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Sugar Chains as the Third Biomolecule, and Post-genome Researches

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1.1 Introduction

In recent years, the sugar chains, the third biomolecule, has been attracting people's attention like the first and second biomolecules, i.e., nucleic acid (DNA) and protein.

Most nucleic acids and proteins have many parts that are commonly found in almost all animal species, so it can be said that studies on those biomolecules are longitudinal types in terms of the evolutionary process of all species of animals. On the other hand, considering the fact that the structures and functions of sugar chains not only differ among different animal species but also vary even in the same species in accordance with organs, tissues or types of cells, it can be said that studies on sugar chains are cross-sectional types, in terms of the evolutionary process, aiming to clarify fundamental mechanisms underlying the biodiversity.

Therefore, it can be said that the study on sugar chains represents one of the significant challenges to be dealt with in parallel with the post-genome researches mainly concentrated on nucleic acids and proteins.

This article discusses the current state of studies on the functions and structures of sugar chains, and the future prospect of sugar chain studies.

1.2 What is the sugar chain like?

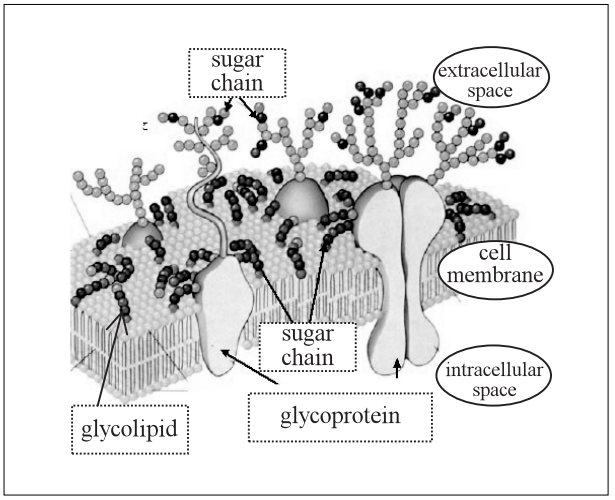
The human body is a huge cellular network consisting of about 60 trillion cells, and all of which have many sugar-chain molecules on their surfaces (Figure 1). ABO blood types, for example, are dependent on the antigenic properties of sugar chains on cell surfaces.

Sugar chains are involved in intercellular recognition and interaction, and play important roles in cellular network. Therefore, disturbance of cellular networks will result in the occurrence of, for example, cancer, chronic diseases, infectious diseases, senile changes, abnormalities in the immune system, brain, development, etc.

For example, cancerization of cells is known to be associated with structural changes of sugar chains. In addition, it is also known that pathogens such as Vibrio cholerae and influenza virus invade and infect host cells by recognizing specific sugar chains on cell surfaces and binding to them.

It is expected that the results of studies on sugar chain functions will be applied to various areas. For example, elucidation of sugar chain functions is expected to lead to the development of pharmaceutical and food products based on new theories, and contribute to the prevention and treatment of diseases.

Figure 1: Sugar chains on the cell membrane



Source: Press release issued by RIKEN (the Institute of Physical and Chemical Research) on November 20, 2001.

Table 1: Structure of components of organisms

Component	Constituent chain molecule	Basic unit of structure (chain)	Modes of binding between basic units
Nucleic acid	polynucleotide chain	nucleotide	phosphodiester bond
Protein	polypeptide chain	amino acid	peptide bond
Glucide	sugar chain (oligosaccharide chain, polysaccharide chain)	monosaccharide	glycosidic bond

Source: Authors' compilation based on the report (1990) on "Strategies for promoting comprehensive research and development in terms of the establishment of foundations of glycotechnology" (Request for advice No. 14) submitted by the Council on Avionic and Electric Technologies.

1.3 Structure of sugar chains

Major components of living organisms other than water include nucleic acid, protein, glucide and lipid. Fundamental data on the structures of nucleic acid, protein and glucide are shown in Table 1.

Sugar chains have bonded covalently with proteins and lipids in living organisms. About 60% of the proteins that makes up the bodies of living organisms takes the form of glycoprotein, which is produced through the covalent bonds of sugar chains with proteins.

Such sugar chains are often composed of two or more kinds of glucides. The human body contains 9 kinds of glucides, and they form various patterns of monosaccharide sequence. For example, for two molecules of a monosaccharide, 1,116 patterns of sequence can be created, and for three molecules of a monosaccharide, 119,736 patterns can be achieved.

In addition, when allowing not only for the sequence of monosaccharides in a sugar chain, but also for the manner(s) and site(s) of bonding of monosaccharides in a sugar chain, length and manner(s) of branching of a sugar chain, conformational structure of a sugar chain, etc., it can be easily conceivable that sugar chains assume far more complex structures as compared with nucleic acids (DNA) and proteins. Therefore, structures of sugar chains contain a wider variety of biological information than those of nucleic acids (DNA) and proteins.

However, because of the structural complexity and diversity of sugar chains, studies on them have lagged behind those on nucleic acids or protein, in spite of the recognition of the importance of such studies.

1.4 Current state of sugar chain studies in Japan

Figure 2 shows the major themes of sugar chain studies, which have been conducted with governmental support in Japan.

With the support given by government agencies, sugar chain studies in Japan have been on the top world-class level. For example, among the 110 sugar chain-related genes that have been discovered up until now in the world, 54 genes were identified in Japan.

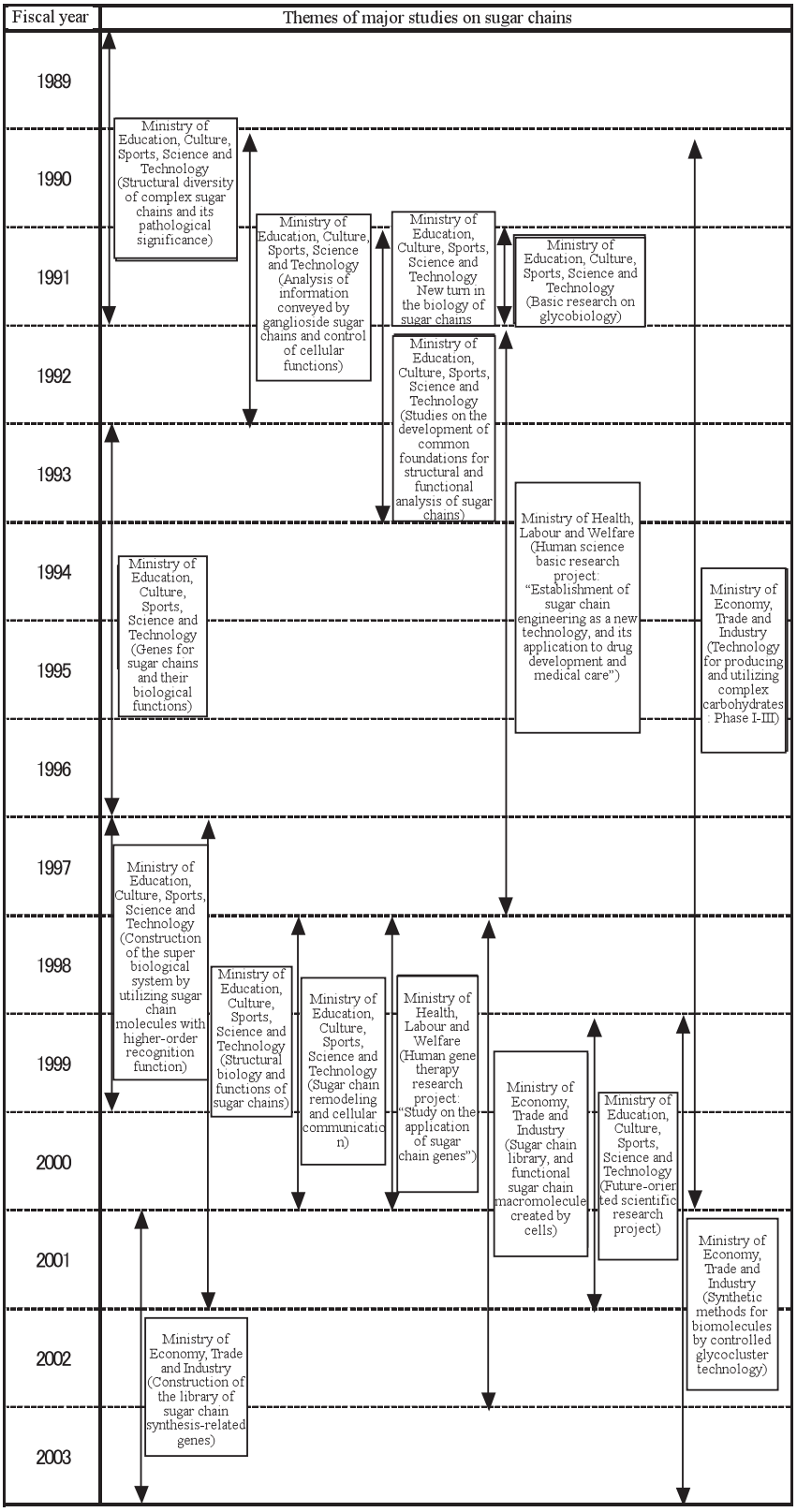
In fiscal year 2001, the Ministry of Economy, Trade and Industry started the program of the "construction of sugar chain synthesis-related genes library" as one of the "study programs for the foundations on which to do biotechnology research targeted at the maintenance and promotion of public health" and submitted a 500 million-yen fiscal 2001 budget request. The program aims to accomplish the cloning of about 300 genes for enzymes essentially involved in sugar chain synthesis as well as to conduct functional analysis of those genes to construct a functional database of them.

Furthermore, the Institute of Physical and Chemical Research (RIKEN) decided to include the "study on super-biomolecular system research" in the second-generation frontier research systems in October 1999. Under the project, RIKEN has pursued studies in the field of integrated sugar chain biology to clarify, for example, the contribution of sugar chain recognition and the mechanism of expression of sugar chain-related genes by the cells in the immune and nervous systems.

At present, it is earnestly hoped that automated sugar chain sequencers and automatic

synthesizers of selected sugar chains will be developed that may form the technological foundations of future studies on sugar chains. However, many challenges are to be addressed before the development of such technologies because of, for example, the highly complex structures of sugar chains and the difficulty of the extraction of sugar chains that sparsely exist intracellularly.

Figure 2: Themes of sugar chain studies in Japan



Source: Authors' compilation by making reference to the materials provided by Yoshitaka Nagai, director of the Mitsubishi Kagaku Institute of Life Sciences.

1.5 Future prospects of sugar chain studies

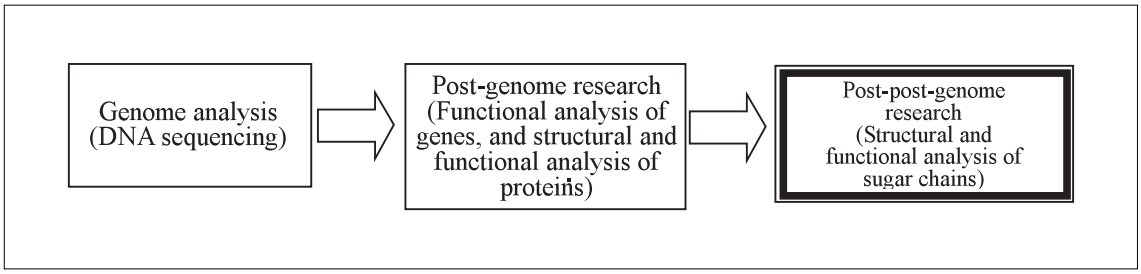
The study on sugar chains can be regarded as a category of the post-post-genome research following the post-genome researches that were pursued with gene function analysis as well as functional and structural analysis of proteins as the core (Figure 3).

A conceptual illustration of future prospects of sugar chain studies is given in Figure 4. Future studies on sugar chains can be roughly classified into 4 categories including "studies targeted at the elucidation of sugar chain structures," "studies targeted at the elucidation of sugar chain functions," "studies targeted at sugar chain synthesis" and "studies targeted at the application of the results to medicine."

Such studies on sugar chains are expected, for example, to lead to the elucidation of the mechanisms underlying fundamental life phenomena or become able to be applied to medicine through work in cooperation with researchers in other fields of life science.

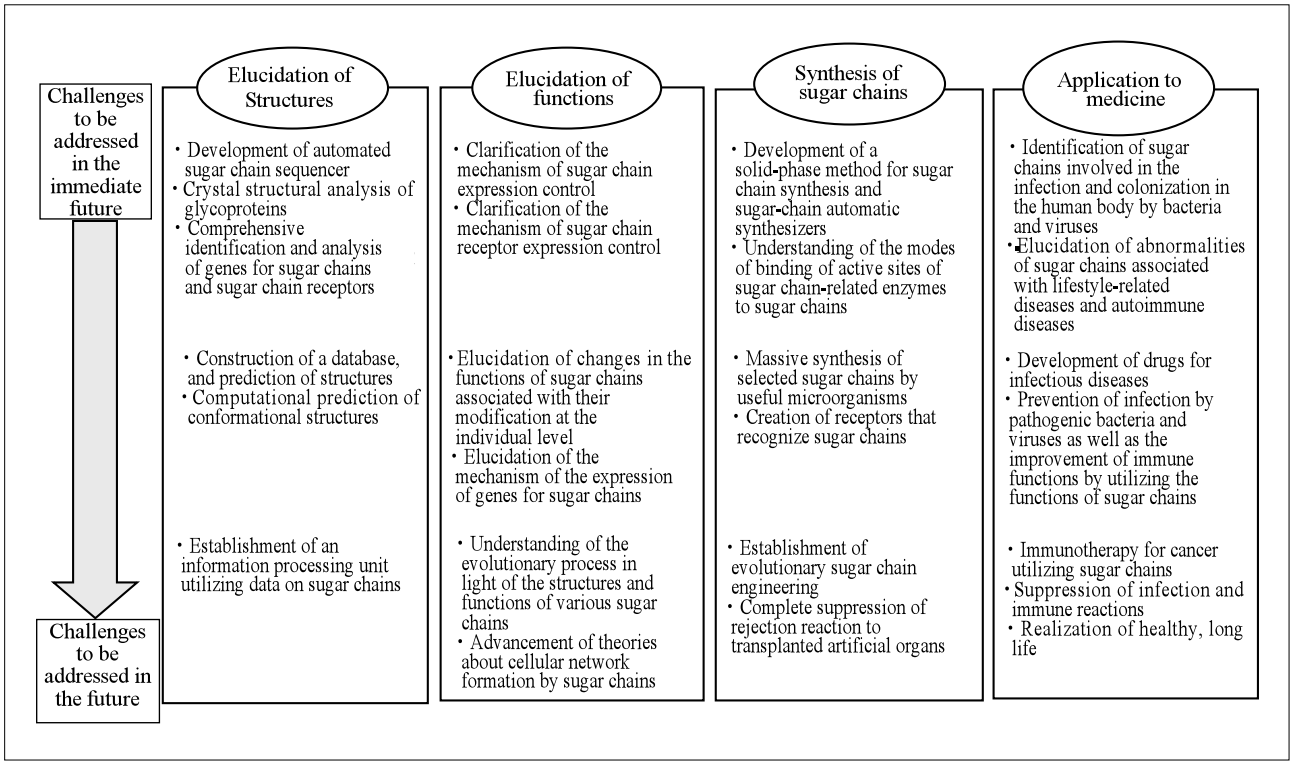
In the United States, efforts to promote sugar chain studies have been undertaken. For example, the National Science Foundation (NSF) held a workshop under the theme "Frontiers in Glycoscience" in May 2000. The report on this workshop points out that sugar chain studies in Japan are in an advanced state, and refers to the

Figure 3: Sugar chain studies as the post-post-genome research



Source: Authors' own compilation

Figure 4: Future prospects of sugar chain studies



Source: Authors' compilation by making reference to the materials provided by Yoshitaka Nagai, director of the Mitsubishi Kagaku Institute of Life Science

necessity of establishing programs and providing financial support for the purpose of promoting joint research in the United States by people in different academic fields (chemists and biologists), and summarizes the suggestions made in the workshop, for example, that construction of sugar chain-related databases in the United States should be promoted. In addition, the National Institute of Health (NIH) announced that it would start a project for promoting sugar chain studies on a 5-year budget of 4.4 billion dollars. Therefore, it can be said that, also in the United States, increasingly earnest efforts have been made to foster research on sugar chains.

1.6 Conclusion — suggestions for the promotion of sugar chain studies —

Recently, government support has been provided mainly for challenges to be dealt with in this era of post-genome research including the functional analysis of genes as well as the structural and functional analysis of proteins. Since studies on sugar chains may represent one of the important categories of post-post-genome research, which should be pursued from the present time when post-genome research is being carried forward, promotion of the employment of the following strategies is desired:

- **Recruitment of competent personnel from a wide variety of academic areas**
  Studies on sugar chains are accompanied by difficulties arising from their structural complexity and diversity. Hence, sugar chain studies need to be pursued comprehensively and strategically by tapping into the collective knowledge of people not only in the areas of biology, such as molecular biology and cell biology, but also by those in other various academic areas including chemistry, physics, engineering and agriculture.
- **Development of research systems**
  Studies on sugar chains in Japan have been on the top world-class level. In order not only to maintain the current level of research into the future, but also to elucidate the roles of sugar chains in life phenomena before any other countries, it may be effective to establish research systems under which world-class personnel can be assembled. It can be expected that products of sugar chain research will synergistically facilitate advancement in post-genome research.
- **Conceptual designs of the future direction for the promotion of sugar chain studies**
  Figure 4 entitled "Future prospects of sugar chain studies" is a conceptual drawing of the future direction for the promotion of sugar chain studies. It is expected that strategies for promoting sugar chain studies will be devised aiming to attain these goals.

Acknowledgements
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