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Original Article

In silico prediction of T- and B-cell epitopes in PmpD: First step towards to the design of a *Chlamydia trachomatis* vaccine

Romina Cecilia Russi [a], *Elian Bourdin* [b], *María Inés García* [a], *Carolina Melania I. Veaute* [a,*]

[a] *Basic Immunology Laboratory, Faculty of Biochemistry and Biological Sciences, National University of the Littoral, Santa Fe, Argentina*

[b] *Independent professional, C1425BME, Buenos Aires, Argentina*

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ABSTRACT

Background: *Chlamydia trachomatis* is the most common sexually transmitted bacterial infection globally. Currently, there are no vaccines available despite the efforts made to develop a protective one. Polymorphic membrane protein D (PmpD) is an attractive immunogen candidate as it is conserved among strains and it is target of neutralizing antibodies. However, its high molecular weight and its complex structure make it difficult to handle by recombinant DNA techniques. Our aim is to predict B-cell and T-cell epitopes of PmpD.

Method: A sequence (Genbank AAK69391.2) having 99–100% identity with various serovars of *C. trachomatis* was used for predictions. NetMHC and NetMHCII were used for T-cell epitope linked to MHC I or MHC II alleles prediction, respectively. BepiPred predicted linear B-cell epitopes. For three dimensional epitopes, PmpD was homology-modeled by Raptor X. Surface epitopes were predicted on its globular structure using DiscoTope.

Results: NetMHC predicted 271 T-cell epitopes of 9-12aa with weak affinity, and 70 with strong affinity to MHC I molecules. NetMHCII predicted 2903 T-cell epitopes of 15aa with weak affinity, and 742 with strong affinity to MHC II molecules. Twenty four linear B-cell epitopes were predicted. Raptor X was able to model 91% of the three-dimensional structure whereas 57 residues of discontinuous epitopes were suggested by DiscoTope. Six regions containing B-cell and T-cell epitopes were identified by at least two predictors.

Conclusions: PmpD has potential B-cell and T-cell epitopes distributed throughout the sequence. Thus, several fragments were identified as valuable candidates for subunit vaccines against *C. trachomatis*.

* *Corresponding author*. Basic Immunology Laboratory, Faculty of Biochemistry and Biological Sciences, National University of the Littoral, University Campus S3000ZAA, Santa Fe, Argentina.
E-mail address: cveaute@fbcb.unl.edu.ar (C.M.I. Veaute).

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At a glance commentary

Scientific background on the subject

Chlamydia trachomatis infection has a high global prevalence and is associated with serious consequences on reproductive health. Antibiotic therapy is not successful at all, thus, vaccine development is strongly needed. One immunogen candidate is Polymorphic Membrane Protein D, a surface protein, highly conserved among serovars, and target of neutralizing antibodies.

What this study adds to the field

The identification of T- and B-cell epitopes on PmpD allows the selection of several regions that may be used to design subunits vaccines, potentially inducing both humoral and cellular immune responses. Bioinformatics presents powerful tools to the characterization of proteins favoring the rational design of vaccines.

Chlamydia trachomatis (*Ct*) is an intracellular bacterium that is an important cause of sexually transmitted infections (STI) with significant impact on public health. The World Health Organization (WHO) estimates that *Ct* is responsible of almost 106 million of the 500 million new cases of STI reported worldwide annually [1]. *Ct* includes three human biovars composed of different serovars [2] that can infect various cell types in humans. Serovars A-C are responsible for ocular infections that result in trachoma leading to blindness [3]. Serovars D-K causes sexually transmitted diseases such as cervicitis and pelvic inflammatory disease (PID), and globally are an important infectious cause of infertility, ectopic pregnancy [4] and chronic pelvic pain [5] in women. In men it is associated with urethritis, epididymitis and orchitis [6]. Moreover, serovars D-K cause urethritis and neonatal pneumonia [2]. The lymphogranuloma venereum (LGV) serovars L1–L3 not only cause sexually transmitted disease but can also infiltrate local lymph nodes, which ultimately results in systemic infection [7,8]. *Ct* infections can be controlled by antibiotic therapy but the lack of compliance with treatment, the persistence of the infection even after a complete treatment, together with the high prevalence of asymptomatic cases [4] leading to severe reproductive complications strongly support the development of an effective *Chlamydia* vaccine. Currently, there are no vaccines available against *Ct* genital infection despite the many efforts that have been made throughout the years to develop a protective one. A failure of several vaccine designs may be attributed at least in part to the fact that protective immune response may result harmful for the host and the assumption that complete microorganisms could have components that induce both a protective and a immunopathogenic response. Safety concerns may be overcome by using subunit vaccines, but they require a thorough design in order to be efficient.

Among the antigen candidates that have been studied, members of the Polymorphic Membrane Protein family (Pmp A-I) have shown to be promising as vaccine components as they are dominant antigenic targets for cellular immune responses [9–11]. Pmps are a group of membrane bound surface exposed chlamydial proteins [12–19] that have been characterized as autotransporter adhesins. These proteins are involved in the delivery of virulence factors involved in the initial phase of chlamydial infection [2], disease progression and immune evasion [18]. As typical type V autotransporters [20], all Pmps are characterized by containing conserved GGA (I, L, V) and FxxN tetrapeptide motifs, with an amino-terminal (N-terminal) dependent leader sequence, followed by a passenger domain and a carboxy-terminal (C-terminal) β-barrel [2,21,22]. The C-terminal region is incorporated into the outer membrane, forming a pore and allowing the translocation of the N-terminal passenger domain to the bacterial surface [22]. Pmp proteins may also undergo complex infection-dependent post-translational proteolytic processing [8,17,18,23]. These proteins mediate *in vitro* chlamydial attachment to human epithelial and endothelial cells [8,16].

PmpD is the second highest conserved Pmps demonstrating a 99.1% of amino acid identity among *C. trachomatis* serovars [24], and it is a target of broadly cross-reactive neutralizing antibodies [16]. The structural features of PmpD are relatively large size (1530 aa, 160.5 kDa), integrin-binding RGD motif (aa 698 to 670), and a putative nuclear localization signal (NLS; aa 783 to 798) [18] besides of N-terminal GGA(I/L/V) and FxxN tetrapeptide repeats as in all Pmps.

Due to its conserved nature, surface localization, and immunological importance PmpD is an attractive vaccine candidate for the prevention of human infections [16]. However, it has a high molecular weight with a complex structure which makes it difficult to handle by recombinant DNA techniques. Thus, an in-depth study of the molecule is needed in order to make a rational choice of the immunogen taking into consideration the critical epitopes to induce the appropriate immunological reaction. Several authors suggest that immunity against *C. trachomatis* requires CD4+ T cells, (mainly Th1) with INF-γ production and, to a lesser degree CD8+ T cells. Besides, neutralizing antibodies are now the focus of immune protection and vaccine development [16]. One of the major difficulties in developing an effective chlamydial vaccine is identifying the B-cell epitopes and the MHC-bound chlamydial protein epitopes that are recognized by T-cells.

In this context, bioinformatic approaches can contribute to the design of epitope-based vaccines. Therefore, the aim of this study was to perform *in silico* prediction of B and T epitopes within the amino acid sequence of PmpD for the design of a subunit vaccine against *C. trachomatis*.

Materials and methods

Datasets

An amino acid sequence of *C. trachomatis* serovar L2 PmpD available from NCBI (Genbank AAK69391.2) [25] was used for computational prediction. PmpD genes are one the most conserved between *C. trachomatis* serovars (with 99.1%

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