CeRNetwork: A Platform for in silico Discovery and Classification of Competing Endogenous RNA Molecules for Multi-Omic Network Diffusion and Novel miRNA-Sequestering Drug Design

Toomer, David (School: Hayfield Secondary School)

MicroRNAs (miRNAs) are small noncoding RNA molecules that are implicated in many gene expression pathways. Because they can degrade genes before translation, they have been extensively researched recently as new therapeutics. However, this same miRNA-mediated degradation has been correlated to various chronic diseases. A recent hypothesis suggests that miRNA can be regulated by competing endogenous RNAs (ceRNAs) that sequester miRNA from their targets, but there are currently no thorough characterizations of ceRNA molecules in the interactome. Enter CeRNetwork: the first fully diffused multi-omic network model of ceRNAs within the human interactome. CeRNetwork integrates millions of data points taken from seven extensive gene sequencing databases in a quadripartite network linearly associating ceRNA, miRNA, genes, and diseases. A hypergeometric test was used to reduce network size and assign edge weights for a series of six bipartite networks. The majority of both putative ceRNAs and ceRNA-miRNA interactions were classified as circRNAs (49.8% and 86.6%, respectively), but functionalization was also given to sncRNAs, lncRNAs, and pseudogene transcripts. Topological features revealed a distinct, modular bipartite nature in the ceRNA-gene and ceRNA-disease networks, implying that ceRNAs behave in families that could regulate genes associated with chronic diseases. Projections into miRNA space, gene space, and disease space further reveal this community structure. The results from this study support that ceRNAs are major players in gene/disease homeostasis whose clusters could act as positive feedback cascades that lead to amplified disease pathogenesis when perturbed.

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