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Effect of deleterious nsSNP on the HER2 receptor based on stability and binding affinity with herceptin: A computational approach

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Abstract

In this study, we identified the most deleterious non-synonymous SNP of *ERBB2* (HER2) receptors by its stability and investigated its binding affinity with herceptin. Out of 135 SNPs, 10 are nsSNPs in the coding region, in which one of the nsSNP (SNPid rs4252633) is commonly found to be damaged by I-Mutant 2.0, SIFT and PolyPhen servers. With this effort, we modelled the mutant HER2 protein based on this deleterious nsSNP (rs4252633). The modeled mutant showed less stability than native HER 2 protein, based on both total energy of the mutant and stabilizing residues in the mutant protein. This is due to a deviation between the mutant and the native HER2, having an RMSD of about 2.81 Å. Furthermore, we compared the binding efficiency of herceptin with native and mutant HER2 receptors. We found that herceptin has a high binding affinity with mutant HER2 receptor, with a binding energy of −24.40 kcal/mol, as compared to the native type, which has a binding energy of −15.26 kcal/mol due to six-hydrogen bonding and two salt bridges exist between herceptin and the mutant type, whereas the native type establishes four hydrogen bonds and two salt bridges with herceptin. This analysis portrays that mutant type has two additional hydrogen bonds with herceptin compared with the native type. Normal mode analysis also showed that the two amino acids, namely Asp596 and Glu598 of mutant HER2, forming additional hydrogen bonding with herceptin, had a slightly higher flexibility than the native type. Based on our investigations, we propose that SNPid rs4252633 could be the most deleterious nsSNP for HER2 receptor, and that herceptin could be the best drug for mutant compared to the native HER2 target. ***To cite this article: R. Rajasekaran et al., C. R. Biologies 331 (2008).***

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1. Introduction

Monoclonal antibodies have been developed for target cell surface receptor molecules, and they represent the most advanced drugs in clinical investigations. Most kinase inhibitors in clinical development are anticancer therapeutics. Two milestones in drug development have been achieved in this field. In 1998, the monoclonal antibody herceptin (also called trastuzumab, developed by Genentech) directed against the receptor tyrosine kinase (RTK) HER2 has been approved for the treatment of

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breast cancer by the FDA as the first example of a next-generation anti-cancer therapeutic [1].

ErbB2 is a proto-oncogene located on chromosome 17, whose product, a tyrosine kinase receptor (HER2), is a 1255 amino acid glycoprotein of 185 kDa, which belongs to the family of epidermal growth factor receptors [2]. ErbB2 was found to be overexpressed in several types of human adenocarcinomas, especially in tumours of the breast and the ovary [3–5]. The overexpression was correlated with more aggressive tumours and a poorer prognosis [6–8]. Hence, herceptin (trastuzumab), humanized antibody against the overexpressed ERBB2, is proven to be effective in treating breast cancers with ErbB2 amplification, which is directed against a juxtamembrane epitope in the HER2 ectodomain [9]. High-affinity binding of trastuzumab to HER2 results in attenuation of aberrant HER2 kinase-associated signal transduction, with coordinate changes in cell cycle distribution (e.g., decreases in the fraction of cells undergoing the S-phase), specifically in HER2-overexpressing cells [10].

Single nucleotide polymorphism (SNP) accounts for common form of human genetic variation. About 500,000 SNPs fall in the coding regions of the human genome [11]. Among these, the non-synonymous SNPs (nsSNPs) cause changes in the amino acid residues. These are likely to be an important factor contributing to the functional diversity of the encoded proteins in the human population [12]. Discovering the deleterious nsSNPs is the main task of pharmacogenomics. So, the main aim of this study is to identify deleterious nsSNPs associated with HER2 protein and their nature of stability and binding affinity with herceptin. We here report that the most deleterious nsSNP is rs4252633 on HER2 receptor. We modeled the mutant HER2 based on this nsSNP, which showed more structural deviation from native HER2. In addition to that, herceptin is having higher binding affinity with mutant structure than in native HER2. This shows that herceptin is the best drug for the molecular target of HER2 receptor, even with most deleterious nsSNP.

2. Materials and methods

2.1. Datasets

The SNPs and their related protein sequence for *ErbB2* gene were obtained from the dbSNP [13] available at http://www.ncbi.nlm.nih.gov/SNP/ for our computational analysis.

2.2. Predicting stability change on mutation by coding nsSNPs based on support vector machine (I-Mutant 2.0)

Single-base changes in protein coding regions of DNA, which lead to changes in amino acids, have an effect on protein structure and function. However, most of the deleterious non-synonymous single nucleotide polymorphisms (nsSNPs)-associated proteins show less stability [14]. We used the program I-Mutant 2.0 available at http://gpcr.biocomp.unibo.it/cgi/predictors/I-Mutant2.0/I-Mutant2.0.cgi. I-Mutant 2.0 is a support vector machine (SVM)-based tool for the automatic prediction of protein stability changes upon single point mutations. I-Mutant 2.0 predictions are performed starting either from the protein structure or, more importantly, from the protein sequence [15]. This program was trained and tested on a data set derived from ProTherm [16], which is presently the most comprehensive available database of thermodynamic experimental data of free-energy changes of protein stability upon mutation under different conditions. The output file shows the predicted free-energy change value or sign (DDG), which is calculated from the unfolding Gibbs free energy value of the mutated protein minus the unfolding Gibbs free energy value of the native type (kcal/mol). Positive DDG values means that the mutated protein posses high stability and vice versa.

2.3. Analysis of functional consequences of coding nsSNPs by sequence-homology-based method (SIFT)

We used the program SIFT [17], which is specifically aimed to detect the deleterious coding non-synonymous SNPs, available at http://blocks.fhcrc.org/sift/SIFT.html. SIFT is a sequence-homology-based tool, which presumes that important amino acids will be conserved in the protein family. Hence, changes at well-conserved positions tend to be predicted as deleterious [17]. We submitted the query in the form of SNPids or as protein sequences. The underlying principle of this program is that SIFT takes a query sequence and uses multiple alignment information to predict tolerated and deleterious substitutions for every position of the query sequence. SIFT is a multistep procedure that, given a protein sequence, (a) searches for similar sequences, (b) chooses closely related sequences that may share similar function, (c) obtains the multiple alignment of these chosen sequences, and (d) calculates normalized probabilities for all possible substitutions at each position from the alignment. Substitutions at each position with normalized probabilities less than a chosen cut-off

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