Dynamical Ordering of Biomolecular Systems for Creation of Integrated Functions

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Professional Employment
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2018 Professor, Exploratory Research Center on Life and Living Systems

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.

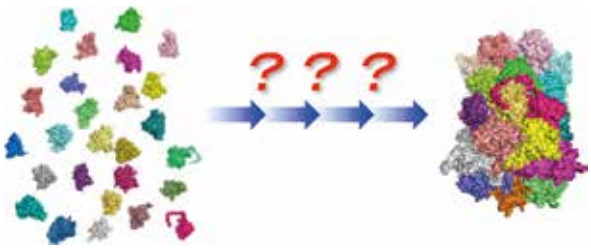

Figure 1. Formation of supramolecular machinery through dynamic assembly and disassembly of biomolecules.

Selected Publications

- S. Yanaka, R. Yogo, R. Inoue, M. Sugiyama, S. G. Itoh, H. Okumura, Y. Miyanoiri, H. Yagi, T. Satoh, T. Yamaguchi and K. Kato, "Dynamic Views of the Fc Region of Immunoglobulin G Provided by Experimental and Computational Observations," *Antibodies* **8**, 39 (2019).
- T. Sekiguchi, T. Satoh, E. Kurimoto, C. Song, T. Kozai, H. Watanabe, K. Ishii, H. Yagi, S. Yanaka, S. Uchiyama, T. Uchihashi, K. Murata and K. Kato, "Mutational and Combinatorial Control of Self-Assembling and Disassembling of Human Proteasome α Subunits," *Int. J. Mol. Sci.* **20**, 2308 (2019).
- S. G. Itoh, M. Yagi-Utsumi, K. Kato and H. Okumura, "Effects of a Hydrophilic/Hydrophobic Interface on Amyloid-β Peptides Studied by Molecular Dynamics Simulations and NMR Experiments," *J. Phys. Chem. B* **123**, 160–169 (2019).
- H. Yagi, S. Yanaka and K. Kato, "Structure and Dynamics of Immunoglobulin G Glycoproteins," in *Glycobiophysics*, Y. Yamaguchi and K. Kato, Eds., Springer Nature; Singapore, pp. 219–235 (2018).
- T. Satoh and K. Kato, "Structural Aspects of ER Glycoprotein Quality-Control System Mediated by Glucose Tagging," in *Glycobiophysics*, Y. Yamaguchi and K. Kato, Eds., Springer Nature; Singapore, pp. 149–169 (2018).

1. Exploration of Protein Assembly Dynamics

We characterized a variety of protein assembly systems using an integrative biophysical approach to provide deeper insights into the biomolecular organization. One of the most striking examples of sophisticated protein assembly is the formation of the proteasome, which is a huge enzyme complex harboring four layers of heteroheptameric rings (*i.e.*, two α and two β rings). We focused on the mechanisms underlying the formation of the α ring that comprises seven different but homologous α subunits. They are correctly assembled via transient interactions with assembly chaperones. We comprehensively characterized the assembly states of the α subunits of the human proteasome, thereby controlled their assembly and disassembly using mutational and combinatorial techniques.[1] In addition, we provided a molecular and structural basis for the mechanism of α subunit assembly mediated by the chaperone complex as a molecular matchmaker[2] (Figure 2).

Our approach has been applied to other protein assembly systems.[3] We successfully characterized the interaction between cyanobacterial clock proteins through the combined use of NMR spectroscopy and native mass spectrometry.[4] Furthermore, we are addressing the molecular mechanisms underlying the environment-dependent self-assembly of proteins into filamentous structures, as exemplified by amyloid formation in microgravity and tardigrade protein assembly occurring during desiccation.

Figure 2. Three-dimensional model of the complex comprising the PAC3/PAC4 heterodimeric chaperon and proteasome subunits α4, α5, and α6.

2. Characterization of Structural Dynamics and Interactions of Immunoglobulin G Glycoproteins

Immunoglobulin G (IgG) molecules play pivotal roles in the immune system as multifunctional glycoproteins, coupling between antigen recognition and effector functions. The Fab region of each IgG binds to its specific antigen, whereas the Fc region interacts with the effector proteins typified by Fcγ receptors (FcγRs), depending on Fc glycosylation, particularly fucosylation. To date, crystallographic studies have been performed to elucidate the molecular mechanisms underlying IgG functions, primarily using isolated Fab and Fc fragments. We aimed to provide dynamic views of IgG-Fc by performing molecular dynamics (MD) simulations, which were experimentally validated using X-ray scattering and NMR spectroscopy. The results indicated that the dynamic conformational ensembles of Fc encompass most of the previously reported crystal structures in the free and FcγR-bound forms, although the major Fc conformers in solution significantly deviated from the crystal structures[5] (Figure 3). Furthermore, we found that glycans restrict the motional freedom of Fc and provide quaternary-structure plasticity via multiple intramolecular interaction networks. Particularly, the fucosylation of Fc glycans restricts the conformational freedom the proximal amino acid residue of functional importance, thereby preventing its interaction with FcγRIIIa, an FcγR isoform that mediates antibody-dependent cellular cytotoxicity. Moreover, based on integrated biophysical experiments, we demonstrated that the Fab portion of IgG is directly involved in its interaction with FcγRIIIa in addition to the canonical Fc-mediated interaction.[6] Our findings could inspire novel therapeutic antibody engineering targeting the previously unidentified receptor-interaction sites in IgG-Fab.

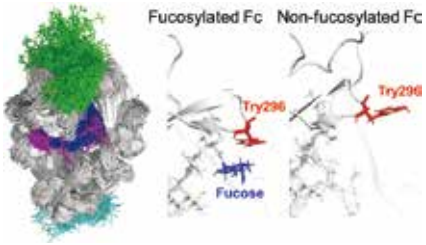

Figure 3. Dynamic views of the Fc region of IgG obtained by experimental and computational observations. This depiction shows the conformational ensemble of IgG-Fc derived from MD simulation (left) and the typical conformational snapshots of the functionally important tyrosine residue (Tyr296) derived from the major conformational states of the fucosylated (middle) and nonfucosylated (right) forms of Fc.

References

1) T. Sekiguchi *et al.*, *Int. J. Mol. Sci.* **20**, 2308 (2019).
2) T. Satoh *et al.*, *Int. J. Mol. Sci.* **20**, 2231 (2019).
3) S. G. Itoh *et al.*, *J. Phys. Chem. B* **123**, 160–169 (2019).
4) Y. Yunoki *et al.*, *Life Sci. Alliance* **2**, e201900368 (2019).
5) S. Yanaka *et al.*, *Antibodies* **8**, 39 (2019).
6) R. Yogo *et al.*, *Sci. Rep.* **9**, 11957 (2019).

Awards

YOGO, Rina; Excellent Student Presentation Award, the 139th Annual Meeting of the Pharmaceutical Society of Japan (2019).
HONDA, Rena; Tokai Branch Chief Award, The Chemical Society of Japan (2019).
SAITO, Taiki; Young Scientist Award, The 6th Joint Nagoya Meeting: Future perspectives on structural/functional analyses and molecular design of biomolecules (2019).
KOFUJI, Kana; The Best Presentation Award, The Tokai Branch Meeting of the Pharmaceutical Society of Japan (2018).
HONDA, Rena; Young Scientist award, The 15th Forum of the Glycoscience base for Chubu (2018).

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