Control of antibody dynamics and activity by glycan modification

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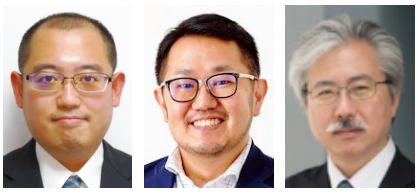

Abstract

Glycans, the third life chain, are involved in many biological phenomena. 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 elucidate and utilize the cell surface glycan function through chemical approach. Considering that glycans are conjugated with proteins or lipids in nature, we are investigating glycan functions by conjugating the synthesized glycans with other biomolecules, such as proteins. In this study, we conjugated the glycan to the antibody drug and successfully improve their immune induction activity by suppressing their internalization into cells. This study proposed a novel approach to exploit glycan functions for controlling protein activity.

Background & Results

Antibody drugs are one of the most important molecular-targeted drugs with high specificity. Conversely, their insufficient efficacy has been a critical issue in many cases. Thus, new trends in molecular-targeted drug development are enhancing the potency of antibody drugs. Here, we aimed to enhance antibody potency by controlling its dynamics on the target cell surface by conjugating glycan. Antibody activity is closely related to its dynamics. For example, when antibodies are taken up into the target cell by endocytosis, they cannot induce adequate immune responses. On the other hand, glycans cover the cell surface as a glycocalyx and interact with various molecules on the membrane, playing an important role in regulating the dynamics of biomolecules on the cell surface, including internalization by endocytosis. Therefore, we utilized the glycan-lectin interaction to regulate antibody dynamics and activity.

In this study, an anti-HER2 antibody, an anti-breast cancer antibody, was conjugated with galactose-containing *N*-glycan, and its internalization was suppressed by interaction with galectin-3, leading to the enhancement of immune induction activity. Although there are many reports on the modification of the inherent *N*-glycan structure of the Asn297 of antibodies, the present approach, in which the glycan was additionally attached to the antibody, proposes a novel approach to modulate antibody activity. To the best of our knowledge, this is the first demonstration of the active control of antibody dynamics by glycan conjugation. Since this method uses endogenous *N*-glycan and employs the glycan-lectin interaction in human bodies, no or few adverse effects are expected. Therefore, this approach might provide an alternative strategy for re-developing therapeutic antibodies and their candidates to improve potency.

Significance of the research and Future perspective

Glycans are the most abundant post-translational modification, and more than 60% of proteins are modified with glycans. The attached glycans regulate protein functions based on their structures. In this study, we propose a versatile method to control protein dynamics and activity by chemical conjugation of glycans, which is expected to be applied to upgrade the functions of various protein drugs.

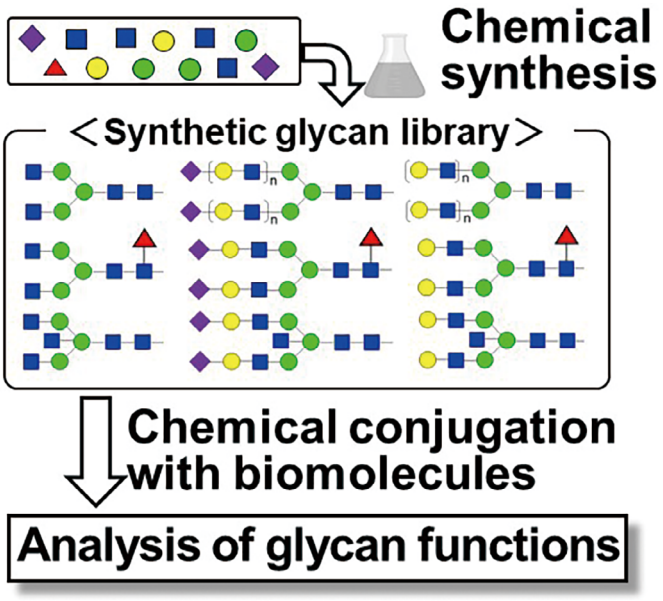

Figure 1 Elucidation and regulation of glycan functions by chemical approach

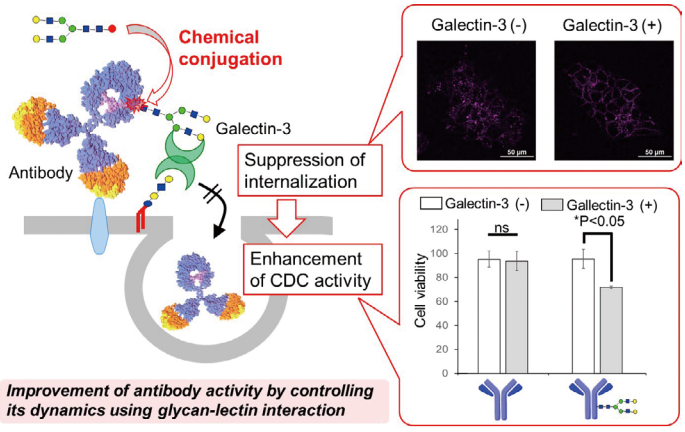

Figure 2 Control of antibody dynamics and potency by conjugating glycan

Patent

Treatise Manabe, Yoshiyuki; Kabayama, Kazuya; Fukase, Koichi et al. Improvement of antibody activity by controlling its dynamics using the glycan-lectin interaction. Angew. Chem. Int. Ed. 2023, 62, e202304779. doi: 10.1002/anie.202304779

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