First publ. in: The journal of immunology 178 (2007), 5, p. 2610

Comment on "Not Lipoteichoic Acid but Lipoproteins Appear to Be the Dominant Immunobiologically Active Compounds in *Staphylococcus aureus*"

Recently, Hashimoto et al. (1) reported that lipoteichoic acid (LTA) extracted from a lipoprotein diacylglycerol transferase deletion (Δ*lgt*) mutant of *Staphylococcus aureus* is immunologically inactive and concluded that the activity of LTA preparations generally lies in lipoprotein contaminants. These conclusions challenge our published (2–5) and unpublished results.

Although referenced, the authors fail to mention that a fully synthetic complete LTA analog reflects the immunostimulatory activity of LTA of bacterial origin (3, 4). This activity cannot stem from lipoproteins.

Since neither the authors nor we see signs of lipoproteins in the nuclear magnetic resonance analysis of butanol-extracted, octylsepharose-purified LTA preparations (1, 2), they would need to prove that purified lipoproteins are at least 100-fold more potent than LTA to be considered relevant immunostimulatory structures. However, they have not been able to isolate or identify such structures.

We prepared LTA from the Δ*lgt* mutant and respective wild-type bacteria by butanol extraction. Although we can confirm that LTA from the mutant does not stimulate the murine macrophage cell line J774A.1, the LTAs of both strains are equipotent in stimulating cytokine release in human whole blood (Fig. 1), arguably the more relevant system.

Whether this difference between the two systems reflects a specific deficiency of the J774A.1 cell line or whether the LTA of the mutant strain is chemically modified, resulting in species-specific macrophage activation, is currently under investigation.

In conclusion, there remains strong evidence that LTAs are major immunostimulatory principles of Gram-positive bacteria. These data caution us from direct extrapolations from mice to humans.

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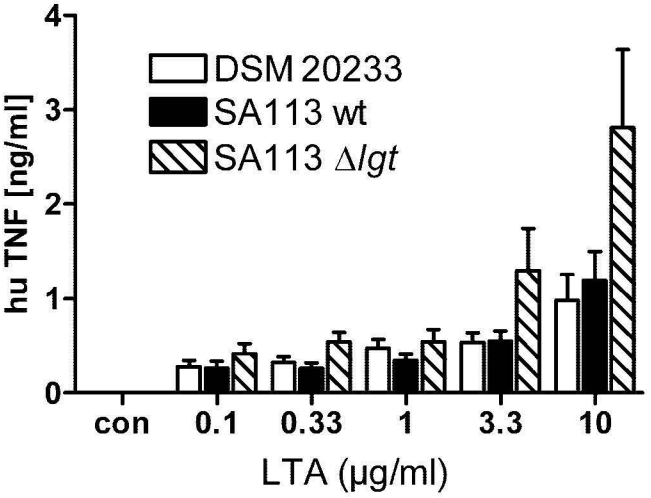

Figure 1. Similar activity of LTA from *S. aureus* DSM 20233, SA113 wild-type, and SA113 Δ*lgt* mutant. Human whole blood, diluted 1/5 in RPMI 1640, was stimulated overnight with LTA prepared as described previously (2). TNF release was measured in the supernatants by ELISA, $n = 12$ blood donors. Data are given as mean ± SEM.

References

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