(1) Submission ID#1527408

Dissecting the role of lipooligosaccharide in the immune response elicited by a Neisseria gonorrhoeae Ng GMMA investigational vaccine

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Background
Therapeutic and prophylactic strategies against N.gonorrhoeae are urgently needed. Generalized modules for membrane antigens (GMMA) are outer membrane vesicles from genetically engineered bacteria that represent an attractive vaccine platform. GSK has developed a GMMA-based investigational vaccine (Ng GMMA), currently in a Phase I/II study, derived from a genetically detoxified Ng FA1090 strain. LOS is the most abundant antigen among the virulence factors present on the Ng membrane and LOS-specific antibodies have been shown to mediate complement activation, bactericidal and opsonic activity. Glycan extensions of LOS α and β-chains is determined by the expression of glycosyltransferases, among which LgtA, LgtC, LgtD

and LgtG encoded by phase variable genes. Diversity of LOS structures/epitopes are expected to have an impact on vaccines targeting this antigen.

Aim/Methods

The role of the LOS component and of different LOS epitopes on functional immune responses elicited by the Ng GMMA investigational vaccine was investigated through a genetic engineering approach applied to different Ng strains. Functional activity was evaluated by serum bactericidal and bacterial adhesion inhibition assays on a panel of Ng strains representing the global variability of gonococcal outer membrane antigens.

Results

GMMA derived from a FA1090 strain engineered to express a highly truncated LOS were used to immunize mice. The obtained sera showed reduced functional activity compared to antisera of the Ng GMMA vaccine against most but not all tested strains, suggesting a key role of anti-LOS antibodies in cross-functional activity but also an additional contribution of other surface antigens. Furthermore, a panel of gonococcal MS11 isogenic mutant strains suitably engineered to express distinct LOS structures was used to dissect the contribution of the different LOS epitopes on GMMA immunogenicity. GMMA obtained from these MS11 mutants were used as competitors in functional assays using sera from mice receiving the Ng GMMA vaccine, as well as to immunize mice for direct immune functional testing. The results elucidated the relative role of antibodies elicited by specific LOS structures in GMMA functional responses.

Conclusions

The data obtained confirmed the relevance of the LOS antigen in the Ng GMMA vaccine and highlighted that cross-strain functional anti-LOS responses were mainly referable to specific structures.