【Grant-in-Aid for Specially Promoted Research】

Science and Engineering (Chemistry)

Title of Project： Chemical Biology of ER Related Glycan Modifications

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Research Project Number：16H06290　Researcher Number：80168385
Research Area：Biological Chemistry
Keyword：Carbohydrate Chemistry/Glycotechnology, Glycoprotein, Glycolipid, The Endoplasmic Reticulum

【Purpose and Background of the Research】

The endoplsmic reticulum (ER) is a venue of protein N-glycosylation as well as other types of glycan modification. For instance, recent study revealed the presence of a peculiar structure of C-mannosylation in various proteins. N-glycosylation of proteins is known to function as a tag that reflect their degree of folding. In the ER, a variety of lectins and enzymes work cooperatively to regulate glycoprotein folding through their ability to recognize specific high-mannose-type glycans, constituting glycoprotein "quality control" machinery.

On the other hand, the role of C-mannosylated tryptophan has been poorly, whereas its involvement in protein quality control mechanism in addition to natural immune signaling control has been implicated. Endoplasmic reticulum is also responsible for the synthesis of various lipids. Most notably, glucose containing novel glycolipids, such as cholesteryl glucoside and phosphatidyl glucoside (PtdGlc) have been found in brain tissue. Very recently, evidences to suggest the role of lyso PtdGlc (LPG) in nerve cell signaling and axon guidance were provided.

Based on these, this project aims to explore common principles among glycan modifications in the ER and ultimately to discover lead molecules for future drug discovery. Main focuses will be placed on 1) functions of glycans in protein folding regulating system in the ER, 2) functional analysis of glucosylation in the ER, 3) modulation of cellular functions through creation of novel LPG related compounds, and 4) relationship between protein C-mannosylation and quality control system.

【Research Methods】

As principal technology, 1) comprehensive synthesis of vesicular type oligosaccharides, 2) chemical synthesis of glycoproteins, 3) protein expression system of ER proteins, 3) carbohydrate-protein interaction analysis system, 4) synthetic method for C-linked mannose-containing glycopeptide, 5) anti-C-mannosiyl tryptophan antibody, 6) synthesis of PtdGlc, lyso PtdGlg (LPG) and their analogues, 7) PtdGlc specific antibody. In addition attempts will made to develop new techniques to facilitate and expand systematic analysis. Effort will be made to secure constant supply of oligosaccharide samples.

【Expected Research Achievements and Scientific Significance】

This project will unravel functions of various sugars signal produced in the endoplasmic reticulum. Establishment of new areas across carbohydrate-lipid-protein, and creation of new molecules having abilities to control cell functions are expected.

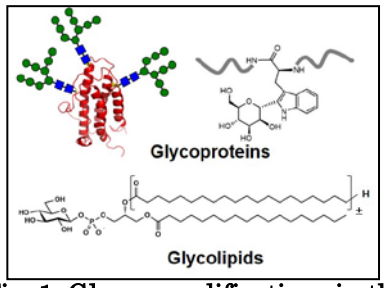

Fig. 1. Glycan modifications in the ER

【Publications Relevant to the Project】

- Y. Ito, Y. Takeda, A. Seko, M. Izumi, Y. Kajihara "Functional anaylsis of endoplasmic reticulum glucosyltransferase (UGGT): Synthetic chemistry's initiative in glycobiology", *Semin. Cell Dev. Biol.*, **41**, 90-98 (2015)
- A. T. Guy, Y. Nagatsuka, N. Ooashi, M. Inoue, A. Nakata, P. Greimel, A. Inoue, T. Nabetani, A. Murayama, K. Ohta, Y. Ito, J. Aoki, Y. Hirabayashi, H. Kamiguchi "Glycerophospholipid regulation of modality-specific sensory axon guidance in the spinal cord", *Science*, **349,** 974-977 (2015)

【Term of Project】 FY2016-2020

【Budget Allocation】 319,400 Thousand Yen

【Homepage Address and Other Contact Information】

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