An Integrative Approach to Constructing MicroRNA-Gene Networks in Ovarian Cancer

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Abstract

Network integration is critical in understanding the underlying mechanisms of human health and diseases. Changes inmicroRNA(miRNA) and mRNA expression are known to be involved in both ovarian cancer development and progression. Pinpointing the exact changes and the relationships that occur between them could lead to advances in how ovarian cancer is treated and diagnosed. Creating an integrated network involving eQTLs, miRNA targets, protein-protein interactions and correlation graphs is one way to explore these relationships. Integrating multiple data sources can thus allow us to create a wider and more holistic view of the genetic network in ovarian cancer. Therefore, we developed a new method of constructing an integrated network by combining the strength of association study and network analysis. Applied to ovarian cancer, our integrated analysis replicated known cancer related miRNAs and genes, in addition to providing new genetic markers.

Results

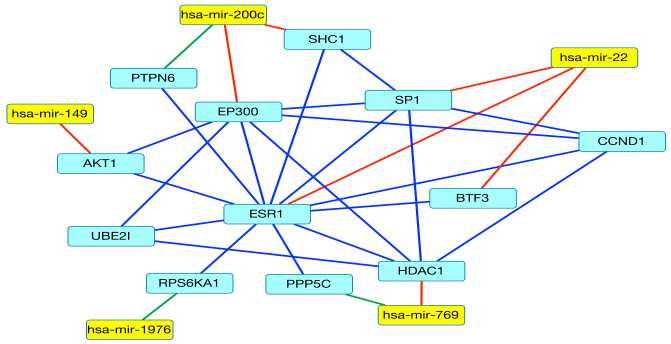

Figure 1: A subnetwork involving AKT1 of our integrated network. *AKT1*, has been implicated in tumorigenesis and specicially in ovarian cancer. Another gene *ESR1* has been associated with breast cancer, and *ESR1* expression has been suggested as a predictor of ovarian cancer survival. The miRNAs (e.g. *hsa-mir-200c* and *hsa-mir-149*) in the network are reported to be associated with ovarian cancer as well. Such a subnetwork allows us to visualize potential downstream effects of these miRNAs and genes. Other miRNAs and genes interacting with known ovarian cancer genes/miRNAs, serve as candidate miRNA and gene markers for tumorigenesis of ovarian cancer.

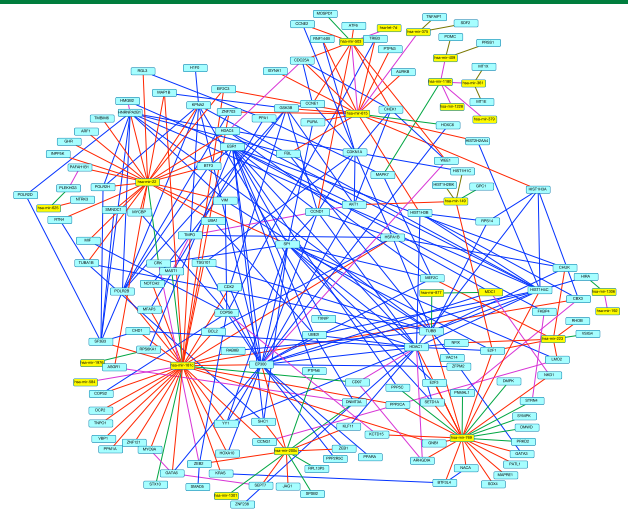

Figure 2: The resulted integrative miRNA-gene network in ovarian cancer. miRNAs are shown in yellow nodes, and genes are shown in light blue nodes. eQTLs are shown as green edges, protein-protein interactions are shown as blue edges, miRNA-target interactions are shown as red edges, MtLasso2G correlation interactions are in purple, and MtLasso2G eQTLs are in gold.

Conclusion

In this study we developed a new method of constructing an integrated network by combining an eQTL mapping and network analysis. We applied our method to TCGA ovarian cancer data and constructed an integrated network of miRNA and gene interactions in ovarian cancer. The generated network contained miRNA to target gene relationships, eQTL associations, protein-protein interactions, the correlations or co-expressions among microRNAs and genes respectively. In the future, we will extend our approach by incorporating multiple resources, other network reconstruction and mining methods. Such an integrative framework can thus exploit the relationships between different molecular components to help understand how ovarian cancer progresses.

Methods

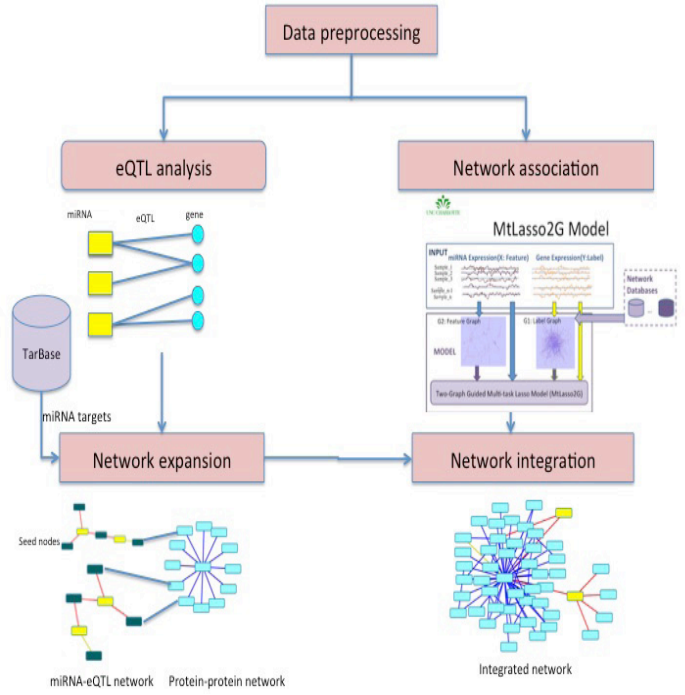

Figure 3: The workflow to create the integrated network.

Phase 1: eQTL analysis - Perform eQTL analysis between miRNAs and gene expression using Matrix eQTL.

Phase 2: Network association - Discover network association between miRNAs and genes using MtLasso2G that captures the co-expression of miRNAs and genes respectively.

Phase 3: Network expansion - Incorporate miRNA-target interactions from TarBase, and expand the genes via a "seed-and-expand" approach by including significantly connected protein protein interactions using DAPPLE.

Phase 4: Network integration - Construct the integrative miRNA-gene network by merging eQTL associations, miRNA coexpression networks, coexpression networks, miRNA-gene interactions, and protein protein interaction networks.

References

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