RESEARCH COMMUNICATION

Predicted B-cell Epitopes of HER-2 Oncoprotein by a Bioinformatics Method: a Clue for Breast Cancer Vaccine Development

Viroj Wiwanitkit

Abstract

Breast cancer is one of the most common cancers in the world and is on the increase. Vaccines are new hopes for primary prevention of this cancer. In the breast cancer case, HER2 is a focus as a target for vaccine development. Here, preliminary data from a computation analysis of this outer membrane protein to find potential B-cell epitopes are described using a new bioinformatics tool. According to the results, 947SRMARDPQRFVVIQNE262 is the peptide with the best binding affinity. These data may be useful for further vaccine development because promiscuous peptide binders allow the total number of predicted epitopes to be minimized without compromising the population coverage required in the design of vaccines.

Key words: Breast cancer - B-cells - epitope -HER2

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Introduction

Breast cancer is one of the most common cancers around the world. Objective and subjective breast cancer risk is associated with impaired immune responses and exaggerated biophysiologic responses in healthy women with a family history of breast cancer (Park and Kang, 2006). Increased psychological distress can contribute further to negative immune responses (Park and Kang, 2006). The ERBB2 proto-oncogene, commonly referred to as the human epidermal growth factor receptor-2 (HER2) gene, encodes a 185 kd receptor tyrosine kinase (Laudadio et al., 2007). Overexpression of the protein leads to constitutive activity of the HER2 receptor and breast tumor development through enhanced cell proliferation, survival, motility and adhesion. Overabundance of the HER2 receptor, typically caused by amplification of the HER2 gene, is present in approximately 10-30% of invasive breast cancers, and is associated with an aggressive disease course and decreased disease-free and overall survival in node-positive patients (Laudadio et al., 2007). The NCCN HER2 Testing in Breast Cancer Task Force was convened to critically evaluate the ability of the level of HER2 expression or gene amplification to serve as a prognostic and a predictive factor in the metastatic and adjuvant settings, to assess the reliability of the methods of measuring HER2 expression or gene amplification in the laboratory, and to make recommendations regarding the interpretation of test results (Carlson et al., 2006). HER2 is also focus as a target for vaccine development for primary prevention of breast cancer.

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, immunomics becomes a new alternative in vaccine development (Brusic et al., 2005; De Groot et al., 2006). Faced with the expanding volume of information now available from genome databases, vaccinologists are turning to epitope mapping tools to screen vaccine candidates (Brusic et al., 2005; De Groot et al., 2006). New databases have been launched in order to facilitate the epitope prediction.

The outer membrane protein may have value as a protective immunogen in novel vaccines (Dakappagari et al., 2000). The main aim of this study was to find potential B-cell epitopes. Here, the author reports preliminary data from a computational analysis of HER-2 oncoprotein to find potential B-cell epitopes using a new bioinformatics tool.

Materials and Methods

Here, the author performed computation analysis of available HER-2 oncoprotein sequence (1225 residues) to find potential B-cell epitopes using bioinformatics tool namely ABCpred Prediction Server (Saha and Raghava, 2006). The ABCpred tool is for prediction B cell epitope(s) in an antigen sequence, using artificial neural network (Saha and Raghava, 2006). This is the first server developed based on recurrent neural network (machine based technique) using fixed length patterns (Saha and Raghava, 2006).

Department of Laboratory Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok Thailand 10330 Email: wviroj@yahoo.com, wviroj@pioneer.netserv.chula.ac.th phone: 662-2564136

Table 1. Predicted B-cell epitopes

Rank	Sequence	Start position	Score
1	SRMARDPQRFVVIQNE	947	0.95
1	CAHYKDPPFCVARCPS	557	0.95
2	YGLGMEHLREVRAVTS	313	0.93
2	AVENPEYLTPQGGAAP	1160	0.93
3	CWMIDSECRPRFRELV	928	0.92
3	YYWDQDPPERGAPPST	1191	0.92
4	AREIPDLLEKGERLPQ	898	0.91
4	LGSGLALIHHNTHLCF	431	0.91
4	EVTAEDGTQRCEKCSK	291	0.91
4	GASCVTACPYNYLSTD	262	0.91
5	YKGIWIPDGENVKIPV	705	0.90
5	AAGCTGPKHSDCLAC	211	0.90

Results

Some 115 peptides were identified . The peptides with the first 5 best orders of predicted binding affinities are presented in Table 1.

Discussion

Breast cancer is a leading cause of cancer-related deaths in women worldwide (Zhou and Zhong, 2004). Although tumorectomy, radiotherapy, chemotherapy and hormone replacement therapy have been used for the treatment of breast cancer, there is no effective therapy for patients with invasive and metastatic breast cancer . Immunotherapy may prove effective in treating patients with advanced breast cancer (Zhou and Zhong, 2004). Breast cancer immunotherapy includes antibody based immunotherapy, cancer vaccine immunotherapy, adoptive T cell transfer immunotherapy and T cell receptor gene transfer immunotherapy . The characterization of tumor antigens recognized by immune effector cells has opened the perspective of developing therapeutic vaccines in the field of breast cancer (Curigliano et al., 2006). Most trials evaluating breast cancer vaccines have been carried out in patients with extended metastatic breast cancer, characterized by aggressive tumors, resistant to standard cytotoxic treatments, so that clinical efficacy was difficult to achieve (Curigliano et al., 2006). Developing the most potent approach for activating antitumor immunity while maintaining the efficacy of standard approaches to breast cancer management will ensure that active immunotherapy is successfully integrated into the standar d of care (Emens et al., 2005). According to a recent study by Dakappagari et al, the engineered, chimeric peptide B-cell immunogen might have applications in the prevention of HER-2-overexpressing cancers (Dakappagari et al., 2000).

Identification of effective epitopes will significantly rationalize the development of epitope-based vaccines. In this work, the author used a new bioinformatic tool to predict potential B-cell epitopes. The technique used in this study is similar to a previous recent report (Wiwanitkit, 2006). The peptides with best binding affinities for each allele are determined. The determined peptides should be useful for further vaccine development because they 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.

In conclusion, a computational analysis was here used to determine potential B-cell epitopes of the HER-2 oncoprotein. According to this work, 947SRMARDPQRFVVIQNE262 is the peptide with the best binding affinity. Of interest, this peptide is different from those candidates of the recent previous reports (316 – 339 and 628 - 647) (Dakappagari et al., 2000; 2003). However, some limitations of this study should be mentioned. The results are only predictions and further confirmation is required. In vitro synthesis of the determined peptide and in vivo experimental study to test the efficacy are future steps for vaccine development.

References

Brusic V, August JT, Petrovsky N (2005). Information technologies for vaccine research. *Expert Rev Vaccines*, **4**, 407-17.

Carlson RW, Moench SJ, Hammond ME, et al (2006). NCCN HER2 Testing in Breast Cancer Task Force. HER2 testing in breastcancer:NCCN Task Force report and recommendations. *J Natl Compr Canc Netw*, **4 Suppl 3**, S1-S22.

Curigliano G, Spitaleri G, Pietri E, et al (2006). Breast cancer vaccines: a clinical reality or fairy tale? *Ann Oncol*, **17**,750-62.

Dakappagari NK, Douglas DB, Triozzi PL, et al (2000). Prevention of mammary tumors with a chimeric HER-2 B-cell epitope peptide vaccine. *Cancer Res*, **60**, 3782-9.

Dakappagari NK, Pyles J, Parihar R, et al (2003). A chimeric multi-human epidermal growth factor receptor-2 B cell epitope peptide vaccine mediates superior antitumor responses. *J Immunol*, **170**, 4242-53.

De Groot AS (2006). Immunomics: discovering new targets for vaccines and therapeutics. *Drug Discov Today*, **11**, 203-9.

Emens LA, Reilly RT, Jaffee EM (2005). Breast cancer vaccines: maximizing cancer treatment by tapping into host immunity. *Endocr Relat Cancer*, **12**, 1-17.

Laudadio J, Quigley DI, Tubbs R, et al (2007). HER2 testing: a review of detection methodologies and their clinical performance. *Expert Rev Mol Diagn*, **7**, 53-64.

Park NJ, Kang DH (2006). Breast cancer risk and immune responses in healthy women.*Oncol Nurs Forum*, **33**, 1151-9.

Saha S, Raghava GPS (2006). Prediction of continuous B-cell epitopes in an antigen using recurrent neural network. *Proteins*, **65**, 40-8.

Wiwanitkit V (2006). Predicted epitopes of H5N1 bird flu by bioinformatics method: a clue for further vaccine development. *Chinese Med J*, **119**, 1760.

Zhou J, Zhong Y (2004). Breast cancer immunotherapy. *Cell Mol Immunol*, **1**, 247-55.