Reverse Vaccinology: Developing Vaccine Against MDR *Acinetobacter baumannii*

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**Abstract**

Emergence of resistance against drugs viz. carbapenems, fluoroquinolones, aminoglycosides is the major problem associated with *Acinetobacter baumannii* infections thus making it imperative to develop a suitable vaccine as an effective treatment option. Previous studies reveal that outer membrane proteins of *A. baumannii* could serve as vaccine candidates and provide partial or complete immunity against lethal doses in various mouse models. Recently, we have shown reverse vaccinology as a powerful tool to identify vaccine candidates. The immunoprotective efficacy of an outer membrane, putative pilus assembly protein, FilF, identified as a potential vaccine candidate was validated in *A. baumannii* associated murine pneumonia model and was found to provide 50% survival against *A. baumannii* lethal doses. NucAb, an outer membrane nuclease identified *in silico* as *A. baumannii* vaccine candidate, provided 20% survival on active and 40% survival on passive immunization.

**Short Communication**

*Acinetobacter baumannii* is a fast emerging nosocomial pathogen that has gained attention of medical fraternity worldwide [1,2]. It infects the patients in hospitals or immunocompromised individuals and makes the treatment difficult due to its multidrug resistance nature [3]. All commonly available antibiotics such as carbapenems, fluoroquinolones and aminoglycosides have failed to control this pathogen [4-7]. Colistin, considered as the last resort of antibiotic treatment, is now used against this pathogen but there are reports of emergence of colistin resistant *A. baumannii* strains [8-10]. Therefore, other than antibiotics, vaccine development appears as the promising and effective treatment option. People in intensive care units or in hospitals for longer durations can be vaccinated prophylactically before admission in order to protect them from this nosocomial pathogen, besides the therapeutic use of vaccine.

Currently, vast information about genomes and proteomes of *A. baumannii* strains is available and promising vaccine candidates can be identified using the computational tools [11-15]. These candidates can further be validated in laboratories using animal models. Highly immunogenic antigens showing little variation among different strains can be determined by conventional techniques but they are time consuming and can be applied only for cultivable microorganisms. Reverse Vaccinology allows a rapid and efficient analysis to find putative immunogenic antigens. This approach can be incorporated in initial study (Figure 1) and can provide such novel proteins which could not be found by conventional vaccinology [16-19]. From the available proteome of pathogen, one can predict putative antigens associated with surface as ideal vaccine candidates. Once shortlisted, these candidates can be cloned and overexpressed in *E. coli* and purified by affinity chromatography. Their immunogenicity can be validated in vivo in suitable animal models.

This approach has successfully led to identification of antigens capable of eliciting protective immunity against *N. meningitidis* group B [15]. Similarly, conserved surface proteins conferring cross-
protective immunity in several pathogens such as Porphyromonas gingivalis [12], Streptococcus pneumoniae [19], Chlamydia pneumoniae [20] and Streptococcus agalactiae [21] have been identified by reverse vaccinology and successfully used. In our earlier published work [22,23], we have analyzed the proteomes of A. baumannii strains and predicted 51 vaccine candidates and validated the immunoprotective potential of two of them (an outer membrane nuclease, NucAb, and FilF, a putative pilus assembly protein) in murine pneumonia model.

FilF is a putative pilus assembly protein that fulfilled in silico the criteria of an ideal vaccine candidate [22]. Its localization in outer membrane makes it interact with host immune system during infection. It has no trans-membrane helix that alleviates the problems encountered in cloning of this protein. And most importantly, its complete dissimilarity with the human and mouse proteome which does not leave any chance of autoimmune response generation by the host. Several other properties of this protein such as high adhesion probability, number of B cell and MHC class I & II binding epitopes and its ability to bind to MHC molecules strongly make it a promising vaccine candidate. The exact role of FilF in A. baumannii is unknown and no information is available how it was named as FilF.

Conservation analysis by BLAST and Multalin shows its exclusive probability, number of B cell and MHC class I & II binding epitopes and its ability to bind to MHC molecules strongly make it a promising vaccine candidate. The exact role of FilF in A. baumannii is unknown and no information is available how it was named as FilF. Conservation analysis by BLAST and Multalin shows its exclusive probability, number of B cell and MHC class I & II binding epitopes and its ability to bind to MHC molecules strongly make it a promising vaccine candidate.

In our studies [22,23], we found that immunization with outer membrane proteins elicited high antibody titer but was unable to provide 100% protection against lethal bacterial dose. There could be several possible reasons for this such as down regulation of certain membrane proteins by bacteria during the acquisition of antibiotic resistance and during the immunity development [36]. Several lines of evidence in our published study [22,23] supported the fact that FilF as sub-unit vaccine could limit the infection and provided protection (50% survival) from lethal bacterial dose challenge. On the other hand, active immunization with nuclease provided 20% survival which increased to 40% after passive immunization. The future of the A. baumannii vaccinology should be focused on a better and clear understanding of the natural infection process in both animal models and human beings. The route of infection and bacterial dose are critical in causing the infection. Appropriate mouse models and more promising vaccine candidates can be explored to develop the best way to protect individuals at high risk. Antigens predicted by reverse vaccinology may represent most appropriate vaccine candidates.

Disclosures

The authors have no conflicts of interest nor any financial interests to disclose.

References


