AN APPROACH FOR EXAMINING LUNG CANCER BY OBSERVING THE MICRORNA IN AN ASSEMBLY OF DRUG INTERACTIONS

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ABSTRACT

MicroRNA is the non-coding RNA in the gene sequences, is the major factor of invoking the oncogenes. Late identification of lung cancer leads to deaths. Multiple studies on miRNAs have made a break through discoveries including their direct and indirect involvements in causing lung cancer. Several miRNAs like miR-21a, miR-196 and miR-69 are identified as bio marking elements of non-small cellular lung cancer few like miR138 and let-7 are considered as anti-cancer agents. This work studies the changes happening to miR-138 in interaction with NSCLC drugs. miRNA use to interact with multiple natural factors, utilizing this property of miRNA we examined the possibility of studying different drug effects on miR-138. Target Scan, Mol View, and free energy calculation algorithm were used for creating an interactive environment for the simulation. From the results, we conclude that miRNAs are reactive to cancer drugs. This could be used for further development of cancer prevention drugs which targets miRNAs rather than oncogenes.

Index Terms—microRNA, Drug Interaction, NSCLC, Cigarette

1. INTRODUCTION

Cigarette smoking was found only in men till 1987, but the shocking survey result which revealed that more than 200,000 women died world-wide due to smoking-induced lung cancer during the period of 1980-1987. In a research, 83% of smoking-induced lung cancer were Non-Small Cell Lung Cancer (NS CLC) which is curable in its initial stages. Tobacco molecules will alter the astrocyte elevated gene-1 in lungs which will invoke NSCLC. Development in bio-informatics and molecular dynamics have verified that microRNAs like miR133a and miR675-5p are effective tumor suppressants which will suppress oncogenes like GPR55 and SUZ12. Currently, most of the lung cancer are treated with chemotherapy and radiotherapy. In this treatment, the chemicals and radiation are used to remove the tumor and suppress oncogenes. However, there is no effective way to keep them in a dormant stage. Chance of reoccurrence of cancer in a recovered person is very high. Micro-RNAs are noncoding genetic sequences, which can change genetic activities. In the research work of Tariq Baig et al., [3] proved that oncogene protein (PDB 5P21) was identified as cancer-causing gene and they monitored the anti-cancer drug interactions.

Various researchers have proved that function of RNAs in post-transcriptional regulation is crucial. Oncogenes have the tendency to be invoked in presence of tobacco smoke. LCmi RNAs regulates oncogenes in cigarette smokers which cause cancer. The common methods to stop NSCLC is initial detection and quick treatment. Preventive measures like stop smoking will also help to an extent. Fanlu Meng et al., [4] suggested that lung cancer can be prevented by suppressing the oncogenes by utilizing miRNAs which prevent regulation. They are miR 133a and miR675. These miRNAs can keep cancer-causing GPR55 and SUZ12 inactive. Analyzing the drug interactions with miRNAs are difficult because of its molecular dynamics and post-transcriptional changes. This keeps most of the cancer preventive drug designs as unapproved.

The proposed system is trying to study the molecular dynamics of miRNA interacting with drugs. The process needs to be validated with multiple conditions including transcription, translation, and replication. Previous studies on protein-drug interactions have shown that drugs are capable of refolding and repairing proteins. However, they failed to prevent further damage or reoccurrence of protein folding. The discovery that not-coding RNA similar to miRNAs are the RNAs responsible protein folding would help to prevent genetic modification from RNA level. Analy-zing miRNA drug interaction will help to create new drugs that will target miRNAs instead of protein. This work proposes to study the structural changes in LC miRNAs and LC suppressing miRNAs by utilizing molecular dynamic algorithms. The results could open a key for further development in cancer treatment. Proper researchers can acquire a cancer free future.

I. LITERATURE SURVEY

Drugs need the genomic expression to find and function in its target. Jakob et al., [5] could design a database for relating miRNA expression linking its drug effects. In the work, they could observe interactions and resistance induced by cisplatin in miR148a. Although this can predict side effects of the drugs it will fail to identify respective miRNA post-transcriptional faces. Erin Gardiner et al., [6] worked on drug interactions on miRNA of T-lymphocytes. From the experiments, they observed the significant effects of antipsychotic drugs on peripheral tissues that are known for poor side effects. Virtual polymerized chain reaction was used to track pre-drug interaction on the miRNA sequences. From the research work of Sudheesh et al., [7] and found the interaction of miRNAs with drug of abuse in the presence of HIV-I virus reviewed and came to a conclusion that drugs of misuse can be treated as an HIV-I deactivator since it can keep the virus in dormant stage with help of HIV-1 miRNAs. We can use the same principle in this work by making drugs targeting miRNAs which are capable of keeping oncogenes in a dormant stage. Analyzing miRNAs and miRNA

polymorphism for identifying their response to drugs was the study of Mu-Peng Li et al., [8]. In this work, research was focused on changes of proteins during drug interacted miRNA polymorphism. Here they used miR18b, miR20b, and miR21 for drug interactions during polymorphism. Tobacco is considered as a major cause of lung cancer, this is due to the character of environmental factor. Since miRNAs interact with the environment it easily reacts to tobacco and other drugs. Chengxiang Qiu et al., [9] made use of this factor of miRNAs to study interactive ranges of natural factors in causing diseases. From this work, they can reverse engineer the miRNAs to stay unaffected to natural causes. They also suggested the probability of creating a mechanism similar to vaccination to ensure the safety of keeping away cancer. Kenneth [10] identifying possible drug targets in specific miRNAs and it was identified as the biomarker for lung cancer. He also studied the effects of multidrug resistance of LC miRNAs while doing chemotherapy. Instead of studying the drug interaction of miRNA while transcription, he worked on analyzing changes of non-coding RNAs during chemo. From the resistance of certain miRNAs in chemotherapy, Kenneth [10] conclude that miRNAs are druggable and can even be treated as the oncogenes suppresser. Work also had another module of identifying druggable targets. From a study on miR34a, miR145, miR29b and miR200c, Jing Xue et al., [11] identified the ability of tumor suppressor miRNAs to act as some drug or therapeutics to treat and cure cancer. Results were obtained from clinical trials on rats and pigs. Still, the human immune-related interactions result of these drugs are unknown. From this work, we could further push the idea of utilizing miRNA drugs to create preventive drugs like vaccines for complete eradication of cancer. From the work of Prashansa Agrawal [12], anticancer drug targets were redesigned changing their targets from oncogenes to miRNA. She also found that non-coding RNAs can bind to antibiotic drugs. This discovery leads to the development of easy target detection using controlled drug testing.

Another common therapeutic experiment on miRNAs is using them for protein interaction. Salim et al., [13] used Hantavirus as the experimental disease for RNA-protein interaction. RNA is the translation carrier of the protein synthesis; thus, RNA has a direct impact on protein generated. From this work, they could design an anti- hantavirus. The applicability of this work in terms of miRNAs are yet to be tested [13]. Diederichs and Daniel [14] calculated the miRNAs sequence variation in lung cancer. Here she altered predicted secondary structure and observed that changes happening to miRNA secondary structure do not affect any protein synthesis. This observation made early detection of lung cancer difficult since we can't predict cancer from secondary structure variations. By screening 15 miRNAs linked to lung cancer, 91 cancer derived call lines were extracted and identified as drug targets.

Knowing about the sequence alignment of micro-RNA is another important aspect of this work. From the primary stage of separately identifying miRNA by extracting sequence and structure alignment. Wang et al., [15] was focusing on the identification and extraction of miRNAs from lung fluids. They also calculated higher sensitivity and comparable sensiti-vity. They identify 59 new miRNA genes. Also, miR-Align was used for aligning the sequence. The rele-vance of this paper is that this method will help to create a drug pathway which can be added to the designed drug. NSCLC survival was surveyed by Hu et al., [16], they utilized genetic variants of miRNA sequences. From the survey on 10 miRNAs, they were able to find that has- mir196a2 may be a prognostic biomarker. He also studied the miRNA changes after radiotherapy and concluded that radiotherapy will not able to change miRNA structures. From the mining of miRNA by Su, et al., [17], they could backtrack almost every cancer to miRNAs. This made it clear that miRNAs are the active biomarker of almost all tumors. This is due to their ability to alter proteins during translation phase of protein synthesis. They also concluded that miR520h, miR133a, miR34, and miR103 as potential therapeutic targets for lung cancer. The downregulation miRNA was observed in rats exposed to cigarette smoke [18]. This concrete the base statement of our work that miRNA can be down regulated or up regulated based on the drug or natural elements. This is an evident concept that makes our idea completely implementable. From the computer simulations, we could recreate the observations made by Alberto [18]. Silviya et al., [1] comparison of the predicted properties suggests that chitosan, which is a natural polymer and has some advantages over others is a promising drug carrier candidate for tumor. Umesh et al., [2] reported S NP, rs1800450 of MB L2 is commonly reported from all major genomic populations in India, and the individuals holding this SNP are prone to the attack of mycobacterium tuberculosis.

II. Problem Formulation

Our former works were focusing on sequence alignment and string matching of DNA and proteins. Using several data mining algorithms to find the perfect match of strings [20]. This work can be further extended to use for comparing same drug sequence at different targets. Another approach for finding drug targets and interactive simulations is using vector position. Adapting this concept from one of our previous paper, this is intended to find the presence of factor 9 gene in DNA sequences at different positions [21].

Most of the miRNA-based studies have discussed their role in protein synthesis and role in causing cancer. However, only a few of them could bring the idea of treating miRNA instead of oncogenes. This could revolutionize cancer treatment. The probability of a future progress in cancer vaccine is high. Instead of using existing high-cost treatment there could be

cheap vaccines in future. The impact of cannabis in oncogenes and miRNAs can also consider for future studies on drug interactions.

III. PROBLEM DEFINITION

Utilizing the property of miRNA which makes it interact with natural factors like tobacco smoke, roofing dust, cooking smoke so on can be used as an advantage to code them to our desire. Proper identification of targets and by injecting a correct dose of the drug to targets can encode miRNAs in a way that protein synthesis will not invoke oncogenes in required conditions. By identifying and trying all possible simulations using external tools analysis can be done. Altering genomic structure is tremendously complex and not affordable for common people. Identifying the natural elements or cheaper drugs that could alter miRNA information can be used as anticancer treatment. Also need to be considered the possibility of not affecting other proteins and other ncRNAs.

IV. METHODOLOGY

MolView: used to view the molecular structure of drugs and miRNA. This tool represents molecules inaccurate bond angles.

DrugBank: this is a repository of the chemical structure of drugs consisting of its bond angle, free energy, thermodynamics, molecular stability, and bond value.

miRBase: this is a complete repository dedicated only for miRNA information. Here the base consists of free energy, bond value, secondary structure, thermal energy of all the miRNAs

TargetScan: this is an online tool which consists of online information of all the targets of genomic sequences. We used to find the targets.

Optimal Drug Target Calculation Algorithm n = Length of the input miRNA sequence m = Length of the Pattern of Drug sequence num = Number of targets based on targetScan match t[n]=array consist of targets

```
1    for 1 to ndo
2    while num reater than 0
3    do
4    if t. next () -> num [n]
5    then
6    if Interact (m, n)
7    then
8    return matched, exit ()
9    else
10   continue
11   end while 13 end for
14   Interact (m, n)
15   do
16   if RMSD(m)->RMSD(n) and FE(m)->FE(n)
17   then
18   generate_structure ()
19   end Interact
```

Structure Prediction: secondary structure of drug-ged miRNA is predicted based on its new sequence length and newly calculated free energy. Prediction consist of two steps

i. FASTA file generation in which sequence are classified based on their bond value.

ii. CT file generation. Here single string which depicts the internal looping structure is predicted by considering free energy differences.

The global optimal algorithm with a complexity of O(n) is used because of its bottom-up local optimal solutions: here we used global optimal alignment for comparing LC-miRNA's secondary structure as well as target strings.

V. FLOW DIAGRAM

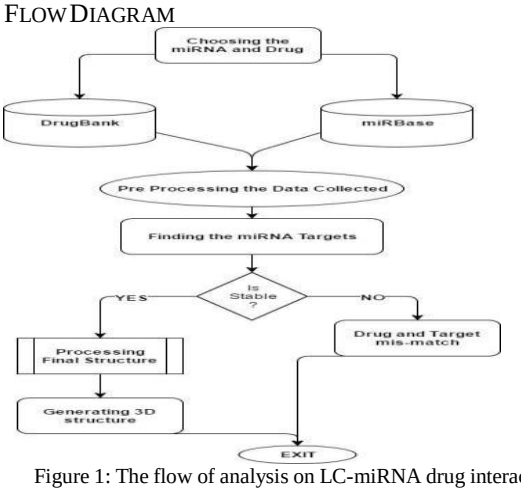

Figure 1: The flow of analysis on LC-miRNA drug interaction.

VI. DATASET

Commonly used drugs for NSCLC are Erlotinib, Afatinib, Gefitinib, Bevacizumab, Crizotinib, and Ceritinib. Collecting of the data was done by giving chemical names to the DrugBank. All the chemical structures were collected as balanced chemical formula and applied to the algorithm. From the work of Ling Xiao, it is found that miR138 is acting as a tumor suppressor of NSCLC [19]. We collected the data sequence from miRBase.

VII. EXPERIMENTAL RESULTS

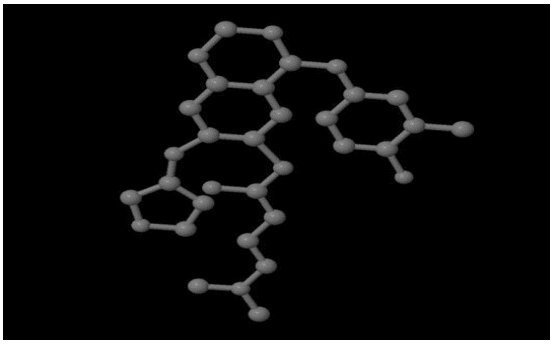

Figure 2: Afatinib is a commonly used drug for controlling oncogenes. The visualization is done using structure viewer.

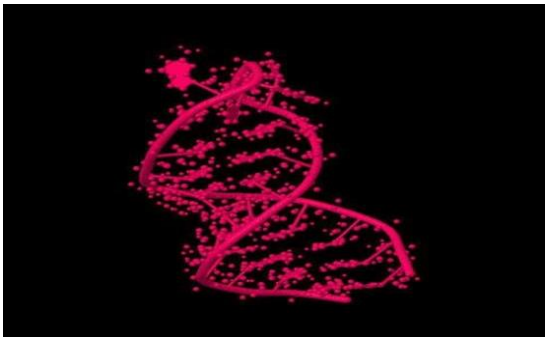

Figure 3: representation of miR138 before undergoing drug interactions.

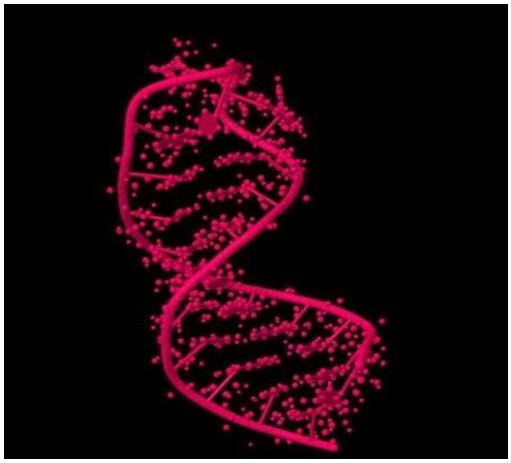

Figure 4: Final observation of changes happened to mir138 after drug interaction.

From these observations, we can find that before and after drug interactions there have been some changes happened to the miRNA. From the structural changes, we can observe the
weak bonding inside the drug, miR138 re-alignment, and changes in free energy value. We got similar observations from all the other drugs undergone the same trial.

VIII. CONCLUSION

MicroRNAs are the basic non-coding genetic material that can alter the protein structure. During translation phase of protein synthesis, miRNAs that are damaged can translate proteins to invoke oncogenes. From this result, we can conclude that use of miRNA targeted drugs will be more efficient and will be more capable of coding miRNAs to suppress oncogenes even while natural factors try to change its structure. This could open an ultimate solution for a deadly disease like cancer. MicroRNAs are highly responsive which makes it more dangerous as well as more controllable genetic material. The future scope of the work is to identify all the noncoding RNAs that can act as cancer suppressors and to redirect them to act against cancer-causing miRNAs.

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