Combining transcriptional and post-transcriptional regulation to predict mutations altering the gene regulatory program in cancer

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Pan-cancer predicted cancer driver miRNAs

- Most somatic mutations are non-coding, a small fraction occurs at transcription factor binding sites (TFBSs).
- Interpretation of the effect of TFBS mutations can be eased by using expression data.
- Most of the known cancer drivers genes are protein-coding, but non-coding genes may also be cancer drivers.
- We mapped somatic mutations to TFBS with experimental and computational evidence derived from UniBind.
- Each TFBS was associated to its potential targets by combining the annotations from geneHancer and associations to the closest TSS.

Dysregulated miRNA-target genes are enriched in key cancer pathways

- We combined transcriptional (TFBS mutations) and post-transcriptional (miRNA networks) information to highlight cancer driver miRNAs across 7 TCGA cohorts.
- We predicted 38 miRNAs in 7 TCGA cohorts. Three well known oncogenic miRNAs (miR-20a, miR-17, miR-92a) were predicted independently in the 7 cohorts. All the predicted miRNAs are annotated as cancer miRNAs in miRCancer.

Predicted cancer driver miRNAs are associated to prognosis

- We used a third, Independent, breast cancer cohort (Metabric, n = 1282) to draw the survival plots.

Conclusions

- By combining transcriptional and post-transcriptional information we highlighted potential cancer driver miRNAs (with mutations at their TFBSs) likely associated to a cascading effect on the miRNA networks.
- Non-coding mutations coupled with gene expression can be explored to highlight cancer driver genes.
- The same methodology also works in TFBS mutations associated to protein coding genes, and could be adapted for other genes such as IncRNAs.