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Integrative Glycobiology and Future Perspectives

Given the fact that over 50% of proteins in eukaryotes are glycosylated, it should be no surprise that the field of glycoscience is now one of the most important fields of research in science. The NAS report on "Transforming Glycoscience: the roadmap in the future" published in 2013 highlights the significance and importance of glycoscience in the future, and it is now clear that glycoscience will have an impact on both basic science and applied science in the fields of glycobiology and glycotechnology.

While the former editor-in-chief of this Journal, Dr. Bill Lennarz, made a number of significant contributions to the field of glycobiology, he stepped down from his position of chief editor of BBRC, even though he continues to serve as a board member. I agreed to serve as the editor of a special issue on glycobiology because it is a subject of great interest to me and it provides me with an opportunity to thank Bill for his continuous support for glycobiology research worldwide.

Ten years ago I served as a co-organizer of the joint meeting of the Japanese Society of Carbohydrate Research (JSCR) and the Society for Glycobiology (SFG) as a representative of JSCR, and Bill also participated in that meeting, where we enjoyed the science as well as a Hula dance at the banquet which was a memorable event for both of us. In November 16–18, as the president of SFG, I will serve as an organizer of a joint meeting of SFG and JSCR in Hawaii. The focus of this meeting is similar to the title of this special issue and is entitled "Integrative Glycoscience from Biology and Chemistry to Medicine". The publication of this special issue on glycobiology could not have come at a more opportune time.

In this special issue I discussed possible authors with Dr. Tadashi Suzuki in our group who used to work with Bill and finally asked those who worked with Bill under his guidance and/or who were collaborators or members in the same department to contribute to this special issue. Fortunately many people, who have published many review articles or contributed to special issues in other journals or other book chapters, accepted my invitation even though they are very busy.

The title of this special issue is Integrative Glycobiology and Future Perspectives. This is because, as we know, glycobiology is related to a variety of research areas, such as developmental biology, iPS/stem cell research, microbiology, immunology, neuroscience, and various medical science fields including biomarker development and therapeutics. However, because of the complexity and heterogeneity of glycan chains as compared to proteins or the genome, convenient techniques found in other research fields such as PCR cloning or protein/DNA sequencers/synthesizers are currently not available in glycobiology. For characterizing glycan structures, techniques such as mass spectrometry, including MALDI-TOF MS, etc. are available, but more in-depth techniques continue to be needed. Therefore, more glycobiologists should be encouraged to actively collaborate with scientists of other areas in order to develop various updated techniques and integrate them into glycoscience. If papers that appear in this special issue will provide us with some hints for future studies in glycoscience, as an editor of this special issue, I will be rewarded.

Going back to basic science in glycobiology, the focus of most data, including mine, have been on changes of a single glycan or a single glycosylatransferase gene and their functionality. However, some of these changes are just a "snapshot" of glycans or glycosyltransferase genes and do not reflect the dynamic life cycles of these molecules in glycan metabolism. A glycomics approach using MALDI-TOF MS or other modern techniques could be used to identify important changes and dynamics in glycans. Also, gene targeting studies of glycosyltransferases in mice have revealed many interesting phenotypes or disease-like abnormalities, but again, these data sometimes reflect a snapshot of a glycan function, and do not fully explain the underlying mechanism of human disease. Therefore, a more dynamic approach by introducing various systems biology techniques is requisite for expanding the field of glycobiology. In this context, we need to develop novel approaches that will permit us to see "a movie" of the whole metabolic process of a glycan in cells.

Many scientists are used to working without thinking of output or applications to society or tax payers and simply enjoy science in a curiosity-driven manner. However modern scientific research requires intense funding because scientists frequently use reagents and modern equipment from commercial sources and also use experimental animals such as KO mice or transgenic mice to save time and all of these are usually very expensive. For these reasons, scientists are continually attempting to attract funding from governmental sources but sometimes the concept of a grant reflects political opinion and is based on various strategic projects proposed by the government in order to explain the output to tax payers or industries rather than pursuing research from a curiosity driven to a translational point of view. This tendency will sometimes cause scientists to become involved in more applied science and not in basic and fundamental science.

For the above reason, the focus of this special issue is mainly on basic research in glycobiology. I briefly describe and highlight each article below.

O.-V. Stichelen, L.K. Abramowits and J.A. Hanover report that the *OGT* gene is located on the X-chromosome near *XIST,* suggesting that *OGT* is subject to X-inactivation and that *OGT* expression could be sex-biased during the first step of embryogenesis. In females, *OGT* may escape X-inactivation, thus altering *O*-GlcNAcylation and disease development. These findings suggest

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that the gender of animals/cells must be considered when conducting *O*-GlcNAcylation studies.

S. Park et al. and J.W. Cho also focused on OGT, a key player in O-GlcNAcylation. Their finding show that its stability is regulated not only by proteasomes but by autophagy, which verified by using inhibitors of autophagy inducers or blocking the autophagy related gene, *Atg* gene. In conclusion protein-O-GlcNAc modification deceases by treatment with mTOR inhibitors (PP242 or Torin 1), and protein levels of OGT and OGA change in opposite directions under mTOR inhibition. In addition, inhibition of autophagy or proteasome restores OGT protein in HepG2 cells.

T. Suzuki and Y. Harada provide a current overview of free oligosaccharides (fOSs) and phosphorylated oligosaccharides (POSs) generated in mammalian cells and *Saccharomyces cerevisiae*. They also report on the underlying mechanism by which these oligosaccharides are generated. fOSs and POSs are liberated from dolichol-linked oligosaccharides at the ER membrane. Meanwhile, fOSs are also generated in cytosol by degycosylation of misfolded N-glycoproteins. The novel pathways constitute the so-called ''non-lysosomal'' degradation pathway for glycans.

V. Sharma, M. Ichikawa and H. Freeze report on some very unique features of mannose which has bimodal properties. For some patients with congenital disorders of glycosylation (CDG) this simple sugar is effective but not for the other CDG patients. Mammalian plasma contains 50-100 micro molar mannose and dietary mannose supplements raise it 3-5 fold. Mutations in mannose-metabolizing enzymes cause CDG, and mannose supplements are used to treat phosphomannose isomerase deficient CDG patients. However, in mouse cases, mannose supplements kill *Mpi*-hypomorphic mouse embryos and blind survivors. Mannose is a routine remedy for urinary tract infections, but caution should be made during the pregnancy.

K. Kitajima and Y. Harada report on the interaction of HSP-90 with glycosaminoglycans such as heparan sulfate, heparin and dermatan sulfate with 2-O sulfated uronic acid residues, which bind tightly to HSP-90 and this will open new avenues for drug discovery. Namely, HSP70 was characterized for interaction with acidic glycans. Interacting directly with acidic glycans with sulfated Gal and GlcNAc residues, Hsp70 forms a large complex with a particular group of GAGs including heparin. The ATPase domain of Hsp70 is responsible for the interaction with acidic glycans. Peptide-binding domain of Hsp70 stabilizes the complex with the particular GAGs.

H. Takeuchi and R. Haltiwanger report on the molecular mechanism by which O-fucose, O-GlcNAc, O-GalNAc and O-glucose glycans affect Notch signaling and also describe the implication of this in various diseases. On the Epidermal Growth Factor –like repeats of Notch in its extracellular domain, these multiple O-linked modifications are found, and Notch signaling is regulated by these glycosylation. Defects in the glycosylation of Notch lead to a variety of human disorders.

D.B. Hizal et al. provide an overview of the significance of sialic acid in potassium and sodium channels which are highly associated with neuromuscular disorders or CDG patients with those disorders. Therefore sialylation may play a significant role in neurological, neuromuscular and cardiovasucular diseases. Alterations in sialylation may have effects on voltage gated ion channel activation and inactivation kinetics. Moreover, changes in glycosylation may have an impact on normal development and aging.

J. Sun, Z. Deng and A. Yan overview the significance of multi-drug resistance to drugs with a particular focus on the inhibition of the efflux pomp in terms of anti-drug resistance intervention. Bacterial multi-drug efflux pumps constitute an important class of resistance determinant. The RND efflux pump utilizes a three-step, functional rotating mechanism to expel drugs. The bacterial efflux pumps have broad physiological functions. Expression of efflux genes is subjected to regulation by local, global and the two component systems. Efflux pump inhibitors present as a promising intervention to treat bacterial infections.

H. Lee and H. Kim provide a mini-review of factors that can serve as determinants of membrane protein topology. Membrane topology is a two-dimensional structural information of a membrane protein. It is influenced by intrinsic protein sequence, translocation machinery and lipids. These factors governing membrane topology and the experimental tools are highlighted.

H. Sagami reports on polyisoprenoid alcohols from livers from various temperate sea fish using 2D-TLC, electrospray ionization (EST) mass spectrometry and NMR methods. The occurrence of novel dolichol derivatives with dehydro molecules in both dolichols and epoxy dolichols were found in fish and these derivatives are involved in the biosynthesis of dolichol-phosphate and, subsequently, dolichol-PP -oligosaccharides.

Frederic Troy and his group report that polysialic acid (PolySia) is expressed on neurons primarily during the early stages of neuronal development. Polysialyted neural cell adhesion molecule is expressed on neural stem cells from adult guinea pig spiral ganglion. PolySia is a biomarker that modulates neuronal differentiation in inner ear stem cells. These new findings suggest that the replacement of defective cells in the inner ear of hearing impaired patients with adult spiral ganglion neurons have the potential to improve the quality of life for patients with auditory dysfunctions and impaired hearing disorders.

Finally I wish to express my sincere thanks to all authors in this special issue for their contributions and to Ms. Fumi Ota, my assistant as well as all BBRC staff members for their efforts in publishing this special issue. Without their tremendous efforts this issue would not have been possible.

Naoyuki Taniguchi