Regulatory Circuit of Human MicroRNA Biogenesis

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Outline

- Introduction
- Goal
- Experiment/Results
- Conclusion
- Questions

Introduction

What are miRNAs?

miRNAs are a class of endogenous, small RNAs that are thought to negatively regulate protein production.

Why are they important?

Aberrant expression of miRNAs is linked to cancer and other diseases.

What is this paper about?

To get a clear understanding of the miRNA pathway to find out more about the role of miRNAs in gene regulation and their causal effects on genetic diseases.

Goal

Hypothesis: a number of known TFs are responsible for the aberrant regulation of miRNAs in cancer and other diseases.

Goal: Identify miRNA regulatory motifs facilitated by a new computational method, K-Factor.

K-Factor?? K-Factor predicts regulatory motifs in a set of functionally related sequences.

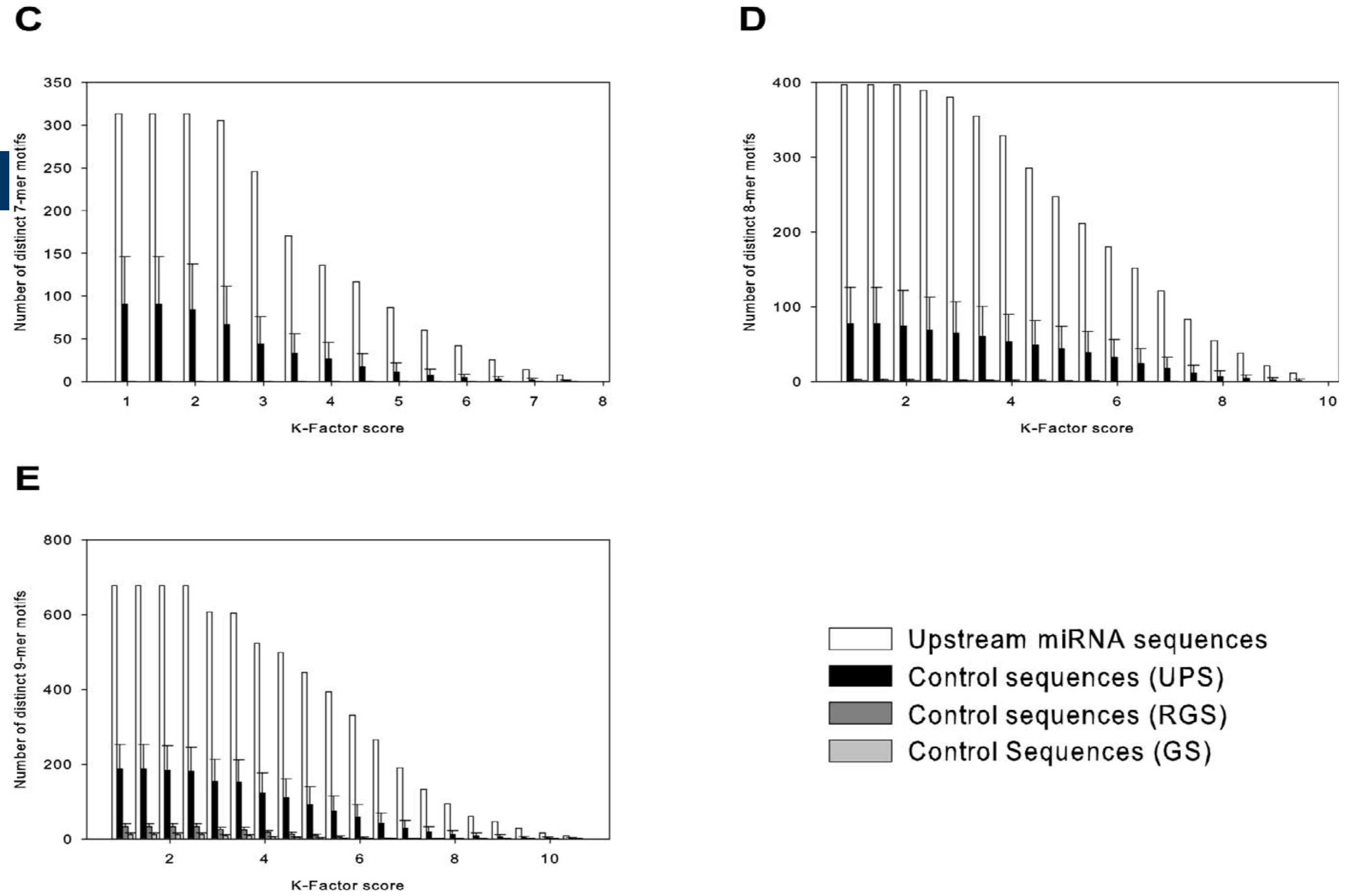
Experiment

- In this report, the concept of using *k*-mers is implemented to identify cis-regulatory motifs(CRMs) that control the transcription of miRNAs.
- K-factor detects over-represented *k*-mers in a set of sequences.

Upstream Sequences of miRNAs Contain Highly Over-represented Motifs

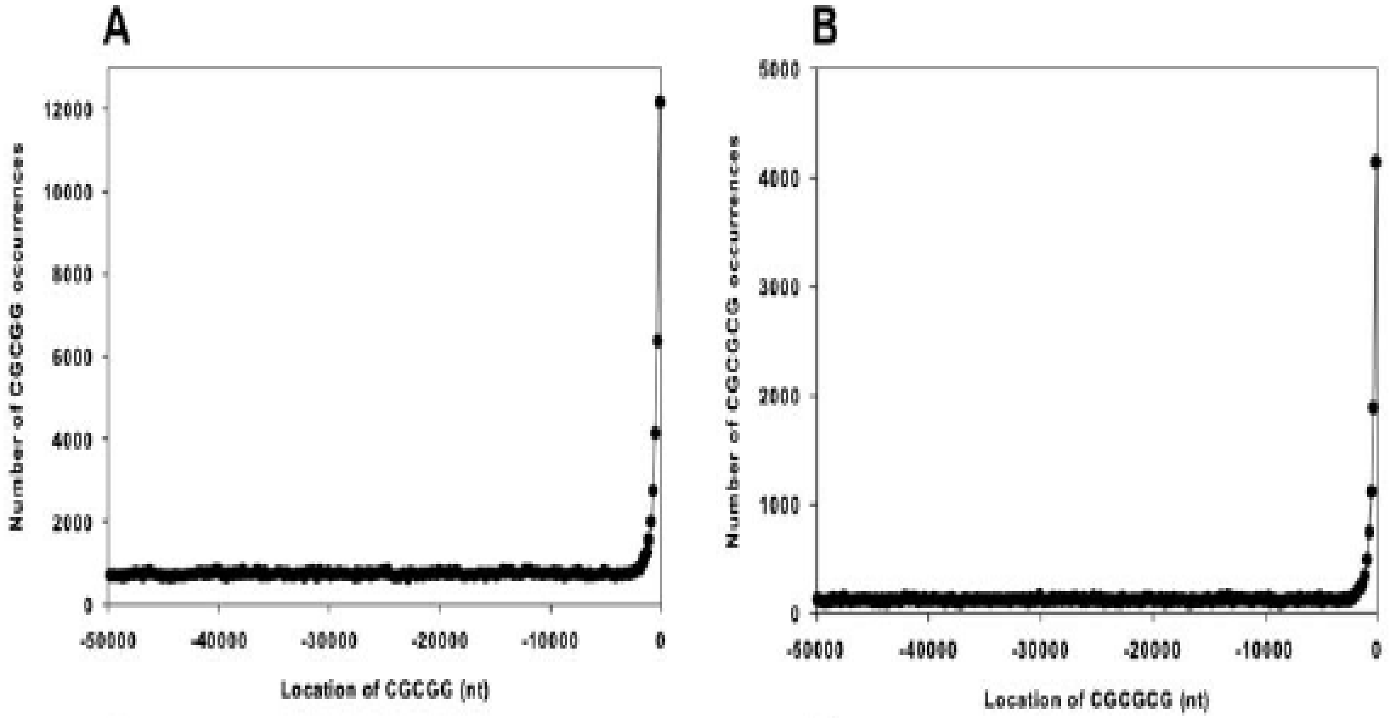
- To identify over-represented k-mers 10 kilobase regions upstream of human miRNA sequences were compared with the same regions in the controls(protein-coding sequences) using K-factor

Upstream Sequences of miRNAs Contain Highly Over-represented Motifs



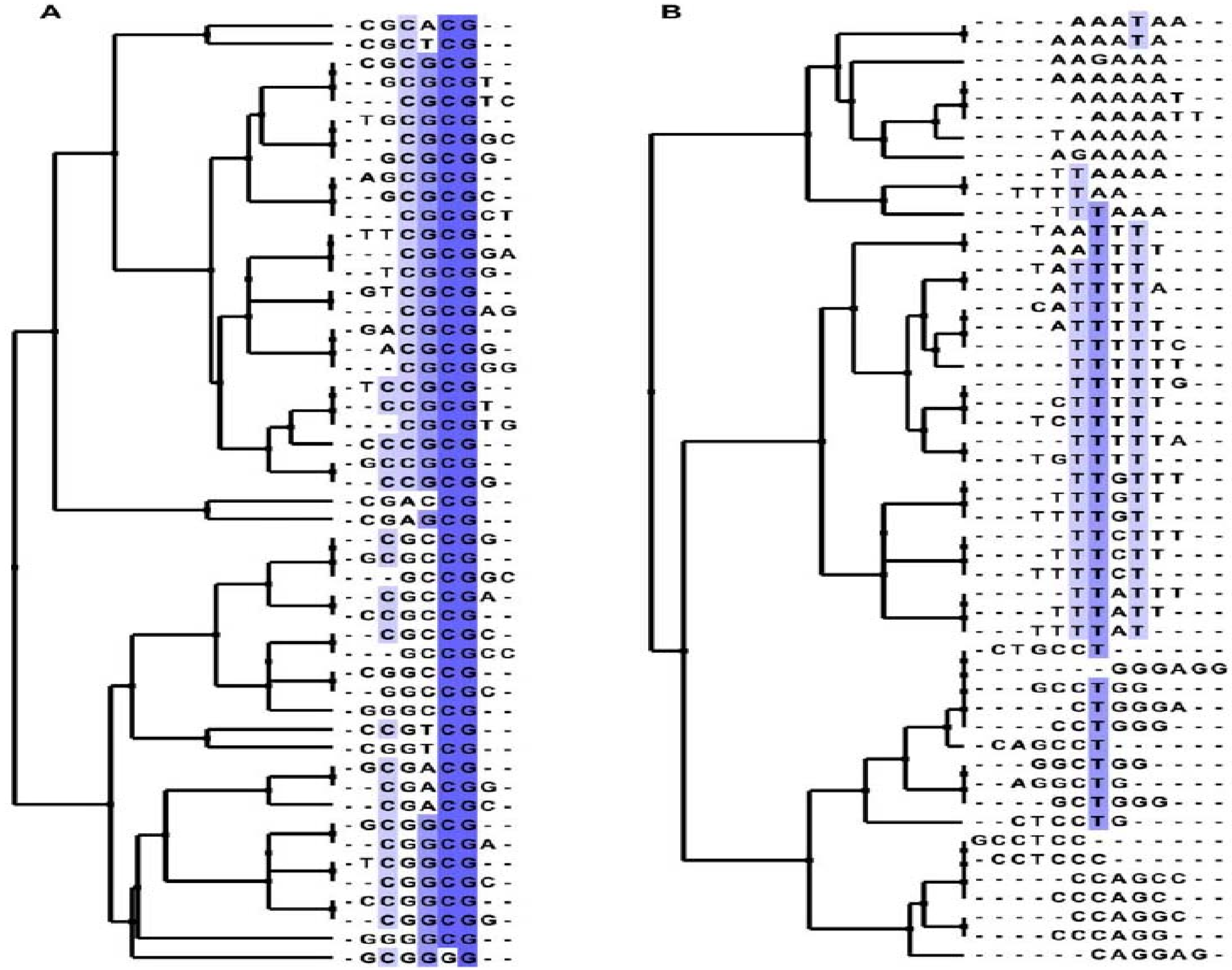
- miRNA upstream regions generally contain more over-represented regulatory motifs in comparison to protein-coding genes.

Motifs That Are Overrepresented Upstream of miRNAs Are Also Preferentially Located within 1 kb of Protein Coding



- ~99% predicted motifs were preferentially located within the first 500 nts upstream of protein-coding genes

Results: all predicted motifs are significantly enriched in G and C nucleotides



Predicted Motifs Are Evolutionary Conserved

- Investigated over-representation of predicted motifs in mouse and opposum.
- Many of the motifs overlapped.
- The significant number of overlaps (evolutionary preservation) of the predicted human miRNA motifs in distantly related species (mouse and opossum) suggested that the conserved motifs are intolerant to mutations.

TF-Motifs Interactions Exert Combinatorial Control on miRNA Expression

- The combined interactions of several TFs are involved regulating the expression of miRNAs.
- For example, *miR-132*, previously shown to be differentially upregulated in six solid cancer types (breast, colon, lung, pancreas, prostate, and stomach carcinomas) is predicted to be combinatorially regulated by 24 CRMs

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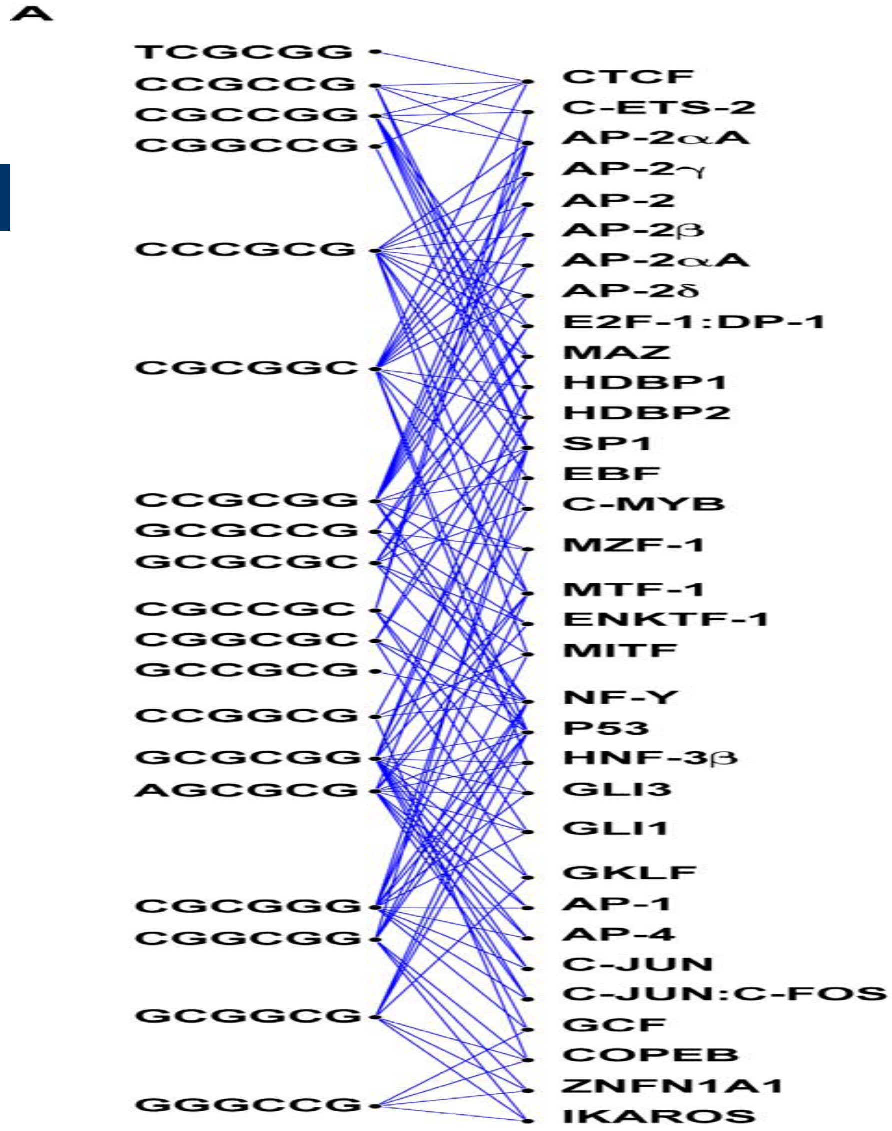

Conclusion

- miRNA expression is regulated by numerous regulatory elements that are in upstream sequences.
- The fact that the predicted motifs to occur near protein-coding genes suggests that transcription of miRNAs and protein-coding genes are controlled by similar factors.