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Quantitative transcriptome-wide analysis of the Myc-miR-17-92 axis

The Myc family oncoproteins are non-canonical transcription factors that regulate greater than 15% of the human transcriptome. Recent work from several laboratories including our own has indicated that some of these unusually broad effects could be mediated through deregulation of a limited number of microRNAs, both Myc-repressed (e.g., miR-34a) and Myc-activated (members of the miR-17-92 cluster). To measure, in an unbiased fashion, the microRNA component of the Myc pathway, we first performed mRNA profiling of human P493-6 lymphoblastoid cells carrying a repressible c-MYC allele. Both Myc-repressed and Myc-stimulated genes exhibited enrichment for predicted binding sites for Myc-regulated miRNAs; however, the miRNAs most enriched for were members of the miR-17~92 cluster. Thus, we repeated the profiling analysis on P493-6 cells saturated with exogenous miR-17-92 mimics to render this miR cluster refractory to changes in c-Myc levels. More than 1400 Myc-repressed genes were found to be stabilized in the presence of steady miR-17~92 levels. Subsequent Gene Set Enrichment Analysis (GSEA) demonstrated that these miR-17~92-dependent Myc targets are selectively enriched in negative regulators of several pathways involved in B-cell proliferation. The significance of these pathways for lymphomagenesis will be discussed.