutic antibodies with tailored interactions.

Moreover, as part of an international collaboration at ExCELLS, we performed dynamic structural analysis of the human ATAD2 AAA+ histone chaperone to elucidate the communication mechanism between subunits.[10)] This work was a joint achievement with Dr. Ji-Joon Song from the Korea Advanced Institute of Science and Technology and the Biomolecular Dynamics Observation Group at ExCELLS.

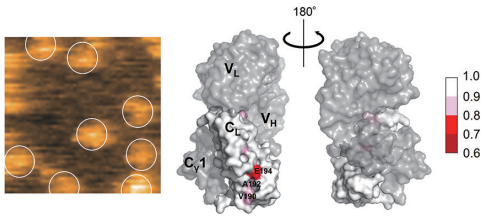


Figure 3. Characterization of interaction between the IgG C_L domain and complement component C1q using HS-AFM (left) and NMR (right) analyses.

References

1) K. F. Aoki-Kinoshita *et al.*, *Glycobiology*, in press (2024).
2) H. Yagi *et al.*, *Biochim. Biophys. Acta, Gen. Subj.* **1868**, 130687 (2024).
3) H. Yagi *et al.*, *Cell Struct. Funct.* **49**, 47–55 (2024).
4) S. Ninagawa *et al.*, *eLife* **12**, RP93117 (2023).
5) T. Satoh *et al.*, *FEBS Lett.* **598**, 2259–2268 (2024).
6) S. Nakagawa *et al.*, *BBA Adv.* **6**, 100118 (2024).
7) S. Nakagawa *et al.*, *J. Bacteriol.* **206**, e0020524 (2024).
8) S. Yanaka *et al.*, *Int. Immunol.* **36**, 405–412 (2024).
9) S. Yanaka *et al.*, *Biol. Pharm. Bull.* **47**, 334–338 (2024).
10) C. Cho *et al.*, *Commun. Biol.* **6**, 993 (2023).

* from Nagoya City University
† from Kyushu University
‡ carrying out graduate research on Cooperative Education Program of IMS with Nagoya City University