Impact of microRNAs on Organization of Protein Interactions and Formation of Protein Complexes

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(Thanks: Wilson Goh, Guimei Liu, Judy Sng)

Motivation

• Typical PPI network
  • Can a protein interact with so many proteins simultaneously?
  • Big “hub” & its “spokes” should be decomposed into subclusters
    – A subcluster is a set of proteins that interact in the same space & time
    – Viz., a protein complex

MicroRNAs

• MiRNAs are small regulatory molecules that act by mRNA degradation or via translational repression
• Do miRNAs have a role in controlling complex formation?
• E.g., diff expression of miRNAs across diff tissues can result in formation of diff protein complexes by repressing expression of some sub-components

Can this happen?

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Hypothesis

• MiRNAs w/ widely diff expression profiles (i.e., anti-coexpressed) control mutually exclusive bio processes; and so result in diff complexes

Results in progress…

• Verify some general properties implied by the Hypothesis
• Check some predictions in experiments

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Terminology

• “Hub” – proteins having ≥50 PPI partners
• “Hub spokes” – PPI partners of a hub
• “Hamming distance” – # of tissues two miRNAs are differentially expressed in
• “Anti-coexpressed” – two miRNAs with Hamming distance ≥35 (out of max of 40 tissues)
• “Co-expressed” – two miRNAs that tend to be expressed in the same tissues

Data Sets

• Biological network info
  – Human Protein Reference Database
• MiRNA expression info
  – 40 normal tissues from Landgraf’s database
• Protein complex info
  – CORUM
• MiRNA target info
  – Prediction by Diana Micro-T

Workflow

Size of hub (i.e., # of neighbors it has) is linearly correlated with ave prob of hub targeted by miRNA

When a miRNA is more likely to target a hub, it is also more likely to target more of its spokes

Freq distribution of Hamming distance based on all miRNA pairs shows that most miRNA pairs are co-expressed
Co-expressed miRNAs are more freq than anti-coexpressed miRNAs

Are hub spokes preferentially targetted by them?

Hub spokes are preferentially targetted by anti-coexpressed miRNAs

Do they work “co-operatively” or “antagonistically”?

Spoke targeting by miRNAs is specific

For a hub, if its spokes targeted by a miRNA (in an anti-coexpressed pair) are removed, can the remaining spokes form protein complexes?

Yes! For every targeting miRNA (in an anti-coexpressed pair), 80-90% of the time, the remaining spokes can form protein complexes

→ Targetting miRNA affects small subset of protein complexes formed by hub spokes
→ Very specific mode of action?

Anti-coexpressed MiRNAs target “hub spokes” more strongly than co-expressed miRNAs

Overlap betw targeted spokes decreases with increasing anti-coexpression

Hub-Spoke targeting by anti-coexpressed miRNAs is specific

In most complexes disrupted by anti-coexpression pairs, there is no third complex that can be formed from components of disrupted complexes

→ MiRNA disruption of complexes is a controlled and specific event
Anti-coexpressed miRNAs target different subsets of complexes controlled by hubs

Do these disrupted complexes have something to do with maintaining tissue-specific function or regulating tissue-specific processes?

Identification of miRNA-regulated complexes

Examine complexes disrupted in a scenario where there is evidence for miRNA upregulation and mRNA downregulation

A downregulated mRNA that is predicted to be targeted by an upregulated miRNA (in an anti-coexpressed pair) is considered to be a real target

Check protein complexes involving real targets
  – Are these expected to be suppressed?

VPA-Treated Mice

Valporic Acid (VPA) prompts differentiation of hippocampal neural progenitor cells into neurons, but they prevent their differentiation into oligodendrocytes and astrocytes

Tx of mice over a 2-day period w/ VPA indicated readjustment of miRNA levels. 136 miRNAs were over-expressed with 1000 targeted genes down regulated

236 genes are high-confidence miRNA targets

The 236 Genes

Genes in this set are involved in
  – Chromatin modification (n= 14, P = 2.12e-05)
  – Nervous system dev (n = 23, P = 0.00077)
  – Cell differentiation (n = 32, P = 0.00129)

These miRNA targets have role in epigenetic regulation in the maturation of neurons from progenitors

Complexes Disrupted

Check against CORUM shows 53 complexes got disrupted via elevated miRNA targeting
  – 15 of these contain HDAC 1 and/or 2.
  – 8 possess Swi/Snf components involved in neuronal differentiation and neurogenesis
  – 5 belong to polycomb family of complexes which are epigenetic regulators, play a role in cell fate transition and neuronal differentiation
  – 8 complexes are SMAD regulators. SMAD can induce proliferation and differentiation of hippocampal neurons

Caveat: These are the best-matching human complexes, not mouse!
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<thead>
<tr>
<th>miRNAs play impt role regulating formation of complexes</th>
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<td>Anti-coexpressed miRNAs tend to regulate direct partners of hubs</td>
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<th>In VPA-treated mice, miRNAs disrupt neuron-specific and neuron-differentiating complexes</th>
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<td>The small # of disrupted complexes, and their precise roles, reaffirms miRNA action as precise</td>
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**Acknowledgements**

- Wilson Goh
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