Synthetic Studies of glycolipid complexes for modulating immunological activities

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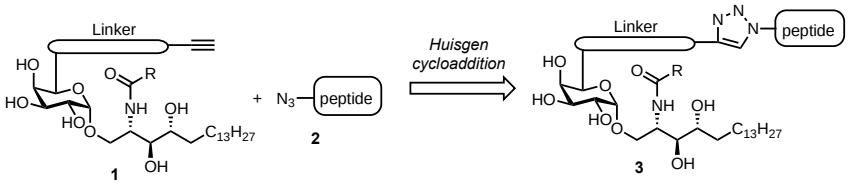
CD1d is a non-polymorphic MHC class I-like molecule on antigen-presenting cells, and its ligand such as α-GalCer (KRN7000) activate NKT cells and act as an immune adjuvant. Recently, we reported that the introduction of amide group to the long fatty acyl chain of α-GalCer affect the immunomodulatory activities,[1,2] the selectivity of Th1/Th2 cytokine introduction. On antigen-presenting cells, both lipid antigens and peptide antigens are recognized to activate the acquired immunity, and conjugation of lipid antigen (α-GalCer) and peptide antigen showed enhanced activity.[3] It suggested the molecular design for activating both NKT cell and T cell, can modulate the immune activation, which would be applicable synthetic vaccine. Based on these findings, we designed and conducted the synthesis of the complexes using α-GalCer derivatives and the peptide antigen, that can be recognized with MHC class I or II molecules.

For the conjugation of α-GalCer and peptide antigen by Huisgen cycloaddition, we introduced azide group to N-terminus peptide, and alkyne containing linker to 6- hydroxy group of GalCer derivative (Scheme 1).

In order to introduce the linker to the 6-OH of GalCer, it was converted to the oxidized form (carboxylic acid), with establishing the condition of GalCer 6-OH selective oxidation, and achieved to synthesize 6-PEGylated GalCer complex **1**. For the synthesis of hydrophobic peptide antigen **2**, we introduced a linker (Ddax-Lys_5),[4] which enhanced water-solubility of the peptide to obtain higher yield. The GalCer-peptide antigen **3** will be used for the investigation of selective immunomodulation.



Scheme 1. Synthetic route of GalCer-peptide complexes as immunomodulator

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