Design of highly specific synthetic miRNAs

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Motivation

MicroRNAs (miRNAs) are small endogenous non-coding RNAs responsible for post-transcriptional gene regulation. In particular a miRNA may target several transcripts leading to their translational inhibition or degradation. The involvement of miRNAs in both physiological and pathological processes has been demonstrated in many species and many computational tools for the prediction of miRNA functions are available online, often through knowledge bases which allow data mining analysis on the validated and predicted data. It has also been reported that synthetic miRNAs may act as powerful switches of gene expression and they may constitute a new class of drugs for targeting several diseases such as cancer. Thus there is the need for computational tools which may help to design effective synthetic miRNAs for specific targets.

Methods

Here we present a new computational method for the design of highly specific synthetic miRNAs. Given a target, one or more miRNAs able to bind it are designed, according to the endogenous miRNAs' mode of action. The main requirements for an effective miRNA are the capability of binding the target at multiple sites, the structural accessibility of the binding sites and the base pairing rules. Our tool first performs a screening for the most accessible regions of the target, by using the *RNAplfold* tool of the *Vienna RNA Package*. Then a search for repeated patterns of about 6~9 nucleotides is performed on the candidate accessible regions. These patterns will constitute the binding sites for the designed miRNA seed. Indeed, the goal is to produce a miRNA which can bind simultaneously to 2 or more sites of the target mRNA. All the patterns which appear in multiple copies in other mRNA sequences are discarded, in order to reduce as much as possible the number of potential off-target genes. The miRNA is then designed, according to the common base pairing rules coming from the experimental observations, and given as output together with the list of all the potential off-target genes.

Results

Given a synthetic miRNA designed by our tool, the corresponding predicted miRNA/target duplexes are energetically stable and satisfy the empirical binding rules inferred from validated pairs, thus confirming the plausibility of the proposed method. The biological validation of the tool is on going.

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