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Drug target identification and homology modeling on glycoprotein 120 and its role in HIV infected human lymphocytes

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ABSTRACT

Human Immunodeficiency Virus (HIV) directly attacks T lymphocyte and brain, kidneys and heart. Our body immune response depends on special type of T and B lymphocytes which helps in fighting infectious diseases and tumors. The HIV binds to CD4+ lymphocytes, which stimulate many immune cells for fighting and neutralizing the invading pathogen. T lymphocytes are required for immunoneutralization of invading pathogens whether it be bacterial or virus, failing which disease develop in our body. The main purpose of this paper was to study the various molecular interactions of HIV to other molecules like receptors CD4+ and also co-receptors like CCR5 and CXCR4. The molecules are going to be modeled by using software known as Swiss PDB Viewer. The first objective is to get the FASTA sequence from the NCBI website. Then we need to paste the sequence onto the Swiss PDB viewer. The requierd protein/molecule is modeled. We are going to follow this method to obtain templates and modles for the following molecukles: HIV, GP120, CCR5 and CXCR4.

KEY WORDS: HIV infection, NCBI database, CD4, gp120 protein, Lymphocytes.

1. INTRODUCTION

In this paper, after getting the models then we will dock the molecukles by using bioinformatics tools. In docking we will test to see the various molecules interacting with each other. We want to dock HIV and GP120 (Fig 1) and save it as a complex and then dock the two chemokine receptors and save it as a complex and then try to dock the two complexes with one another. The mechanism of HIV infection occurs via lysing T lymphocytes as target cells, which results in reduced immune function or lack of immune response. Other white blood cells, without itself undergoing any morphological changes by lysis, they allow viral multiplication.

Figure.1.Picture shows the HIV gp120 protein complex with CD4. The glycoprotein 120 is shown in red; CD4 is shown in yellow

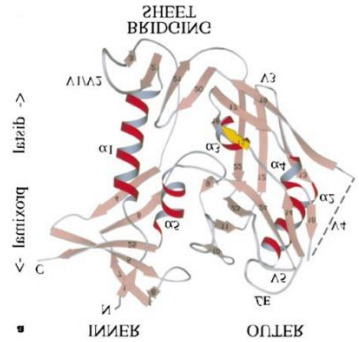

Figure.2.Morphology of gp 120. Further to earlier figure, the morphology or 3D structure has been turned 180

The figure depicts the occurrence of domains in outer and inner sides, and the cavity or groove present between them, which contain the ninding site for CD4/gp120.

2. METHODS

The bioinformatics tools BLAST (Basic Local Alignment Search Tool) is a vital method controlled by National Center for Biotechnology Information (NCBI). Query comparision with database of DNA sequences can be done through BLASt search which promotes easier comparision and operation of software and enables identification of sequences above a certain threshold levels. The BlAST wrapper provides help all types such as tBLASTn, BLASTn, BLASTx, BLASTp and tBLASTx. These possess a query DNA sequence to look and DNA sequence to find against or a DNAdatabase sequence having multiples types of similar DNA sequences.

In bioinformatics tool search, studies in strucutural similarity modeling (Homology) would result in producing high quality structural models, if the search results in closely related target and template, such results has contributed to the formation of consortium on structural genomics assigned to the protein folds with specific representation of experimental structures. The errors in the early stages of sequence alignment and from disordered selection of template results in worsening of DNA sequence similarities leading to inaccuracies in bioinformatics search results. Based on the currently available structural prediction bioinformatics methods, at present homology modeling is monitored half-yearly large scale experiment called as the Critical Assessment of Techniques for Protein Structure Prediction, or CASP.

Ab initio protein modeling: *Ab initio*- or *de novo*- methods of protein modeling look in to construct tertially structure of protein models from scratch, which is developed on the basis of physical principles than previously solved structures. Previous literature has shown a few feasible methods which helps in mimicking protein folding or find positive solutions through stochastic methods. Development of these methods requires large computational resources, and results can be obtained for lower molecular weight proteins. To predict *de novo* protein structure of higher molecular weight or large proteins require better mathematical methods (algorithms) and vast computational resources like Blue Gene or MDGRAP-3 which could be run using supercomputers. Such methods are highly applicable in higher order protein structure prediction or tertiary level interacations between liqands and receptors. Despite availability of open access to lage computational barriers contributing to innovative and advanced drug designing research, the utility of structural genomics results in *ab initio* prediction of secondary and tertiary structures.

3. RESULTS AND DISCUSSION:

Our results show threading of primary amino acid sequence template in concurrence with the structure and two way sequence and spatial configuration obtained from the sequence match arrangements were used for predictions (Figure 3). In our studies, we observed distant homology for the target, protein threading resulting in good predictions. *In silico* model development or prediction of higher order terially structure of a target protein from primary structures of similar proteins for which ther is direct access for NMR structural related studies and X-ray diffraction studies are feasible.

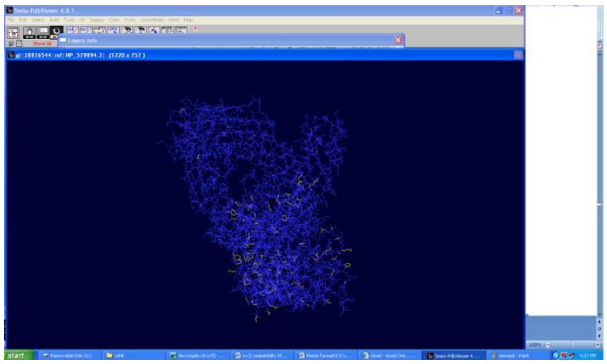

Figure.3. The result of the model displayed using the spdb viewer

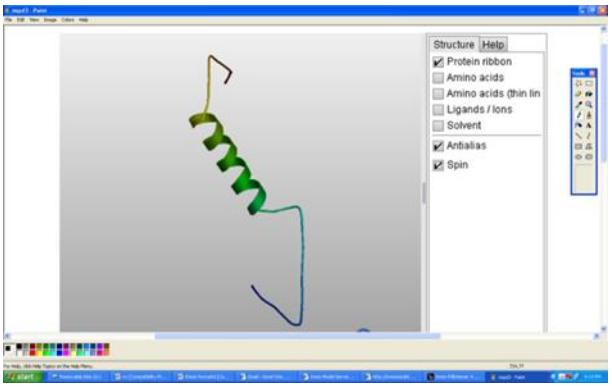

Figure.4. Result of the required molecule. Hex homepage for docking

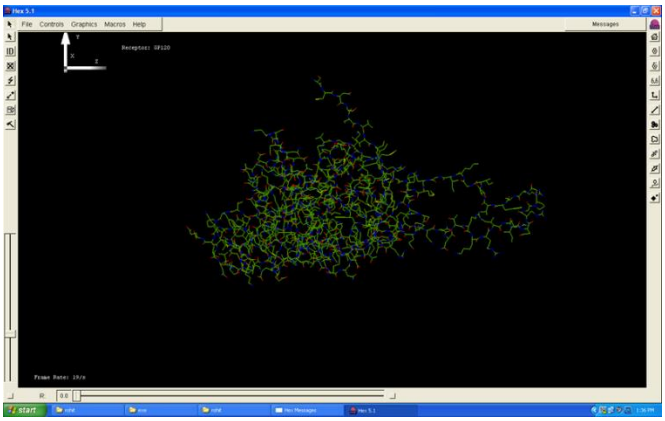

Figure.5. Select the gp120 receptor pdb format file. Image after loading the receptor file Load the ligand from the file menu. Image displying both the receptor and ligand

As per the protein structure prediction methods like Homology Modeling, Threading and Ab initio methods, we are supposed to find the template for our sequence of interest (Figure 4 & 5). While finding the template we have looked for the % identity or similarity between the sequence of interest and template. As per the modeling scenario, if the % identity is more than 60%, we should go for Homology modeling, if is in the range of 25-60%; should go for threading method and if it is below 20-25%; should go for Ab Initio method. As per the % identity we have got from template after sending template selection request either through Swiss PDB viewer or directly through the online Swiss model server, we have chosen the homology modeling method for structure prediction. Modeling for the Sequences of interest has done by Swiss PDB Viewer offline tool or by directly the automated mode for structure prediction available online on Swiss-Model Server. It has given us with the final predicted structure based on the template structure so as to simulate or anticipate the sequence of interest for funcational studies. Here we have got

the structures of HIV1 gp120 on the basis of template 2B4C. And Human CD4+ structure on the basis of the template 1BUO.

In docking, we are supposed to manipulate the receptor and ligand molecules before we will be going for docking. Manipulations are to be done according to the Tool which we are going to use for docking purpose. Here we have used Hex docking platform which has manipulating criteria in terms of enabling solvent, enabling hetero and enabling Arg/Lysine. This has to be done by the enabling all this options so as to create the live environment for docking as that of in vivo process of ligand and receptor binding. When we have started with the docking, first thing we considered is Estart and then simultaneously Emin and Emax. These values are to be considered energy should be minimized so as to make the molecule stable as, more the rotatable bonds in ligand, the more hard the method will be to search suitable binding modes in repeated docking studies. Thus final result that is the Etotal should lie in between Emin and Emax. ETotal should be always less so as to get the maximum stability to docking complex for perfect merge and also less than Estart.

Our result analysis considers scoring function as a pose as input and returns a number indicating the similarities that the pose exhibits a suitable binding interaction. The energy of the pose can be estimated through physics based molecular mechanics resulting in most of the scoring functions. Negative energy shows a standard or unchangeable system thus resulting in a likely binding interaction. Another method is to obtain a mathematical potential for interactins from a big database of ligand- receptor complexes, such as the protein data bank, and assess the suitability of fitness of the pose in accordance to our potential obtained in the results.

T lymphocytes is characterized by presentation of CD4 proteins on its surface, which is a glycoprotein playing an important role in T-cell functions and many white blood cell types. In 1984 T cells CD4 was named after extensive investigatin with monoclonal antibody that specifically recognized this protein and later named it as leu-3 and T4. In humans, the CD4 gene was identified which code for CD4 T cell receptor protein. The protein is responsible for HIV virus to binds to T cells and mediates viral multiplication by depleting T cell population. In silico studies, suitability of functions was identical and percentage identity was investigated. The structure of HIV1 gp 120 and human CD4+ were extensively evaluated using structure prediction methods in silico modeling. In our studies, we observed more than 60% identity, which concludes the sequence similarity of interest as similar function that of the template.

Our computational calculation anlaysis indicated that Etotal for T cells gp 120 and T cells should be lower thatn Estart and should lie in between Emin and Emax. In our Energy calculation studies and docking results we obtained that EStart was 47.50 KJ/mol and our Etotal is-244.0 KJ/mol. Therefore, wich is lower than Estart and depending more towards Emin, which has resulted in formation of stable higher order complex as predicted from docking analysis. Our studies has demonstrated that the complex is very valid and both molecules (gp 120 and cd4+ are having bidning similiarities which is required or the HIV viral infectivity.

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