Using Public Resources for Targeting mRNA-miRNA Interactions

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Introduction

Since the first discovery of lin-4 in the early 1990s, microRNAs have been recognized as one of the key regulating factors for gene expression, and their therapeutic values are under investigation. However, with decades of accumulating data on genetic research, prediction of miRNA-mRNA interaction remains challenging. While most research articles on this topic disclosed the prediction tools for identifying research targets, many of those tools create hundreds, if not thousands of targets, which makes the job of screening become yet another research topic. In this poster, I demonstrated that by utilizing public datasets, one can identify research targets with simple steps and basic programming skills.

Here, three study scenarios are provided as examples. The main purpose is to use zebrafish, one of the most popular models for screening medication and toxicity, to find out the potential harmfulness to embryos from a specific miRNA-based therapy (i.e. exogenously introducing large amount of miRNA). We found that by consulting human data, one can more efficiently identify potential miRNA-mRNA interactions that might lead to specific developmental abnormality in zebrafish.

Resources

- TargetScanFish: http://www.targetscan.org/fish_62/
  - Download Conserved Family Info and Context Scores (release 6.2)
- Bgee: https://bgee.org
  - Download processed dataset GSE39703 (mRNA profiles of zebrafish embryos at multiple stages)
- Ensembl: https://ensembl.org
  - For each expressed genes at 24 hpf in GSE39703,, download records of Gene stable ID, Gene name, Phenotype description, Study external reference, GO term evidence code, GO term name, GO term accession from BioMart (GRCz11)
- miRTarBase: https://mirtarbase.cuhk.edu.cn/
  - Download MTI.xlsx (release 8.0)

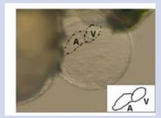
Methods

- Scenario I
  1. Extract human and zebrafish rmiRTarBase records from MTI.xlsx
  2. Screen for conserved microRNAs based on “Conserved Family Info” from TargetScanFish
  3. Extract records of miRNAs for chd7 from 2.
- Scenario II
  1. Extract records with the word “heart” and evidence codes IDA, IPI, IMP, and IGI from the BioMart file
  2. Extract target mRNAs from “Context Scores” file and the processed MTI file (follow step 2 in Scenario I)
  3. Screen records from step 1 with genes in step 2
- Scenario III
  1. Extract target mRNAs from the processed MTI file (follow step 2 in Scenario I) for miR-19
  2. Extract BioMart records based on the mRNAs in step 1
  3. Sum up the phenotype records for all of the records from step 2.

Results

Scenario I: identify regulating miRNAs

Chd7 — Expect to see tubular heart

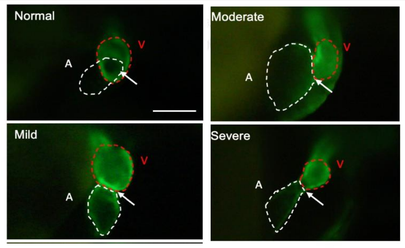


Patten et al., 2012

TargetScanFish — ~ 21 out of 82 conserved microRNA families

TargetScanFish + miRTarBase — let-7, miR-124, miR-129 , miR-155, miR-181, miR-192, miR-219, miR-454

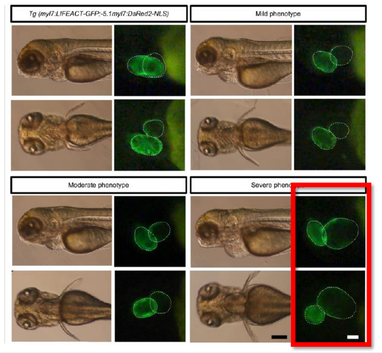
AB at 96 hpf



Tg(BMP4:EGFP) at 48 hpf

Scenario II: search for target mRNAs

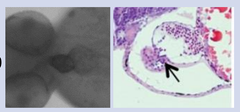
miR-19d



Ensembl + TargetScanFish — 225 genes, where 109 genes with experimental evidence for cardiac phenotypes

Ensembl + miRTarBase — 28 genes, where only 6 genes with experimental evidence for heart looping issues

Follow the reference — atg5
ZDB-GENE-040801-149
Lee et al., 2013



Scenario III: predict possible phenotypes

miR-19d — To be overexpressed in zebrafish embryos

Ensembl + miRTarBase
- ✓Evidence for interaction between miRNA and mRNA
- ✓Evidence for relationship between mRNA and phenotypes

- More than 1000 phenotypes!
- Including heart, fin, vessel, eye, liver, head, brain, trunk, blood…

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Discussion

1. With abundant records of experiments shared online, target prediction (identification) has become possible with simple steps and reasonable hit rates, while phenotype prediction is still challenging
2. Why is it important for experiment design?
   - Save time!
   - To avoid unwanted effects and to induce phenotypes of interests
   - Especially important when developing therapeutic applications
3. Results in zebrafish from consulting human data might be more readily generalizable to human medications

Reference

- Patten, Shunmoogum A., et al. "Role of Chd7 in zebrafish: a model for CHARGE syndrome." *PLoS One* 7.2 (2012): e31650.
- Lee, Eunmyong, et al. "Autophagy is essential for cardiac morphogenesis during vertebrate development." Autophagy 10.4 (2014): 572-587.