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Proteome-wide identification of epitope-based vaccine candidates against multi-drug resistant *Proteus mirabilis*

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ABSTRACT

Proteus mirabilis is one of the important pathogens of urinary tract and exhibits resistance to multiple drugs. Development of vaccine tends to be the most promising and cost-effective remedy against the said pathogen. Herein, we implement a combinatorial approach for screening proteins harboring potential broad-spectrum antigenic epitopes in the proteome of *P. mirabilis*. The targets are host non-homologous, essential and virulent, and have localization in the extracellular and outer membrane. Immuno-informatics revealed antigenic, surface exposed and broad-spectrum B-cell derived T-cell epitopes for three membrane usher family candidates: AtfC, PMI2533 and PMI1466, which could evoke a substantial immune response. Protein-protein interactions of targeted three proteins have shown their involvement in biologically significant pathways indispensable for the growth and survival of the pathogen. The antigenic epitopes are conserved among all completely annotated strains and docked deeply in the binding cavity of the most prevalent allele-DRB1*0101 in human population. Future work is necessary to characterize the shortlisted proteins and epitopes for immune protection in animal models.

1. Introduction

Urinary tract infections (UTIs) are the infections due to the presence of microbial pathogen within the urinary tract [1]. *Escherichia coli* being the major causative agent of UTIs accounts for 90% of the cases [2]. *Proteus mirabilis* along with other family members of Enterobacteriaceae are the foremost reason of infectious diseases in community and health-care settings [3]. The pathogen is responsible for kidney stone formation, acute pyelonephritis, wound and bloodstream infections (BSI) [3–5]. *P. Mirabilis* accounts for 1–10% of all UTIs [5] and is difficult to treat as 48% of its strains are resistant to broad-spectrum antibiotics [5,6], therefore the development of an effective vaccine is urgently required.

Vaccines are considered as safe and efficacious means of preventing human population from infectious diseases [7]. Development of conventional vaccines such as those including whole cell organisms (inactivated or live attenuated) are not preferred due to unnecessary antigenic load that leads to non-specific immune responses [8–10]. Additionally, such vaccines are associated with allergenic and reactogenic responses, which further complicate the situation [8]. Likewise, subunit-based vaccines harbor different antigenic epitopes and not all of them are required [8]. One of the rationale left behind is the designing of epitope-driven or peptide-based vaccines. Compared to whole cell or subunit vaccines, peptide-based vaccines are highly specific, easy to design, and formulate [8–10]. With growing trends of bacterial whole genome sequencing and advancement in bioinformatics, the field of vaccinology is revolutionized to “Reverse Vaccinology (RV)” [11,12]. RV is a series of *in silico* filters that prioritized protein candidates in the pathogen proteome based on several parameters: non-homology with the host proteome, aid in bacterial virulence, essential for survival, localized in the extracellular matrix or outer membrane, antigenic and have broad-spectrum conservation

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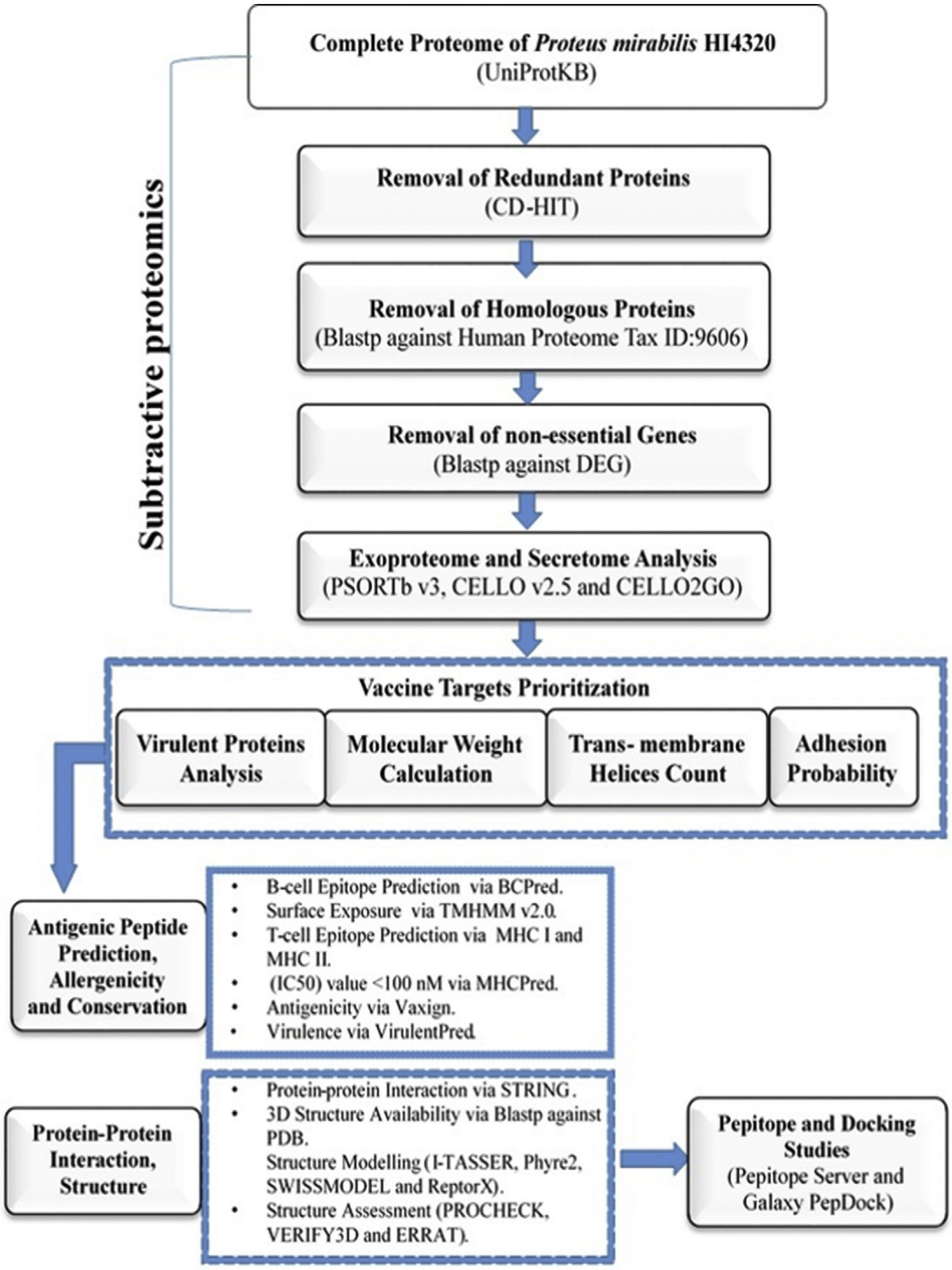

Fig. 1. Workflow for prediction of potential subunit and epitope-based vaccine targets against *P. mirabilis*.

[9,10,13]. RV predicts potential vaccine candidates by minimizing the problems of cultivating the pathogen, time and cost, and opens up new doors of solution for problems where traditional methods failed [9,10,14]. In the past, RV was used to design a successful vaccine to prevent, by active immunization, invasive disease caused by *Neisseria meningitidis* serogroup B (MenB) in individuals of 10 through 25 years of age [15]. Additionally, RV expedited preclinical (before start of clinical trials) and clinical vaccine targets against *Staphylococcus aureus* and *E. coli* [12]. The current research utilizes RV in combination with proteome mining for identifying proteins that harbored antigenic and specific epitopes that can elicit both humoral and cell-mediated immunity. The proteins can be used in subunit vaccine while the antigenic peptides can be used in peptide vaccine designing. Outcomes of the study can be targeted in future for experimental validations to unveil their roles in immune protection.

2. Materials and methods

The overall scheme of the study is presented in Fig. 1.

2.1. Prioritizing vaccine proteins

Complete reference proteome of the pathogen, *P. mirabilis* HI4320, was retrieved from UniProtKB (http://www.uniprot.org) [16] and subjected to CD-Hit server (http://weizhongli-lab.org/cdhit_suite/cgi-bin/index.cgi?cmd=cd-hit) [17] for removal of paralogous proteins sharing identity of 60% [9,10]. Paralogous proteins have redundant function and are evolutionary less conserved among bacterial species [18]. On the other hand, orthologous (non-redundant) proteins are evolutionary more conserved and tend to be attractive targets for vaccine designing [9,10,18]. To avoid cross-reactivity with the host proteins, pathogen specific (host non-homologous) proteins with