Synthesis and functions of symbiotic bacterial lipid A for safe vaccine adjuvant development

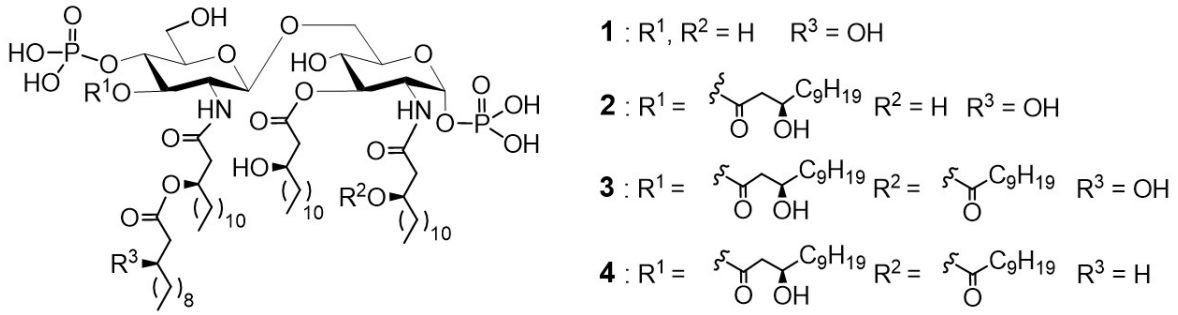
Atsushi SHIMOYAMA [1], Haruki YAMAURA [1,2], Koji HOSOMI [2], Azusa SAIKA [2], Flaviana DI LORENZO [3], Alejandra MATAMOROS-RECIO [4], Sonsoles MARTÍN SANTAMARÍA [4], Jun KUNISAWA [1,2], Antonio MOLINARO [3], Koichi FUKASE [1]

[1] Graduate School of Science, Osaka University, JAPAN; [2] National Institutes of Biomedical Innovation, Health and Nutrition, JAPAN, [3] Department of Chemical Sciences, University of Naples Federico II, ITALY, [4] Spanish National Research Council, SPAIN

ashimo@chem.sci.osaka-u.ac.jp

Lipopolysaccharide (LPS) is a major glycoconjugate in outer membrane of Gram-negative bacteria and canonical *Escherichia coli* LPS activate innate immunity to induce lethal strong inflammation. The terminal glycolipid lipid A is the active principle of LPS. Low inflammatory lipid A have been expected as adjuvants.

We hypothesized that co-evolved parasitic and symbiotic bacterial components should modulate host immunity moderately with low toxicity. We synthesized parasitic [1] and symbiotic [2] bacterial lipid A and elucidated the molecular basis of immunoregulation and developed safe and useful adjuvants. In this lecture, we introduce the structure determination, chemical synthesis, and structure-activity relationship studies of lipid A from *Alcaligenes faecalis* inhabiting gut-associated lymphoid-tissue (GALT) that is responsible for the mucosal immunity regulation. We synthesized *A. faecalis* lipids A **1**-**3** with diverse acyl group patterns and identified the active center as hexa-acylated **3** [2]. Lipid A **3** was confirmed to exhibit non-toxic but useful adjuvant function (enhancing antigen-specific IgA and IgG production) [3-6], and that vaccine model using **3** was found to be significantly protective against bacterial infection [4]. Since IgA is responsible for mucosal immune homeostasis, by focusing on GALT symbiotic bacteria, we found promising adjuvant that can safely regulate mucosal immunity. Furthermore, lipid A **4**, which lacks the hydroxy group in the acyl chain, was found to be less active than **3** [7], and the molecular basis of the adjuvant function is also becoming clear.



Chemical structure of gut-associated lymphoid-tissue (GALT) resident A. faecalis lipids A 1-3 and its derivative 4

Bibliographic references:

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