International Journal of Computational Bioinformatics and In Silico Modeling
Vol. 2, No. 4 (2013): 180-185
Review Article
Open Access

ISSN: 2320-0634

Web Based Tools and Databases for Epitope Prediction and Analysis: A Contextual Review

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Received: 29 June 2013 Accepted: 12 July 2013 Online: 16 July 2013

ABSTRACT

Vaccinomics is new branch of bioinformatics that deals with the designing of a candidate vaccine against a pathogen which is produced in less time as that of conventional vaccinology. This new beginning of the vaccine research in past few decades has led to several new approaches towards vaccine development. These include synthetic peptides that able to stimulate immune system of host. Hence epitope prediction and epitope mapping are most important steps in designing of the synthetic vaccine. Epitope prediction and Epitope mapping can be done by various tools and software that runs on various algorithms that are most useful for prediction; giving appropriate value by considering each amino acid.

Keywords: Vaccinomics; synthetic peptides; Epitope prediction; epitope mapping; algorithms

INTRODUCTION

When the conventional ways fail to develop the vaccine then non conventional ways are to be followed for their preparation. Till now genome sequences of more than 500 pathogens including bacteria and viruses are available on National Institute of Health (NIH) list [1]. As the techniques are available for host- pathogen interaction, whole genome, each and unique gene studies, thus, the work is now focused on the development of epitope driven vaccine that are target specific.

Epitope is an antigenic determinant that plays an important role in immunity of an organism. These are present on the surface of organism that can be detected by the antibody [2]. As reverse vaccinology deals with computational analysis of organism genome that can be used for the prediction of the epitopes that is surface protein [3]. So the epitopes play an important role in development of candidate vaccine. The major role in immune system is played by B- and T- lymphocytes. B-cells are important in recognizing the epitopes of the antigen that can be identified by the paratopes of antibody; while in some cases T-cells play role in cell mediated immunity as the processed antigenic peptides interacts with the T-cell when they are presented in context of T-cell [4]. So the prediction of the epitopes of T-cells and B-cells play an important role in determination of the candidate vaccine. The epitope prediction plays an important role in designing of epitope based vaccine [5].

Immunological Reaction [6]

Antigen is a protein molecule but whole of it is not presented to immune cells especially T- and B-lymphocytes. Antigen is processed and converted to antigenic peptides; these peptides are then capable of stimulating the immune system of the host. The antigenic peptides are generated by various enzymes. After which it gets associated with Transporter Associated Proteins (TAP), to get transported to endoplasmic reticulum and then interact with Major Histocompatibility Complex (MHC). These antigenic peptides, in the context of MHC, are then presented to T cells. As there are two kinds of MHC molecules present, so the antigen processing is classified as

1. Endocytic pathway
2. Cytosolic pathway

Hence to design an efficient vaccine the epitopes must have to be predicted that can bind to MHC molecules

[7]. There are many tools that can predict the epitopes as MHC binder. These tools run on various matrices and algorithm. In these methods each amino acid is given a particular value [8]. For the prediction of the epitopes data must have to be there in database and if the new epitopes are predicted then this data is deposited at several databases. Several databases are present on web as depositories of epitopes that bind to Major Histocompatibility Complex class I and class II, B-cell epitopes and Transporter Associated Proteins (TAP).

Immunological Databases:
Several databases are present on web that gives the whole immunological information. These databases store the information about T cell epitopes, B cell epitopes, TAP binding sequences etc

Immune Epitope Database (IEDB) [9]
The database is developed by National Institute of Health and it is now the major database on web that store total information about immunology informatics. It is collection of the various prediction and analysis tools that predicts the targets for T-cell and B-cell immune responses. These tools can be grouped as follows based on their immune targets

1. MHC- peptide binding
2. Antigen processing
3. Antibody processing
4. Epitope analysis tools

The database runs on various algorithms that are used for the analyses of various immune responses related to T-cell, B-cell and epitope interactions. Table 1 shows the entries of the database.

Table 1. List of entries at Immune Epitope Database

Entries	Count
Peptidic Epitopes	98883
Non-Peptidic Epitopes	1892
T Cell Assays	204953
B Cell Assays	156268
MHC Ligand Elution Assays	8046
MHC Binding Assays	238205
Epitope Source Organisms	3026
Restricting MHC Alleles	647

SYFPEITHI [10]
It contains the information about peptide sequence, anchor position, specificity of MHC source organism. Each and every amino acid is taken into consideration in anchor position and auxiliary anchor position. The database contains naturally processed peptides as that of others. The score of each amino acid is calculated by following Table 2.

Table 2. Score value for each residue at SYFPEITHI

Ideal anchor	10 points
Unusual anchor	6 to 8 points
Auxiliary anchor	4 to 6points
Preferred residues	1 to 4 points
Negative effect as binding	-1to -3 points

SVM Server [11]
This is a support vector machine which is used for the prediction of the epitopes against MHC class I and MHC class II. It is used for prediction of the most likely binders in protein sequence and also investigates the effect of single nucleotide polymorphism in terms MHC peptide binding.

MHCPEP [12]
It is major database comprising of sequence of near about 13,000 peptides that can bind MHC molecules both class I and class II. These entries were compiled from submission of the experimental data with each peptide sequence having MHC specificity, observed activity and binding affinity. The present format of databases allows text string matching searches but can easily be converted for the use in conjunction with sequence analysis.

JenPep [13]
It is family of rational databases supporting the growing community of immunoinformatics. It consists of quantitative data of peptide that binds to MHC molecule and to transmembrane peptide transporter and also consists of T-cell epitope list. It consist of 6000 peptide sequences that binds MHC I and MHC II, and set of over 400 peptide that binds to Transporter Associated Protein (TAP).

FIMM [14]
It contains relevant functional data about molecular immunology focusing cellular immunology with the complete data of antigens, MHC molecules, MHC associated peptides and their respective references. The source of data which is incorporated in FIMM is literature, public databases, and HLA workshop reports.

MHCBN [15]
The database contains sequence of peptides of MHC binders and MHC non-binders. It is comprehensive database comprising over 25,857 peptide sequences including 1,053 entries of TAP binding peptides. The entries are compiled from literature and immunological databases. It consists of various tools for analysis and recovery of the information of antigenic regions and allele specific datasets. Table 3 shows the entries of this database.

Table 3. List of entries at MHCBN

Data	Entries
MHC binders	20717
MHC non binders	4022
TAP peptides	1053
T- cell epitopes	6722
Antigenic sequences	3754
MHC allele sequences	1420
MHC structure	119
MHC linked disease	20

EPIMHC [16]
It is relational database of MHC binding peptides and T-cell epitopes. It consists of 4867 entries of peptide sequences including 84 tumor associated antigen.

HIV Molecular Immunology Database [17]
The database contains all information about the sequence diversity of HIV, T-cell epitopes (CD4+ and CD8+) and antibody interactions sites. It provides a complete list of HIV epitopes with full information.

Epitope Mapping
Vaccines are biological preparations that consist of either killed or attenuated pathogens. But it could be desirable to use peptide vaccines that don't contain any harmful agent for safety purpose. Such vaccines contain peptides representing B-cell epitopes and T-cell epitopes that able to stimulate immune system of host [18]. So the epitope based vaccine will be a good choice for designing a candidate vaccine. Epitopes are antigenic determinants which are made up of protein and some accessory factors [19]. As there are two important cells of immune system that are most responsible for host immunity. Thus the epitopes are classified as:

1. T cell epitopes
2. B cell epitopes

Epitope mapping tool provides a better understanding of all molecular features of protein including discovery of drug, vaccine targets etc.

T-Cell epitope mapping and prediction
T cell plays an important role in cellular immunity with accountability for the removal of acute viremia. So the vaccine which is developed against T cell will be able to prevent the cause of disease in days to come [5]. T cell recognizes the antigenic peptides only when are presented by MHC I or II, with the help of the CD4 and CD8 molecule [20]. T-cell epitopes are short linear peptides as they are cleaved by antigenic proteins [8]. There are so many web based tools available for the prediction of the epitopes.

Web based tools and databases for T-cell epitope prediction
A successful peptide-based vaccine must include immune dominant epitopes [21, 22]. One of the problems faced due to traditional vaccines is the lack of a broad cell-mediated immune response against variable pathogens [23-25]. Knowing the importance of T-cell responses in controlling viral infections, the larger number of T-cell epitope mapping and prediction algorithms are available [26, 27]. So many tools and databases are there for the epitope prediction against T cell. So epitope can be predicted with the ability to bind with MHC class I and MHC class II molecules. Promiscuous HLA presentation and epitope prediction offers a rational strategy for creation of T cell vaccines. These tools provide extensive listings of T cell epitopes and HLA-binding peptides as well as non binding peptides, which are an important resource for motif resolution and epitope prediction. Epitope prediction assists the detection of new epitopes, vaccine design, site-directed mutagenesis (for making less immunogenic proteins) and potential autoantigen identification [18].

IEDB analysis Resources [9]
IEDB analysis is the major database available on web that contains various tools for antigen processing including the T cell and B cell epitope prediction. Several programs run this database which can be arranged in increasing order of performance for both MHC- I and MHC-II molecules.

For MHC-I: CombLib < Net MHCpan < SMM < NetMHC < consensus

For MHC-II: CombLib < SMM align < NN align < Net MHCII pan < Consensus

PREDEPP [28]
In this method MHC groove peptide structure is used as template on which compatibility of peptide binding is evaluated by statistical potential. It also relies on conservation and interaction of peptide- MHC complexes. Binding compatibility of peptide is evaluated statistically by pairwise potential. It is also useful for prediction of proteosomal cleavage site.

Epipredict [29]
It is quantitative method used to describe peptide libraries. The binding contribute each amino acid in side chain as described by allele specified 2 dimensional database.

Predict [30]
In this tool neural networks are used for the prediction of MHC class I and MHC class II and TAP binders. The software able to predict:

- MHC class I binders.
- MHC class II binders.
- Proteasomal/immunoproteasomal processing of antigens.
- Peptide-TAP binding.
- Exclude peptides shareing local similarity with human proteins from the set of predicted epitopes.
- Assess expected population coverage by the selected set of peptides.
- Assist you in identifying the minimal set of peptides covering the most MHC class I alleles chosen for prediction.
- Analyze a batch of antigen sequences at once.
- Process antigen sequences, written either in Fasta or GenBank format.

MHCpred [31]
It predicts protein- ligand energetics relating free energy of binding taking into consideration of each single amino acid and side chain interactions. The original and mutated peptides are compared for the prediction of the high affinity binding peptides. It is composed of no. of allele specific QSAR model created using PLS a multivariable statistical method used for prediction of binding 11 different MHC class I and 3 different MHC class II molecules.

NetMHC [32]
Neural networks and position specific score matrix (PSSM) are used for prediction of HLA-A2 binding peptides. It is a quantitative method used for prediction of binding affinity. Neural network consist of data with 55 MHC alleles and PSSM consist of 122 alleles.

PREDIVAC [20]
It is CD4+ T cell epitope prediction tool that covers about 95% of HLA class II DR protein diversity. It is useful for designing the particular candidate vaccine that covers most of HLA allele. The software runs on Perl language. High affinity binding peptides and specificity determining residues are main purpose of the Predivac DB database. The data is taken from IEDB, MHCBN, and EPIMHC. For T cell epitope prediction, it consist of about 1325 entries of MHC class II restricted T cell epitope that account for 43 MHC class II HLA alleles. It has the ability to identify immunodominant and promiscuous epitope.

RANKPEP [33]
It is online resource that uses position specific scoring matrices for prediction of peptide that can bind MHC class I and MHC class II. Currently 88 entries of MHC I and 50 different entries of MHC II molecules that are targeted for peptide binding prediction are available on RANKPEP.
It is most powerful tool that allows:

1. Prediction of peptide able to bind to MHC I and MHC II molecules using motif profile.
2. Highest specificity of CD8 T-cell epitope prediction by combined proteosomal cleavage site prediction.
3. Prediction of conserved epitope.

EpiMatrix [34]
EpiMatrix tool set is competent in predicting epitopes against more than 100 different MHC class I and class II alleles. In a typical EpiMatrix analysis, the protein sequence is broken down into overlapping 9-mer frames. Each of the derived 9-mer frames is then screened for predicted affinity against MHC class I and/or class II alleles. The resulting scores can be directly compared across HLA alleles. The ability to rate putative epitopes on a common scale is described as an exclusive feature of the EpiMatrix system [35].

The EpiMatrix platform is also closely tied with additional computational tools such as ClustiMer (scans EpiMatrix results for T-cell epitope 'clusters'), BlastiMer (automated BLAST search tool), OptiMatrix (involved in de-immunizing sequences), Conservatrix (involved in finding conserved epitopes) and Vaccine CAD (an *in silico* vaccine design algorithm) [34].

B-cell epitope mapping and prediction
Antigen antibody interaction plays an important role in immunity, binding takes place at antigenic determinant also known as B-cell epitopes. The B-cell epitopes are defined by a specific surface region of an antigenic protein, and may be divided into two different types of epitopes: linear epitopes and conformational epitopes [36].

The linear epitopes are short peptides while conformational epitopes composed of amino acid folded in 3- dimensional protein structure [37]. The mapping of the B cell epitopes can be done by various techniques. The focus of the scientist is only on the determination linear B cell epitope [38]. The propensity value of amino acid plays an important role in determination of its position in B cell epitopes. It was introduced by Hopp and Woods. They utilized the Levitt hydrophobicity scale for the determination of the propensity value for each amino acid [37]. But till today several tools are available for the prediction of linear B cell epitopes, these are PREDITOPE [39], PEOPLE [40], BEPITOPE [39] and BcePred [41] (with the determination of) that determines the propensity value for the epitopes. ABC pred [41] uses the machine learning based method for the prediction of the linear B cell epitopes. The conformational B cell epitope prediction can be done by:

Sequence based prediction method: - Does not require a known target antigen structure [37].
Structure based prediction method: - Depends on the determination of the antigen antibody complexes using X- ray crystallography. DiscoTope is used for the determination of the conformational B cell epitope prediction. PEPITOPE uses combination of propensity value and half sphere exposure value of amino acid residues [37].
Mimotpoe analysis based prediction method: - It combines both computational and experimental techniques for B cell epitope mapping. It determines the organization of the genuine epitopes [37].

Web based tools and servers for B-cell epitope prediction
Bepitope [42]
It is the server which provides continuous protein epitopes for highly specific monoclonal antibodies. It also suggests the epitope list which can be synthesized. It includes whole genome treatment and also uses defined pattern for glycosylation site.

BcePred [43]
This tool evaluates the existing Linear B cell prediction method based on physicochemical properties. It consists of 1029 B cell epitopes like hydrophobicity, flexibility, accessibility and polarity turns. It is capable of predicting epitope with 58% accuracy using flexibility hydrophobicity, polarity and surface protein.

Pepitope [44]
It is B cell epitope prediction tool is that used for predicting discontinuous epitope that have affinity against monoclonal antibodies. It runs on PepSurf and Mapitope algorithm. It is useful when 3D structure of protein sequence is known.

Ellipro [45]
Ellipro is tool designed by IEDB web server that is used for prediction of discontinuous B cell epitopes. It is best and gives AUC (area under curve) value of 0.7332. It based on 3 algorithms:

1. Approximation of the protein shape as an ellipsoid
2. Residue protrusion index calculation
3. Clustering of neighboring residues based on PI value

The first two algorithms consider each residue centre of mass and third algorithm is for clustering residues that is for discontinuous epitope. It is web based tool for the prediction of antibody epitope in protein antigen of a given sequence or structure.

Epitopia [46]
It is web based server that is used to predict immunogenic regions in 3D protein structure as well as machine learning algorithm giving immunogenic potential of each and every single amino acid. It contains 66 entries of non redundant epitope sequences derived from antigen antibody co-crystal structure and 194 entries of non redundant sequences derived from antigen sequences.

ABCpred [47]
It allows the prediction of continuous B cell epitopes. One can easily input the query sequence using threshold value and result will appear in tabular form and in overlap display. It uses neural network for prediction of epitope. It contains 1400 entries of B cell epitopes and non-epitope peptides.

FBCpred [48]
The implementation of FBCpred is available on BCEPREDS. It compares different algorithm for the prediction of B cell epitopes which is most reliable method than individual prediction. This tool is useful for prediction of linear flexible length B cell epitope.

Discotope [49]
The method is used for the prediction of B cell epitopes. It uses 3 parameters for prediction:

1. Statistical difference in amino acid composition
2. Spatial neighborhood for interacting log odds
3. Surface measure

It acts by probing carbon backbone of protein structure. It uses propensity score and half spheres exposure as surface measure. It defines epitopic residues from combination of surface exposure and log odds propensity scores.
List containing web addresses are given in Tables 4-6.

CONCLUSION

Epitope prediction and epitope mapping are most important tools in development of epitope based vaccine which is a very good approach as it may eliminate adverse effect of pathogens. It is possible to use no. of epitopes at once to overcome the problem of hypervariable sequences. Such vaccines contain B-cell and T-cell epitopes. The software given in this review are mostly important for designing the epitope as there is need of epitope based vaccine now a day's against pathogens for which vaccine is not available. Concluding this review, it shows that IEDB analysis resources is a best tool available on net for in silico vaccine designing as it consists of many links about epitope prediction, epitope analysis, homology mapping, conservation analysis etc. IEDB analysis resources are freely available web server to accessible for every user easily.

Table 4. Immunological databases and their links

Immunological Databases	URL
Immune Epitope Database	http://www.iedb.org
SYFPEITHI	http://syfpeithi.bmi-heidelberg.com/scripts/MHCServer.dll/home.htm
SVM Server	http://sysbio.unl.edu/SVMTriP.
MHCPEP	http://wehih.wehi.edu.au/mhcpep
JenPep	www.jenner.ac.uk/JenPep
FIMM	http://sdmc.krdl.org.sg:8080/fimm
MHCBN	www.imtech.res.in/raghava/mhcbn
EPIMHC	http://mif.dfci.harvard.edu/Tools/db_query_epimhc.html
HIV Molecular Immunology Database	http://hiv-web.lanl.gov/content/immunology/

Table 5. Softwares and their links for prediction of T-cell epitope prediction (MHC binding peptides)

Epitope prediction Tools	URLs
IEDB analysis Resources	http://tools.immuneepitope.org/mhc/
PREDEPP	http://bioinfo.md.huji.ac.il/marg/Teppred/mhc-bind
Epipredict	www.epipredict.de/index.html
Predict	http://sdmc.krdl.org.sg:8080/predict-demo
MHCpred	www.jenner.ac.uk/MHCPred
NetMHC	www.cbs.dtu.dk/services/NetMHC
PREDIVAC	http://predivac.biosci.uq.edu.au
RANKPEP	http://bio.dfci.harvard.edu/RANKPEP/
EpiMatrix	www.epivax.com

Table 6. Softwares and their links for prediction of B-cell epitope prediction

Epitope prediction tools	URL
Bepitope	http://www-dsv.cea.fr/en/institutes/institute-of-environmental-biology-and-biotechnology-ibeb/services2/department-of-biochemistry-and-nuclear-toxicology-sbtn/molecular-recognition-and-interactions-laboratory-lirm/research/software/bepitope
BcePred	http://www.imtech.res.in/raghava/bcepred/
Pepitope	http://pepitope.tau.ac.il/
Ellipro	http://tools.immuneepitope.org/tools/ElliPro.
Epitopia	http://epitopia.tau.ac.il
ABCpred	www.imtech.res.in/raghava/abcpred
FBCpred	http://ailab.cs.iastate.edu/bcpreds/
Discotope	www.cbs.dtu.dk/services/DiscoTope-2.0.

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