Dynamical Ordering of Biomolecular Systems for Creation of Integrated Functions

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.

Selected Publications

1. Design and Creation of Neo-Glycomolecules Based on Knowledge of Conformational Dynamics of Oligosaccharides

Exploration of the conformational spaces of flexible oligosaccharides is essential to gain deeper insights into their functional mechanisms. We characterized dynamic conformation of a high-mannose-type dodecasaccharide with a terminal glucose residue, a critical determinant recognized by molecular chaperones.1) The dodecasaccharide was prepared by our developed chemoenzymatic technique, which uses 13C labelling and lanthanide tagging to detect conformation-dependent paramagnetic effects by NMR spectroscopy. The NMR–validated molecular dynamics simulation visualized the dynamic conformational ensemble of the dodecasaccharide, thereby delineating the spatial distribution as well as the glycosidic linkage conformation of the terminal glucose determinant. Moreover, comparison of our results with previously reported crystallographic data indicates that the chaperone binding to its target oligosaccharides involves an induced-fit mechanism (Figure 2). Furthermore, our crystallographic data of glucosidase II revealed how the catalytic subunit recruits the regulatory subunit for cooperative recognition of the glucosylated high-mannose-type oligosaccharide, thereby providing structural basis of glycoprotein quality control in the endoplasmic reticulum.2)

We also attempted to design and develop cyborg supra-molecular systems having unique molecular recognition properties. We successfully created a self-assembled, Lewis X-expressing glycoccluster by hybridizing a spherical metal–organic complex with a synthetic oligosaccharide derivative.3) The self-assembled glycocclusters exhibited homophilic hyper-assembly in aqueous solution in a Ca2+-dependent manner through specific carbohydrate–carbohydrate interactions, offering a unique structural scaffold for functional biomimetic systems (Figure 3).

Figure 2. Comparison of our NMR-validated simulation results (right) with the previously reported crystallographic data (left) indicate that the chaperone binding to its target oligosaccharides involves an induced-fit mechanism.

Figure 3. Ca2+-dependent hyper-assembly of self-assembled glyco-clusters mediated by specific carbohydrate–carbohydrate interactions.

2. Dynamical Structures of Biomolecules toward Understanding the Mechanisms Underlying Their Functions

Here we summarize our recent findings obtained by employing integrative biochemical and biophysical approaches for structural characterization of various biomolecular systems that involve proteins, including NMR spectroscopy, X-ray crystallography, solution scattering, and mass spectrometry (MS).

We determined a crystal structure of the human proteasome assembling chaperone PAC4 and characterized the interaction with its binding partner PAC3.4) Furthermore, we applied native MS and small-angle neutron scattering data to structural characterization of the circadian clock protein complex.5) Moreover, we successfully addressed the functional roles of the enzymes related to dystroglycanopathy, which is a major class of congenital muscular dystrophy caused by a deficiency of functional glycans on α-dystroglycan (αDG) with laminin-binding activity. By employing nanoLC-MS/MS analytical workflow in conjunction with a panel of mutated cells deficient in one of these enzymes, we revealed additional modifications on phosphorylated O-glycans of αDG, suggesting functional interplay among these enzymes through their interactions.6)

References

Awards
YOGO, Rina; The Best Poster Award, OIIB retreat (2016).
YUNOKI, Yasuhiro; The Young Scientist Award, The 4th Joint Nagoya Meeting: Future perspectives on structural/functional analyses and molecular design of biomolecules (2016).
YOGO, Rina; Poster Award, The 81st Annual Meeting of Chubu Branch, the Japanese Biochemical Society (2017).
YUNOKI, Yasuhiro; Poster Award, The 81st Annual Meeting of Chubu Branch, the Japanese Biochemical Society (2017).

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