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, microRNA 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 activity of other endogenous RNAs. Here we present a new computational method to microRNA expression, mRNA target availability, binding affinity, and competing

Datasets

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

- Sequencing data of CLASH experiment that including 18,514 high-confidence microRNA-mRNA interactions
- Binding site information of 150 transcription factors from 686 ChIP-Seq experiments in ENCODE project
- Multi-dimensional genomic information including microRNA and RNA expressions, transcription factor binding 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 microRNA regulation in the context of dynamic gene regulation network.

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 microRNA-mRNA interactions based on binomial test
  - Calculate regulatory score of miRNAs by integrating competitive binding
  
  \[ P_{m_j}(g_i) = \frac{C_{g_i}}{(C_{g_i} + M_j)(C_{g_i} + M_j)} \sum_{m=1}^{N} MFE_{m} \times \binom{P_{m_j}(g_i)}{N} \]

  - Estimate regulatory potentials of TFs to each genes:
    - Calculated the distance (\(d\)) between the binding site to TSS from ChIP-Seq data
    
    \[ S_j(g_i) = e^{-\left(\frac{(d - 2000)^2}{10000}\right)} \]

    \[ S_{TF}(g_i) = 1 - \prod_j (1 - S_j(g_i)) \]

- Regulator detection based on a regression model:
  - Frisch-Waugh-Lovell Regression Model
  
  \[ M_{Y} = X_1 \beta_1 + X_2 \beta_2 + \epsilon \]

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

Results

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

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

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