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Outer membrane vesicle vaccines isolated from an unencapsulated, genetically-detoxified Neisseria meningitidis strain exhibit potent, cross-reactive seroresponses

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Background

For decades, outer membrane vesicle (OMV) vaccines have been used to effectively reduce the incidence of disease caused by meningococcal serogroup B (MenB) outbreak strains. As part of the OMV isolation procedure, detergent detoxification is required to reduce the high levels of lipooligosaccharide (LOS) present on the vesicle surface, a process that results in removal of cross-reactive immunogenic antigens that are loosely associated with the outer membrane. In previous reports, we described elicitation of highly cross-reactive antibodies upon immunization with ΔABR, an OMV vaccine isolated from a MenB mutant strain deleted for the major outer membrane proteins (OMPs) PorA, PorB, and RmpM. While functional, anti-ΔABR OMV antibodies in general killed MenB strains at low titers, and OMP deletion rendered the bacterial membrane unstable upon detergent treatment, suggesting low vaccine potency was likely a result of protein loss/membrane disruption.

Aim/Methods

To study the impact of detergent detoxification on OMV immunogenicity, we first generated markerless, genetically-detoxified ΔABR OMV vaccine strains, with the aim of modifying the native LOS structure to sufficiently diminish OMV toxicity in the absence of detergent treatment; strains lacking capsule expression were also constructed to assess the impact of anti-capsular antibody responses. Markerless mutants were obtained utilizing a positive/negative selection cassette, with deletion confirmed via sequencing, immunoblot analyses, and in vitro TLR4 stimulation assays. Detergent-detoxified and genetically-detoxified OMVs were isolated and used to immunize mice and rabbits, with immunogenicity examined by immunoblot and human complement serum bactericidal assays (hSBAs).

Results
Genetically-detoxified ΔABR OMVs induced cross-reactive anti-MenB seroresponses, with a sera from immunized animals exhibiting bactericidal activity against a greater number of strains compared to sera from animals immunized with detergent-detoxified ΔABR OMVs. An additive effect was observed when OMVs were isolated from a vaccine strain that was both genetically-detoxified and unencapsulated, with higher overall hSBA titers reported. Equivalent serological responses were observed when OMVs were detergent treated, independent of genetic modification.

Conclusions
OMVs isolated from the genetically-detoxified, unencapsulated ΔABR strain induced potent heterologous vaccine-specific seroresponses. Genetic detoxification likely resulted in maintenance of (a) cross-reactive antigens and (b) membrane integrity, while capsule deletion may have increased antigen availability.