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Studying microRNA-target interactions using gene expression data

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Short Abstract: We investigated the effect of microRNAs on mRNA target stability using transcript sequence and steady-state expression data from normal human tissues. Activity levels of miRNAs inferred from the differential expression of putative targets revealed tissue-specific regulation in several tissues and helped distinguish functional targets from non-functional ones.

Long Abstract:

Thirteen years after their discovery in the context of C. elegans larval development, microRNAs (miRNAs) are now recognized as ubiquitous regulators of gene expression in plants, animals, and even viruses. Mature miRNAs are typically 21-25 nucleotide long non-coding RNAs that post-transcriptionally downregulate potentially hundreds of target genes. This repression appears to mediated by the RNA-induced silencing complex (RISC), which is recruited by the miRNA to its mRNA target after recognizing and base pairing to the 3' UTR of its targets.

To date there are few experimentally validated miRNA-target interactions, and so there remain many unanswered questions about the mechanism and extent of downregulation. In particular, target mRNAs may be translationally repressed, cleaved by the RISC protein Argonaute, or destabilized through some other process. The particular fate chosen is thought to depend on the nature of the miRNA-target interaction.
For example, if a miRNA has full complementary to its target (i.e. all 21-25 bases match), the target mRNA is usually (though not always) cleaved. Though commonly observed in plants, such full complementarity is seldom seen in animals. Instead, computational and experimental studies have suggested the importance of a 6 or 7 bp “seed sequence” at the 5' end of the miRNA as being a critical determinant for target recognition in vertebrates. This rule is presumably incomplete, however, since human 3' UTRs are rather long (~1500 bp) and the chance of a random 7-mer match is quite high.

As a first step towards understanding some of these issues, we investigated the effect of miRNAs on the stability of their mRNA targets using transcript sequence and steady-state expression data from normal human tissues. Genes regulated by a particular miRNA are expected to have lower expression than non-targeted genes in tissues where the miRNA is active. This difference in expression is a proxy for the miRNA's activity profile (miRAP). Such a miRAP tells us in what tissues and/or conditions a miRNA is functionally active, without having to rely on the expression level of the miRNA itself.

We obtained miRAPs for each known human miRNA by performing a simple t-test between the expression levels of putative targets and non-targets in each tissue assayed. Putative

targets were defined simply as genes harboring a perfect match to the miRNA's 7-mer seed sequence. miRAPs derived in this fashion made novel predictions in addition to confirming a great deal of 'known' biology. For example, hsa-miR-124 showed the greatest activity in brain regions, where it is thought to be specifically expressed. Similar results were obtained for a number of other miRNAs. We find that the accuracy of miRAPs is greatly improved when the potentially confounding factor of 3' UTR length is accounted for.