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Designing a multi-epitope vaccine for cross-protection against *Shigella* spp: An immunoinformatics and structural vaccinology study

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ABSTRACT

Shigellosis is a severe diarrheal disease with high mortality and morbidity rate. Until now, there is no approved vaccine against the disease. Therefore, the present study was planned to design a novel multi-epitope vaccine against *Shigella* spp., the causative agents of the disease based on the immunoinformatic tools. For this end, firstly seven conserved antigens of the bacteria, including IpaA, IpaB, IpaC, IpaD, OmpC, OmpF and VirG were selected. Then, linear B-cell epitope mapping of these proteins was carried out and top-ranked and shared epitopes were selected based on antigenicity, allergenicity, stability, toxicity and physicochemical properties for further analysis. In next step, B-cell derived T-cell epitopes were determined and appropriate epitopes were selected for incorporation into the final construct. Moreover, the selected epitopes and two mucosal adjuvants including ctxB and LT-IIc were joined using appropriate linkers. The three dimensional structure of the final construct was modeled and evaluated in term of structural quality and presence of conformational B-cell epitopes. Furthermore, binding affinity of the proposed vaccine to MHC I and II molecules were evaluated through molecular docking method using Hex 8.0. as well as the stability of the vaccine-MHC complexes was monitored by molecular dynamics method using the NAMD graphical user interface embedded in visual molecular dynamics. Finally, to evaluate the immunogenicity of the designed protein, the protein was administered to BALB/c mice and the serum IgG was determined by ELISA. The results indicated that the proposed vaccine has high structural quality and binding affinity to both MHC I and II molecules. Moreover, molecular dynamics studies confirmed that the vaccine-MHC docked complexes were stable during simulation time. Animal study showed that the proposed protein is able to evoke mice's humoral immune response. In sum, the results suggested that the proposed candidate vaccine could be considered as a promising anti-shigellosis vaccine.

1. Introduction

Shigellosis is an intestinal infectious disease caused by the gram negative bacteria of *Shigella* spp. Despite the great efforts made in the field of prevention, diagnosis and treatment of shigellosis, the disease is still a significant public health problem, especially in developing countries. It is estimated that approximately 1.1 million deaths occur due to *Shigella* infection annually (Schroeder and Hilbi, 2008). The genus *Shigella* has 4 species or subgroups (A, B, C, and D) and 43 serotypes that among them *S. dysenteriae*, *S. flexneri*, *S. boydii* and *S. sonnei* are able to cause the disease in human (Niyogi, 2005). Symptoms of shigellosis typically start 1–2 days after exposure and include: diarrhea, abdominal pain, fever and tenesmus. Shigella transmission can occur through direct person-to-person contact or via the contaminated food and water (Bennish, 1991). Depending on the severity of the disease, patient's condition, age and gender, various strategies are used for the treatment of shigellosis, from antibiotic therapy for the severe cases to consumption of fluids and rest in moderate ones (Steffen, 1990). Although, antibiotic therapy may be useful for severe cases of shigellosis and can reduce the duration of symptoms, but there are increasing antibiotic resistance among Shigella spp. so that antibiotic treatment frequently fails (Murray et al., 2017). Due to wide spread antibiotic resistance as well as costly, time-consuming and low effectiveness of antibiotic therapy, many efforts have been done to introduce effective vaccine against *Shigella* spp. (Kaminski and Oaks, 2009; Levine et al., 2007; Hajizade et al., 2016). However, despite many efforts on the

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