Available online at www.sciencedirect.com

ScienceDirect

Biomedical Journal

journal homepage: www.elsevier.com/locate/bj

Original Article

Computational prediction of vaccine potential epitopes and 3-dimensional structure of XAGE-1b for non-small cell lung cancer immunotherapy

Mohammad M. Tarek [a,*], *Ayman E. Shafei* [b], *Mahmoud A. Ali* [b], *Mohamed M. Mansour* [c]

[a] *Bioinformatics Department, Armed Forces College of Medicine (AFCM), Cairo, Egypt*
[b] *Biomedical Research Department, Armed Forces College of Medicine (AFCM), Cairo, Egypt*
[c] *Ain Shams University (ASU), Faculty of Computer Information Sciences (FCIS), Bioinformatics Program, Cairo, Egypt*

ARTICLE INFO

Article history:
Received 6 January 2017
Accepted 12 April 2018
Available online xxx

Keywords:
Epitope prediction
NSCLC immunotherapy
Bioinformatics
Peptide vaccines
Cancer/testis antigen
XAGE-1b

ABSTRACT

Background: XAGE-1b is shown to be overexpressed in lung adenocarcinoma and to be a strong immunogenic antigen among non-small cell lung cancer (NSCLC) patients. However, 3D structure of XAGE-1b is not available and its confirmation has not been solved yet.
Methods: Multiple sequence alignment was run to select the most reliable templates. Homology modeling technique was performed using computer-based tool to generate 3-dimensional structure models, eight models were generated and assessed on basis of local and global quality. Immune Epitope Database (IEDB) tools were then used to determine potential B-Cell epitopes while NetMHCpan algorithms were used to enhance the determination for potential epitopes of both Cytotoxic T-lymphocytes and T-helper cells.
Results: Computational prediction was performed for B-Cell epitopes, prediction results generated; 3 linear epitopes where XAGE-1b (13-21) possessed the best score of 0.67, 5 discontinuous epitopes where XAGE-1b (40-52) possessed the best score of 0.67 based on the predicted model of the finest quality. For a potential vaccine design, computational prediction yielded potential Human Leukocyte Antigen (HLA) class I epitopes including HLA-B*08:01-restricted XAGE-1b (3-11) epitope which was the best with 0.2 percentile rank. Regarding HLA Class II epitopes, HLA-DRB1*12:01-restricted XAGE-1b (25-33) was the most antigenic epitope with 5.91 IC50 value. IC50 values were compared with experimental values and population coverage percentages of epitopes were computed.
Conclusions: This study predicted a model of XAGE-1b tertiary structure which could explain its antigenic function and facilitate usage of predicted peptides for experimental validation towards designing immunotherapies against NSCLC.

* *Corresponding author*. Bioinformatics Department, Armed Forces College of Medicine (AFCM), Egypt, Ehsan Abd Al Kodoos, Mansheya El-Bakry, Heliopolis, Cairo, Egypt.
E-mail address: mohammadtareq459@gmail.com (M.M. Tarek).
Peer review under responsibility of Chang Gung University.
https://doi.org/10.1016/j.bj.2018.04.002

At a glance commentary

Scientific background on the subject

XAGE-1b has been identified as an overexpressed surface antigen in NSCLC cells and has been shown to be immunogenic. The quest for designing immunotherapies as peptide vaccines based on XAGE-1b has been challenged by the lack of detailed structural and sequence based information regarding its immunogenic properties.

What this study adds to the field

This study provides an extensive computational analysis of XAGE-1b that provides essential antigenic data that could aid in the development of immunotherapies against NSCLC. The paper also provides detailed structural as well as sequence based properties for each antigenic determinants on XAGE-1b.

Lung cancer is the primary cause of cancer death among both genders. An estimated number of 158,080 deaths are expected to occur in 2016 approximately quarter of the expected number of deaths to be caused by cancer. The most common type of lung cancers is Non-small cell lung cancer (NSCLC) as it accounts for about 84% of lung cancer cases [1]. About 70 cancer/testis (CT) antigens have been identified by immunological or genetic approaches [2–4] and have been shown to generate humoral and cell-mediated immune responses in cancer patients [5]. Because they are limitedly expressed in normal tissues and show great antigenicity, CT antigens are interestingly being attractive targets for cancer vaccines [6–10]. PAGE/GAGE-related genes were investigated using an expression sequence tag database [11] where XAGE-1 was found to have similar characteristics to CT antigens [12–14]. Four transcript variants of XAGE-1 were identified which are XAGE-1a, XAGE-1b, XAGE-1c, and XAGE-1d and were shown to be expressed in lung cancers as well as metastatic melanoma, breast cancer, Ewing sarcoma and prostate cancers [15–18]. XAGE-1b protein has been shown to be located in the cellular nuclei, using Immuno-histochemical nuclear staining methods. XAGE-1b was observed to be expressed strongly in 53% of lung adenocarcinomas; XAGE-1b expression was also immunogenic where most mRNA-positive specimens have been shown to express XAGE-1b protein [19]. The relevance of the XAGE-1b antigen expression was observed in Caucasian NSCLC patients [20]. XAGE-1b overexpression in adenocarcinoma cases of NSCLC is considered one of the most immunogenic antigens and a promising target for lung adenocarcinoma immunotherapy which requires determination of antigenic epitopes and tertiary structure of that antigen that may be addressed by computational tools which could pave the way for experimental validation and designing an epitope-based vaccine for NSCLC [21,22].

Materials and methods

Retrieval of 9kD cancer/testis-associated protein XAGE-1b protein sequence

The antigenic protein sequence of 9kD cancer/testis-associated protein XAGE-1b protein was retrieved by accessing the NCBI databases [23] with 81 amino acid sequence in order to study the antigenicity and solvent accessible regions which permits potential vaccine targets to recognize active sites against NSCLC and then submitted to IEDB tools and other bioinformatics methods in order to computationally predict 3-dimensional model, assess modeling quality, and perform computational epitope prediction.

Homology modelling

Synthesizing peptides does not depend on the secondary structure of the protein, instead of that, it completely depends on the primary structure. Subsequently it does not indicate that the tertiary structures of the Antigen. Synthesis of XAGE-1b Antigenic peptides have been reported in the literature [20] However, peptide synthesis does not indicate that the 3D structure of XAGE-1b conformational epitopes have been solved. Furthermore in order to be able to study the immune interaction between XAGE-1b epitopes and HLA molecules, we need to study the 3D structure of the Surface antigen and the conformations of the epitopes. The prevalence of XAGE-1b antigen in different populations including Caucasians [20] supports that screening capabilities of immunoinformatics approaches could be helpful to provide large scale immune interaction analysis of XAGE-1b interaction with HLA class I and II as well as the structural analysis that may be implemented for further immune interaction studies or more interestingly peptide vaccine design.

Homology modeling is a comparative method of building an atomic-resolution model of a target protein sequence using an experimental 3-dimensional structure of a homologous Template. It depends on the identification of template structures resembling the target structure of the input sequence, doing an alignment that compares the input sequence to the template sequence. The rationale behind homology modelling is that Protein structures are proved to be more conserved than protein sequences among homologues, but proteins of sequence identity less than 20% can have non-homologous structure. Evolutionarily related proteins show similar amino acids sequences while naturally occurring homologous proteins have correlated 3-dimensional structure, so 3-dimensional protein structure is more conserved than expected on the basis of sequence conservation alone. Multiple Sequence alignment and template structure could be both used to produce a structural model of the target.

Despite its importance in Cancer research, the 3-dimensional structure of this protein is not available on bioinformatics databases (NCBI) (PDB) and it is confirmation has not been solved experimentally yet. Similarity alignment was done to select different reliable modeling templates and Top models were generated and tested according to SWISS-Model [24] parameters such as QMEAN which is a combined scoring

Please cite this article in press as: Tarek MM, et al., Computational prediction of vaccine potential epitopes and 3-dimensional structure of XAGE-1b for non-small cell lung cancer immunotherapy, Biomedical Journal (2018), https://doi.org/10.1016/j.bj.2018.04.002