

Regulation of Bacterial Lipid A-Induced Innate Immune Activation by Endogenous Amphiphilic Molecules

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Innate immunity is activated by pathogen-associated molecular patterns (PAMPs) derived from bacteria, viruses, fungi, etc. as well as by damage-associated molecular patterns (DAMPs) released from damaged cells. The representative PAMPs are lipopolysaccharides from Gram-negative bacteria and their active principle lipid As (*E. coli* lipid A **1** is depicted in Fig. 1), which are the potent ligands of TLR4. We previously reported that aggregate formation of lipid A and the composition and state of mixed aggregates with other lipids significantly affect its activity¹. In this study, the effect of fatty acids on lipid A activity was investigated in relation to the composition of aggregates using *E. coli* lipid A **1** (Fig. 1), saturated fatty acids **2-5** (Fig. 2), and unsaturated fatty acids **6-10** (Fig. 3). Fatty acids, which are neither PAMPs nor DAMPs, are involved in the regulation of TLR4 function.

Mixed aggregates of lipid A **1** and fatty acids were prepared by two different methods: simple mixing method (SMM) and homogenized mixing method (HMM). SMM tends to form separate aggregates composed of single components, whereas HMM tends to form homogeneous aggregates composed of both lipid A and fatty acids molecules.

Immunological assay for SMM samples between *E. coli* lipid A **1** and saturated fatty acids **2-5** or unsaturated fatty acids **6-10** showed no effect on lipid A's immune function. However, HMM samples prepared using saturated fatty acids **2-5** showed a concentration-dependent attenuation effect on the activity of lipid A. Attenuation effect decreases as carbon chain length of fatty acid decreases. In the case of HMM samples using unsaturated fatty acids **6-10**, a concentration-dependent attenuation effect was observed at high fatty acid concentration, while a boosting effect was observed at low fatty acid concentration.

1) Mueller, M., Lindner, B., Kusumoto, S., Fukase, K., Schromm, A. B., Seydel, U. *J. Biol. Chem.* **2004**, *279*, 26307-26313.

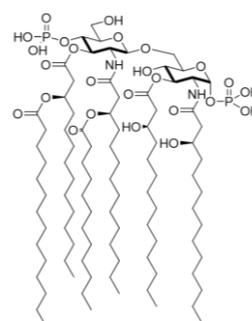


Fig 1. Structure of *E. coli* lipid A **1**

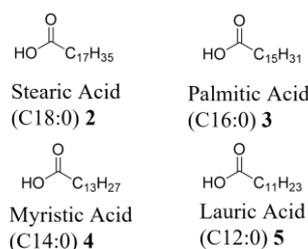


Fig 2. Structures of saturated fatty acids

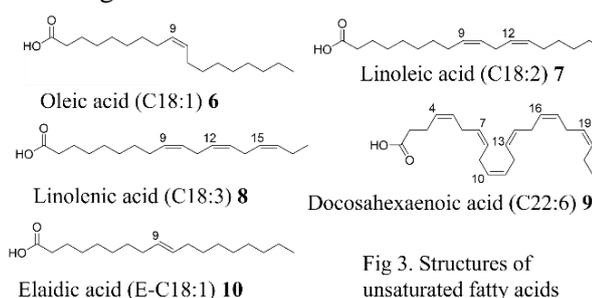


Fig 3. Structures of unsaturated fatty acids