Computational Biology and Chemistry 65 (2016) 110–116

Contents lists available at ScienceDirect

Computational Biology and Chemistry

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

Research Article

In silico designing breast cancer peptide vaccine for binding to MHC class I and II: A molecular docking study

Manijeh Mahdavi[a,*], Violaine Moreau[b]

[a] Applied Physiology Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
[b] CNRS UMR 5048-UM-INSERM U1054, Centre de Biochimie Structurale, 29, rue de Navacelles, 34090 Montpellier Cedex, France

ARTICLE INFO

Article history:
Received 18 July 2016
Received in revised form 17 October 2016
Accepted 19 October 2016
Available online 19 October 2016

Keywords:
HER2 receptor
Docking
MHC
Bioinformatics
Peptide vaccine

ABSTRACT

Antigenic peptides or cancer peptide vaccines can be directly delivered to cancer patients to produce immunologic responses against cancer cells. Specifically, designed peptides can associate with Major Histocompatibility Complex (MHC) class I or II molecules on the cell surface of antigen presenting cells activating anti-tumor effector mechanisms by triggering helper T cell (Th) or cytotoxic T cells (CTL). In general, high binding to MHCs approximately correlates with *in vivo* immunogenicity. Consequently, a molecular docking technique was run on a library of novel discontinuous peptides predicted by PEPOP from Human epidermal growth factor receptor 2 (HER2 ECD) subdomain III. This technique is expected to improve the prediction accuracy in order to identify the best MHC class I and II binder peptides. Molecular docking analysis through GOLD identified the peptide 1412 as the best MHC binder peptide to both MHC class I and II molecules used in the study. The GOLD results predicted HLA-DR4, HLA-DP2 and TCR as the most often targeted receptors by the peptide 1412. These findings, based on bioinformatics analyses, can be exploited in further experimental analyses in vaccine design and cancer therapy to find possible proper approaches providing beneficial effects.

1. Introduction

Most current treatments of cancers involve surgery, chemotherapy, radiation and hormone therapy (Garrett, 2007; Jones, 2007). While these initial therapies are successful, some problems remain, such as drug resistance to current treatments and the risk of cancer recurrence (Calabrich et al., 2008). Today, in order to find new cancer drugs, cancer vaccines are active therapeutic approaches designed to trigger the immune system through the recognition of antigens (Xiang et al., 2013). Peptide vaccines are an attractive alternative strategy which employs short peptide fragments to engineer the generation of highly targeted immune responses (Weidang et al., 2014; Pedro et al., 2014). Peptide vaccines contain the 8–11 amino acid epitope of an antigen for inducing positive, desirable T and B cell mediated immune response (Slingluff, 2011).

In T cell mediated immune responses, the peptide antigens are presented on the surface of cancer cells to specific T-cell receptors (TCR) by MHC (Major Histocompatibility Complex) class I and II molecules (Zhang, 2013). The short peptides with 8–10 amino acids primarily derived from endogenously proteolysed proteins which are presented in association with Class I MHC molecules, recognized by CD8+ cytotoxic T lymphocytes (CTL) (De Groot et al., 2001; Bian et al., 2003). While, the long peptides (typically 12–28 amino acids) mainly derived from exogenous antigens which are associated with Class II MHC molecules, identified by helper (CD4+) T-cells (Martin et al., 2003).

Crystallographic analyses of class I MHC/peptide complexes have shown that the peptides are bound in an extended conformation through conserved networks of hydrogen bonds with the C- and N-terminal charges compensated by complementary MHC residues (Garboczi et al., 1996). The nature of the peptide side chains is not the only reason for hydrogen bonding and electrostatic interactions (Patronov et al., 2012). Whereas, binding specificity is regulated by the interactions of the charged peptide amino acids and carboxyl-termini with polar residues at the two ends of a binding groove with MHC residues (Jardetzky et al., 1996). After forming the MHC–peptide complex, most of the central residues of the peptides exposed in the MHC complexes are recognized by TCRs (Tong et al., 2004).

In the design of peptide vaccines, for efficient induction of either B-cell or cytotoxic T cell responses, the induction of a strong helper T cell responses is an important prerequisite (Dakappagari

* Corresponding author.
E-mail addresses: mahdavi@pharm.mui.ac.ir (M. Mahdavi), violaine.moreau@cbs.cnrs.fr (V. Moreau).

http://dx.doi.org/10.1016/j.compbiolchem.2016.10.007
1476-9271/

et al., 2000; Mahdavi et al., 2013). Thus, to find a peptide that induces specific immune responses, the challenge would be to detect the precise epitope that can activate T cells conferring protective immunity (Wang et al., 2010; Sundaram et al., 2004). The most important issue to be considered is the association of the candidate peptide vaccine by antigen presenting cells in MHC heterogeneous human populations. The fast and reliable identification of epitopes-based vaccines is of great importance as it will reduce the time-consuming and expensive process due to the large number and diverse nature of MHC alleles and candidate peptides (Flower, 2003).

The molecular docking is a fundamental structure-based method with significant efficacy in drug design, and bioinformatics. It has now become a proper tool, capable of application to solve the problem of binding prediction for MHC molecules. The docking method has succeeded in the area of identifying small molecule ligands of macromolecular targets, and subsequently can help identifying MHC binders. Generally, molecular docking has been broadly tested on both peptide-MHC class I and II complexes. As an approach to predict peptide binding to MHCs, it has confirmed to be rapid, accurate, and reliable (Young, 2009; Patronov et al., 2011).

In our previous study (Mahdavi et al., 2013), a library of novel "discontinuous–continuous peptides" from 3D structure of subdomain III of Human Epidermal Growth Factor Receptor 2 (HER2) extracellular domain (ECD) subdomain III were predicted by PEPOP (Moreau et al., 2008). The predicted peptide 626 could stimulate HER2 specific antibodies especially IgG isotype, in a population of mice with a potential to inhibit the growth of HER2 over expressing SK-BR-3 breast cancer cells (Mahdavi et al., 2014). In the present study, we applied a molecular docking procedure to assess the binding affinities of the predicted peptides with MHC molecules. This technique was also used to model the interactions between the selected peptide with TCR α and β.

2. Methods

2.1. Discontinuous B-cell epitope peptides prediction

Using PEPOP (Moreau et al., 2008), the epitopes were selected, as previously described (Mahdavi et al., 2013), following a three step strategy: (1) 3D structure selection of HER2 ECD, (2) Peptide design from the 3D structure of the targeted protein using methods based on the clustering of the surface accessible segments according to their spatial distances, (3) Peptide selection.

2.2. 3D structure prediction of the peptides

The 3D structure of the epitope-based peptides were predicted by PEP-FOLD server (Maupetit et al., 2009). Visualization of all the models was made in Pymol V1 (De Lano, 2002). Next, for selecting the best model of each peptide, the GROMOS96 force field application in SPDBV was used to minimize the energy of each models (Scott et al., 1999; Guex and Peitsch, 1997).

2.3. Theoretical physicochemical properties of the peptides

The theoretical physicochemical properties of the peptides such as isoelectric point, and hydrophobicity were evaluated using the Prot Param algorithm. The GRAVY index designated the hydrophobicity of the peptides and was measured as the sum of the hydropathy values of the constituting amino acids, divided by the number of residues in the sequence. Peptides with negative GRAVY index are hydrophobic whereas peptides with positive GRAVY index are hydrophilic (Lebreton et al., 2011).

2.4. MHC–peptide complexes selection

We have tested the molecular docking tool on two class I and seven class II MHC-peptide complexes at and below 3.00 Å. Table 1 details the MHC complexes used in this study. The pdb files used in this research were obtained from the Protein Data Bank (pdb). When more than one PDB structure is found, the highest quality structure with the highest resolution is selected. When more than one ligand was available in the selected crystal structure, the ligand that generated the best binding site for the tested peptides is selected.

2.5. The docking of predicted peptides

The full license version of Genetic Optimization for Ligand Docking (GOLD) 5.4 was applied for the molecular docking (Jones et al., 1997, 1995). The Hermes visualizer in the GOLD Suite was used to further preparing the receptors for docking. The binding site used for GOLD docking was defined as all the protein residues within the 10 Å of the reference ligands that accompanied the downloaded protein structure complexes. Default values of all other parameters were used and all solutions are scored according to Piecewise Linear Potential (CHEMPLP) fitness function. According to CHEMPLP, the steric complementary between protein and ligand is calculated while the distance and angle dependent hydrogen and metal binding terms are considered. Empirical parameters used in the fitness function are hydrogen bond energies, atom radii and polarisabilities, torsion potentials, hydrogen bond direction abilities.

3. Results

PEPOP predicted 12 peptides from 3D structure of HER2 ECD subdomain III. Firstly, it identified 116 segments gathered in three clusters according to their spatial distances. PEPOP methods of extension were run on the whole protein with the requested length of 16 amino acids. Optimized Nearest Neighbor (ONN), Optimized Flanking Nearest Neighbor (OFN), and Optimized Patched segments Path (OPP) methods predicted peptides based on segments identification and clustering, while Traveling Salesman Problem (TSP) and Shortest Path (SHP) methods can predicted peptides based on segments or amino acids. Then, the predicted peptides which did not relate to HER2 ECD subdomain III were removed and finally 12 peptides as listed in Table 2 remained.

The peptides conformation plays a significant role in their presentation by helper T-cells to MHC molecules and in epitope recognition by antibodies. Moreover, the direction in which atoms should be displaced in order to reach a lower energy state is important. Thus, the best prediction result was considered to be the most stable predicted structure for each peptide, i.e. the peptide having the minimum total energy (Table 2). Energy minimization can repair distorted geometries by moving atoms to

Table 1
MHC class I and II complex crystal structures used in this study for molecular docking.

Class	MHC alleles	PDB	Resolution (Å)
I	HLA-A*0201	1AO7	2.6
I	HLA-A*0201	1I4F	1.4
II	HLA-DP2	3LQZ	3.25
II	HLA-DQ8	1JK8	2.4
II	HLA-DR2	1BX2	2.6
II	HLA-DR2	1FV1	1.9
II	HLA-DR3	1A6A	2.75
II	HLA-DR4	1J8H	2.4
II	HLA-DRA10101-DRB50101	1H15	3.1