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

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SUMMARY

miR10b, miR335, and 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 microRNAs have direct interactions with proteins and that they are able to inhibit/activate 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 (oncogenic and suppressor proteins) included the BRCA1, BRCA2, p53, p21, by processing the Docking and matching tools using especially Hexli and HADDOCK server. Mathematically, The Hidden Markov models were used to the algorithm of Harrison et al in order to study and validate the interactions and bonds between the protein and mirRNAs. The main results demonstrated the ability of miR10, miR335, and miR21 to create direct linkages with 3D protein structures. Furthermore, these interactions with vivo-oncogenic and oncogenic proteins were observed as 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 life-threatening 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 geographically unknown 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 signature of cancer, will allow once the profile established an early and selective diagnosis of cancer.

AIMS OF THE STUDY

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

MATERIALS & METHODS

- **Data set:**
  - The sequences of mir10b, miR335, and miR21 are collected from MiRNA data base miRBase.
  - 2D and 3D structures are predicted using miRBase protein.
  - To predict 2D structures of mir10b, mir335 and miR21 used RNA structure software and miRNA RNA RNA Web Service.
  - **Target prediction:**
    - We investigated the direct interactions proteins-miRNA in order to determine other possible targets and the mechanism of regulation
  - **Interaction protein-miRNA**
    - In the context, we used the Aith algorithm tool in the objective to study the possible interactions between proteins and miRNAs, based on molecular modeling using docking protein-RNA and matching protein-RNA, HADDOCK 3.2 (De Vos, 2010), and Pro 3.0 to predict these interactions.
  - **Validation by hidden markov model between protein-RNA**
    - In the present study, we used the Aith algorithm based on HMM (Harrison 2016) and the Panoaldi 2011 in order to validate the results using the HMM coupled to bayesian models.

RESULTS

- **Mir10b:**

  ![Figure 1: miR10b binding to BRCT in the same site of DNA](image1)

  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.](image2)

DISCUSSION

Results of figure 1 and 2 show that the mir10b as example 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 functionality. Those results were in agreement with study conveyed by Jiang et al. (2013) about association of microRNA with Argonaute proteins. Furthermore, according to all these references (2,3,4,5,6) we can reject the idea that microRNA 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 microRNAs can make interactions with whole proteins and causing either stimulating activity or inhibiting it.

REFERENCES