A preliminary report on predicted epitopes of malarial VAR2CSA by bioinformatics method: a clue for further vaccine development

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Abstract

Malaria is an important tropical infection. Development and approval of new vaccines are the hope for infectious control of the possible emerging pandemic of this pathogen. Malarial VAR2CSA may have value as a protective immunogen in novel vaccines. Here, the author reports the preliminary data from the computation analysis of VAR2CSA to find potential T-cell and B-cell epitopes using new bioinformatics tools. According to this work, the possible alternatives are reported. These data are useful for further vaccine development because these promiscuous peptide binders allows to minimize the total number of predicted epitopes without compromising the population coverage required in the design of vaccines.

Key words: *malaria, VAR2CSA.*

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Introduction

Malaria is an important tropical infection [1]. It is an important potentially deadly mosquito-borne disease in the tropical countries. Despite decades of control success and a competent network of country-wide health infrastructure, malaria remains an important health threat in many countries [2]. Development and approval of new vaccines are the hope for control of the possible emerging pandemic of this infection. Based on the advance in bioinformatics, the immunomics becomes a new alternative in vaccine development [3, 4].

Advanced technologies for vaccine development, such as genome sequence analysis, microarrays, proteomics approach and high-throughput cloning and bioinformatics database tools and computational vaccinology can be applied for vaccine development of several diseases including to emerging diseases. Prediction of peptide binding to major histocompatibility complex (MHC) molecules is the basis for epitope discovery-driven vaccine development). Current developments in computational vaccinology mainly support the analysis of antigen processing and presentation and the characterization of targets of immune response. Databases and data mining are the two principal weapons at the disposal of the in silico vaccinologist. Faced with the expanding volume of information now available from genome databases, vaccinologists are turning to epitope mapping tools to screen vaccine candidates [3, 4]. New databases have been launched in order to facilitate the epitope prediction.

Malarial VAR2CSA may have value as a protective immunogen in novel vaccines [5]. The main aim of this study is to find potential T-cell and B-cell epitopes of. Here, the author reports the preliminary data from the computational analysis of VAR2CSA to find potential T-cell and B-cell epitopes using new bioinformatics tools.

Material and Methods

Prediction for T-cell epitopes by MHCPred

First the author performed a database search on PubMed (www.pubmed.com) to find the amino sequence of

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VAR2CSA malaria. According to the search, there are 88 natural sequences. The author investigated all sequences and selected the longest sequence for further analysis. Then the author performed computation analysis of the proper VAR2CSA sequence (accession number = ABK91145, 316 residues) to find potential T-cell epitopes using bioinformatics tool namely MHCPred (available from the URL: http://www.jenner.ac.uk/MHCPred) [6]. The MHCPred tool is a partial least squares-based multivariate robust statistical approach to the quantitative prediction of peptide binding to major histocompatibility complexes (MHC), the key checkpoint on the antigen presentation pathway within adaptive cellular immunity [6]. MHCPred implements robust statistical models for both Class I alleles (HLA--A*0101, HLAA* 0201, HLA-A*0202, HLA-A*0203, HLA-A*0206, HLA-A*0301, HLA-A*1101, HLA--A*3301, HLA-A*6801, HLA-A*6802 and HLA-B*3501) and Class II alleles (HLA-DRB*0401, HLA-DRB*0401 and HLA-DRB*0701) [6]. The results of computational analysis included peptides and their corresponding IC50 values, which implies the binding affinity. Usually, peptides with predicted binding affinities <500 nM are good binders, whereas those with binding affinities >5000 nM are considered non binders [7].

Prediction for B-cell epitopes by BepPred

In addition to T-cell epitope prediction, the author also performed a B-cell epitope prediction using another bioinformatic tool namely BepPred (available from the URL: http://www.cbs.dtu.dk/services/BepiPred) [8]. This tool combines the hidden Markov model with one of the best propensity scale methods. It is accepted as the best tool for prediction of B-cell epitope at present [8]. The results of computational analysis included peptides and their corresponding threshold scores. The higher threshold score mean higher specificity and binding affinity.

Deriving for a consensus prediction by other alternative tools

To derive a consensus prediction, the author performed additional T-cell epitope prediction (for the identified candidate HLAs) by SYFPEITHI [9] and B-cell epitope prediction by ANTIGENIC [10].

Table 1. Peptides with the best predicted binding affinities for each allele

Alleles	Peptides	ic50 value
A0101	109ILGTSVNIY117	4.02
A0201	287LLKENYPEC295	24.95
A0202	166KSGIKTIKK174	23.88
A0203	122KLQEDIKKI130	3.58
A0206	173KKQKKNGTY181	23.82
A0301	168GIKTIKKQK176	11.53
A1101	298ANFDFIFND306	8.39
A3101	13LWDKRYGGR21	63.8
A6801	300FDFIFNDNI308	15.38
A6802	164AVKSGIKTI172	27.54
B3501	292YPECISANF300	145.88
DRB0101	40IQKETELLY48	2.73
DRB0401	280VGKSASDLL288	39.26
DRB0701	51HDKGTAIIS59	23.33

Results

Prediction for T-cell epitopes by MHCPred

For T-cell epitope prediction, the alleles selected for binding affinity prediction are A0101, A0201, A0202, A0203, A0206, A0301, A1101, A3101, A6801, A6802, B3501, DRB0101, DRB0401 and DRB0701. According to the analysis, peptides with the best predicted binding affinities for each studied are presented in table 1. Among all alleles, the results from DRB0101, A0203 and A0101 show significant lower IC50 than other alleles.

Prediction for B-cell epitopes by BepPred

For B-cell epitope prediction, there are 7 identified peptides (table 2). According to the analysis, the 63NPMKEGGEDGKGKQKEGGEKANNNKNSNGLPKGFCHAVQRSFID94 presents the higher score.

Table 2. Peptides with the acceptable predicted binding affinities

Peptides	Threshold score
1IPPRTQN7	0.383-1.430
17RYGGRSNIKNHTKESL32	0.431-1.110
63NPMKEGGEDGKGKQKEGGEKANNNKNSNGLPKGFCHAVQRSFID94	0.535-2.266
138QNGKTVGSGADKVNDWWKEIE158	0.526-2.076
179GTYTGNECGVSPPTGNDEDQSVSWFKEWGEQF210	0.387-2.761
23LNGKKCINSKSGQGDKVEGACKRKCEKYKKYI261	0.361-1.562
273TKYENKYVGKSASDLLKENYPEC295	0.359-1.363

Deriving for a consensus prediction by other alternative tools

Using SYFPEITHI in T-cell epitope prediction, 54EGGEDGKGK63 (6th rank), 125DIKKIIEKG134 (2nd rank) and 116IYEYIGKLQ124 (9th rank) can be predicted as good candidates for DRB0101, A0203 and A0101, respectively. Using ANTIGENIC in B-cell epitope prediction, 93IDYKNMILGT102 (1st rank) can be predicted as good candidate.

Discussion

Malaria is still an important problematic mosquito-borne infection at present. For vaccine development it is important to define the antigenic targets for protective antibodies and to characterize the consequences of sequence variation [5]. VAR2CSA is a polymorphic protein of approximately 3,000 amino acids forming six Duffy-binding-like (DBL) domains [5]. Duffy et al proposed VAR2CSA as a pregnancy-specific malaria vaccine [11]. Conclusively, VAR2CSA is accepted as a target for vaccine development at present [5, 12].

Identification of epitopes capable of binding multiple HLA types will significantly rationalize the development of epitope-based vaccines [13]. In this work, the author used a new bioinformatic tool to predict potential T-cell epitopes. The technique used in this study is similar to a previous recent report [14]. In this work, the author firstly performed an internet search to find the proper VAR2CSA sequence using the standard database, PubMed. Only natural sequences are focused for further studying. Indeed, the choice for this type of study should be the natural sequence from a laboratory isolate with a full length sequence. In this work, the author selected the VAR2CSA with the longest length. Indeed, there might be some sequences with longer lengths from some laboratories but they have not been included into PubMed. For the selected VAR2CSA (ABK91145), the peptides with best binding affinities for each allele are determined. In addition, the author also verifies the selected tools by performing a consensus prediction by other alternative tools. Of interest, peptide candidates predicted by alternative methods, although not the best ones but in the first top ten, in the nearby regions to those predicted by MHCPred and BepPred can be derived. Indeed, the difference in consensus prediction can be seen due to the difference basic technique of the tools. However, the used tools are the standard tools and accepted as the best tools in immunoinformatics at present.

The determined peptides are useful for further vaccine development because it can reduce the time and minimize the total number of required tests to find the possible proper epitopes, the target for vaccine development. The design of multi-epitope vaccines can also based on these identified epitopes. Conclusively, the author used a computational analysis to determine the potential T-cell and B-cell epitopes of VAR2CSA. For T-cell epitope prediction, 40 IQKETELLY48 corresponding to DRB0101 allele is the peptide with the best binding affinity. For B-cell epitope prediction, 63NPMKEGGEDGKGKQKEGGEKANNNKNSNGLPKGFCHAVQRSFID94 is the peptide with the best binding affinity. Of interest, these predicted epitopes are described for the first time and can be the good preliminary data for further studies. In addition, this study can be a good example of using basic bioinformatics techniques in epitope prediction, called "epitope informatis" at present [15]. However, some limitations of this study should be mentioned. The results from this study are only predicted results. Further confirmation is required. Further in vitro synthesis of the determined peptide and in vivo experimental study to test the efficacy are the recommended as the future steps to this preliminary study for vaccine development.

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