Insight into the Intermolecular Recognition Mechanism between HLA-A*24:02 and Antitumor Peptides against Breast Cancer

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Abstract

Passive immune therapy with “trastuzumab” have been proven to be useful to treat HER-2/neu overexpressing breast cancers. However, serious problems such as recurrence presumably due to the resistance acquisition occasionally occur. Therefore, several peptide vaccines have been studied to overcome the problems. Several peptides have been shown to elicit specific immune response and expected to confer a clinical benefit. The interactions between the peptides and specific HLA molecules are crucial for the proper immune response. Hence, understanding the detailed molecular mechanisms of the interactions are of particular interest from the view point of designing better peptide vaccines. In this study, the interaction modes between these peptides and HLA-A*24:02 which is the most common allele in Japanese populations were elucidated by docking simulations. The roles of each amino acid of these peptides in immunization deduced from the present study would be useful for designing more potent and specific peptide vaccines.

Key Words: vaccination, antitumor, peptides, breast cancer, HER-2/neu, docking simulations

Area of Interest: Molecular Recognition

1. Introduction

Breast cancer is the most common malignancy in women. HER-2/neu is a tumor-associated antigen that is overexpressed in approximately 30% of breast cancer patients [1] and correlates with more aggressive tumor behavior [2]. Passive immune therapy with “trastuzumab” has been proven to be powerful for treating breast cancers overexpressing HER-2/neu. However, since occasional recurrence has been observed, active immune therapies using immunogenic peptides have been tried in order to substitute trastuzumab therapy.
Among several immunogenic peptides derived from HER-2/neu, at least two peptides of E75 and GP2 have shown to be effective in raising HER-2/neu immunity. Tsuda et al. found that a 20-mer peptide containing a B cell receptor epitope of anti-HER-2/neu monoclonal antibody “CH401” possesses potential of a general breast cancer vaccine [3].

E75 and GP2 are human leukocyte antigen (HLA)-A2 restricted and stimulate cytotoxic T lymphocytes to recognize and lyse HER-2/neu-expressing cancer cells [4][5]. As CH401 MAP reacts with a vast majority of human lymphocytes of Japanese cancer patients, HLA-A2 should be one of its major targets [3].

Specific interactions between HLA and immunogenic peptides are crucial for immunization. Understanding the detailed molecular mechanism of the interaction between a specific HLA molecule and immunogenic peptides is particular useful to design better peptide vaccines. Since HLA-A*24:02 is the most frequently observed allele in Japanese, it is of interest to understand how these peptides are recognized by the allele.

In this study, we have predicted a possible mechanism of intermolecular recognition between HLA-A*24:02 and the above three peptide vaccines by docking simulations in order to disclose whether there is a common recognition mechanism.

2. Methods

The X-ray crystal structure of the HLA-A*24:02 molecule (PDB ID: 4F7T) deposited at the Protein Data Bank [6] was used as the initial structure of HLA-A*24:02. The structures of the complexes between HLA-A*24:02 and the peptides were calculated by use of HLA-Modeler [7]. The main function of HLA-Modeler is building homology models of HLA molecules based on given amino acid sequences. HLA-Modeler also can optimize the structure of a peptide placed at the antigenic-peptide binding cleft. The binding affinity of a peptide to HLA-A*24:02 was judged by a scoring function of GBVI/WSA_dG which is considered to express protein-ligand binding free energy [8]. A software system MOE (molecular operating environment) [9] was used throughout this study.

Although CH401 MAP is a 20-mer, the region actually recognized by HLA-A2 should be a contiguous nine amino acid residue. Therefore, all possible 9-mers derived from CH401 MAP were considered. The 9-mer with the lowest GBVI/WSA_dG value was regarded as the peptide primarily recognized by HLA-A*24:02.

3. Results and Discussion

The 9-mer derived from CH401 MAP with the highest calculated affinity to HLA-A*24:02 has the sequence of DTILWKDIF. Tsuda et al. predicted [3] the recognition site of the CH401 MAP peptide by HLA using the algorithm for epitope prediction implemented in SYFPEITHI[10], which is a database based on previous publication on T-cell epitopes and major histocompatibility complex ligands. The predicted sequence recognized by HLA-A*24:02 was DTILWKDIF and conforms to the sequence predicted in this study.

The GBVI/WSA_dG values for the complexes between HLA-A*24:02 and the three peptides of E75, GP2 and DTILWKDIF are -15.60, -14.65 and -18.54 kcal/mol, respectively. Atomic coordinates of these complexes are deposited as Supplementary Materials. Fisk et al. reported that E75 has a high binding affinity for the HLA-A2 and is considered the immunodominant peptide of the HER-2/neu protein, whereas GP2 with a lower binding affinity is considered a subdominant
The binding affinity calculated for these peptides by HLA-Modeler explains the experimental observation. Judging from the results, the DTILWKDIF peptide with the highest calculated binding affinity can be an immunodominant one. The amino acid residues at the antigenic-peptide binding cleft of HLA-A*24:02 commonly observed around these peptides are E63, K66, H70, N77, T143, K146, W147 and Y159. These amino acids residues should play important roles to recognize and tether these immunogenic peptides.

In addition to the affinity to HLA-A*24:02, adequate interactions with the T-cell receptors (TCR) are crucial for the immunogenic potency. The amino acids residues protruding from the surface of the complex should take part in the interactions with the TCR. In order to feature these amino acids, non-hydrogen atoms of HLA-A*24:02 in the three complexes are superposed as shown in Figure 1.

Figure 1. Comparison of the binding modes of three peptides to HLA-A*24:02.

The structures of HLA-A*24:02 are depicted in cartoon mode, and the peptides in ball-and-stick representations. The carbon atoms of the DTILWKDIF, E75 and GP2 peptides are colored in cyan, green and light pink, respectively. A cross-eyed stereoscopic drawing.

As shown in this figure, there are at least three sites facing the TCR. The main chain carbonyl oxygen atoms of L4, G4 and A4 in the DTILWKDIF, E75 and GP2 peptides, respectively, form Site 1. The side chains of K6, L6 and V6 in the DTILWKDIF, E75 and GP2 peptides, respectively, form Site 2. Since the side chain of lysine has significant hydrophobic character, this site should be hydrophobic. Site 3 is formed by the side chains of I8, F8 and I8, in the DTILWKDIF, E75 and GP2 peptides, respectively. The common disposition of atomic groups observed in the three complexes indicates that the amino acid residues in the 4th, 6th and 8th position of the 9mer peptide play important roles in recognizing the TCR.
In this study, the detailed molecular mechanisms of recognition of HLA-A*24:02 by these peptides were disclosed. It is highly expected that based on the recognition mechanism peptide vaccines with greater clinical potential would be designed for preventing recurrence of breast cancer.

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Supplements

Supplemental data are available at: http://cbi-society.info/supplement/10.1273/cbij-15-1/

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