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The influence of alternative splicing on microRNA regulation and the role of coding regions

MicroRNAs (miRNAs) are small non-coding RNA molecules that regulate gene expression after transcription. They target specific sequences - binding sites - on mRNAs and silence them by degradation. In complex diseases, such as cancer, epigenetic dysregulation including miRNA dysregulation plays a significant role. Epigenetic therapy targets these regulatory mechanisms, but a better understanding of the epigenetic processes and their changes in complex diseases is necessary to develop effective treatments.
Alternative splicing enables the expression of a variety of isoforms coding for functionally diverse proteins from a single gene. This mechanism can produce a mRNA transcript excluding the exon with the miRNA binding site thereby unresponsive to miRNA regulation. According to most studies miRNAs are thought to preferably bind to 3'-untranslated regions of mRNA. In this work, we study the role of miRNA binding sites in coding regions. Our hypothesis is that splicing out exons with binding sites affects miRNA regulation of transcript expression. We tested this hypothesis using four cancer data sets from The Cancer Genome Atlas: Brain lower grade glioma, Kidney chromophobe carcinoma, Kidney renal cell carcinoma, and Liver hepatocellular carcinoma.
We predicted miRNA binding sites on mRNAs from their sequence using TarPmiR. For our analysis we trained linear regression models to predict miRNA expression from transcript expression. Using the nested models approach, we compared to which extent the expression of transcripts with miRNA binding sites in the coding regions may predict miRNA expression compared to transcripts without binding sites. For all four cancer datasets, we showed that transcripts with binding sites could predict the expression of the corresponding miRNAs significantly better. We conclude that splicing-induced regulatory/functional miRNA binding sites in coding regions are more common than previously thought. Consequently, it is likely that alternative splicing interferes with miRNA regulation by differential splicing of exons with miRNA binding sites.

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