Decoding glycocode using synthetic glycans

Department of Chemistry, Graduate School of Science
Assistant Professor Yoshiyuki Manabe Researchmap https://researchmap.jp/researchmap_manabe
Professor Koichi Fukase Researchmap https://researchmap.jp/read0076573

Abstract

Glycans, the third life chain, are involved in many biological phenomena, including infection, cell adhesion, immune response, and cancer. On the other hand, the diversity and heterogeneity of glycan structures make their functional analysis and regulation difficult. Thus, pharmaceutical applications of glycans have been limited. We aim to decode and utilize the glycan information (glycocode) based on our technology of precise glycan synthesis (Fig. 1). We hope that our project will lead to the creation of novel glycodrugs. We have achieved a practical synthesis of *N*-glycans (Fig. 2), which are representative post-translationally modified glycans, and have been studying their functions using synthetic compounds.

Background & Results

N-Glycans have diverse structures and exhibit various functions based on their structures. For example, sialic acids, which are located at the non-reducing end, provide a recognition site to many pathogens to be closely related to various infectious diseases. In addition, they also control immune responses through the recognition by their recognition lectins (Siglecs). We have been working on the chemical synthesis of *N*-glycans for analyzing their functions at the molecular level. A key step in *N*-glycan synthesis is the construction of branched structure. We employed the convergent route; the non-reducing end fragments are glycosylated at the 3- and 6-positions of branched mannose, respectively. These key glycosylations involve difficulties because the large fragments are linked at the sterically hindered positions. We have achieved these glycosylation in high yields by using ether solvents effect, which promoted the desired glycosylation by stabilizing the oxocarbenium ion intermediate. Furthermore, perfect stereoselectivity of these glycosylations was achieved by utilizing remote participation. These investigations realized practical synthesis of *N*-glycans. Here, we analyzed the molecular basis of sialic acid recognition by neuraminidase, which has important role in influenza infection (Fig. 3). To investigate the difference in recognition of the non-reducing terminal branches of *N*-glycans, we synthesized **1** and **2**, in which only one of the branches was labeled with deuterium. In addition, to evaluate the effect of the branching number (= number of sialic acids) on neuraminidase recognition, a tetraantennary *N*-glycan **3** was also synthesized. Analysis using these synthetic glycans revealed that the neuraminidase preferentially recognizes the sialic acid on the lower branch and that the number of branches has little effect on substrate recognition by the neuraminidase.

Significance of the research and Future perspective

Glycans are closely related to various diseases. For example, many diseases are caused by disturbances in homeostasis, and glycans play an important role in maintaining the homeostasis. Therefore, glycans are widely used as diagnostic biomarkers. We believe that elucidation and regulation of the glycan functions enables to restore the homeostatic disturbances in various diseases, including cancer, immunological disorders, and neurological disorders. Such unprecedented approach is expected to lead innovative glycodrug development.

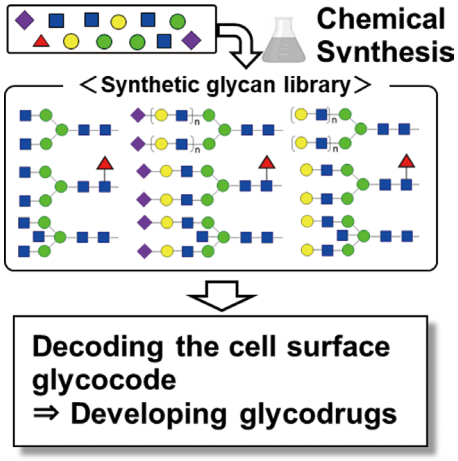

Fig. 1

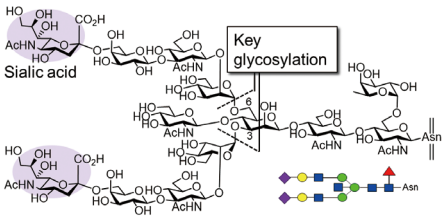

Fig. 2

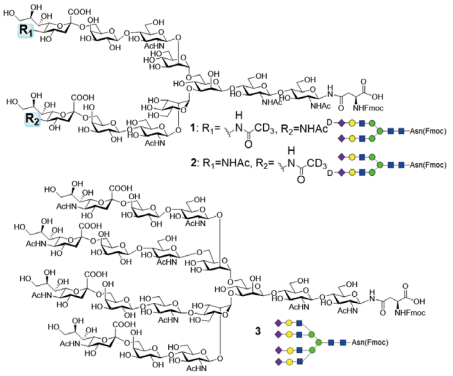

Fig. 3

Patent
Treatise Shirakawa, A; Manabe, Y; Fukase, K et al. Chemical Synthesis of Sialyl N-Glycans and Analysis of Their Recognition by Neuraminidase. Angew. Chem. Int. Ed. 2021, 60, 24686-24693, doi: 10.1002/anie.202111035
URL
Keyword glycocode, carbohydrate synthesis, glycan, *N*-glycan, immunity