#234

Computational characterization of microRNA-mediated association between Obesity and Cancer

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Abstract

MicroRNAs control gene expression in many fundamental cellular processes that are associated with pathogenesis of human cancer and obesity. However, the microRNA-mediated association between cancer and obesity is largely under-investigated, in spite of the emerging evidences indicating 1) a higher risk of pancreatic cancer and breast cancer in obese people 2) a novel mechanism to understand the links, e.g. upregulation of insulin-like growth factor-1 (IGF-1) in overweight individuals may promote pancreatic cancer 3) IGF-1 regulation of tumor suppressive miRNAs such as miR-15b, miR-98, miR-195, miR-200b, let-7c and let-7g. Considering our current knowledge of the relationship between obesity and cancer is very limited, we have applied an omics-driven integrative approach to systematically study the regulatory roles of microRNA in cancer and obesity and to elucidate the association between these two types of diseases from the microRNA-mediated gene regulation perspective. Specifically, we have collected large-scale genomics data on obesity and three types of cancer, namely, pancreatic cancer, gastric cancer and ovarian cancer in this analysis, which are subject to sophisticated bioinformatics analysis including microRNA co-regulatory modules identification, targets prediction and functional enrichment analysis.

Our statistical analysis has identified a list of obesity-associated microRNAs (e.g. miR-146b, miR-223, miR-125b, etc.), part of which shows strong association with cancers under investigation. Using the experimentally-detected miRNA-mRNA interactions from CLASH data, we are able to identify the potential miRNA modules that include miRNAs co-regulating the same set of gene target. Through analysis on the targets, we have identified functional crosstalk between obesity and cancers, as well as specific regulation pattern in each disease. Overall, we demonstrates such integrative study using computational modeling and omics information can effectively facilitate the discovery of disease-related microRNA regulation network and bring new insights into understanding of the association between obesity and cancer.

Datasets

The data in this study was collected from the following resources:

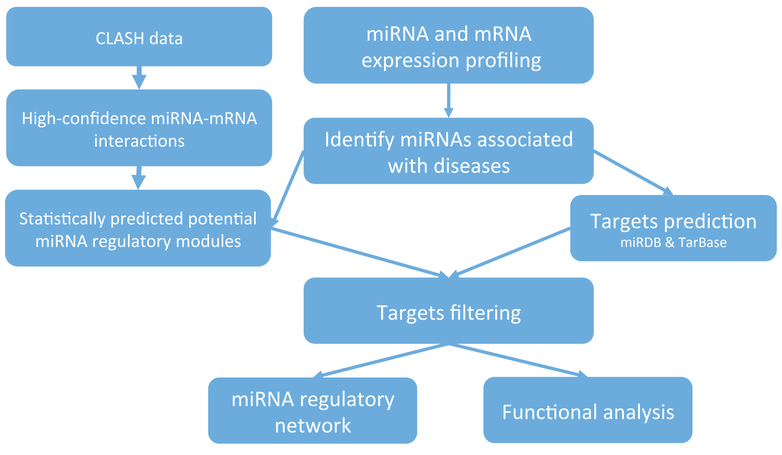
- **CLASH[1] dataset that provides more than 18,000 high-confidence miRNA-mRNA interactions;**
- **miRNA and mRNA expression data from GEO and TCGA database on four types of diseases**

	Obesity		*Pancreatic cancer*	*Gastric cancer*	*Ovarian cancer*	
miRNA	GSE53377	GSE25470	GSE32678	GSE41369	TCGA-BATCH 57 & 12	TCGA-BATCH 11 & 9
mRNA	GSE53376	GSE25401	GSE32676	GSE41368	TCGA-BATCH 57 & 12	TCGA-BATCH 11 & 9
# of Samples *(Disease vs Normal)*	16, 16 sample paired	30, 26	25, 7	9, 9	31, 38	39, 9

Bioinformatics analysis

miRNA cooperative regulation predication

Regulatory network of miRNAs in Obesity and Cancers



miRNA cooperative binding

Identify potential miRNA co-regulatory modules[2]:

- **Among CLASH data, find *n* mRNAs that interacts with same group of *i* miRNAs**
- **For each miRNA (m_i) in the group, calculate the probability (p_i) of randomly bound on a mRNA, which is 1/N, where N is the number of mRNA targets of m_i.**
- **Test the statistical significance of miRNA group:**
  - **For this miRNA group, the probability (*P*) of randomly bound on the same mRNA is $P = \prod_{i=1} p_i$.**
  - **To evaluate the significance of each miRNA group, binomial tail probability of observing *n* mRNAs are bound by same group of miRNAs is calculated as:**

$$p - value = 1 - pbinomial(i-1, G, P)$$

  G is number of total mRNA that in CLASH data.
  - **Multiple comparison correction method is applied to control the false discovery rate.**
- **Any miRNA groups that satisfies FDR < 0.05 cutoff are considered as a miRNA module. There are 507 miRNA modules are detected in this study.**

Results

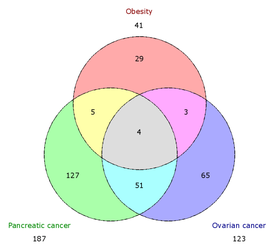
Predicted miRNA co-regulatory modules:

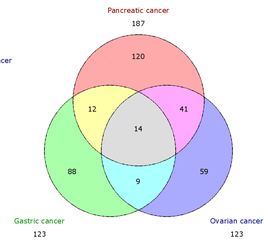
- **507 miRNA modules were accessed in four diseases:**
  - **Theoretically, if the regulatory relationship is remained for a validated miRNA-mRNA interaction in the different phenotypes, it should lead to negative correlation coefficients between miRNA and mRNA on its expression level.**
  - **However, this is not always presented in our study, for example:**

	Obesity			Pancreatic cancer			Gastric cancer			Ovarian cancer		
	miR-125b	miR-484	miR-92a	miR-125b	miR-484	miR-92a	miR-125b	miR-484	miR-92a	miR-125b	miR-484	miR-92a
ADRM1	0.67	0.62	0.17	-0.33	0.25	0.33	-0.09	0.10	-0.23	-0.41	0.22	-0.10
GANAB	0.43	0.26	-0.09	-0.51	0.09	0.00	-0.42	0.07	-0.10	0.13	0.25	0.12
UBAP2L	0.09	0.06	-0.22	-0.38	-0.21	-0.18	-0.24	0.19	0.07	0.10	0.06	-0.51
EMD	0.54	0.77	0.27	-0.69	-0.18	-0.33	-0.45	0.03	0.00	-0.17	0.02	0.23
ACLY	0.21	0.60	0.09	-0.14	-0.12	-0.34	-0.04	0.00	0.01	-0.20	-0.09	-0.21
	miR-125b	miR-320a	miR-615-3p	miR-125b	miR-320a	miR-615-3p	miR-125b	miR-320a	miR-615-3p	miR-125b	miR-320a	miR-615-3p
WNK1	-0.16	-0.07	0.39	-0.05	0.33	-0.06	-0.11	-0.47	0.48	0.22	-0.15	-0.12
MLL2	-0.20	0.30	0.48	0.44	0.58	-0.11	-0.39	-0.26	0.31	0.55	-0.26	-0.42
SPEN	-0.31	-0.10	0.60	0.21	0.41	0.01	-0.06	-0.24	-0.33	0.24	0.10	-0.38
FRAT2	-0.20	-0.02	0.40	-0.03	0.56	-0.03	-0.47	-0.03	-0.52	-0.22	0.13	0.22
PCBP2	-0.26	-0.07	-0.09	0.10	0.32	-0.09	-0.11	-0.39	0.57	-0.02	0.19	0.13
SRRM2	-0.39	0.39	0.56	0.54	0.37	0.01	-0.39	-0.12	0.75	0.37	-0.02	-0.41
TAF15	-0.26	-0.06	0.26	-0.10	0.47	-0.07	-0.48	-0.34	0.30	-0.07	0.18	0.05
ATP5B	-0.26	-0.01	0.03	0.16	0.30	-0.08	-0.25	0.29	-0.15	-0.05	0.25	0.14
KPNB1	-0.12	-0.11	0.12	-0.09	0.46	0.07	-0.43	-0.02	-0.18	-0.08	0.11	0.15
BCOR	-0.31	-0.26	0.10	-0.42	0.52	-0.06	-0.11	-0.17	-0.70	-0.35	0.14	0.01

  - **This observation may suggest that:**
    - **miRNAs cooperative binding and regulation do exist;**
    - **the regulatory patterns of miRNA-mRNA binding may vary in different biological conditions;**
    - **to carry out downstream functional analysis, filtering based on miRNA and mRNA expression analysis is necessary to only keep reliable miRNA-mRNA interaction.**

Identify differential expressed miRNAs for each diseases:



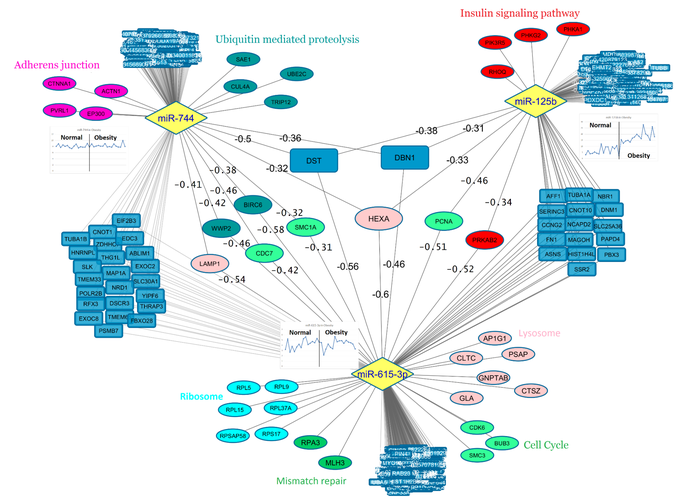


miRNA regulation in obesity and cancers

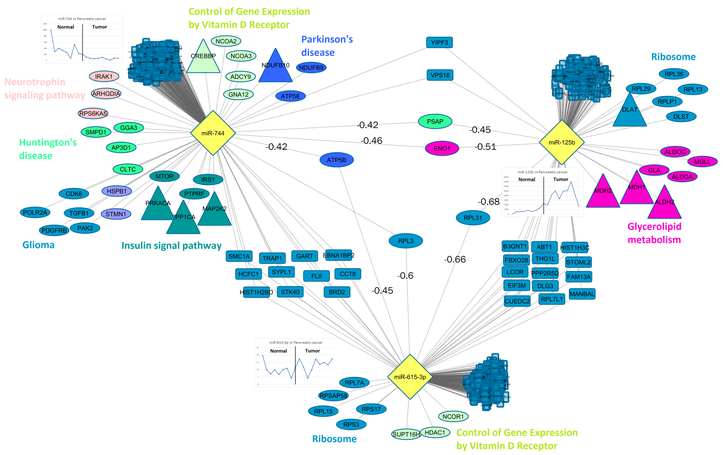
Here, a miRNA module is used as an example to show the connection between obesity and cancers:

- **miR-125b: diff. expressed in both obesity (fc=2) and pancreatic cancer(fc=5.8);**
- **miR-744: diff. expressed in pancreatic cancer(fc=-3.8);**
- **miR-615-3p: no significant effects are observed;**
- **all the predicted targets were collected from miRDB and TarBase, which then pass the correlation filtering process;**
- **Insulin signaling pathway was enriched in two diseases, regulated by different miRNAs among the same module.**

miRNA module regulation in obesity



miRNA module regulation in cancer



References & Acknowledgement

[1] Helwak, A., Kudla, G., Dudnakova, T., & Tollervey, D. (2013). *Mapping the human miRNA interactome by CLASH reveals frequent noncanonical binding*. Cell, 153(3), 654-665.

[2] Ding, J., Li, X., & Hu, H. (2014). *MicroRNA modules prefer to bind weak and unconventional target sites*. Bioinformatics, btu833.

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