Regulation of Excessive Inflammation Using Lipoteichoic Acid (LTA) from *Lactobacillus plantarum* via Toll-Like Receptor Signaling

Dae-Kyun Chung[1, 2 *], Han-Geun Kim[1], Jung-Min Lee[1, 2], Na-Ra Kim[1], Mi-Yeon Ko[1], Hea-Young Lee[1], Chul-Min Kim[3], and Seung-Hyun Han[4]

[1] *Graduate School of Biotechnology and Institute of Life Science and Resources, Kyung Hee University, Yongin 449-701*
[2] *Skin Biotechnology Center, Kyung Hee University, Youngin 449-701*
[3] *RNA Inc., #308 College of Life Science, Kyung Hee University, Yongin 449-701*
[4] *Laboratory of Microbial Infection and Immunology, Seoul National University School of Dentistry, Seoul 110-749*

Bacterial cell wall components such as peptidoglycan, lipoteichoic acid, lipopolysaccharide (LPS) and lipoproteins are recognized by the host's innate immune system. This process is mediated by the Toll-like receptor (TLR), which induces inflammation by activating nuclear factor (NF)-κB. Excessive activation of monocytes by TLR ligands leads to serious inflammatory diseases such as septic shock and atherosclerosis. Many studies have tried to regulate excessive inflammatory responses using LPS tolerance [1-3]. Clinically, LPS tolerance is thought to be an important factor in the susceptibility to reinfection in patients treated for severe sepsis. However, this clinical experiment has many limitations because LPS is very toxic [4, 5].

In this study, we examined the effects of lipoteichoic acid (pLTA), isolated from *Lb. plantarum*, on the inhibition of endotoxin (LPS)-mediated TNF-α production and endotoxin shock in mice, and its role in tolerance mechanism. Unlike other bacterial cell walls such as *Staphylococcus aureus* LTA, LPS, and lipoproteins, pLTA had low cytotoxicity, and did not induce excessive inflammation [6], which means that pLTA has no risk of harmful side effects. In particular, pLTA significantly reduced the excessive TNF-α production caused by endotoxin, and increased the survival rate of endotoxin shock mice [7]. These inhibitory effects were induced by the complex mechanism of i) the inhibition of intracellular signaling pathways such as MAP kinases and NF-κB; ii) the reduction of sepsis-related PRRs such as TLR4, NOD1, and NOD2; and iii) the induction of IRAK-M. The alteration of these mechanisms reduced LPS-induced TNF-α factor (LITAF) expression, and resulted in the inhibition of excessive LPS-induced TNF-α production.

This study will extend our understanding of the pLTA tolerance mechanism, which is related to the inhibition of LPS-induced endotoxin shock, and suggest that pLTA may have promise as a new therapeutic agent for endotoxin-induced septic shock.

Acknowledgements

This work was supported by the 21C Frontier Microbial Genomics and Application Center Program, Ministry of Education, Science and Technology and Innovation Center Grant RIC 07-06-04 (Skin Biotechnology Center),

funded by the Ministry of Knowledge Economy, Republic of Korea.

References

[1] Ginsburg I. *Lancet Infect. Dis.* **2:**1717, 2002.

[2] Jacinto R, Hartung T, McCall C, and Li L. *J. Immunol.* **168:**6136, 2002.

[3] Sugawara S, Arakaki R, Rikiishi H, and Takada H. *Infect. Immun.* **67:**1623, 1999.

[4] Yang S, Tamai R, Akashi S, Takeuchi O, Akira S, Sugawara S, and Takada H. *Infect. Immun.* **69:**2045, 2001.

[5] De Kimpe SJ, Kengatharan M, Thiemermann C, and Vane JR**.** *Proc. Natl. Acad. Sci. USA* **92:**10359, 1995.

[6] Kim HG, Gim MG, Kim JY, Hwang HJ, Ham MS, Lee JM, Hartung T, Park JW, Han SH, and Chung DK. *FEMS Immunol. Med. Micobiol.* **49:**205, 2007.

[7] Kim HG, Kim NR, Gim MG, Lee JM, Lee SY, Ko MY, Kim JY, Han SH, and Chung DK. *J. Immunol.* **180:**2553, 2008.