Principles of Interplay Between miRNAs and TranscriptionFactors in The Cancer Genome

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Abstract

miRNAs are small non-coding RNA that play a vital role in post-transcriptional gene regulation. They are involved in several important biological processes; hence their dysregulation has been associated with several diseases. In this study we propose a novel method to identify dysregulated miRNAs using tumor matched expression data. Applying the method to expression datasets of nine cancers from TCGA we identify dysregulated miRNAs in each of these cancers. In six cancers we see that more than 50% of the dysregulated miRNAs are up-regulated, suggesting a general trend of upregulation. We then identify transcription factors (TFs) that control the expression of dysregulated miRNAs in cancer by footprinting their upstream regions in order to build a high confidence transcriptional regulatory network contributing to the dysregulation of miRNAs. We observe that these TFs are predominently responsible for up-regulation of miRNAs across cancers. In addition, we find that TFs that are identified in six or more cancers have different network centralities in the TF-Tf regulatory network when compared to TFs identified to contribute to dysregulation of miRNAs in a single cancer. Finally, we build cancer specific dysregulated TF-miRNA networks and identified several novel motifs including feedback loops involving TFs and miRNAs. These patterns of interactions show how TFs and miRNAs interact in a cancer specific manner and how dysregulation at one level affects the other.

Materials

Expression data used in the study is downloaded from TCGA using the datamatrix. Only tumor matched expression datasets were used in the analysis. TF binding sites are taken from Jolma et.al 2013.

Cancer	#miRNA samples	#mRNA samples
BRCA(Breast Invasive Carcinoma)	81	NA
LIHC(Liver Hepatocellular Carcinoma)	49	NA
HNSC(Head and Neck Squamous Cell Carcinoma)	38	31
KIRP(Kidney Renal Papillary Cell Carcinoma)	25	NA
KIRC(Kidney Renal Clear Cell Carcinoma)	67	65
THCA(Thyroid Carcinoma)	43	NA
PRAD(Prostate Adenocarcinoma)	50	NA
LUSC(Lung Squamous Cell Carcinoma)	35	17
LUAD(Lung Adenocarcinoma)	39	25

Table1: Number of miRNA and mRNA samples used in the analysis for each of the nine cancers

Methods

For each miRNA or mRNA the ration between expression in tumor and normal tissue is calculate and log transformed, this value is called fold-change. A miRNA or mRNA is dysregulated in a patient if its fold-change is greater than average fold change. A p-value is calculated using t-test. We call a miRNA or mRNA dysregulated in a cancer if it is dysregulated in 50% of the patients and p-value is less than 0.01. These dysregulated miRNAs and mRNAs are used to build cancer specific TF-miRNA networks.

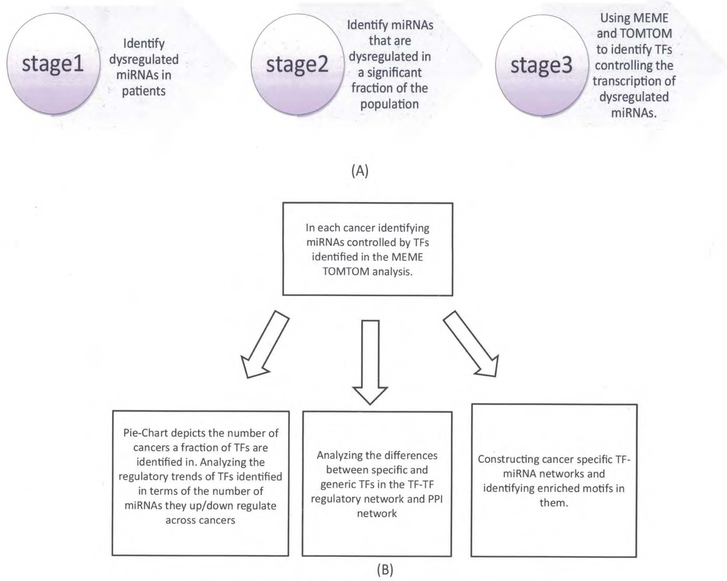

Figure1: (A) The Pipeline (B) Flow chart describing the analysis

Results

a) Dysregulated miRNAs are Predominently upregulated.

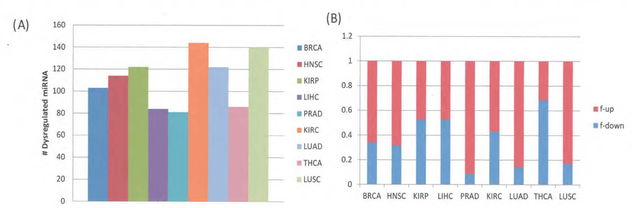

Figure 2: (A) Number of dysregulated miRNA in each cancer (B) Fraction of up and down regulated miRNAs in each cancer

b) TFs are Predominantly Responsible for Up-regulation of Dysregulated miRNAs.

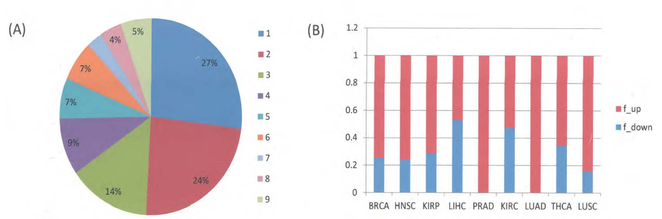

Figure 3: (A) Fraction of TFs identified in a given number of cancers (B) Fraction of up and down regulating TFs in each cancer

c) Generic and Specific TFs Exhibit Differential Transcriptional Wiring.

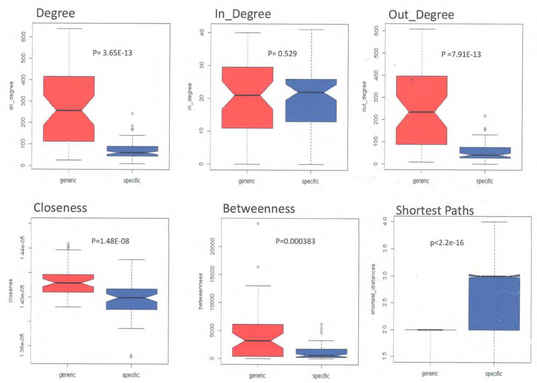

Figure 4: Comparision of network centralities of Generic and Specific TFs.

d) Motifs In Cancer Specific TF-miRNA Networks.

Cancer specific TF-miRNA networks are built to study the interactions between dysregulated TFs and miRNAs. TFs targeted by miRNAs are identified using miRanda and miRNA targets of TFs are identified based on the predictions of MEME and TOMTOM.

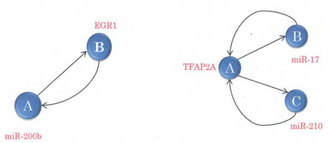

Figure 5: Two Motif instances of interest

Conclusions

In this study we present a novel method that uses tumor matched expression data to identify dysregulated miRNAs in cancers. Using this method we identify dysregulated miRNAs in nine cancers. We also identify TFs controlling the expression of these miRNAs. We find that TFs that are identified across several cancers are very generic in their function and are central in the TF-TF regulatory network. We also build cancer specific TF-miRNAnetworks in four cancers and identify motifs in these networks. We find several feedback motifs involving miRNAs and TFs among them. This suggest a strong coupling of dysregulation at the transcriptional and post-transcriptional level.

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