Structural Basis for Membrane Receptor Activity of Ganglioside GM3 Regulated by Lipid-Lipid Interactions

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Ganglioside is one of the key components in the bio-functional membrane domains, so called lipid rafts. As the structural feature, ganglioside consists of hydrophobic ceramide and hydrophilic glycan moieties (Fig.1). This amphiphilic molecule is involved in various biological functions, one of which is binding activity for exogenous proteins, such as viral spike-proteins and bacterial toxins. Cholesterol-ganglioside interaction occurring in the lipid rafts has been thought to regulate the protein-ganglioside interplay by altering orientation of the ganglioside head group.[1] However, there are few reports on the experimental evidence supporting this orientation change.[2]

To elucidate the mechanism in regulating affinity between glycan-binding proteins and ganglioside GM, we here examined their interactions with the focus on the three-dimensional structure of the glycan moiety. The binding event of membrane GM3 with a fluorescence-labeled lectin was evaluated with the lipid bilayer models mimicking the rafts or the non-rafts. As a result, the binding affinity of them was found to be affected by membrane ordering with cholesterol. For the orientational analysis, ^{2}H-labeled GM3 probes were synthesized and incorporated in the lipid bilayer models mimicking the rafts and the non-rafts. We observed the orientational difference of the sialic acid moiety of GM3 in the different membrane conditionsby solid state NMR. The solid-state ^{2}H NMR results suggested that the orientation of the sialic acid moiety of GM3 was different depending on the membrane environment.

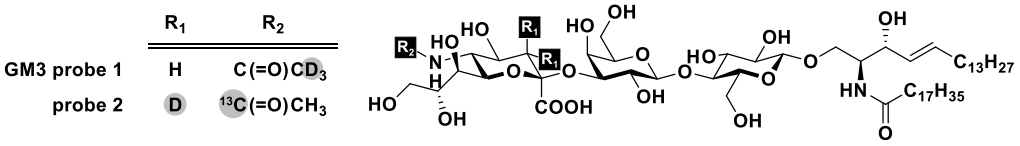

Fig.1 Design of Isotopic-labeled Ganglioside GM3

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[2] Takahashi, M.; Shirasaki, J.; Komura, N.; Sasaki, K.; Tanaka, H.; Imamura, A.; Ishida, H.; Hanashima, S.; Murata, M.; Ando, H. *Org. Biomol. Chem*. **2020**, *18*, 2902–2913.