ISSN: 2467-9283

OPEN ACCESS

Indexing & Abstracting

Open Academic Journals Index (OAJI), InfoBase Index, Cosmos, ResearchGate, CiteFactor, Scholar Stear, JourInfo, ISRA: Journal-Impact-Factor (JIF), Root Indexing etc.

Impact Factors*

IBI factor: 3

Impact factor (OAJI): 0.101

SEM-Biotech Publishing

*Kindly note that this is not the IF of Journal

INTERNATIONAL JOURNAL OF GRADUATE RESEARCH AND REVIEW

Vol-3, Issue-2

June 2017

Research Article

In-silico Drug Discovery approach to Cancer

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Abstract

Cancer is the abnormal proliferation of cells, when there is an internal or external agent, physical, biological or chemical agent involved. Cancer can be due to viruses, radiations, chemical or sometimes even genetic. This particular paper shows a few tools that were used in determining the to study and analyse a few different bioinformatics tools to come to study about an in-silico drug discovery approach. A few tools that were used were RAMPAGE- to obtain the Ramachandran plot, RCSB- to obtain the 3-D structure of the protein, RasMol- to visualize and obtain the proteins and ligands that can bind to it, PubChem- to obtain the 3-D structure, physicochemical and ADMET properties of the drug, HEX- to visualize and study the binding and docking properties of the drug with the target protein sand gene receptor, Superpose- to study multiple sequence alignment data and superpose with other proteins using homology modelling.

Keywords: Epigenetics; Transcriptional silencing; DNA methylation; CTCF

Introduction

Cancer is the abnormal increase in cell number due to various physical, chemical or biological factors like radiations, chemical compounds like nicotine, or biological agents like a few adeno and retroviruses. There are many types of cancers like leukemia, melanoma, carcinoma etc. The disease is named based on the part where the tumour is formed for example, lung cancer, breast cancer, colon cancer etc., in common tongue (Welsh *et al*., 2017). The difference between a normal tumour and a cancerous cell (carcinogen) is that the carcinogens are able to metastasize which means they move to different parts of the body. There are two types of tumours a benign tumour, which is harmless and a malignant tumour which might prove to be detrimental, if ignored. The initial symptoms of cancer include unexplained weight loss, change in bowel movements, bleeding, prolonged cough although these are only the speculated clinical symptoms. There is no other way to confirm that a person suffering from this disease other than performing a biopsy of the tissue. This remains an area of intense research. There is no exact cure to this disease or for the complete mechanisms and the exact pathophysiology of this disease is not yet known. The available management techniques include radiation therapy, immunotherapy, chemotherapy surgery all of which have adverse side effects (Miyata & Yahara, 2000).

Motivation

People suffer from this deadly disease daily and undergo very a huge suffering in this year alone 8.2 million people fell prey to this disease. Hence we, decided to choose this topic and look into it further and hopefully manufacture a drug that can be a cure for this deadly disease one day.

Future Aspects

With increase in technology, we hope to use this data will be useful in further research for the in-silico approach of a few drugs related to cancer and the molecular mechanisms. We also plan to continue with this research and synthesize a new drug that will one day eradicate the disease.

Theory

Tumor suppressing genes are those that code for proteins that restrict the proliferative and survival capacity of a cell.

The above paper is on the epigenetic silencing of tumour suppressor gene. With the identification of chemical agents, surgery and viral oncogene, these information can help in development of small molecules at the restoration of tumour cells in order to limit cell proliferation. The agents identified should be associated with a dynamic reprogramming of the epigenetic code primarily in the promoter region of affected genes. This paper outlines basic five mechanisms which can be performed using the agents along with drug to suppress the tumour gene and the changes observed with respect to these regions . The basic five mechanisms specified here are:

1) Defects in the transcriptional process
2) Overexpression of DNA methyltransferases
3) Dysfunction of CTCF
4) Overexpression of the polycomb protein Ezh2, and
5) Aberrant expression of long noncoding RNAs

There are also two new recent report on the primary anti proliferative effect of nucleoside by activation of antiviral response.

Materials and Methods

Tools Used

Some of the tools like **RasWin** for 3D structure determination, **PubChem** to get the properties of the chemical agent, **Open Bable** to find out how the ligands are bound to protein, **Hex** used for protein docking, **Ramachandran plot** used to compare the after and before effects of drug . **RCSB** used for protein structure determination. **JPRED** used to determine protein secondary structure.

1) The required sequence was identified for *TP53* gene using **BLAST** tool.
2) Identification of chemical agents that can be a effectively used with drug in order to suppress the tumour genes
3) On finding out cyclophosphamide as one of the alkylating agent, the structure and chemical properties, ligand protein interaction.
4) After figuring out the required information about the chemical, this can be used as alkylating agent in performing DNA methylation and prevent transcription and translation.
5) Using open bible CTCF binding was predicted and this identified chemical is successful in
6) Disrupting CTCF binding.
7) Molecular docking is done to see how the ligand binds to the protein and successfully performs the above mentioned mechanisms.
8) Ramachandran's plot is made to find out the effect of the drug with and without the chemical agent after and before binding.

Results and Discussion

The 3D structure of *TP 53* gene of human being, which is known for tumour protein p53, was plotted using RasWin, windows version of the software RasMol (Fig. 1). To know the interaction with cyclophosphamide, a drug for tumour gene, RasWin software was used and structure is shown in Fig. 2.

The docking mechanism between gene (*TP53*) and the protein (Cyclophosphamide) is shown in Fig. 3.

Plot of the *TP53* gene bound to SV40 virus (Covey *et al*, 1984). The binding of every single residue is in the allowed region and hence the binding between the two is facilitated.

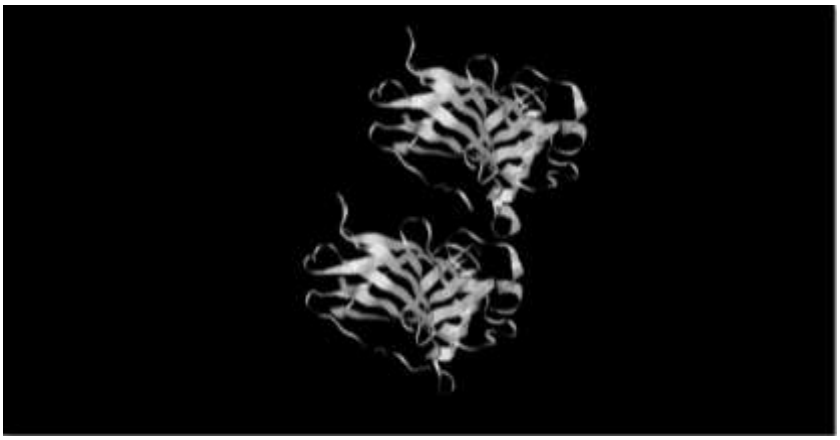

Fig 1: The *TP 53* gene product using RasWin

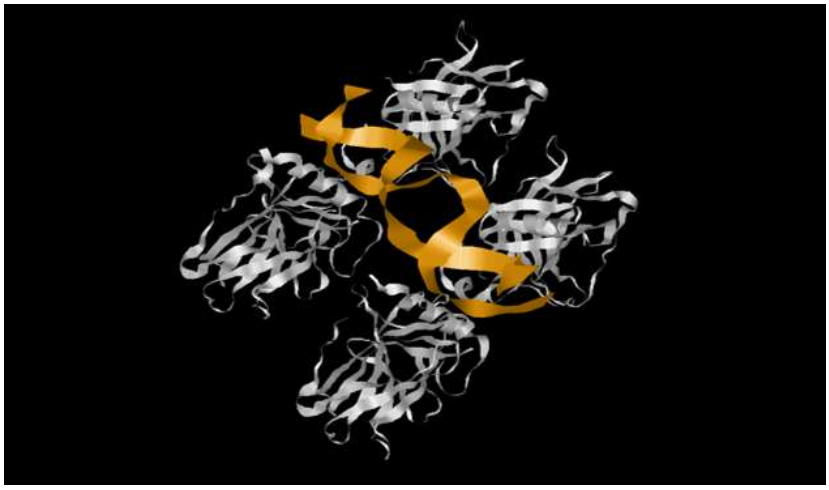

Fig. 2: The structure of TP 53 when bound to the respective DNA using RasWin.

Fig. 4 & 5 illustrate the the Ramachandran plot used to find the accuracy of the structure when DNA is not bound and the Ramachandran plot used to find the accuracy of binding of the DNA to the TP53 gene responsible protein called tumour protein p53 respectively.

The *TP53* gene provides instructions for making a protein called tumour protein p53 (or p53). This protein acts as a tumour suppressor, which means that it regulates cell division by keeping cells from growing and dividing too fast or in an uncontrolled way. The bending energy being a large negative value makes the binding of cyclophosphamide highly stable (Manos *et al*., 1984).

The drawback of the drug being it has a high toxicology

The p53 protein is located in the nucleus of cells throughout the body, where it attaches (binds) directly to DNA. When the DNA in a cell becomes damaged by agents such as toxic chemicals, radiation, or ultraviolet (UV) rays from sunlight, this protein plays a critical role in determining whether the DNA will be repaired or the damaged cell will self-destruct (undergo apoptosis). If the DNA can be repaired, p53 activates other genes to fix the damage. If the DNA cannot be repaired, this protein prevents the cell from dividing and signals it to undergo apoptosis. By stopping cells with mutated or damaged DNA from dividing, p53 helps prevent the development of tumours (Napoli and Flores, 2017).

Because p53 is essential for regulating cell division and preventing tumour formation, it has been nicknamed the "guardian of the genome."

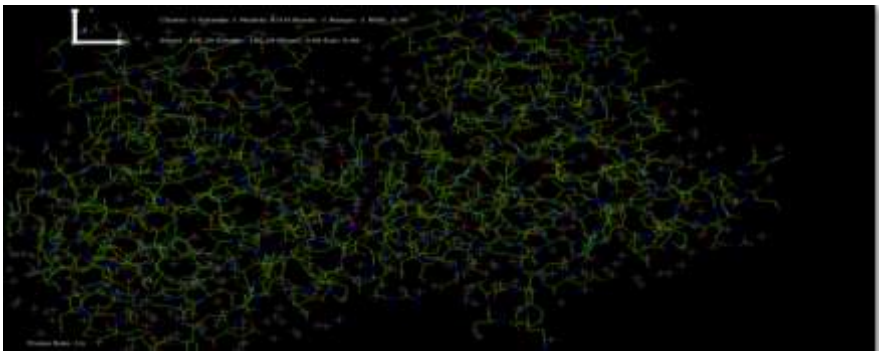

Fig. 3: The docking mechanism between gene (TP53) and the protein (Cyclophosphamide). B.umps= -1 E=-165.6

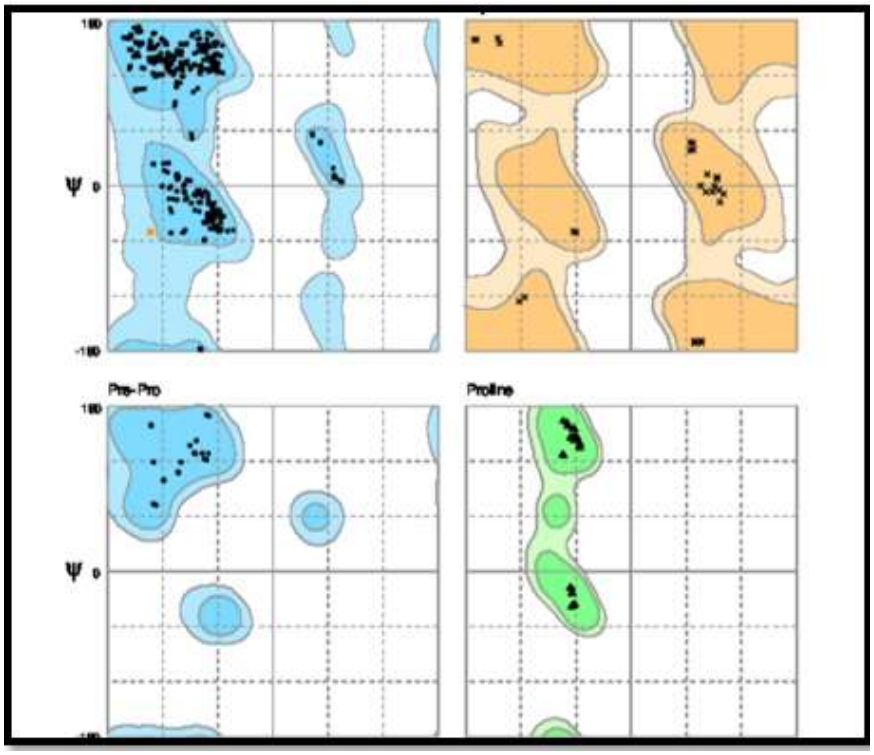

Fig. 4: The Ramachandran plot used to find the accuracy of the structure when DNA is not bound

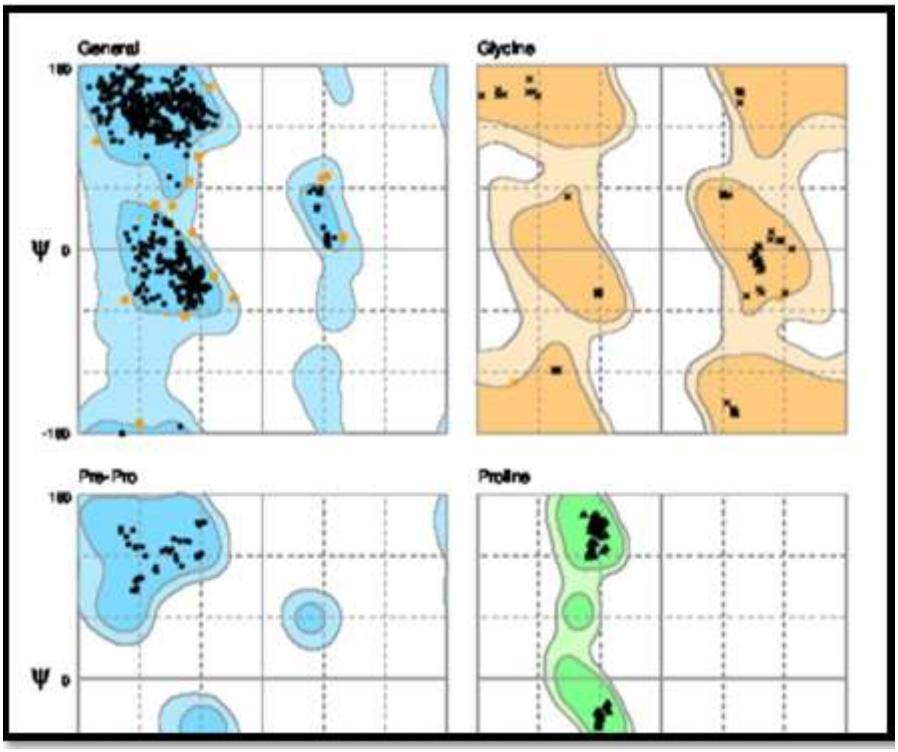

Fig. 5: The Ramachandran plot used to find the accuracy of binding of the DNA to the *TP53* gene responsible protein called tumour protein p53

Conclusion

The tools we used for interpretation of the drug supported the five mechanisms as per the research paper. We determined what the tumour-suppressing drug might contain and predicted its structure and integration with the viral cells. Hence, we proved that cyclophosphamide could be a potential chemical agent in the drug.

Acknowledgment

We would like to express our heartfelt gratitude for the support provided by our mentor Dr. Savithri Bhat who guiding us. Our heartfelt gratitude to our institution, BMS College of Engineering for the encouragement and support they provide in all our endeavours.

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