RESEARCH COMMUNICATION

Intramolecular Antigenicity of MUC1, a Candidate for Cancer Vaccines

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Abstract

Cancer is a big public health problem as well as a medical challenge. The tumor-associated carbohydrate antigens and glycopeptide antigens derived from, for example, the MUC1 mucin glycoprotein or tumor mucin antigen, are attractive targets for the immunotherapy of cancer, owing to their expre ssion by malignant cells. MUC1 glycoprotein is present in endometriotic lesions and overexpressed in many cancers and the MUC1 immune response is known to provide a protective host defense mechanism against cancer. In this work, the author studied the antigenicity pattern within the MUC1 molecule by an advanced bioinformatics method. It can be seen that the amino acid in the middle portion of the sequence pose high antigenicity. This part could be selected for further vaccine development.

Keywords: MUC1 - antigenicity - vaccine development

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Introduction

Cancer is a big public health problem as well as a medical challenge. A lot has been learned about the process of transformation of a normal cell into a tumor cell by studying genes and proteins that regulate this process either in cis or in trans, however, whether these molecular mechanisms succeed in fulfilling their potential to give a clinically evident (Finn, 2006). The tumor-associated carbohydrate antigens and glycopeptide antigens derived from, for example, the MUC1 mucin glycoprotein or tumor mucin antigen, are attractive targets for the immunotherapy of cancer, owing to their expression by malignant cells (Liakatos, 2007).

MUC1 glycoprotein is present in endometriotic lesions and overexpressed in epithelial ovarian tumors (Vlad et al., 2006). Vlad et al recently mentioned for the MUC1 antigen as the potential for immune therapy/prevention with MUC1 in both diseases (Vlad et al., 2006). In addition, MUC1 also plays important roles in breast cancer (Apostolopoulos et al., 1999). Recently, it have demonstrated that mannan, a polymannose carbohydrate is an effective carrier for MUC1 in eliciting a cellular immune response (Apostolopoulos et al., 1999). Generally, MUC1 loses apical distribution and is hypoglycosylated (Limacher and Acres, 2007). These cancer-associated changes render it antigenic and make it an attractive target for a specific cancer immunotherapy (Limacher and Acres, 2007). In this work, the author studied the antigenicity pattern within the MUC1 molecule by an advanced bioinformatics method.

Patients and Methods

A bioinformatic tool, namely JaMBW (Toldo, 1997) was used with the ANTIGENIC PLOT function was selected for this study. Given a sequence of aminoacids, this program computes and plots the antigenicity along the polypeptide chain, as predicted by the algorithm of Hopp and Woods (1981). After application of the template sequence into the system, the result can be generated in the form of antigenic index chart. The chart displays the variation of the antigenic index as function of amino acid position. The higher the antigenic index, the more likely should be that antibodies would “see” those groups of residues.

Results

The derived sequence for MUC1 from database searching is presented in Figure 1. The resulted antigenic index chart for MUC1 is presented in Figure 2. It can be seen that the amino acid in the middle portion of the sequence (around 100 - 260) pose high antigenicity.

Discussion

The gene MUC1 encodes a large membrane-associated glycoprotein, previously termed polymorphic epithelial mucin and now known as MUC1 [8]. The majority of the extracellular domain is made up of tandem repeats of 20 amino acids (Miles and Taylor-Papadimitrios, 1999). In some epithelial malignancies,

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1 mtpgtqspff lllltvltv vtgsghasst pggeketsat qrssvpsste knavsmtssv 61 lsshspgsgs sttqgqdvtl apatepasgs aatwgqdvts vpvtrpalgs ttppahdvts 121 apdnkpapgs tappaqgvts apetrpppgs tappahgvts apdnrpalas tappvhnvts 181 asgsasgsas tlvhngtsar atttpaskst pfsipshhsd tpttlashst ktdassthhs 241 tvppltssnh stspqlstgv sfffsfhis nlqfnssled pstdyyqelq rdisemvsig 301 lsfpmlp

Figure 1. Sequence of MUC1 (AAB59612)

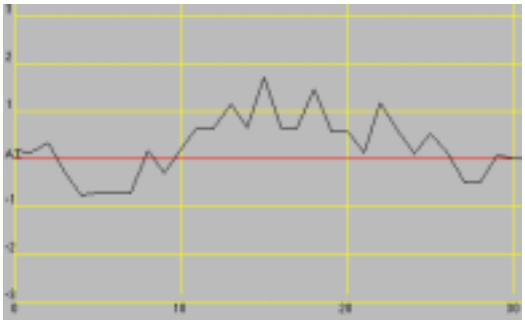

Figure 2. The Resultant Antigenic Index (the X axis represents amino acids (x 10) and the Y axis the antigenic index (x 1)

MUC1 is up-regulated, and as a result of changes in glycosyl and sialytransferases, the complex carbohydrate side chains are truncated, leading to exposure of novel peptide and carbohydrate epitopes (Miles and Taylor-Papadimitrios, 1999). The MUC1 is established as a marker for monitoring recurrence of breast cancer and is a promising target for immunotherapeutic strategies to treat cancer by active specific immunization (Hanisch and Ninkovic, 2006). Natural human immune responses to the tumor-associated glycoforms of the mucin indicate that antibody reactivities are more directed to glycopeptide than to non-glycosylated peptide epitopes (Acres and Limacher, 2005).

The MUC1 immune response is known to provide a protective host defense mechanism against cancer (Vlad et al., 2004). Preliminary clinical results to show that vaccine-based immunotherapy with MUC1 does have an impact on the therapy of cancer (Denda-Nagai and Irimura, 2000). To design a new vaccine candidate, the antigenic study of the selected peptide molecule is needed. In this work, the author used the bioinformatics study to find the intramolecular antigenicity for MUC1 and it was found that the middle part of MUC1 has the highest antigenicity. This part could be selected for further vaccine development.

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