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Outer membrane vesicles: A novel particle of next generation Shigella vaccine

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The Gram-negative bacterium *Shigella* secretes outer membrane vesicles evidently during normal growth condition. We have observed under electron microscope a distinctive vesicle secretion of different sero-groups. Among them, *Shigella boydii* type-4 BCH 612 strain releases outer membrane vesicles (OMVs) more vigorously during growth than the other strains, selected for this experiment. In this study, we immunized female adult mice by the intra-gastric route with purified single outer membrane vesicles (SOMVs, 32 µg per 100 µl), isolated from *Shigella boydii* type 4 BCH 612 strain. Immunized mice induced specific, high-titer immune responses against a variety of antigens present in the OMVs. After the 4th and last immunization, the half-maximum total immunoglobulin titer was stable over a 3-month period for IgG, IgA and IgM indicating that the immune response was long lasting. We challenged the offspring of immunized female mice with *Shigella* sp. of four serogroups via the oral route in two consecutive periods, approximately 70th and 120th day after the 4th and last immunization. The offspring was protected against colonization with homologous strain, *Shigella boydii* and also heterologous strains *Shigella dysenteriae* 1, *Shigella flexneri* 2a and *Shigella sonnei* in challenge experiments. Our results showed that 100% homologous protection was quite satisfactory, 75% average heterologous protective efficacy bestowed by the OMVs of *S. boydii* was not at all promising from the purview of disease prevalence and severity. Then, we have advanced our research by formulating multi-serotype outer membrane vesicles (MOMVs), mixing the OMVs of *Shigella dysenteriae* 1 stx, *Shigella flexneri* 2a, 3a and 6, *S. boydii* type 4 and *Shigella sonnei* to achieve a broad spectrum protection against Shigellosis. Adult mice were immunized orally with 50 g of MOMVs, four times at weekly intervals. Immunological parameters were observed at various time points, before, during and after immunization, in adult mice. Passive protection was examined in their offspring by measuring protective efficacy and studying intestinal colonization, after challenging with various *Shigella* strains. Immunized dams exhibited a consistent broad spectrum antibody response. 3–4 day-old offspring of immunized dams showed significant long term passive protection against wild type *S. flexneri* 2a, 3a, and 6, *S. boydii* type 2 and *S. dysenteriae*. Their stomach extracts, essentially containing mother's milk, have also exhibited significant levels of anti-MOMVs immunoglobulins. In conclusion, MOMVs formulation represents an easy, safe immunization strategy that was found suitable to provide complete passive protection to the neonatal mice against all four serogroups of Shigellae. In this study, we observed the inefficient of *Shigella* to secrete significant amount of outer membrane vesicles naturally, during growth, making the study very time consuming and costly. To overcome this trouble, we disrupted tolA gene, necessary to maintain outer membrane integrity, from *Shigella boydii* type 4 BCH612 strain. 60% increase of OMVs secretion was noticed (80 mg/500 ml culture) in the tolA mutant than the wild type (50 mg/500 ml culture). Moreover, ΔtolA-OMVs played better stimulatory role to macrophage and epithelial cells inducing more IL-8, TNF-α, IL-1β, IL-12, IL-18, IL-6, IL-10, IFN-γ and IL-4 secretion than the wild type OMVs. General Cytokine profile has made clear the Th1/Th2 based immune response by OMVs of *Shigella*. This study has efficiently established a new technique for better cost effective production of OMVs in shigellae. ΔtolA-OMVs was showing valuable role in the field of next-generation non-living vaccine against human shigellosis in near future.

Biography

Hemanta Koley, MSc, PhD is a Scientist in the Division of Bacteriology. After completion of his Master degree in Physiology from Calcutta University, he joined in National institute of Cholera and Enteric Diseases, Beliaghata, Calcutta for his PhD. In 1996, he joined as Associate Professor in Dept. Physiology, College of Medical Sciences-Nepal, where he devoted entire heartily in teaching medical students till 2000. He worked in Rutgers-The State University of New Jersey, New Brunswick, USA. He also worked in Gastroenterology Section, Harvard Medical School as Research Associate. His present research interest is to understand signal transduction pathways in immune and inflammatory cells during diarrhea and also to study the nature of protection against diarrheal pathogens like *Vibrio cholerae, Salmonella, E. coli and Shigella* in different animal model. He has published 57 original papers and more than 42 abstracts presented different national and international conference. He has secured patent for a process for the preparation of Cholera Vaccine-VA1.3 (European Patent Office; Patent No- 97309957.5-2105 on 19/05/98) and Shigella Vaccine (Patent application no. 1652/Del/2013 dated 31.05.2013). He received different awards among them Young Scientist Award received in IUPS, New Zealand in the year 2001.

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