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研究課題：スフィンゴ糖脂質とコレステロール間の代謝クロストークによる新規糖脂質産生と生物機能

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Grant Title: Novel glycolipids generated by crosstalk between sphingolipid and sterol

Abstract:

Cholesterol is an essential component for maintaining the structure and function of biological membranes, and the pathway of its synthesis has already been elucidated completely. The concentration of cholesterol (Chol) in the biological membrane is thought to be tightly regulated in response to the organelle function of the cell. On the cell biological membrane, Chol associates with glycosphingolipids to form small lipid domains, so-called lipid rafts, which play an important role in cell-cell interaction, intracellular vesicle trafficking, and the transmission and reception of intracellular and extracellular information. The discovery of phosphatidylglucoside, biologically active lipid component in the nervous system, has prompted us to study the whole picture of glycosylated lipids in the brain. As a result, we found that glucosylated Chol is present in the fraction of cerebroside (GalCer), which is a major brain glycolipid, and clarified its structure and biosynthetic pathway. Interestingly, the glycosylation of Chol is carried out by retained trans-glycosylation reaction by GBAs (GBA1 and 2), glucosylceramide (GlcCer)-degrading enzymes. In this study, we have demonstrated that GBAs act not only on GlcCer but also on GalCer to biosynthesize galactosylcholesterol (GalChol). Unexpectedly, GBAs act on GalCer as well as on GlcCer to synthesize GalChol (Akiyama, et al.; *JBC* 2020). We also examined the effect of 3-O-glucosylation on the ordering and lipid interactions of Chol in artificial membrane composed of brain major lipid, N-stearoyl sphingomyelin (SSM). MD simulation suggested that GlcCho has reduced umbrella effect from the phosphocholine headgroup of SSM due to the hydrophilic Glc moiety, probably affecting the distribution and localization of the sterol core in biological membranes (Hanashima *et al.*, *BBA, Biomembranes* 2021).

In the course of our studies, we found the existence of alpha-linked disaccharide (Gb2: Gal-GalCer) glycosphingolipid in addition to GlcChol and GalChol in human cerebrospinal fluid (CSF). We expect that these new types of glycolipids are useful as biomarkers for neurological diseases such as Parkinson's disease, ALS and Alzheimer diseases (Akiyama *et al.*, BBRC 2021).

(1) Akiyama H, *et al.* (2021) "Galabiosylceramide is present in human cerebrospinal fluid." *Biochem Biophys Res Commun.* 536:73-79. (2) Hanashima S, *et al.* (2021) "β -Glucosylation of cholesterol reduces sterol-sphingomyelin interactions." *Biochim Biophys Acta Biomembr.* 1;1863(2):183496. (3) Akiyama H, *et al.* (2020) "Glucocerebrosidases catalyze a transgalactosylation reaction that yields a newly identified brain sterol metabolite, galactosylated cholesterol." *J Biol Chem.* 295(16):5257-5277.