"Elucidation of microRNA Control of Cell Signaling and Apoptosis Pathways"

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Abstract: microRNAs (miRNAs) are a large family of ~22 nucleotide (nt) regulatory RNAs that collectively have substantial impact on transcriptome activity. Consequently, miRNA dysfunction may underlie diverse human diseases, including cancer. However, computational predictions do not readily identify key miRNA activities, since individual miRNAs have hundreds of targets, and most transcripts contain conserved miRNA binding sites. Therefore, there is a great need for rational, directed strategies to identify cancer-relevant miRNAs, beyond using target predictions. Most of the fundamental cell signaling pathways are not only linked to mammalian oncogenesis, but are also rich in dose-sensitive phenotypes. We hypothesized that this makes them especially sensitive to miRNA dysfunction, and we indeed observe that the Drosophila Notch, Wnt, Ras, Hippo, and apoptosis pathways are regulated by specific miRNAs. Remarkably, activation of these miRNAs induces animal phenotypes that specifically mimic the activation or repression of these signaling pathways, although these miRNAs have tens or hundreds of other conserved targets. On this basis, we propose a series of directed screens in mammalian cells to identify miRNAs that modulate these highly cancer-relevant signaling pathways. To the extent possible in this initial grant, we will investigate the activity of miRNA hits in mouse models, and characterize their relevant targets. We also propose complementary Drosophila investigations to elucidate general principles underlying the incorporation and influence of miRNAs on complex systems, and develop novel methods for interrogating miRNA activity. This knowledge will improve the design of our mammalian miRNA screens and aid the functional characterization of mammalian hits.