Development of cancer immunotherapy using antigen glycan

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Abstract

Glycans, the third life chain, are involved in many biological phenomena. Especially, glycans cover the cell surface as glycocalyx and provide the milieu for the first contact of the cell with the outside environment, and therefore, they are closely related to self- and non-self-recognition processes, including immune responses. 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 functions by editing the glycocalyx using synthesized glycans. We herein introduced antigen glycan, whose antibodies abundantly exist in our body, to the cell surface and successfully induced strong immune responses to the target cancer.

Background & Results

Glycan antigens such as α-gal (trisaccharide structure) and α-rhamnose (α-Rha) are present in many organisms, such as bacteria, but humans do not have these glycans. Instead, humans have a large number of natural antibodies against these glycans. Therefore, these glycan antigens act as markers of non-self to induce strong immune responses. In this study, we utilized these antigen glycans for cancer immunotherapy. Namely, we introduced glycan antigens on the cancer cell surface to induce immune responses by recruiting their natural antibodies. After metabolic incorporation of azido-sugar to the cell surface glycocalyx followed by α-Rha introduction by the click chemistry, immune response was induced. To enhance the practicality of this method, we herein employed caged strategy, in which tentatively protected α-Rha was activated by photo-irradiation after the α-Rha introduction on cell surface. This strategy enhanced the efficacy of click chemistry by preventing the capture of α-Rha by their antibodies under promiscuous conditions. Furthermore, this strategy enables the switching of glycan functions by photo-irradiation. Considering that glycans function through the interactions with various biomolecules, spatiotemporal control of such interactions is essential for exploiting glycan functions and was achieved using the caging strategy.

Significance of the research and Future perspective

Glycans cover the cell surface and interact with many biomolecules to regulate various biological phenomena. Therefore, the technology to edit the glycan structures of the cell surface provides a new approach to control the event on bio-membranes, including immune responses, intercellular communication, and signal transduction. In this study, we proposed a versatile method to regulate the glycan functions of the cell surface by combining metabolic glycan-labeling and caged strategy. We believe that this approach enables practical functional control of cell surface glycan to provide an innovative method for realizing glycodrugs.

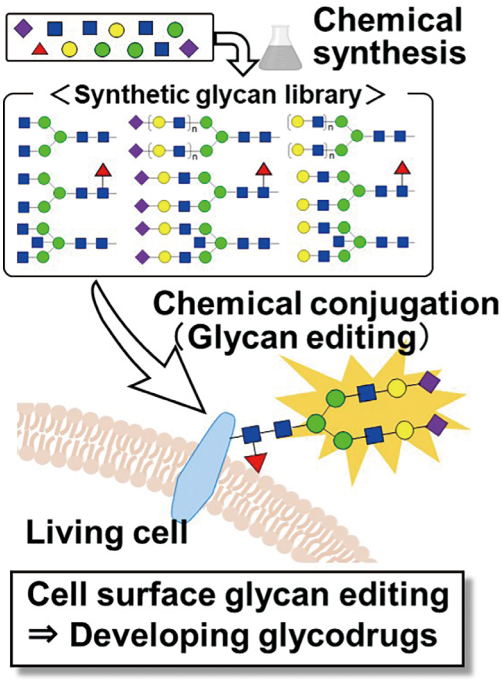

Figure 1 Functional analysis and regulation of cell surface glycans by chemical approach

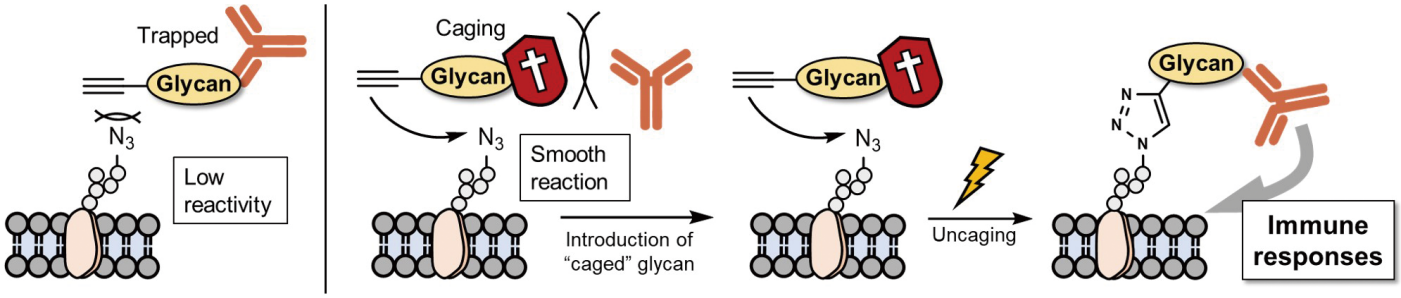

Figure 2 Immune induction through antibody recruiting strategy using caged glycan

Patent

Treatise Manabe, Yoshiyuki; Fukase, Koichi et al. Practical antibody recruiting by metabolic labeling with caged glycans. Angew. Chem. Int. Ed. 2023, 62, e202303750. doi: 10.1002/anie.202303750
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URL

Keyword glycan, antibody, immunity, photo-switching