Reconstruction and Analysis of Dynamic microRNA Regulation in Cancers

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Abstract

MicroRNAs, a class of short non-coding RNAs, are able to regulate more than half of human genes and affect many fundamental biological processes. Compelling evidence has shown that the microRNA-mediated gene regulation is a complex dynamic process, where the interactions are highly dependent on several conditional factors, such as microRNA expression, mRNA target availability, binding affinity, and competing activity of other endogenous RNAs. Here we present a new computational method to stratify the dynamic gene regulation network with focus on uncovering the microRNA regulatory impact under given conditions.

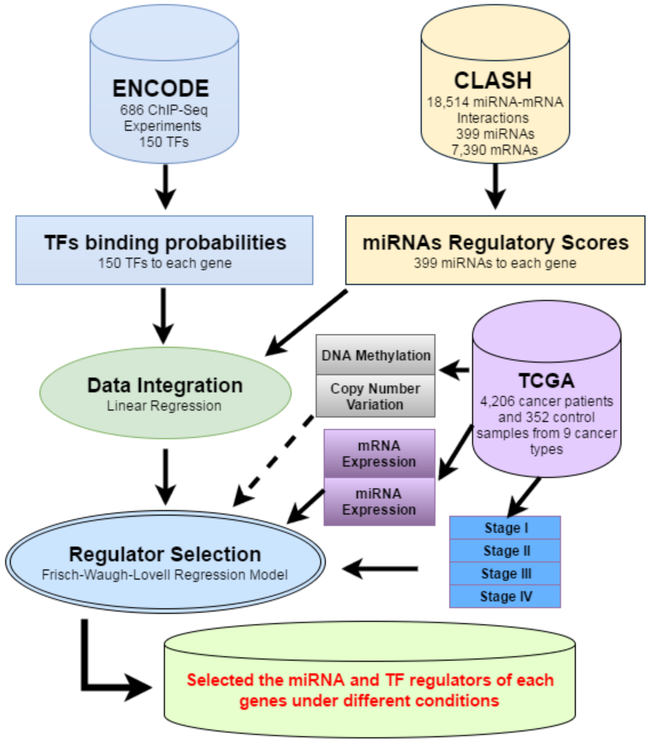
Specifically, we applied a large set of microRNA-mRNA interactions detected by CLASH experiment and integrated a heterogeneous set of multi-dimensional genomic information including microRNA and RNA expressions, transcription factor biding sites, DNA copy number variation, and methylation data from nine types of solid cancers, into a regression-based pipeline to estimate the microRNA-mediated gene regulation during cancer progression. Our method provides a promising new tool for studying the condition dependent miRNA regulation in the context of dynamic gene regulation network.

Datasets

The data for this study was collected from the following resources:

- Sequencing data of CLASH experiment that including 18,514 high-confidence miRNA-mRNA interactions
- Binding site information of 150 transcription factors from 686 ChIP-Seq experiments in ENCODE project
- Multi-dimensional genomic information of 4,206 cancer and 352 control patients in 9 solid cancers from TCGA
  - mRNA and microRNA expressions
  - DNA methylation data
  - Gene copy number variation

Workflow



Highlights of Methods

- Estimate regulatory potentials of miRNAs to each targets:
  - Re-analyzed raw sequencing data of CLASH and examined three types of reads
  - Purified miRNA-mRNA interactions based on binomial test
  - Calculate regulatory score of miRNAs by integrating competitive binding

$$P_{m_i}(g_t) = \frac{C_{ij}}{(C_{i\bullet} + M_{i\bullet})(C_{\bullet j} + M_{\bullet j})} \qquad S_{m_i}(g_t) = \frac{\sum_{k=1}^{N} |MFE_k| \times (P_{m_i}(g_t))_k}{N}$$

$$S'_{m_i}(g_t) = \frac{S_{m_i}(g_t)}{\sum (S_{m_i}(g_n))}$$

- Estimate regulatory potentials of TFs to each genes:
  - Calculated the distance (*d*) between the binding site to TSS from ChIP-Seq data

$$S_i(g_t) = e^{-(0.5+4(\frac{d}{100kb}))} \qquad S_{TF}(g_t) = 1 - \prod_i (1 - S_i(g_t))$$

$$S'_{TF}(g_t) = \frac{S_{TF}(g_t)}{\sum (S_{TF}(g_n))}$$

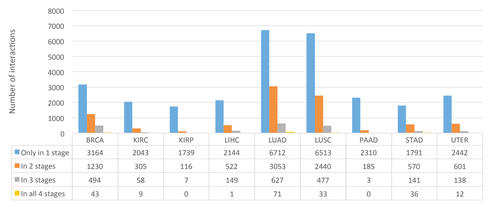
- Regulator detection based on a regression model:
  - Frisch-Waugh-Lovell Regression Model

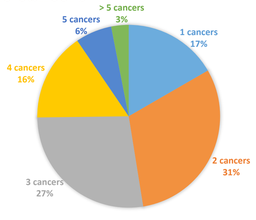
$$M_{X_1} = I - X_1(X_1^T X_1)^{-1} X_1^T$$

$$Y = X_1\beta_1 + X_2\beta_2 + \varepsilon \longrightarrow M_{X_1}Y = M_{X_1}(X_2\beta_2 + \varepsilon)$$

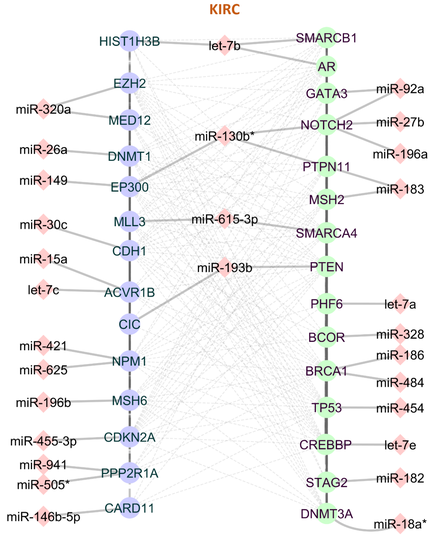
Results

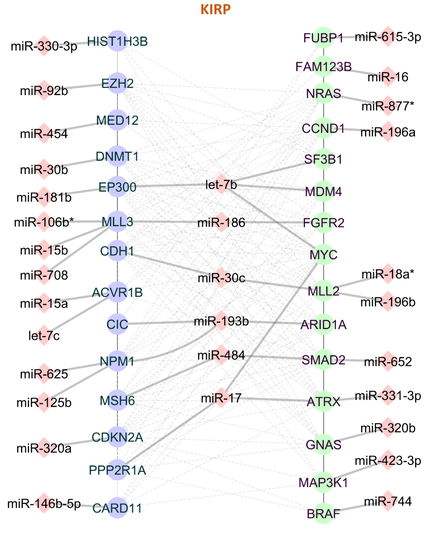
- Majority of miRNA-mRNA interactions were only occurred in one stage of cancer
- Some miRNA-mRNA interactions were shared by multiple cancers





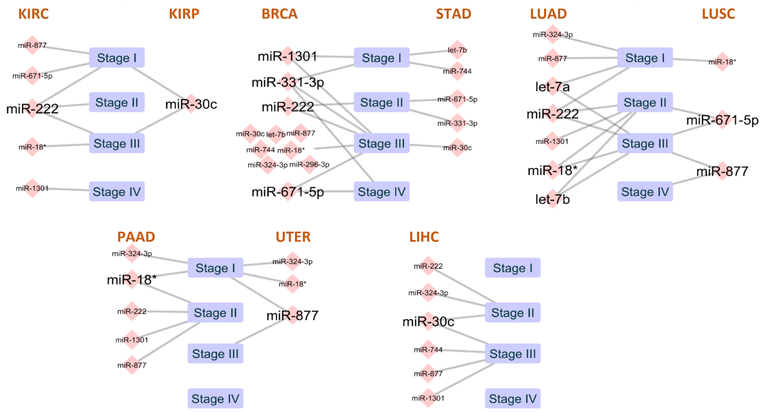
- Different miRNA regulation of featured cancer genes in two cancers in Kidney



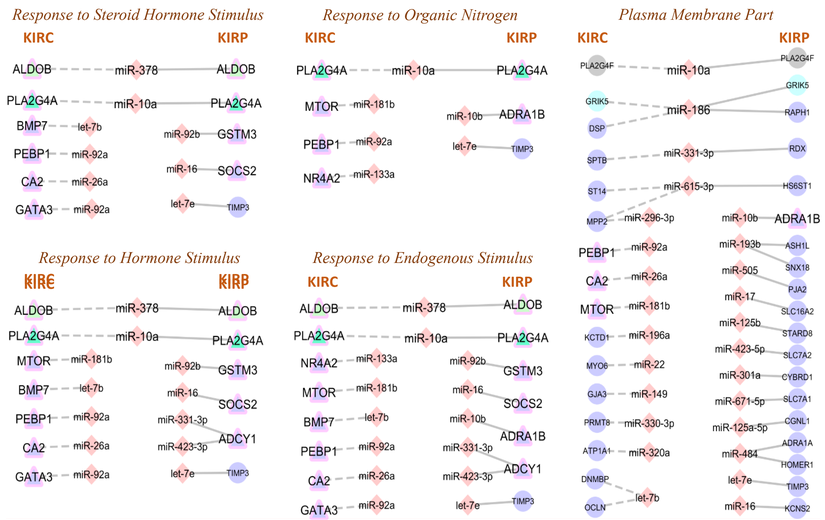


- miRNAs form regulatory modules across different cancers

  HMGA1 (High mobility group AT-Hook gene 1)
  - Repressor of P53 family members and a key contributor in NF-κB signaling pathway
  - Was regulated by the combinations of 12 miRNAs in different stages of nine cancers



- Functional Impacts of miRNA Cooperative Regulation
  - Five common enriched biological processes in Stage I of KIRC and KIRP



Summary

- microRNA-mRNA interactions are highly condition dependent
  - Genomic information is demanded to precisely identify the microRNA regulation network under a given condition
  - During the tumor progression, most of microRNA-mRNA interactions only occurred once
  - Cancers shared a limited commonality in microRNA regulation
- microRNA dynamic regulation is a functional-oriented mechanism
  - microRNAs formed modules to consistently repress the common targets across different stages and cancers
  - Different microRNAs control the similar biological processes through regulating different genes

Acknowledgement

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