Dynamic MicroRNA Regulation in Human Gene Network

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Background

Micro-RNA (miRNA) is group of small (~20nt) non-coding RNAs that is widely found in post-transcriptional gene regulation. The major functions of miRNA include:

- Inhibiting the translation process of target messenger-RNA (mRNA);
- Directly cleaving the target mRNAs.

In the past decade, miRNAs have been discovered to actively regulate more than 30% of human genes and get involved in most of biological processes, including cell proliferation, death, and metabolism. Thus, the study of miRNA regulation represents one of the most important researches for achieving insights in biological systems. However, the progress has been hindered by the limitation of lab techniques that can be used for large scale study. For example, most of the miRNA-mRNA interactions studies were done by computational predictions based on the static complementary base pairing of short sequences, which however produce large numbers of false positive errors.

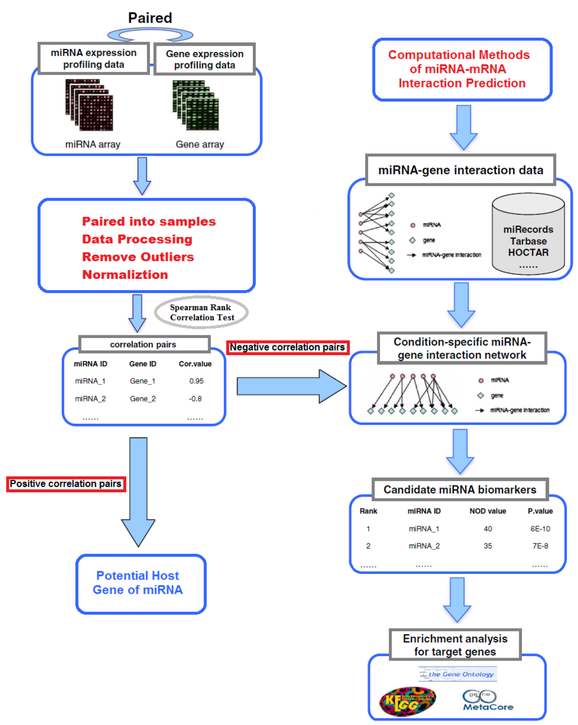
Here we present a novel computational approach which integrated both computational prediction and Omics data analysis, specifically, utilizing the miRNA microarrays and gene expression data from *The Cancer Genome Atlas (TCGA)* to construct dynamic miRNA regulatory network across different cell types, followed by the functional inference to elucidate the impact of dietary miRNAs in human heath through gene regulation.

Preliminary Study in Cancer

Research questions:

- Does the miRNA regulation contribute to cancer progression?
- Does gene the miRNA-regulated gene network alter over different cancer stages?

Method



Datasets

We analyzed 547 Ovarian Cancer samples that were obtained from *TCGA*:

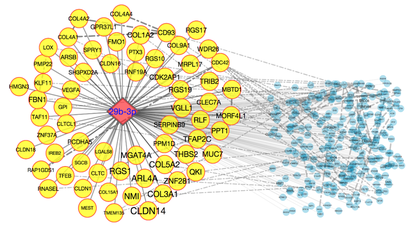
- Both of miRNA microarray and gene expression data were paired for each sample
  - 723 miRNAs and 12,042 human genes
- 8 organ-specific control samples and 539 ovarian cancer samples

	CONTROL	STAGE I	STAGE II	STAGE III	STAGE IV
TUMOR SAMPLES	8	16	24	424	83

- For each miRNA, we utilized the target prediction from *TargetScanDB* for preliminary analysis:
  - 11,161 unique human target genes in total

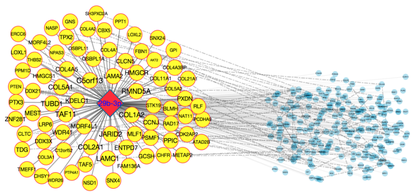
Overview of the Dynamic Regulatory Network in Five Ovarian Cancer Stages

Here, *miR-29b-3p* (◆) is used as an example to illustrate the dynamic regulatory network of miRNA (301 predicted target genes):



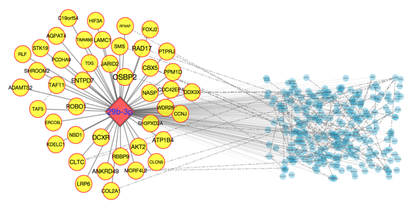
STAGE 0 (Organ-Specific Control Samples):

Initial regulatory network of *miR-29b-3p*.
Strong Negative Associated Targets: 65
Range of p-values: 3.65E-05 ~ 3.32E-03



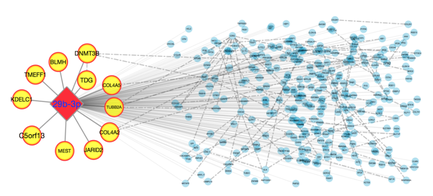
STAGE I (Early Stage Samples):

Strong Negative Associated Targets: 78
Range of p-values: 4.49E-05 ~ 3.32E-03



STAGE II (Early Stage Samples):

Strong Negative Associated Targets: 43
Range of p-values: 6.51E-05 ~ 3.31E-03



STAGE III (Late Stage Samples):

Strong Negative Associated Targets: 11
Range of p-values: 3.22E-07 ~ 3.27E-03

STAGE IV (Late Stage Samples):

Strong Negative Associated Targets: 28
Range of p-values: 1.53E-05 ~ 3.32E-03

shows the STRONG negatively associated target genes;
shows the WEAKLY associated target genes;
indicates the miRNA-mediated gene interaction;
indicates the protein-protein interaction among genes;

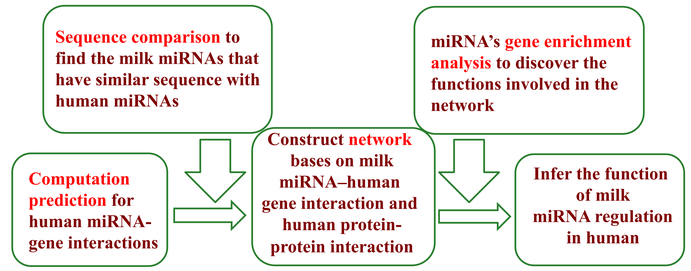
The bigger font size of gene symbol means a stronger negative association between gene and miRNA.

Preliminary Study in Milk miRNAs

Research questions:

- Does human absorb miRNA from milk supplement?
- Whether these milk miRNAs regulate human gene network and therefor cause phenotypic alterations or not? how?

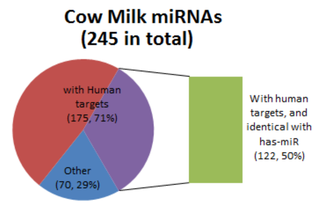
Proposed Approach



Martials

We analyzed 245 miRNAs in raw milk[1] and found:

- A total number of 10,104 human genes can be regulated by these 175 milk miRNAs;
- Moreover, 122 milk miRNAs have sequences identical or highly similar to their human orthologs.



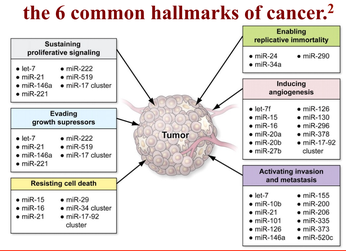
Future Steps in the Pipeline

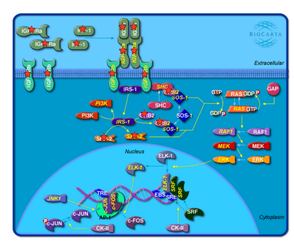
Probabilistic Method for prediction of miRNA binding sites:

- Development of a probabilistic model for the inference of miRNA binding sites, which consider both the collaborative and competitive miRNA binding, which means that multiple miRNAs can binding to the same mRNA while one single miRNA can bind to multiple mRNAs.

Inference of Milk miRNA regulated Functional Processes in Human:

- Aberrant miRNA expression and regulation in different human phenotypes may reflect signaling or metabolic pathways that contribute to the development of human diseases such as cancers. For example, the representative miRNAs below act as oncogenes or tumor suppressors to affect the 6 common hallmarks of cancer.[2]





Summary

- With the expression data of miRNA and gene, we are able to construct a reliable regulatory network by using computational methods;
- miRNA regulatory network changes over different conditions;
- Milk miRNAs heavily overlap with human miRNAs, the function of this group of miRNAs in humans could be discovered by pathway analysis.

Acknowledgements:

Gene expression and miRNA microarray data are obtained from The Cancer Genome Atlas (TCGA).

[1] Chen, X. et al (2010). Identification and characterization of microRNAs in raw milk during different periods of lactation, commercial fluid, and powdered milk products. Cell research, 20(10), 1128-1137.
[2] Ross, SA. *et al* (2011). MicroRNA, nutrition, and cancer prevention. Advances in Nutrition: An International Review Journal, 2(6), 472-485.