

Widespread inference of weighted microRNA-mediated gene regulation in cancer transcriptome analysis

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MicroRNAs (miRNAs) comprise a gene-regulatory network through sequence complementarity with target mRNAs. Previous studies showed that mammalian miRNAs decrease many target mRNA levels and reduce protein production predominantly by target mRNA destabilization. However, it has not yet been fully assessed whether this scheme is widely applicable to more realistic conditions with multiple miRNA fluctuations. Here we developed GSEA-FAME analysis (GFA), which enables prediction of miRNA activities from mRNA expression data, using rank-based enrichment analysis and weighted evaluation of miRNA-mRNA interaction. This cooperative approach delineated a better widespread correlation between miRNA expression levels and predicted miRNA activities in cancer transcriptome, thereby providing proof-of-concept of the mRNA-destabilization scenario. We also showed that GFA-based inference of miRNA activity could be utilized for selection of prognostic miRNAs in development of cancer survival prediction models. This approach proposes next-generation strategy for interpretation of miRNA function and identification of target miRNAs as biomarkers and therapeutic targets. We also discussed our current approach for dissection of context-dependent miRNA function in various cellular conditions such as stimulation with TGF- β .