Competing interactions of Mirnas and proteins: miR10b, miR335, miR21 in breast cancer

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SUMMARY

MiR10b, miR335, miR21 are a class of microRNAs that are overexpressed in breast cancer. These microRNAs are significantly correlated to stage of metastasis. Thus, in our study we aimed to test the hypothesis that miRNAs have direct interactions with proteins and that they are able to inhibit/active the functional site of proteins and enzymes. For that, we have chosen this 3 miRNAs related to breast cancer and studied interactions with some proteins associated with this cancer (onco-protein and suppressor proteins) included the BRCA1, BRCA2, palb2.., by processing the Docking and matching tools using especially Hex8 and HADDOCK sever. Mathematically, The Hidden Markov models were realized using Matlab script according the algorithm of Harrison *et al.*in order to study and validate the interactions and bonds among the protein and miRNAs. The main results demonstrated the ability of miR10, miR335 and miR21 to create direct linkages with 3D protein structures. Furthermore, these interactions with viro-oncogenic and oncogenic proteins were observed at the RNA-Protein docking level. These direct interactions allowed us to conclude that the influence levels of microRNAs are marked not only at the genomic level but can reach proteomic levels.

INTRODUCTION

- Currently, cancer is still one of the most common lifethreatening diseases worldwide. Breast cancer (BC) is the most common form of cancer and the second most common cause of cancer death in women. In recent years, BC incidence rates are increasing in the majority of countries.
- Despite significant advances in research in the development and improvement of means of diagnosis, monitoring and therapeutic management of breast cancer, these molecular methods only allow late diagnosis involving advanced stage of the disease, especially in rural areas where the awareness and information of the population is lacking.
- Thus, several research is directed towards the molecular signatures of different cancers including research on newly discovered and highlighted biomarkers called MiRNAs.These biomarkers , an early molecular signatures of cancer , will allow once the profile established an early and selective diagnosis of cancer .

AIMS OF THE STUDY

❑ Establish to hypothesis that miRNAs that microRNAs has another targets other than mRNAs especially proteins
❑ Investigate direct interactions between miRNAs and proteins and their ability to inhibit/active the functional site of proteins and enzymes

MATERIALS & METHODS

❑ **Data set**
- The sequences of mirR10b mir335, and miR 21 are collected from MicroRNA data base *miRBase*.

❑ **2D and 3D structures prediction of mir-10b**
- To predict 2D structures of mir10b ,mir335 and mir21 we used RNA structure software and ViennaRNA Web Service

❑ **Target prediction**
- We investigated the direct interactions protein-microRNA in order to determinate other possible targets and the mechanism of regulation

❑ **Interaction protein-microRNA**
- In this context, we used chemoinformatics tools in the objective to study the possible interactions between proteins and miRNAs, based on molecular modeling using docking protein-RNA and matching protein-RNA, HaDOCK 3.2 (De Vries,2010), and Hex 8.0 to predict these interactions.

❑ **Validation by hidden markov model bayesian protein-RNA**
- In the present study, we used the aPPRove algorthim based on HMM (Harrison 2016) and the Pancaldi 2011 in order to validate the results using the HMM coupled to baysiean models.

RESULTS

- **Mir10b:**

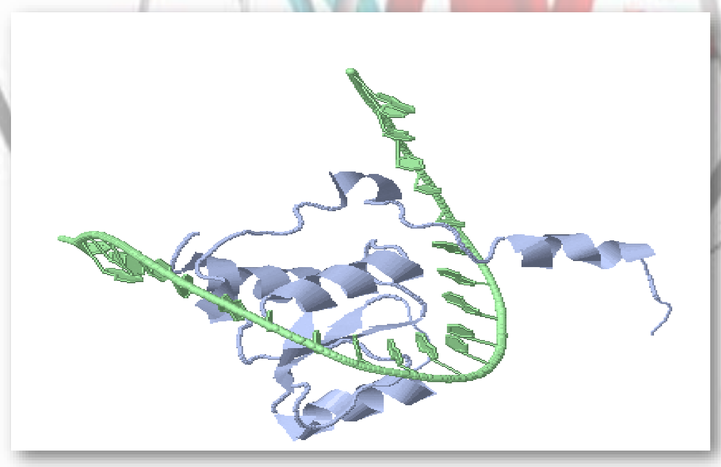

Figure 1: Mir10b binding to BRCT in the same site of DNA.
Covalent and hydrogen bonding was constructed between amino acids and nucleotides leading to blockage of the active BRCT site

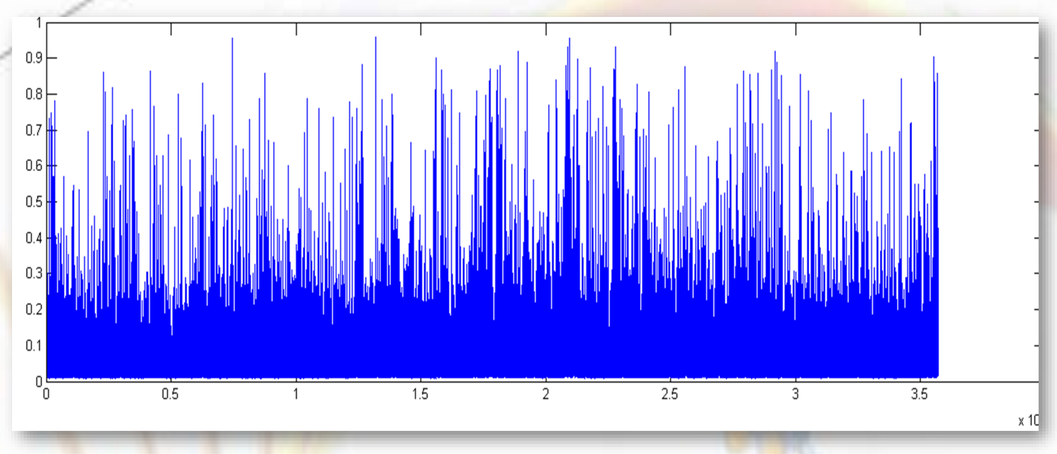

Figure 2: Prior HMM Model demonstrate the binding probable region between the Mir10b and BRCT in the same site of DNA.

DISCUSSION

Results of figure 1 and 2 show that the Mir10b as exemple is probably binding to BRCT in the same site of DNA.the Thereby, miRNA don't only regulate expression of gene by binding to mRNA but also to the 3D structural protein in order to regulate the functionment, Those results was in agreement with study convyed by jiang et al. (1) about association of microRNAs with Argonaute proteins. Furthermore, according to all those references (2,3,4,5,6) we can reject the hypothesis that miRNA are binding only to mRNA.

This new pathway should be more improved and studied so as to understand more this mechanism of regulation.

CONCLUSION

We can conclude from computational analysis via docking, and a model HMM (Markov Hidden Model) that many micorRNAs can make interactions with whole proteins and causing either stimulating activity or inhibiting it.

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