miRNA-mRNA integrative data analysis in primary breast cancer

INTRODUCTION

Deregulation of micro-RNAs (miRNAs) has been increasingly implicated in cancer. Several miRNAs have aberrant expression profiles in breast cancer and the expression of some has been correlated to specific clinical features of breast cancer. miRNA dependent regulation is mediated through changes in mRNA levels and function, and miRNA:mRNA interaction in the context of breast cancer highlights clinically relevant pathways.

It is hoped that molecular profiling can help tailor treatments for breast cancer [1]. With the help of novel genome-wide technologies, miRNA expression profiles have joined the list of methods for describing the molecular portraits of breast tumors.

DATASET AND METHODS

In this study we present and analyze data derived from expression profiling of 799 miRNAs (Affymetrix U133) in 103 primary human breast tumors, along with genome-wide miRNA profiles and extensive clinical information. We investigate the relationship between these molecular components, in terms of their effect on clinical characteristics and cellular processes. We identify statistically significant differential expression of miRNAs between molecular intrinsic subtypes, and between samples with different levels of proliferation.

In this work we introduce a systems biology approach to examine the cumulative relationship between miRNA and miRNAs using statistical enrichment methods. Results from this study have been published in [2].

RESULTS (continued)

We identify miRNAs that are associated with cellular processes involved in tumorigenesis, like proliferation, immune response, and cell adhesion, and miRNAs associated to TP53 mutational status.

Biological results, discovered through the use of this methodology, include:

• A strong association of miRNAs with cell-cycle gene modules. We also show that the level of cell-cycle association is monotonically related to the miRNA differential expression between low proliferating and high proliferating samples. For example, we observed a strong association of miR-17/19 family cluster with proliferation. We further validate the role of miR in regulating proliferation using high-throughput (transfection)-miRNA on cell lines including a direct effect of miR-19a.

• An association between miR-150 and the immune response activity that is independent in any known subtype characterization of the tumors. We further show that miR-150 expression, a good marker of the immune response, is associated to disease free survival in HER2/ER+. samples.

Proliferation vs. Enrichment

miRNA association with cell-cycle is reflected in their expression in proliferating cells. X-axis: the enrichment level (log p-value) of the cell-cycle GO term in miRNA correlated genes.

Association of miR-29c to cell-adhesion

miRNAs associated with cell-cycle and were expressed in high proliferating cells were transfected to breast cancer cell lines. Cell lines were tested for proliferation using K67/HCC 422 or 72H after transfection. Presented are miRNAs that showed a direct effect on proliferation in cell lines as proposed by our methodology.

miRNA transfection in cell line

CONCLUSIONS

• We developed a framework for jointly analyzing miRNA and mRNA data. This is an enable for usage of related measurement technologies such as microarrays or high throughput sequencing.

• We identify novel miRNAs associated to breast cancer subtypes and cancer progression processes, including:

  Immune response: e.g. miR-150
  Cell adhesion: miR-29c
  TP53 status: e.g. miR-342-3p
  Survival: e.g. miR-377, miR-378

ACKNOWLEDGMENTS

Israel Steinfeld’s work is supported by an Agilent Technologies University Relations GIT. This project is supported by grants from the Norwegian Cancer Society and from The Functional Genomics Program (FUGE) of the Norwegian Research Council, and Norwegian Radium Hospital.

REFERENCES

