Integrated analysis of microRNA and gene expression data to reconstruct regulatory networks

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Motivation

MicroRNAs (miRNAs) are an abundant family of small non coding RNAs that play an important role in gene expression regulation. By base pairing to mRNAs, microRNAs control genes expression at post-trascriptional level, regulating the stability of RNA messenger (mRNA) and their traslational efficiency. MiRanda, TargetScan, Pictar and Pita are the most popular algorithms for predicting miRNA target genes, based on sequences complementarity. In spite of differences in design and efficiency, miRNA-target relationships predicted using each of these programs include many false positives. The integrated analysis of miRNA and gene expression data may provide a criterion to identify those subsets of miRNA-target relationships more likely functional in a specific biological contest.

Methods

The purpose of this work is to present a computational framework for the integrative analysis of miRNA and mRNA expression profiles which helps shedding light on the regulatory circuits of gene transcription. The integration of miRNA and target expression levels is achieved using GenMiR++ (Huang et al., 2007). GenMiR++ relies on a probabilistic model that, on the base of expression data, refines miRNA-target relationships predicted by bioinformatics tools. Specifically, the model combines predictions with miRNA and mRNA expression profiles under the assumption that, since miRNAs tend to down-regulate their targets, expression profiles of miRNA and real targets are expected to be anti-correlated. GenMiR++ outputs an adjacency matrix whose values indicate the strength and reliability of each miRNA-gene relationship based on expression profiles and can be used to reconstruct networks of miRNA-target interactions. The integrative framework also comprises methods to inspect miRNAs and genes expression profiles, moving along the arcs of the miRNA-target networks. Moreover, it allows the reconstruction of a multi-relational network of miRNA and genes, in which arcs connecting miRNA and gene nodes represent regulatory relationships, whereas gene-gene edges represent co-expression relationships or functional similarity.

Results

The study of these networks allowed identifying inner structures, as components and islands. The latter are composed of groups of genes regulated by sets of shared miRNAs and miRNA sets regulating similar genes and demonstrated that pair-wise co-expression in genes, which are common targets of miRNAs, is significantly higher than in genes which do not share any target site. The integrative pipeline and the modules for network analysis have been tested on miRNA and mRNA expression data regarding myeloid suppressor cells, T cells and multiple myeloma samples.

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