Synthesis of a fluorescent ganglioside probe using late-stage sialylation and its behavior analysis

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Gangliosides form functional domains (lipid rafts) with proteins in cell membranes. To study lipid rafts in detail, we developed fluorescently labeled gangliosides (ganglio-, and globo- series), and observed their behaviors by single-molecule imaging technique.[1] For inclusive understanding of ganglioside behaviors, this study focused on lacto-, and neolacto- series gangliosides, which have never been analysed.

For the synthesis of ganglioside probes in an efficient way, we designed a late-stage α-sialylation strategy of glycolipid acceptors using a fully stereoselective α-sialylation method.[2] To improve the aggregation property of glycolipid derivatives, we developed a glycolipid acceptor, which was multiply protected with TBBz groups.[3] As a result, α-sialylation of the glycolipid acceptor provided a ganglioside framework in high yield.[4]Based on this result, we next examined the synthesis of the lacto-series ganglioside probe. α-Sialylation of a Lc_4Cer acceptor by a C9-NHTFAc bicyclic sialyl donor provided the ganglioside framework successfully. Finally, global deprotection and fluorescent labeling of C9-NH_2 afforded $NeuLc_4Cer$ probe.[5] Similarly, Neolacto-series ganglioside probe was synthesized. The single-molecule imaging of the fluorescent $NeuLc_4Cer$ first revealed its colocalization with a major raft molecule CD59. Furthermore, $NeuLc_4Cer$ formed transient homodimers, which are commonly observed in other gangliosides examined previously. In conclusion, we have demonstrated the utility of the fluorescent ganglioside for studying their dynamic interactions on cell membranes.

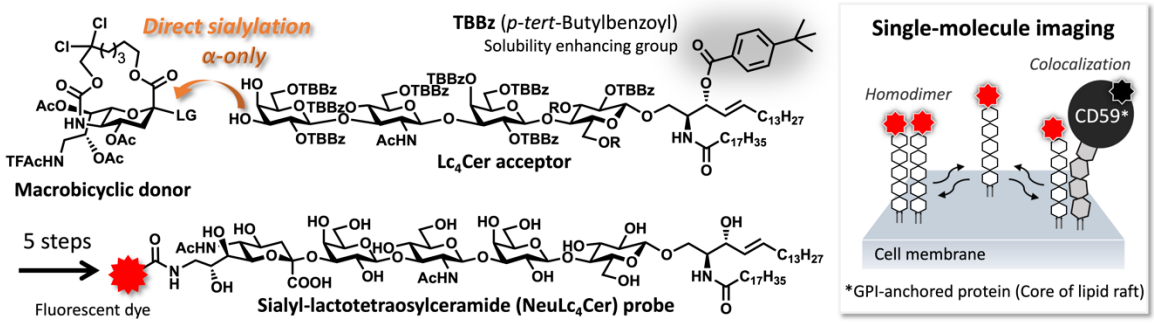

Figure. Chemical synthesis of the fluorescent ganglioside and its single-molecule imaging on living cells

Bibliographic references:

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2. N. Komura et al. (2019), Science (364) 677-680.
3. S. Asano et al. (2019), Org. Lett. (21) 4197-4200.
4. M. Takahashi et al. (2020), Org. Biomol. Chem. (18) 2902-2913.
5. M. Takahashi et al. (2022), RSC Chem. Biol. (3) 868-885.