Title: miREA: a network-based tool for global and cancer-specific miRNA-oriented enrichment analysis

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Abstract
MicroRNAs (miRNAs) are small non-coding RNAs that play a critical role in post-transcriptional gene regulation by binding to complementary sequences on target mRNAs, resulting in translational inhibition or mRNA degradation. Dysregulated miRNAs and their downstream targets have proved to be crucial biomarkers in various human cancers. With the increasing availability of high-throughput sequencing data, pathway enrichment analysis has become essential to elucidate the biological functions of miRNA-gene regulatory networks. However, traditional approaches in the past decade predominantly infer miRNA functions through indirect annotations that retrieve their target genes and perform gene set enrichment analysis at the genome level, which introduces bias and fails to capture the convinced regulatory roles in diverse biological pathways. To overcome these limitations, we will develop miREA, a web-based miRNA-gene interaction-oriented enrichment analysis tool that enables functional analysis of miRNAs at the pathway level. By integrating generic miRNA-gene interactions, cancer-specific transcriptome profile, and employing statistical or network-based methods, miREA will identify enriched miRNA-gene interactions based on interaction overlap, regulatory strength score, and topology structure. Moreover, various advanced visualization will provide explicit insights into how specific miRNA-gene interactions regulate distinct pathways rather than single gene targets. miREA will offer a reliable and user-friendly platform for performing miRNA-oriented enrichment analysis, thereby enhancing the accuracy of both generic and cancer-specific functional annotations of miRNAs.