International Journal of Advanced Science and Technology
Vol. 29, No.02, (2020), pp. 1141-1147

AN INITIATION TOWARDS IDENTIFYING A NEW CHEMICAL ENTITY TO TREAT CANCER BY HOMOLOGY MODELLING AND DOCKING OF COLCA2

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ABSTRACT

Colorectal cancer is a cancer of colon or rectum, it's a deadly disease and occurs majorly due to proliferation.GWAS is an observational study of genetic variants for different individuals to identify variants in a trait, the associations between the single-nucleotide polymorphisms (SNPs) and also major human diseases. COLCA2-colorectal cancer associated gene 2 is a protein coding gene that is involved in various molecular functions, biological processes. Homology modeling is the prediction of resolution model of the "target" protein from the sequence of amino acid based on the experimental three-dimensional structure of a related homologous protein using Galaxyseok lab server which is based on template based modeling(TMB). The protein model obtained from the above server was then checked for quality using the Rampage server. This server gives a plot called the Ramachandran plot which shows the quality of the models. Peptide-protein interactions are very prevalent for most of the biological processes such as signal transduction, protein trafficking and etc. Peptide protein docking was done from cabs dock. Interaction of theGGST and GGTS peptide were observed.. Interaction of the GGST peptide where seen those residue((Receptor residue,Peptide residue)(TYR A 153,THR B 4)(ASP A 150,SER B 3)(TYR A 143,GLY B 1)(GLU A 62,SER B 3)(PRO A 61,GLY B 2)(PRO A 14,THR B 4)(ILE A 151,THR B 4)(TYR A 143,GLY B 2)(ASN A 63,GLY B 1)(GLU A 62,GLY B 1)(PRO A 57,THR B 4)(TYR A 153,SER B 3)(ASP A 150,GLY B 2)(TYR A 64,SER B 3)(GLU A 62,GLY B 2)(SER A 58,THR B 4)).Interaction of GGTS peptide where seen those residue((Receptor residue,Peptide residue)(TYR A 153,THR B 3)(ASP A 150,GLY B 2)(THR A 139,GLY B 1)(ASN A 63,GLY B 2)(GLU A 62,GLY B 2)(PRO A 14,SER B 4)(ALA A 13,THR B 3)(ASP A 150,THR B 3)(TYR A 143,GLY B 1)(TYR A 64,GLY B 1)(GLU A 62,THR B 3)(HIS A 15,SER B 4)(ALA A 13,SER B 4)(ILE A 151,THR B 3)(ASP A 150,GLY B 1)(TYR A 64,GLY B 2)(ASN A 63,GLY B 1)(PRO A 57,SER B 4)(PRO A 14,THR B 3)).

KEYWORDS: *COLCA2,GWAS,Homology Modelling, Molecular docking and SNP,*

INTRODUCTION

Cancer is caused by unchecked division and survival of abnormal cells.Cancer is made up of trillions of cells and can occur anywhere in the human body. Abnormal growth in colon or rectum results in

ISSN: 2005-4238 IJAST

the Colorectal cancer(CRC).The combination of colon and rectum forms the large intestine which is mainly responsible in food processing and elimination of solid waste i.e.,fecal matter. Colorectal cancer (CRC) is one of the biggest killers worldwide, with the highest incidence and prevalence in economically developed countries. In the United States CRC is the third most common type of tumor and the second most common cause of death [1].

Countries with the highest incidence rates include Australia, New Zealand, Canada, the United States, and parts of Europe. The countries with the lowest risk include China, India, and parts of Africa and South America[2].

Different populations worldwide experience different incidence rates of colorectal cancer, and these rates change with time. In parts of Northern and Western Europe, the incidence of colorectal cancer may be stabilizing, and possibly declining gradually in the United States. In the United States, male and female colorectal cancer incidence rates declined from the mid-1980s to the mid-1990s, followed by a short period of stabilization. From 1998 to 2005 incidence rates have again declined—an average of 2.8% per year for men and 2.2% per year among women[3].

METHODS

Bioinformatics is vital to significantly improve the position and function of molecules in binding and simulation. In bioinformatics, the process of computer-aided drug design (CADD) exists as a specialized discipline to use the computational [4] methods to simulate theinteractions between a drug and a receptor. CADD methods are heavily dependent on bioinformatics tools, applications, and databases.GWAS is an observational study of genetic variants for different individuals to identify variants in a trait, the associations between the single-nucleotide polymorphisms (SNPs) and also major human diseases.Modeling of target protein: Template-based modeling (TBM), also called homology modeling or comparative modeling, is a structure prediction method applied in this case using similar proteins as templates. GalaxyTBM program and its web server (http://galaxy.seoklab.org/tbm) are based on the TBM method, which was used to predict the structure of the target protein. The 3D structures were downloaded in pdb format.Virtual screening and Docking: Molecular docking would describe the ―best-fit‖ orientation of a peptide that binds to the target protein and is used to predict the structure of the inter-molecular complex formed between the two molecules.Protein–protein docking based on the flexible docking of a SLiM fragment (peptide) to a protein receptor without using any information about the SLiMs structure or a binding site is performed using the CABS-dock online docking server [5,6] (available at http://biocomp.chem.uw.edu.pl/CABSdock/) that employs an efficient peptide docking scheme.Since the human genome was first sequenced in 2003, almost 3700 genome-wide association studies (GWAS) have agnostically identified thousands of genetic risk variants and their biological

function[7,8]. There are several possible mutual conformations in which binding may occur. [9]Protein-peptide interaction using LIGPLOT: The LIGPLOT program automatically generates schematic 2-D representations of protein-peptide complexes [10]. The output is a color, or blackand-white, PostScript file giving a simple and informative representation of the intermolecular interactions and their strengths, including hydrogen bonds, hydrophobic interactions. The target ligand interactions were studied using this program.

RESULTS

The protein sequence of COLCA2 were obtained from Uniprot in FASTA format. >sp|A8K830|COLC2_HUMAN Colorectal cancer-associated protein 2 OS=Homo sapiens OX=9606 Gn=Colca2Pe=2Sv=1mhpepllnstqsaphhfpdsfqatpfcfnqslipgspsnssilsgsldysyspvqlpsyapenynspasldtrtc gyppedhsyqhlsshaqyscfssattsicycasceaedldalqaaeyfypstdcvdfapsaaatsdfykretncdicys

This amino acid sequence of COLCA2 protein was then submitted to Galaxy Seok lab software for Modelling based on template.

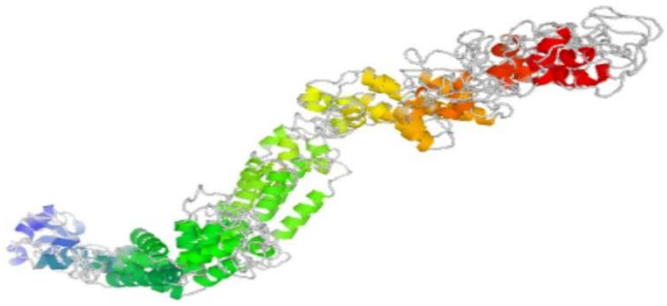

Fig.1. Predicted structure of COLCA2

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The quality of the predicted structure was then checked using Ramachandran plot using Rampageserver.

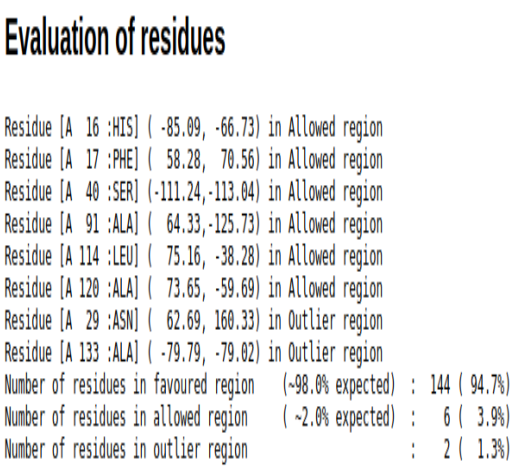

Fig.2. Evaluation of Ramachandran plot

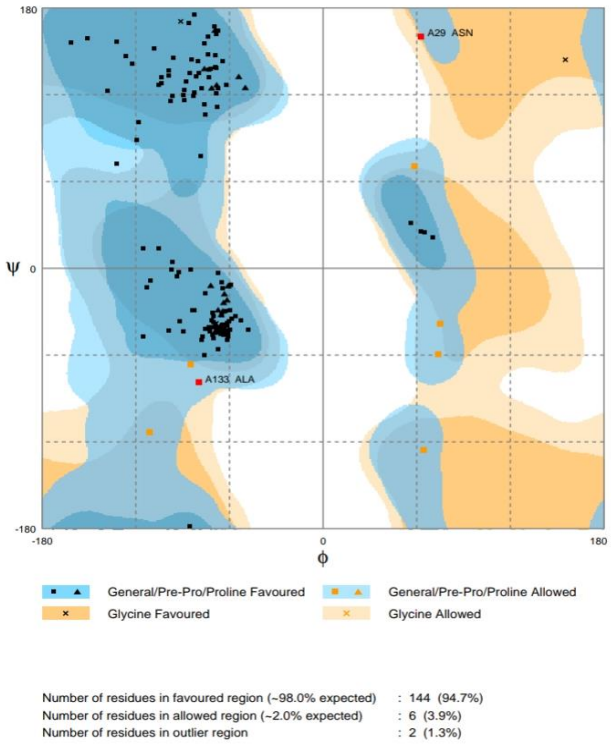

Fig.3. Ramachandran plot

This structure is then docked with GGST and GGTS peptide obtained from GWAS. The docking is carried out using CABS dock server. The interaction between the peptide and the protein is observed using Ligplot software.

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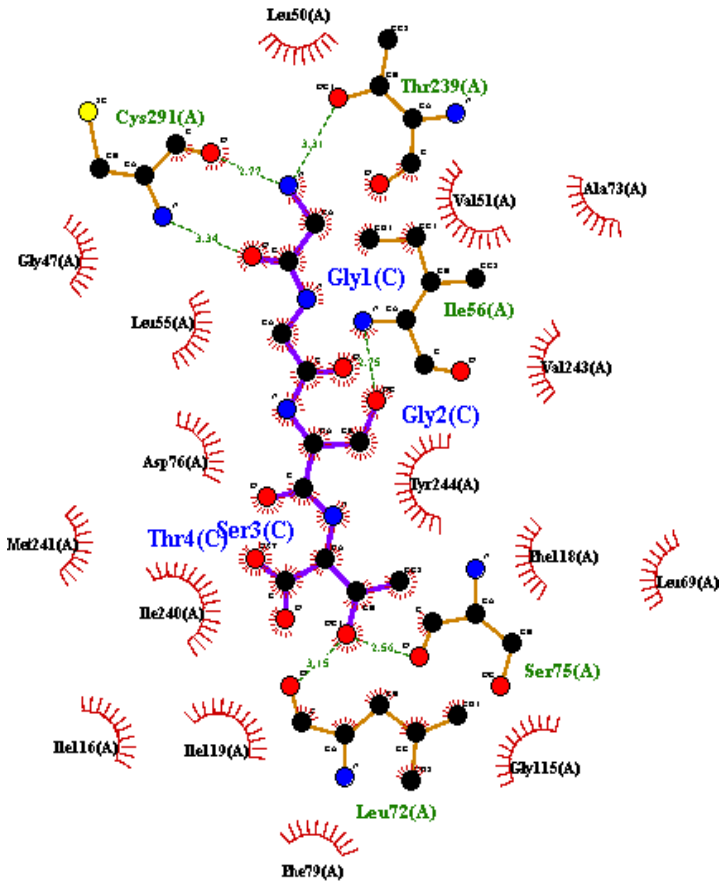
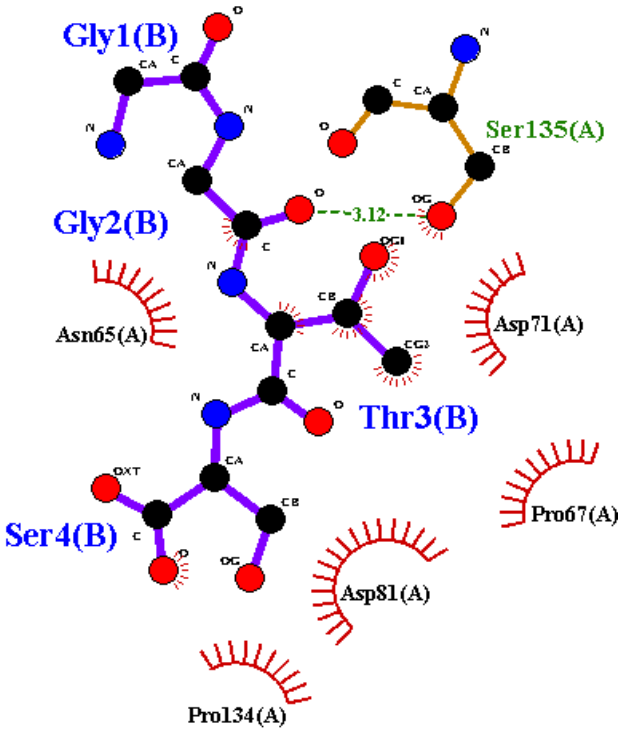


Fig.4. Interaction of COLCA2 with GGST

Fig.5. Interaction of COLCA2 with GGTS



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CONCLUSIONS

Colorectal Cancer is a cancer of colon or rectum, it's a deadly disease and occurs majorly due to proliferation. COLCA2- Colorectal cancer Associated 2 Protein is co-regulated with COLCA1 gene. It is an intracellular protein, found in the cytoplasm and is involved in various Molecular cell functioning. The function include catalytic activity, signaling, transporter activity, DNA binding, RNA binding, metal ion binding, carbohydrate binding, lipid binding, cell death, cell differentiation, immune system processes, nervous system processes and other biological processes.

In this paper, we are using bioinformatics tools for the prediction, modeling and studying interaction between the protein and the peptide.Virtual screening and molecular docking approaches are widelystudied nowadays to find protein-ligand, protein-protein and protein-peptide interactions and to identify peptides that can inhibit atarget protein. Interaction of theGGST and GGTS peptide were observed.. Interaction of the GGST peptide where seen those residue((Receptor residue,Peptide residue)(TYR A 153,THR B 4)(ASP A 150,SER B 3)(TYR A 143,GLY B 1)(GLU A 62,SER B 3)(PRO A 61,GLY B 2)(PRO A 14,THR B 4)(ILE A 151,THR B 4)(TYR A 143,GLY B 2)(ASN A 63,GLY B 1)(GLU A 62,GLY B 1)(PRO A 57,THR B 4)(TYR A 153,SER B 3)(ASP A 150,GLY B 2)(TYR A 64,SER B 3)(GLU A 62,GLY B 2)(SER A 58,THR B 4)).Interaction Of GGTS Peptide Where Seen Those Residue((Receptor Residue,Peptide Residue)(TYR A 153,THR B 3)(ASP A 150,GLY B 2)(THR A 139,GLY B 1)(ASN A 63,GLY B 2)(GLU A 62,GLY B 2)(PRO A 14,SER B 4)(ALA A 13,THR B 3)(ASP A 150,THR B 3)(TYR A 143,GLY B 1)(TYR A 64,GLY B 1)(GLU A 62,THR B 3)(HIS A 15,SER B 4)(ALA A 13,SER B 4)(ILE A 151,THR B 3)(ASP A 150,GLY B 1)(TYR A 64,GLY B 2)(ASN A 63,GLY B 1)(PRO A 57,SER B 4)(PRO A 14,THR B 3))

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ISSN: 2005-4238 IJAST