Dynamical Ordering of Biomolecular Systems for Creation of Integrated Functions

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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

- 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. Zhang, T. Yamaguchi and K. Kato, "New NMR Tools for Characterizing the Dynamic Conformations and Interactions of Oligosaccharides," *Chem. Lett.* **42**, 1455–1462 (2013).
- 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).
- K. Kato and Y. Yamaguchi, "Glycoproteins and Antibodies: Solution NMR Studies," in *Encyclopedia of Magnetic Resonance*, John Wiley; Chichester, **vol.3**, pp. 1779–1790 (2012).
- O. Serve, Y. Kamiya and K. Kato, "Redox-Dependent Chaperoning, Following PDI Footsteps," *Proteomics Res. J.* **3**, 69–79 (2012).
- Y. Kamiya, M. Yagi-Utsumi, H. Yagi and K. Kato, "Structural and Molecular Basis of Carbohydrate–Protein Interaction Systems as Potential Therapeutic Targets," *Curr. Pharm. Des.* **17**, 1672–1684 (2011).

1. Dynamic Orchestration of Proteasomes

Recently accumulated evidence has demonstrated that the assembly of the eukaryotic 26S proteasome is not due to spontaneous self-organization but due to an ordered process assisted by several proteins called 'proteasome assembly chaperones' that transiently associate with the assembly intermediates at certain steps in the proteasome assembly pathway.

To provide structural basis for quaternary structure formation of the proteasome and its consequent activation, we conducted structural study by employing X-ray crystallography and NMR spectroscopy. By inspection of our structural data, a working model is proposed in which the proteasome assembly chaperones Pba3-Pba4 and Nas2 act as molecular matchmakers and offer checkpoints, respectively, during the proteasome formation (Figure 2).[1,2] The proteasome assembly chaperones can be potential therapeutic targets for drug discovery.[3]

We also performed conformational characterization of an intrinsically disordered protein in complex with an archaeal proteasome activator, PbaB, by NMR spectroscopy combined with small-angle neutron scattering using an inverse contrast matching method.[4]

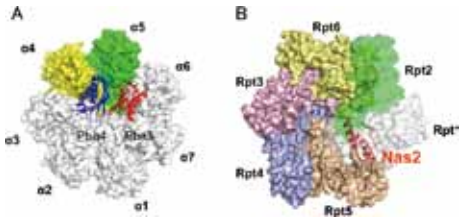

Figure 2. 3D models of (A) the proteasome α-ring complexed with the Pba3–Pba4 heterodimer and (B) the proteasome ATPase ring complexed with Nas2.

2. Functional Mechanisms of Glycans

The carbohydrate chains displayed on proteins play pivotal roles in a variety of molecular recognition events on cell surfaces as well as in intracellular environments. The intermolecular interaction systems involving the carbohydrate moieties could be potential therapeutic targets for various diseases.

In the early secretory pathway, *N*-glycans serve as tags recognized by cargo receptors having lectin activities. Our crystallographic data provide structural basis for disparate sugar-binding specificities in the homologous cargo receptors ERGIC-53 and VIP36, the former of which shows a broader specificity and lower binding affinity to the high-mannose-type oligosaccharides, irrespective of the presence or absence of the nonreducing terminal glucose residue at the D1 arm (Figure 3).[5]

Dystroglycanopathy is a major class of congenital muscular dystrophy that is caused by a deficiency of functional glycans on α-dystroglycan (α-DG) with laminin-binding activity. We demonstrated that a product of a recently identified causative gene for dystroglycanopathy, AGO61, is indispensable for the formation of laminin-binding glycans of α-DG. Furthermore, our results indicate that functional α-DG glycosylation was primed by AGO61-dependent GlcNAc modifications of specific threonine-linked mannosyl moieties of α-DG. These findings provide a key missing link for understanding how the physiologically critical glycan motif is displayed on α-DG and provides new insights on the pathological mechanisms of dystroglycanopathy.[6]

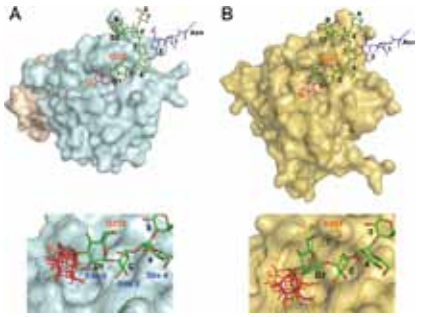

Figure 3. Structural models of the lectin domains of (A) ERGIC-53 and (B) VIP36 with monoglucosylated high-mannose-type oligosaccharides.

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Awards

YAMAGUCHI, Takumi; Presentation Award, The 7th Symposium on Biofunctional Chemistry (2013).
YAMAGUCHI, Takumi; The 3rd NINS Prize for Young Scientists (2014).

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