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EDITORIAL

Introduction to the special issue on chemical glycobiology: all the aspects are important

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Biological reactions and interactions occurring in cells, in organs, in organisms, and between different species are chemical processes. The mechanisms underlying such interactions and transformations involved in individual processes are all considered under the purview of chemical biology.

The historical record indicates that carbohydrate chemistry has been important in developing an understanding of chemical aspects of biology. The mutarotation phenomenon was discovered in the nineteenth century; it was later understood to be caused by the anomerization, equilibrium of the intramolecularly formed hemiacetals and aldehyde. This phenomenon was closely related to a process for quality control of sugar, which was an important commercial product of the time. The stereochemistry of carbohydrates has formed the foundation of organic stereochemistry. In due course, our knowledge of biological molecules was greatly expanded. In the twentieth century, structures of blood-type determinants were determined to be glycans, which were then used as synthetic targets. Since the biological roles of many glycans have been elucidated, synthesizing probes to investigate their functions further has become a major trend. The field of chemical biology has emerged recently because of the advent of the use of synthetic molecules to probe biological systems. This change in research trends, although not limited to this, reflects an expansion of research direction and recognition of the necessity of investigating the dynamic process of carbohydrate transformation in living systems.

In chemical biology investigations, various aspects of orthogonality play conceptually important roles. First, a chemical handle, which should not affect endogenous reactions but have a unique reactivity enabling introducing a reporter group such as fluorescent group for imaging, has to be introduced into a probe molecule. The probe molecule or its metabolites can be now visualized. The detection process should not interrupt any ongoing chemical or biological reactions as well. Considering properties such as spatiotemporal resolution, non-invasiveness, and accessibility, confocal fluorescence scanning microscopy is often used for cell imaging. Moreover, other aspects such as methodological developments and improvements, chemical synthesis of probe molecules, and advancement of the analysis platforms are crucial.

In recognition of the above aspects in chemical biology, this special issue is formed to cover (1) chemical ways to visualize cell-surface glycans by using a series of chemically functionalized monosaccharides, called metabolic oligosaccharide engineering (or metabolic glycoengineering), (2) lipo-chitooligosaccharide that is important in symbiotic relationship between nitrogen-fixing bacteria and plant, and (3) methodology development in various aspects including glycoarray, targeting and imaging live animals taking advantage of glycoclusters, a new photochemical approach for the specific glycan cleavage, and an NMR method utilizing paramagnetic probes to investigate dynamism of glycoconjugates. These mini-reviews and review articles are followed by four original articles dealing with the metabolic oligosaccharide engineering, the enzyme-mediated activation of radical sources for the analysis of neighboring proteins, chemical synthesis of UDP-Gal analogue as a useful probe protein *O*-GlcNAcylation investigation, and a design and synthesis of hyaluronan-related pentasaccharide derivatives to improve affinity towards CD44.

M. R. Pratt and K. N. Kelly provide an overview of chemical methods that enables visualization of the major types of mammalian cell surface glycoproteins. Monosaccharides with

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preinstalled chemical reporter groups, which are bioorthogonal to cellular reactions, are summarized. Investigations using analogues of ManNAc, as the sialic acid precursors, sialic acid, GalNAc, and Fuc, are summarized. K. J. Yarema and colleagues introduce less explored bacterial metabolic glycoengineering. In comparison to the mammalian metabolism, specific difficulties and challenges are summarized. Incorporation of the chemical reporter group into cell wall-related compartments such as LPS and peptidoglycan using bacteria-specific monosaccharide analogues and derivatives was described. Furthermore, future prospects for the technology are discussed.

J. Fliegmann and J.-J. Bobo describes the lipochitooligosaccharides, known as Nod factors, produced by nitrogen-fixing rhizobia, signaling molecules involved in the establishment of a symbiosis with plants. Unlike modern chemical biology approaches, the approaches used in the investigation of Nod factors are rather classical, but they surely are regarded as chemical biology. The receptors of Nod factors as discovered by genetic and biochemical approaches are also presented.

In the "functional glycomics," a variety of methodological investigations are necessary. Such investigations include (1) glycoarray technology, (2) method of preparation of glycans either by chemical synthesis or by isolation from natural sources, (3) structural analysis method, and (4) functional analysis method.

X. Song and colleagues provide an overview of the glycoarray technology with a highlight on methodological aspect for the preparation of necessary glycans. An entry of a chemical method using *N*-bromosuccinimide is summarized. Furthermore, an introduction of a fluorescent reporter group at a position between the individual glycans and support material enables faster access to the affinity studies. The reporter group is also useful in structural analysis. The method forms a foundation of functional glycomics. K. Toshima and D. Takahashi introduce a new chemical way of releasing glycans by cleaving a specific glycosidic bond by means of a mild photochemical process with the aid of specific boronate or hydrogen bond formation. X.-L. Sun and colleagues describe the recent developments of glycoarray investigations with highlights on "glyco-macroligands." With a recognition of important issues of 2D arrays including sensitivity problem and three-dimensional presentation properties, the mini-review summarizes the investigations on multimeric glycan presentation using glycopolymers, dendrimers, neo-glycoproteins, nanoparticles, and liposomes. K. Tanaka and colleagues summarize their targeting and imaging approach utilizing complex yet accessible conjugates of glycoclusters and radioactive chelate. The use of glycoclusters instead of monomers is advantageous for targeting by enhancing their specific bindings and incorporation. With incorporation of radiolabels, the positron emission tomography enables the delivery kinetics study in live animals.

To facilitate functional glycomics research, the structural analysis is of extreme importance. Such analysis methods typically include X-ray crystallography, mass spectrometry (MS), and nuclear magnetic resonance (NMR). Although the special issue could not cover the crystallography and MS of which importance is very much obvious, an NMR method was included. K. Kato and T. Yamaguchi describe the applications of paramagnetism-assisted NMR techniques in the elucidation of glycan structure. Incorporation of a paramagnetic probe at the reducing end of glycan affects the signal intensities and/or chemical shifts depending on the distance between the probe and individual protons, which resolve the peak overlap problems often found in glycan NMR spectra. Taking advantage of the long-range atomic distance information, the method is useful in obtaining the overall structure and/or dynamic nature of a glycan.

This special issue also includes a series of original articles describing metabolic oligosaccharide engineering, enzyme-mediated activation of radical sources, and chemical synthesis of compounds those might be useful in this field such as UDP-Gal analogue and hyaluronan-related pentasaccharides.

J. J. Kohler and colleagues describe a different metabolic outcome depending on the cell types employed. They point out the efficiency of enzymes such as cytosolic esterases, kinases, and phosphatases acting on the probe molecules differs, which further suggests future research directions to improve or enhance the metabolic oligosaccharide engineering technique.

Finding specific partners that interplay important biological functions is very important in glycobiology or any biology research area. To facilitate the type of investigations, a method forming chemical bond between molecules acting together is often utilized. K. Honke and colleagues describe a modified method of investigating associating proteins that they termed as enzyme-mediated activation of radical sources (EMARS). A fluorescein coupled to tyramide was successfully used in conjunction with HRP fusion protein. In the presence of hydrogen peroxide, adjacent protein to HRP is specifically labeled by fluorescein-tyramide enabling live cell imaging.

Y. Sakamoto and colleagues describe efficient synthesis of a potent chemical probe molecule, namely UDP-2-(ketopropyl)galactose, which has been used in the investigation of *O*-GlcNAcylated proteins by introducing a chemical handle for further tagging. X. Lu and X. Huang describe synthesis of hyaluronan (HA)-related pentasaccharide library and inhibition results against HA-CD44 binding. Non-reducing tetrasaccharide used as the starting material is prepared from HA by means of hyaluronidase, which was coupled with a series of reducing end monosaccharides carrying substituent groups.

Glycoconjugates play pivotal roles in cytosolic and luminal fluids, on the membrane, and at extracellular space. Many such compounds still require further investigation for a better understanding of biological systems. One of the problems in

glycoscience might relate to the difficulty pointing an example of single function of the glycoconjugate. This may hinder recognition of the importance of the field to non-specialists. However, this does not deny the importance of glycoscience of course. Most of the glycoscience researches are more or less basic researches. Basic researches often spread its direction into diversity, which itself, I believe, is important. Diversity is the basis of a blossom that comes afterward. I hope that this special issue in chemical glycobiology, comprising of a small collection of review, mini-reviews, and original articles, helps shed light on the complexity of cellular systems.

To conclude, I would like to thank all the contributors of this issue. I also thank the reviewers who gave helpful discussions. The role as a guest editor has special meaning for me, because the Institute of Glycoscience where I belong is going to close with a recognition that its first objective has been accomplished in our university. Professor Akemi Suzuki, former President of the institute, gave me an opportunity in this occasion, and Editor-in-Chief Professor Hans Vliegenthart agreed to this idea of course. At last, I sincerely thank both professors for kindly providing me an opportunity and hand-to-hand guidance.