Center for Bioinformatics
生物信息中心
CBI
HUAZHONG AGRICULTURAL UNIVERSITY

Characterizing the role of miRNAs within gene regulatory networks using integrative genomics techniques

Group Members:刘骏武
靳文启

Background：

- miRNAs：内源性的单链小分子RNA片段（~22nt）
  - 在多物种间参与多种途径的调节途径；
  - 据预测，人类约1/3基因受miRNAs调控；
  - miRNAs的调控机理复杂；

当前认为的调控机制：

组装由RNA诱导的沉默复合体，通过碱基互补配对的方式识别靶mRNA，并根据互补程度的不同指导沉默复合体降解靶mRNA或者阻遏靶mRNA的翻译。

预测miRNA潜在的靶标：假阳性（～22-39%）；假阴性（～35-52%）

Purpose：

Explore the association between miRNAs and their target mRNAs using an integrative genomics approach.

Methods:

- Integrative genomics and genetic approaches
- eQTL:expression QTL

作者Schadt在03年于鼠的肝组织中检测23574个基因的表达情况，并采用区间作图法进行 e QT L 定位，发现在第2 、6 、7、9、1 0 、1 6和 1 7号染色体上存在 e QT L热点区域,并找 到 了一 个 与小 鼠肥胖有关的候选基因 Mup I.

Materials：

- *C57BL/6J and DBA/2J*

- *127 male mice for miRNA and mRNA expression profiling*

- *Collect both mRNA expression and genotype information from mice liver(From miRBase 187 miRNAs ~31% in release 15).*

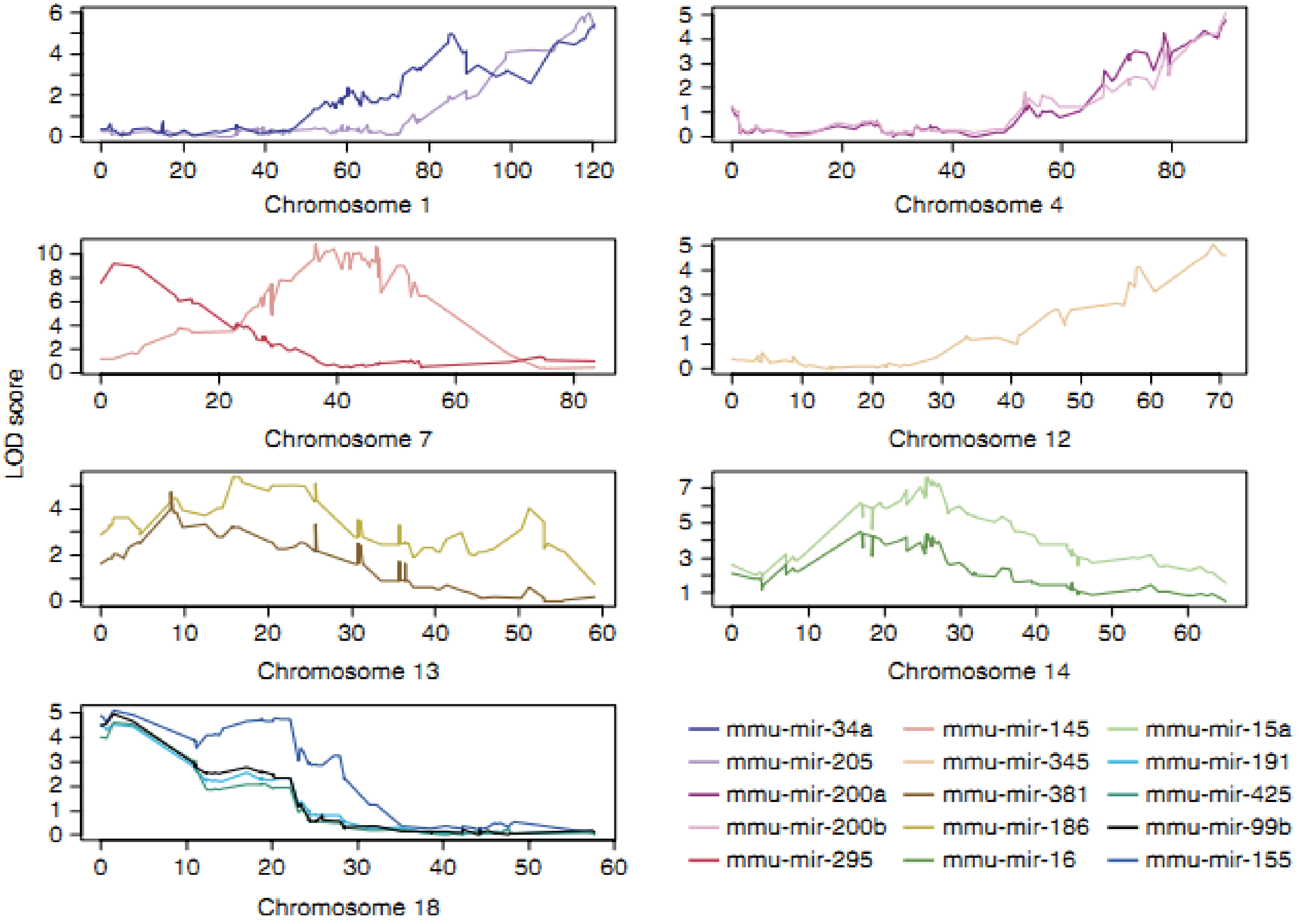
Results：

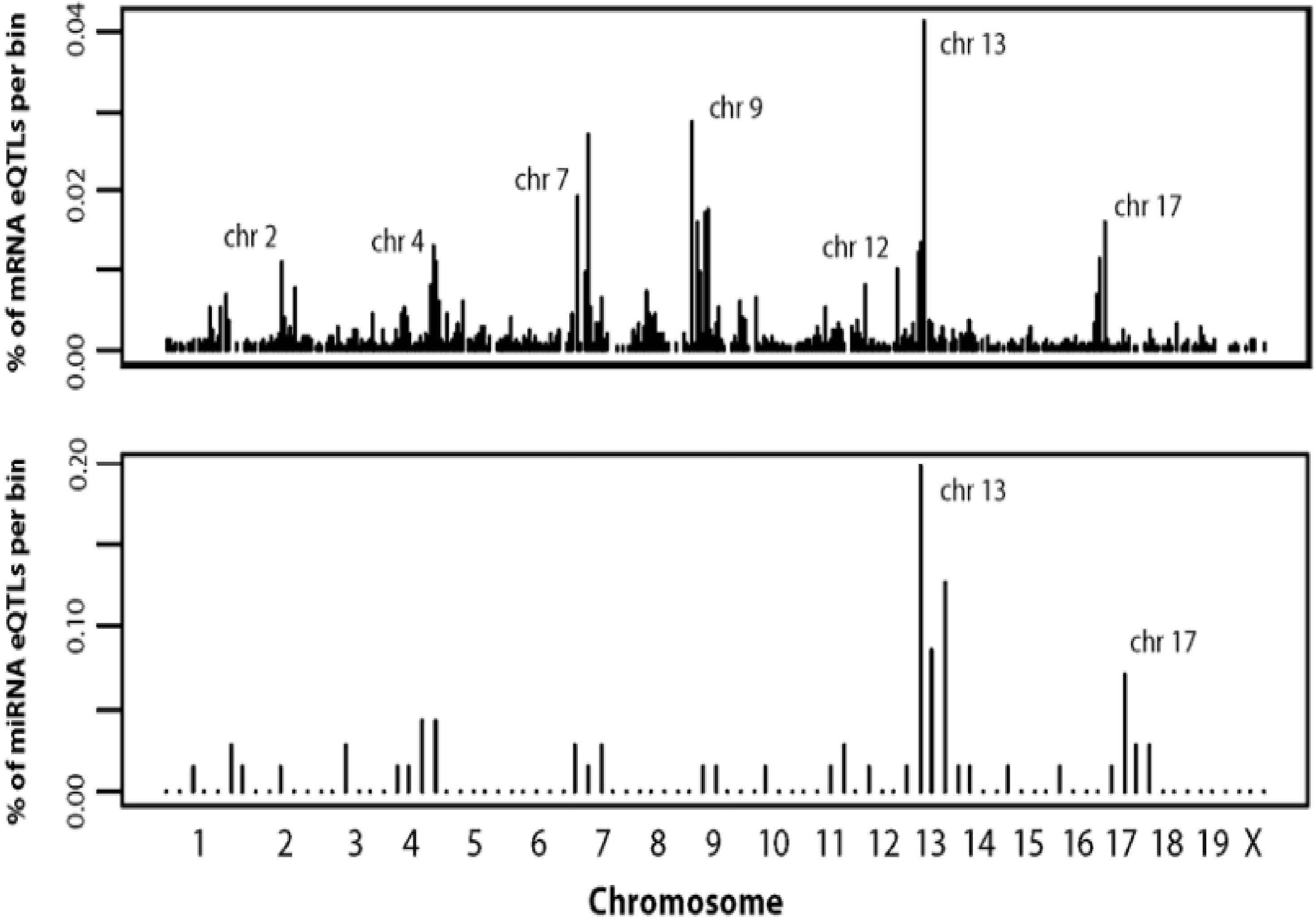
1. *eQTL mapping study;*

2. *Correlation analysis between miRNA and mRNA expression level in mice*

3. *Causal associations between miRNA and mRNA*

一:


LOD score
Chromosome 1
Chromosome 4
Chromosome 7
Chromosome 12
Chromosome 13
Chromosome 14
Chromosome 18
mmu-mir-34a
mmu-mir-205
mmu-mir-200a
mmu-mir-200b
mmu-mir-295
mmu-mir-145
mmu-mir-345
mmu-mir-381
mmu-mir-186
mmu-mir-16
mmu-mir-15a
mmu-mir-191
mmu-mir-425
mmu-mir-99b
mmu-mir-155


% of mRNA eQTLs per bin
0.00
0.02
0.04
chr 2
chr 4
chr 7
chr 9
chr 12
chr 13
chr 17
% of miRNA eQTLs per bin
0.00
0.10
0.20
chr 13
chr 17
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
X
Chromosome

二：

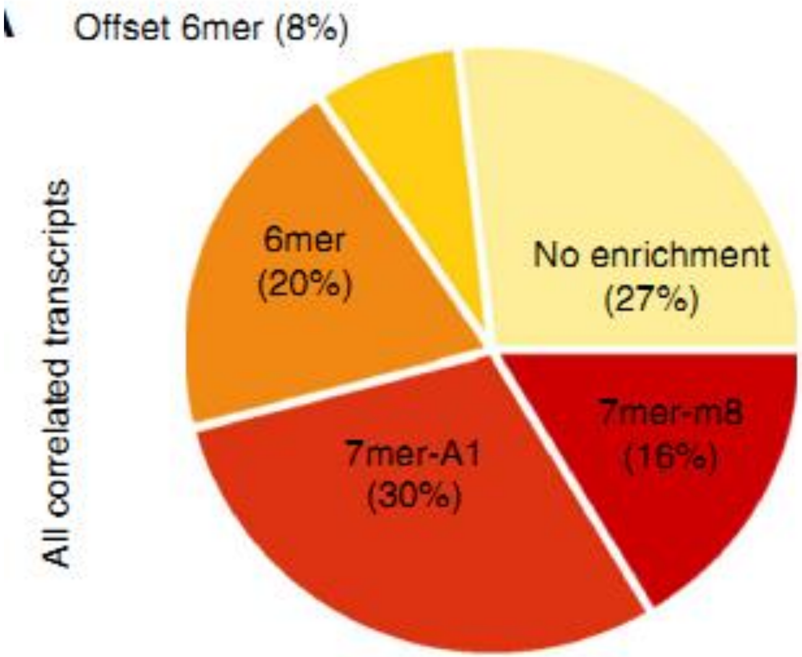
Offset 6mer .... TTGACG..

6mer ....TGACGA.

7mer-A1 ....TGACGAT

7mer-m8 ....TTGACGA.

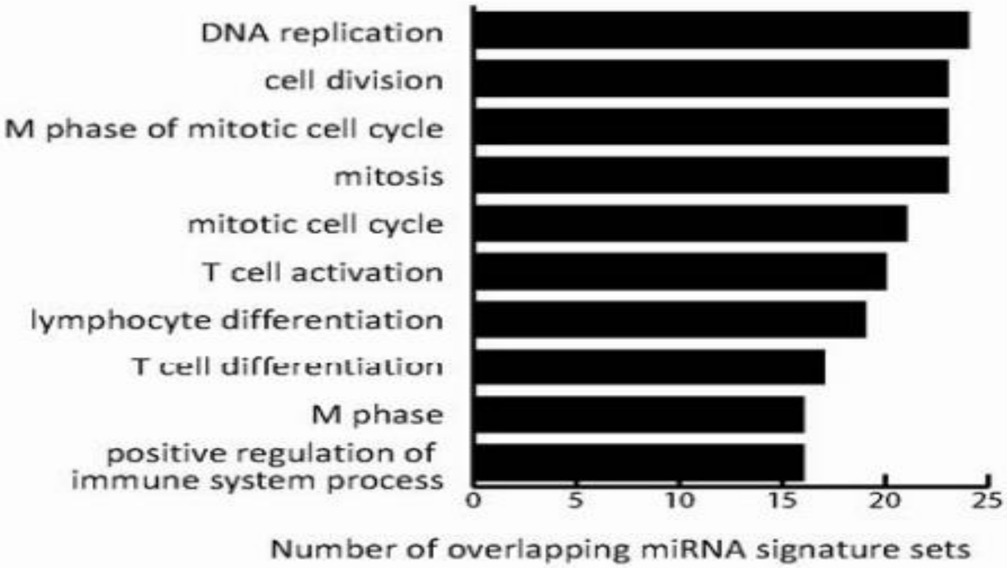
miRNA 3′-NNNNNAACTGCTA-5′



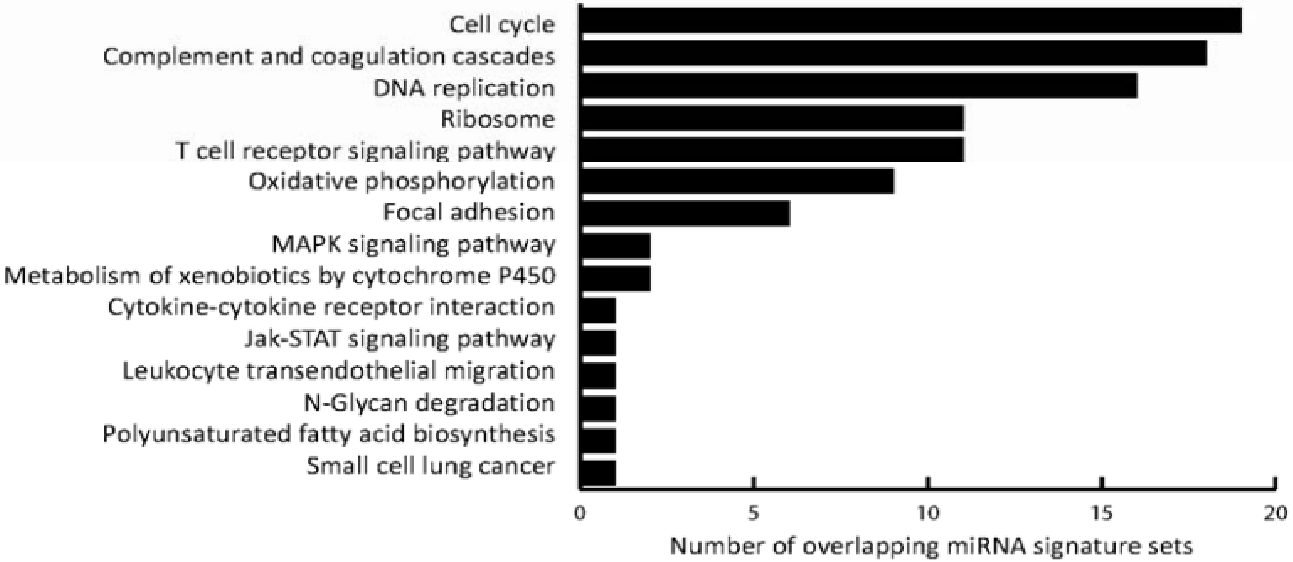
And...

- 1.A number of miRNAs were very broadly connected to thousands of mRNA.
  - a.表明miRNA在肝组织的基因调控网络中相当于中心节点;
  - b.平均每个miRNA与2545mRNA有重要关联;
  - c.有8个miRNA与超过10000mRNA有重要关联。
- 2.mRNA —>miRNA
  - 平均每个mRNA转录与19个miRNA相关联;
  - 63%的转录本至少与1个miRNA相关联。

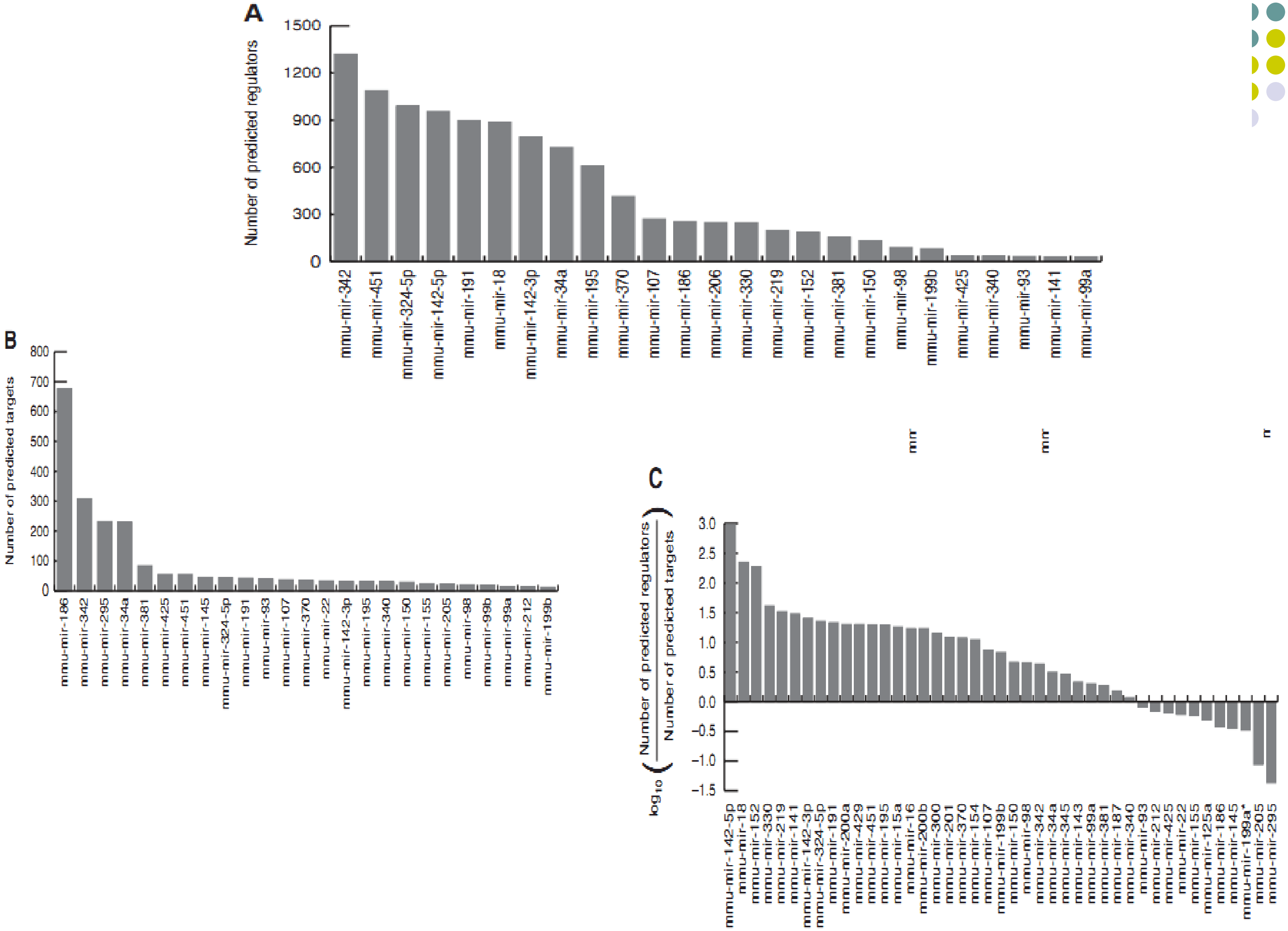
B


DNA replication
cell division
M phase of mitotic cell cycle
mitosis
mitotic cell cycle
T cell activation
lymphocyte differentiation
T cell differentiation
M phase
positive regulation of immune system process
0
5
10
15
20
25
Number of overlapping miRNA signature sets

C


Cell cycle
Complement and coagulation cascades
DNA replication
Ribosome
T cell receptor signaling pathway
Oxidative phosphorylation
Focal adhesion
MAPK signaling pathway
Metabolism of xenobiotics by cytochrome P450
Cytokine-cytokine receptor interaction
Jak-STAT signaling pathway
Leukocyte transendothelial migration
N-Glycan degradation
Polyunsaturated fatty acid biosynthesis
Small cell lung cancer
0
5
10
15
20
Number of overlapping miRNA signature sets

三:


A
Number of predicted regulators
1500
1200
900
600
300
0
mmu-mir-342
mmu-mir-451
mmu-mir-324-5p
mmu-mir-142-5p
mmu-mir-191
mmu-mir-18
mmu-mir-142-3p
mmu-mir-34a
mmu-mir-195
mmu-mir-370
mmu-mir-107
mmu-mir-186
mmu-mir-206
mmu-mir-330
mmu-mir-219
mmu-mir-152
mmu-mir-381
mmu-mir-150
mmu-mir-98
mmu-mir-199b
mmu-mir-425
mmu-mir-340
mmu-mir-93
mmu-mir-141
mmu-mir-99a
B
Number of predicted targets
800
700
600
500
400
300
200
100
0
mmu-mir-186
mmu-mir-342
mmu-mir-295
mmu-mir-34a
mmu-mir-381
mmu-mir-425
mmu-mir-451
mmu-mir-145
mmu-mir-324-5p
mmu-mir-191
mmu-mir-93
mmu-mir-107
mmu-mir-370
mmu-mir-22
mmu-mir-142-3p
mmu-mir-195
mmu-mir-340
mmu-mir-150
mmu-mir-155
mmu-mir-205
mmu-mir-98
mmu-mir-99b
mmu-mir-99a
mmu-mir-212
mmu-mir-199b
C
log10 (Number of predicted regulators / Number of predicted targets)
3.0
2.5
2.0
1.5
1.0
0.5
0.0
−0.5
−1.0
−1.5
mmu-mir-142-5p
mmu-mir-18
mmu-mir-152
mmu-mir-330
mmu-mir-219
mmu-mir-141
mmu-mir-142-3p
mmu-mir-324-5p
mmu-mir-191
mmu-mir-200a
mmu-mir-429
mmu-mir-451
mmu-mir-195
mmu-mir-15a
mmu-mir-16
mmu-mir-200b
mmu-mir-300
mmu-mir-201
mmu-mir-370
mmu-mir-154
mmu-mir-107
mmu-mir-199b
mmu-mir-150
mmu-mir-98
mmu-mir-342
mmu-mir-34a
mmu-mir-345
mmu-mir-143
mmu-mir-99a
mmu-mir-381
mmu-mir-187
mmu-mir-340
mmu-mir-93
mmu-mir-212
mmu-mir-425
mmu-mir-22
mmu-mir-155
mmu-mir-125a
mmu-mir-186
mmu-mir-145
mmu-mir-199a*
mmu-mir-205
mmu-mir-295

剧情回顾：

- ✓ *Examined expression level of 187 within the context of a mouse liver gene regulatory network;*

- ✓ *The results suggest that the transcript abundances of these miRNA are under more complex regulation than those previously observed for mRNA abundances.*

- ✓ *The data further suggest that many of the surveyed miRNAs are co-expressed with mRNAs involved in DNA replication and the cell cycle in liver tissue.*

- ✓ *Demonstrate that a number of miRNAs detected typically exist as highly connected hub-nodes within the liver transcriptional network that respond to perturbations in mRNA transcript levels and drive changes in mRNA expression profiles.*

- ✓ *For the majority of surveyed miRNAs, the number of mRNA statistically supported as causalfor regulating miRNA transcript exceeds the number of downstream mRNA transcripts predicted to respond to changes in miRNA levels, illustrating the complexity of miRNA-mediated regulation.*

The End ~