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Nanodisc-displayed MtrE vaccine elicits immune responses that accelerate Neisseria gonorrhoeae clearance from lower genital tract in mice

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Background

We are focusing on developing a gonorrhea subunit vaccine comprised of MtrE in nanodiscs (MtrE-NDs). MtrE is a highly conserved β-barrel outer membrane protein and a component of the MtrCDE, FarAB, and MacAB efflux pumps. These pumps are critical for infection in the female mouse model and protect Neisseria gonorrhoeae from progesterone, antibiotics, and antimicrobial peptides. We have used NDs, which are lipid bilayers encircled by two molecules of amphipathic membrane-scaffold protein, to enable functional presentation of MtrE and improve vaccine efficacy.

Aim/Methods

1) To generate MtrE-NDs; 2) to assess dose-dependent immune responses elicited by MtrE-NDs in the presence of adjuvants; and 3) to test the efficacy of the most promising MtrE-ND formulation in challenge studies in the murine model of lower reproductive tract gonorrhea infection.

Results

MtrE was expressed in the outer membrane of E. coli, purified, mixed with the membrane-scaffold protein and phospholipids, and the resultant MtrE-NDs were purified by gel filtration. To assess immune responses elicited by different doses and formulations, BALB/c mice (n=5/group) were inoculated subcutaneously with MtrE-NDs (2.5, 5, and 10 µg) in Alum, CpG, or MPLA. Immunoblot analysis demonstrated that all vaccines-induced antigen-specific IgG in pooled sera and vaginal lavages recognized rMtrE and MtrE from the panel of the 2016 WHO Ng strains. Antibody titers were significantly higher in mice immunized with MtrE-NDs in Alum or CpG (10 µg) in comparison to all other groups. In challenge trials, mice (n=20/group) were given MtrE-NDs formulated with Alum, CpG, or Alum+CpG. Immunization with MtrE-NDs significantly increased clearance of Ng H041 (WHO X) in infected mice over the course of infection compared to controls (PBS, NDs+CpG+Alum). The number of gonococci recovered from vaginal swabs over time was also significantly reduced in mice inoculated with MtrE-NDs+Alum or MtrE-NDs+Alum+CpG; whereas bioburden measured as area under the curve was reduced in MtrE-NDs+Alum-vaccinated mice. A comparable neutrophil influx was observed between all experimental groups. Biological replicate immunization/challenge experiments are underway.

Conclusions

MtrE-ND vaccine formulated with Alum elicited a protective immune response that significantly increased Ng clearance and decreased bioburden.