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Grant Title: Synthesis and Functional Analysis of Glycoconjugates for NKT Cell Activation

Abstract

Microbial surface lipid-conjugates often show immunomodulatory activities by the recognition of innate immune receptors or lipid-antigen binding proteins, such as TLRs (eg. TLR1, 2, 4, and 6), CLRs and CD1 family proteins (eg. CD1a~d).

In order to modulate the NKT-cell-mediated cytokine induction via CD1d-ligand recognition, we have synthesized several natural compounds from both human and microbes, and also designed to control the binding affinity of the ligand to enhance and to modulate the activity. One series of the target natural compounds are the inositol phospholipids as the partial structure of GPI anchor, which are abundant in eukaryotes in both unicellular or macrocellular organisms. As one of unique microbial GPI-anchor type inositol phospholipids, we have synthesized inositol phospholipid moieties, EhPIa and EhPIb from *Entamoeba histolytica* [1,2]. EhPIa and EhPIb contain characteristic long fatty acids such as C28:0 or C30:1, and the unique structures lead to the selective cytokine induction via NKT-cell activation in a CD1d dependent manner, along with TLR2 recognition. We have also synthesized the inositol phospholipids from human, and showed that the molecules induce definite NKT-cell-mediated cytokine induction. The results suggested that the lipid part of the GPI anchor plays an important role in the endogenous modulation of the NKT cell activation.

On the other hand, we have also designed and synthesized a series of lipid conjugates as the CD1d ligands, which have special affinity in the binding site of the CD1d, for modulation of the NKT-cell-mediated cytokine induction [3]. The biological activities and the molecular dynamics calculations were analyzed for the understanding of the binding mode of lipid-conjugates in the receptors.

References

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