Dysregulated Subnetwork Markers: miRNA-Disease Associations

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For Nets subgroup

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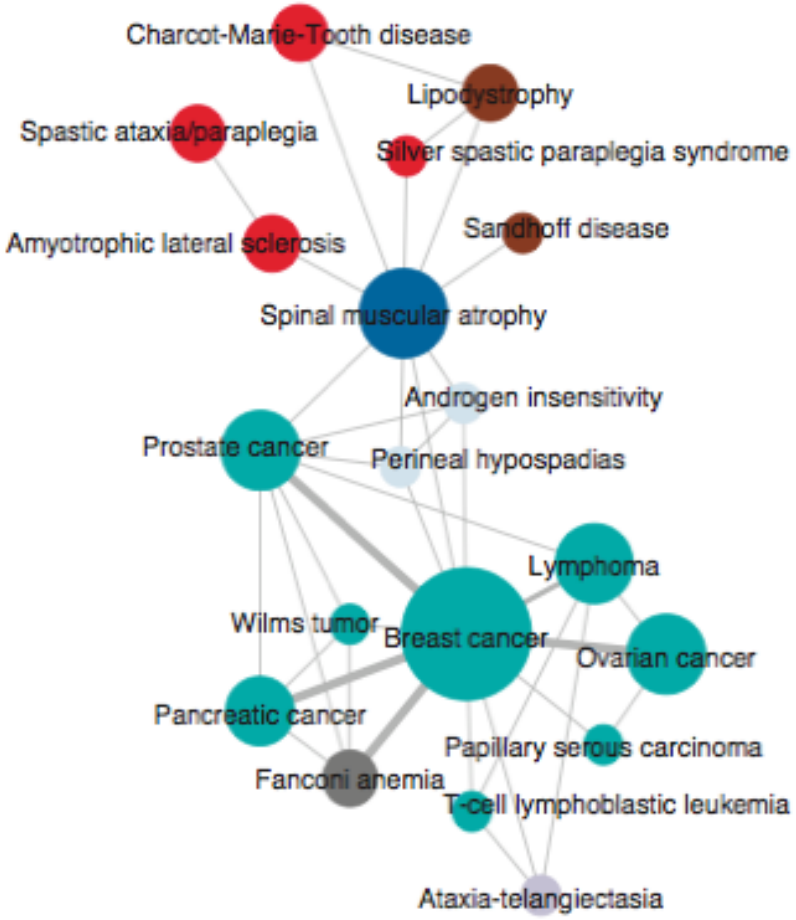
Quick Recap

- Supernetwork integrating three types of networks
  - PPI, TF regulation, and miRNA regulation
- Whole genome mutation data
  - 7 prostate (Rubin)
  - 9 colorectal (Peter Good)
  - 44 colon adenocarcinoma (COAD) (TCGA public)
  - 126 glioblastoma multiforme (GBM) (TCGA public)
  - 59 acute myeloid leukemia (AML) (TCGA public)
  - 142 ovarian serous cystadenocarcinoma (OV) (TCGA public)
  - 35 rectum adenocarcinoma (READ) (TCGA public)

Overview

- Map mutation data onto the supernetwork and find subnetworks of mutated genes
- For each cancer, one large subnetwork (Dysregulated Subnetwork Marker: DSM) was produced (some had a few really small subnetworks in addition to the main one)
- GOAL: Find how many [genes, TFs, miRNA] intersect multiple cancer DSMs
  - Hoped that pairwise intersection data could be used to develop a “second-order diseasome network”
- GOAL: Functionally characterize the [genes, TFs, miRNA] of the DSMs

Human Diseasome Network

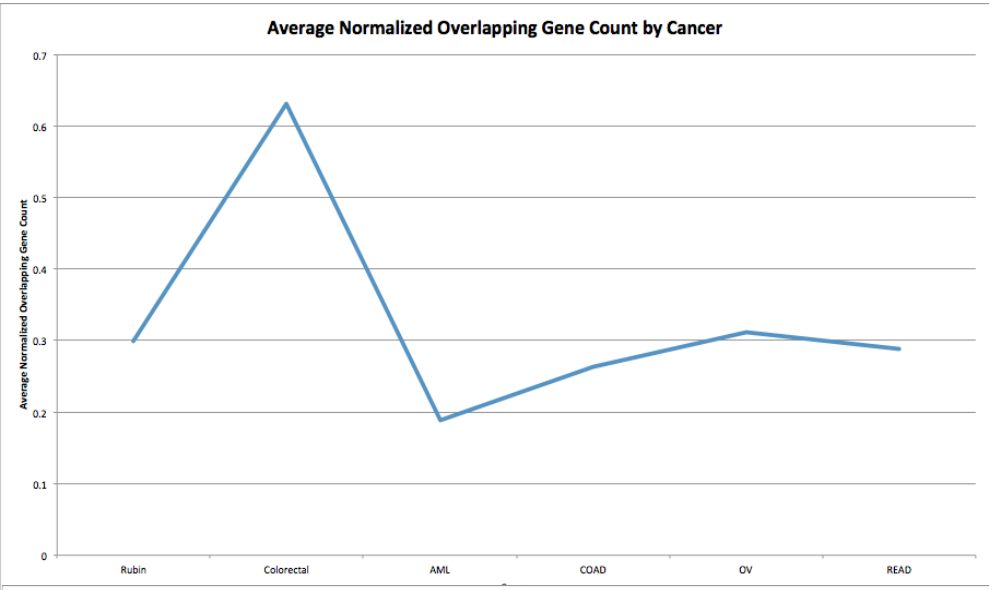


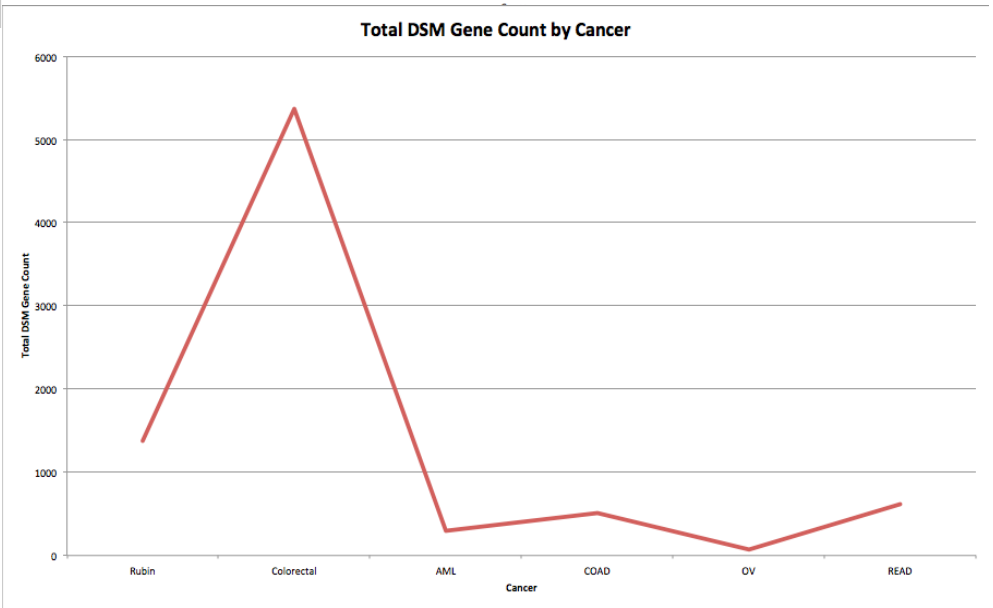
Goh *et al*. "The human disease network." *PNAS May 22, 2007 vol. 104 no. 21 8685-8690*

Intersection Results

- DSM first-neighbor miRNA typically included at least 2/3 of all known human miRNA, if not all
  - Not very informative
- Switched focus to DSM member genes
  - Pairwise intersection sizes were proportional to the # of DSM genes
  - Found very strong correlation between the average normalized overlapping gene count and DSM gene count

Intersection Results





Top graph:
Average normalized overlapping gene count by cancer
(for each cancer, start with the number of genes in each pairwise intersection, divide by total gene count, and find arithmetic mean)

Bottom graph:
Total DSM gene count by cancer

Correlation: 0.952

Summary of DSM miRNA

Shared by 3 cancer DSMs

- hsa-miR-1267 – Colorectal, AML, prostate

Shared by 2 cancer DSMs

- hsa-miR-1302 – Colorectal, prostate
- hsa-miR-548f/h/q – Colorectal, prostate

Singletons

- hsa-miR-1185 - colorectal
- hsa-miR-142-3p - AML
- hsa-miR-142-5p - AML
- hsa-miR-1973 - colorectal
- hsa-miR-320d - colorectal
- hsa-miR-548a-3p - prostate
- hsa-miR-891a - AML
- hsa-miR-921 - colorectal

miRNA Functional Characterization

- Looked in miRNA databases to see what was already known about these miRNA
- Found miR-Ontology
  - Data warehouse developed at the Univ of Cantania in Italy
  - Integrates all sorts of data on miRNA, including sequence features, expression data, experimental and predicted targets
  - Includes disease associations --> targets' disease annotations are applied to parent miRNA

miRNA Functional Characterization

- miR-Ontology confirmed the disease associations of almost all miRNA discovered through DSMs
- With 3 exceptions:
  - hsa-miR-1973 in colorectal cancer
  - hsa-miR-548q in colorectal and prostate cancer
  - hsa-miR-891a in AML
- Hence, we can conclude that many of the miRNAs implicated in DSMs have genuine associations with their respective diseases
- And there is the potential for DSMs to implicate miRNA not previously implicated

miRNA targets: DSMs vs. miR-Ontology

miRNA	Cancer Type	DSM #	miR-Ontology #	Intersection #
hsa-miR-1185	Colorectal	756	4	1
hsa-miR-1267	AML	64	1	0
hsa-miR-1267	Colorectal	1145	6	4
hsa-miR-1267	Prostate	338	7	0
hsa-miR-1302	Colorectal	854	13	3
hsa-miR-1302	Prostate	234	10	2
hsa-miR-142-3p	AML	50	1	0
hsa-miR-142-5p	AML	128	2	1
hsa-miR-1973	Colorectal	144	0	0
hsa-miR-320d	Colorectal	1567	20	5
hsa-miR-548-3p	Prostate	639	16	0
hsa-miR-548f	Colorectal	2322	20	9
hsa-miR-548f	Prostate	624	18	0
hsa-miR-548h	Colorectal	2302	28	14
hsa-miR-548h	Prostate	663	12	0
hsa-miR-548q	Colorectal	779	0	0
hsa-miR-548q	Prostate	223	0	0
hsa-miR-891a	AML	14	0	0
hsa-miR-921	Colorectal	859	15	2

- For each miRNA found in a DSM, find how many targets appear in its DSM and how many appear in miR-Ontology (also find how many in the intersection set)
- DSMs have far more targets than miR-Ontology
  - Did the DSM algorithm find many targets not previously implicated in disease?
- Also have many targets in miR-Ontology not in DSMs
  - Poor sensitivity?

DSM transcription factors

TF	# of Cancers	Cancers
Elf1	3	Prostate, colorectal, AML
Taf1	3	Colorectal, COAD, READ
Zeb1	3	Prostate, colorectal, COAD
Max	2	Colorectal, AML
Tcf12	2	Colorectal, READ
Bclaf1	1	Colorectal
Brca1	1	OV
Ets1	1	Colorectal
Nrf1	1	Colorectal
Pbx3	1	Colorectal
Smc3	1	AML
Stat1	1	Colorectal
Stat3	1	Colorectal
Tbp	1	Colorectal
Zbtb33	1	COAD
Znf143	1	Colorectal
Zzz3	1	Colorectal

- List of all transcription factors that appear in DSMs
- Ordered by # of cancers involved
- Indicates shared and unique components of cancer regulatory disruptions
- Most cancers appear to affect a unique part of the network (lots of singletons)

Future Work

- Functionally characterize the intersecting components of DSMs
- Map additional cancer data to the supernetwork
- Investigate correspondence of DSM components to pathways and complexes

Acknowledgements

- Sign up on the Gdoc:
  - http://goo.gl/ukUB9