

Title: miREA - A Network-Based Tool for Cancer-specific miRNA-Oriented Enrichment Analysis

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Abstract

MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression at the post-transcriptional level. Pathway enrichment analysis is essential to elucidate biological functions, understand the regulatory mechanisms, and discover therapeutic targets of miRNAs. However, conventional node-based approaches predominantly focus on either miRNA's target genes or miRNAs for enrichment and treat them independently. These approaches introduce significant bias and often fail to capture the complex roles for miRNAs for ignoring the regulatory strengths of miRNA-gene interactions (MGIs) and neglecting the network topology of pathways. Here, we develop MiREA, a network-based miRNA enrichment analysis tool at the MGI edge level. Specifically, MiREA provides four categories of edge-based methods for MGI enrichment analysis including (i) an overlap-based method that defines differentially expressed MGIs (DEMGIs) and test their significance using the Fisher's exact test, (ii) scoring-based methods that calculates enrichment score through ranked MGI scores list and the two-dimensional coordinate system, (iii) topology-based methods that incorporates MGIs' centralities in the pathway network and their scores, and (iv) network-based methods that distinguish whether a pathway is strongly associated with DEMGIs by Random Walk with Restart algorithm. By integrating cancer-specific MGI networks with transcriptomic profiles from TCGA and GTEx, we apply MiREA to identify enriched pathways across 17 cancer types. To evaluate MiREA's ability to uncover functional pathways, we benchmark its sensitivity and specificity through known, annotated cancer-related pathways and randomly generated pathways. Moreover, we provide advanced visualization of the results and an R package for other researchers to gain insights into MGIs at the pathway level. Taken together, MiREA is a powerful and reliable tool for performing miRNA-oriented enrichment analysis, thereby enhancing the accuracy of both generic and cancer-specific functional annotations of miRNAs.