Grid docking simulations for comparative ligand binding of neuraminidase structures

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Motivation

The influenza neuraminidase (NA) is a viral surface glycoprotein which cleaves terminal sialic acid from glycoconjugates and is essential for virus proliferation. At present, two distinct groups of NA are known: group 1 that includes the subtypes N1, N4, N5, N8 and group2 containing the subtypes N2, N3, N6, N7, N9. N1 subtype is present, for example, in the avian in?uenza virus that currently threatens a new pandemic (H5N1).

The neuraminidase viruses has long been considered a valid target for antiviral drugs. Among these, the most widely used are the inhibitors oseltamivir carboxilate and zanamivir. The design of these drugs is based on the structure of group 2 NA, assuming that the overall characteristics of the active site were conserved among the subtypes. However, recently determined x-ray structures of group 1 NA showed that two different conformations of a loop adjacent to the active site (the so called loop 150) can be detected, depending on ligand concentration (1). In the apo-form, or at low ligand concentration, the loop assumes an open conformation that forms a large cavity near the active site. High ligand concentration induces a conformational change of loop 150, that closes up the cavity on the ligand. This closed conformation corresponds to the structure observed in the group 2 NA. This finding raises the concern for the efficacy of the above mentioned medications to control a pandemic and for the need to obtain more specific drugs to fill the open cavity. Moreover, the development of drug resistance, determined by aminoacidic mutations of virus proteins, requires an accurate evaluation of ligand affinity in the variant structures. In this work, we have screened, by docking simulation on a grid platform, a large set of compounds in the open and closed wild-type structures and in five of the most frequent disease-related aminoacidic variants, modelled in the open conformation of N1 neuraminidase. The results allow the evaluation of the relative binding affinity for the tested ligand. Critical residues involved in the ligand-protein interaction were also identified.

Methods

The dataset used for the screening was downloaded from the site http://blaster.docking.org/dud (2). It included 49 ligands and 1874 decoy molecules designed in order to match the physical properties of the specific ligand for the neuroaminidase target with pdb code 1a4g. The target structures correspond to the pdb entries 2hu0 and to 2hu4 for the open and closed conformation, respectively. The variants E119A, E119D, H274Y, H274F, R292K were obtained by homology modelling on the 2hu0 structure. The docking experiments were performed with AutoDock 3.05 with 50 runs. During this screening a total of 1544 jobs were distributed on 30 Grid CEs. The 2-weeks long activity has covered the computing power of about 135 days and it produced around 4 GB of docking results. The management and analysis of parsed data from docking results were rationalized in a relational database.

Results

The whole dataset binds the NA active site of the two wild-type conformations with comparable energies but with a different ranking. In the top 5% of the docked dataset, 25% and 12% of the natural ligands were found in the closed and open conformation, respectively. This suggested the possibility of different binding properties of the active site in the two conformations. The binding mode of the best 10 ligands for each conformation was analyzed in order to understand the structural differences. In the open structure, all the ligands were superposed in the same position within the active site making the typical electrostatics interactions of the NA known inhibitors. In the closed conformation, some are oriented towards loop 150. The different binding mode involves distinctive residues: R156 establishes hydrogen bonds in the open conformation and D151 in the closed conformation. In the closed conformation, most of the non-bond interactions are centred near the loop 150, while in the open conformation, the residues involved occupy the active site. We also analysed the ligand interaction with the mutants of the open conformation and we found that the E119 and H274 substitutions imply a change of interaction pattern compared to wild type, by the gain of a new interaction with the Y406. Moreover, we found that the E227 is an exclusive residue of the interaction in the binding site of E119A mutant. The information derived by this comparative study can be useful for the selection and rational drug design of high affinity inhibitors for group I neuroaminidase.

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