【Grant-in-Aid for Scientific Research (S)】

Broad Section G

Title of Project：Biology of sugar-alcohol modification in glycan

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Research Project Number：19H05648　Researcher Number：30168827
Keyword：glycosylation, sugar-alcohol, post-translational modification

【Purpose and Background of the Research】

Glycosylation is an important post-translational modification of cell surface and intercellular molecules, regulating various physiological processes, such as molecular interactions and intracellular communications. We have found novel glycan modifications by sugar-alcohol phosphates (ribitol-phosphate and glycerol-phosphate) in mammals (Ref. 1,3). We also identified several enzymes involved in the sugar-alcohol phosphate modifications and revealed that a defect in ribitol-phosphate modification causes severe disorders such as congenital muscular dystrophy with brain malformation (Ref. 1,2). In the sugar-alcohol phosphate modification, ribitol or glycerol binds to saccharide through phosphodiester linkage, while typical glycans are formed by glycosidic linkage between monosaccharides. The sugar-alcohol phosphates have long been known as a component of bacterial cell wall, teichoic acid, but they have never been found in mammals. Interestingly, the mammalian sugar-alcohol phosphates are conserved as molecules with a function disinct from that in bacteria and are related to diseases. However, details of the metabolic pathway of mammalian sugar-alcohol phosphates are poorly understood. Additionally, the advantage of the usage of phosphodiester linkage in glycosylation is also unclear. In this study, we aim to elucidate the biological significance of sugar-alcohol phosphates modification in glycan formation.

【Research Methods】

In this study, we will focus on the following subject areas to elucidate the biological significance of sugar-alcohol phosphate modification:

1. Physicochemical characteristics: we will synthesize a series of glycans containing sugar-alcohol phosphate and examine their physicochemical properties.
2. Molecular basis of sugar-alcohol phosphate modification: the mechanism of modification will be elucidated by studies on the structural biology of related enzymes.
3. Metabolic pathway of sugar-alcohol phosphate modification: the enzymes responsible for synthesis and metabolism of sugar-alcohol phosphate will be elucidated by biochemical assays.
4. Target molecules of sugar-alcohol phosphate modification: specific detection methods for the modified glycans will be developed using chemical biology and antibodies or lectin-like molecules.
5. Biological function: the effects of sugar-alcohol phosphate deficiency on biological functions will be examined using genetically modified cells/animals.

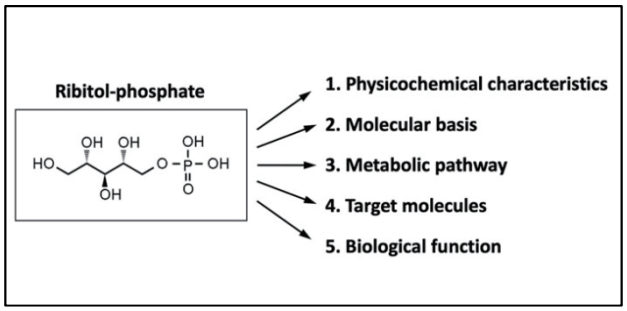

Figure 1. Research methods

【Expected Research Achievements and Scientific Significance】

The underlying molecular mechanism of sugar-alcohol modification and its biological significance will be elucidated by this study. Furthermore, the results will provide a pathomechanism of congenital muscular dystrophy and aid in the development of therapies.

【Publications Relevant to the Project】

1. Kanagawa M. et al. (2016) Identification of a post-translational modification with ribitol-phosphate and its defect in muscular dystrophy. *Cell Rep.*, 14, 2209-2223
2. Kuwabara N. et al. (2016) Carbohydrate-binding domain of the POMGnT1 stem region modulates *O*-mannosylation sites of α-dystroglycan. *Proc. Natl. Acad. Sci. USA*, 113, 9280-9285
3. Imae R. et al. (2018) CDP-glycerol inhibits the synthesis of the functional *O*-mannosyl glycan of α-dystroglycan. *J. Biol. Chem.*, 293, 12186-12198

【Term of Project】

FY2019-2023

【Budget Allocation】

135,000 Thousand Yen

【Homepage Address and Other Contact Information】

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