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Effects of bacteria lipopolysaccharides on the activation and activity of coagulation factor XII

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Abstract

Background:

Lipopolysaccharides (LPS), the major outer wall component of Gram-negative bacteria, plays a critical role in the pathogenesis of sepsis and are known to contribute to the development of disseminated intravascular coagulation (DIC) syndrome. Since LPS aggregates are negatively charged, we hypothesized the LPS may directly interact with and activate the contact pathway coagulation factor (F) XII as part of the pathogenesis of DIC.

Aims:

To investigate the mechanisms of interaction and activation of FXII by LPS chemotypes. Methods: The physicochemical properties of different LPS chemotypes were determined by dynamic light scattering, zeta potential (ZP), and fluorescence spectroscopy. Fluorescence spectroscopy were employed to study the interaction of LPS with FXII. FXII autoactivation and FXIIa activity were measured using a chromogenic assay.

Results:

The LPSs O111:B4, O26:B6, and Rd2 produced aggregates with hydrodynamic diameters of 123. 213. And 201 nm; and ZP of -0.414, -23.0, and -55.0 mV, respectively. Intrinsic tryptophan fluorescence experiments demonstrate similar quenching of FXII in the presence of LPSs which similar apparent binding affinity (K_{Dapp}) of 0.206, 0.304, and 0.3391 μM, respectively. We observed a red shift of $\Delta\lambda \sim 13$ nm in the emission of FXII in the presence of O26:B6, suggesting a modification in the secondary structure. FXII was not activated by O111:B4 and Rd2, while it was more efficiently activated by O26:B6. O26:B6 showed a bell-shaped dose-response curve, suggesting a template mechanism of autoactivation. The amidolytic activity of FXIIa was not affected by O111:B4, but FXIIa activity was increased in the presence of RD2 or O26:B6, suggesting a positive allosteric modulation. However, higher concentrations of O26:B6 decreased FXIIa activity, suggestive of protein structural modifications.

Conclusions:

Select chemotypes of LPS have differential impacts on the structure and function of FXII, providing a mechanism-of-action for I initiating DIC via the contact pathway of coagulation.