Ultrasensitivity and Bistability arising from miRNA-mRNA Reciprocal Interaction

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***Short Abstract* —It is found that miRNA and mRNA reciprocally regulate each other. However, the functionality of this mutual regulatory relationship is not fully understood. Here, through mathematical modeling, we found that depending on the recycle ratio of miRNA, the reciprocal regulation between mRNA and miRNA shows subsensitive activation, ultrasensitive and subsensitive inhibition. Bistability is generated when the ultrasensitivity from the miRNA-mRNA reciprocal regulation is equipped with a positive feedback loop. Furthermore, the degree of ultrasensitivity is amplified when a stronger competitor (ceRNA) is involved. Interestingly, bistability can also be generated from mRNA-miRNA reciprocal interactions when considering more than one binding sites.**

Keywords — Reciprocal, miRNA, mRNA, ultrasensitivity, bistability, recycle ratio.

I. INTRODUCTION

In the gene regulatory networks, miRNAs serve as important post-transcriptional regulators of gene expression to control a large variety of essential cellular processes, such as EMT [1]. During the last decade, there are accumulated studies on the basic molecular mechanisms of miRNA biogenesis, function and degradation.

Through base-pairing interactions, miRNA inhibits its target mRNA by two modes, translational repression and mRNA degradation. Furthermore, under some circumstance, miRNAs can stimulate mRNA translation. Quantitative measurements show that miRNA regulation establishes a threshold level of target mRNA [2]. However, the functionality of the gene expression threshold regulation by miRNAs remains to be established.

Furthermore, recent results also provide evidence that mRNA targets can reciprocally control the stability and function of miRNAs. Kinetic analysis already provided support that miRNA could be recycled following regulating mRNA [3]. However, the endogenous functions of mRNA-directed miRNAs degradation remain elusive. Interesting, it is also found that target interaction could stabilize miRNA by preventing its release from Ago and subsequent destabilization. Furthermore, each miRNA may target tens or hundreds of mRNA molecules, enabling cross-talk between competing endogenous RNAs (ceRNAs) targeted by the same miRNA. This appreciated reciprocal regulation between miRNAs and their targets adds a significant level of complexity to the miRNA-mRNA relationships. Thus, how the ceRNAs cross-talk and the miRNA-mRNA reciprocal regulation tune the miRNA-mediated regulation need to be further elucidated.

Acknowledgements: The research was supported by the U.S. National Science Foundation (DMS-0969417).

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II. MODEL AND RESULTS

To explore the features of the regulations between mRNA and miRNA, we built a mathematical model by considering the formation of mRNA-miRNA complex via base-pairing with complementary sequences, degradation of the complex and the recycle ratio of miRNA during the degradation.

First, regulation of mRNA by miRNA generates ultrasensitivity in a recycle ratio dependent manner. The larger of the recycle ratio, the less sensitive inhibition of mRNA by miRNA and vice versa. That is, ultrasensitivity is generated by sacrificing efficiency.

Second, regulation of miRNA by mRNA also generates ultrasensitive inhibition under small recycle ratio, subsensitive inhibition under large recycle ratio, or protection under near complete recycle.

Taken together, the regulation between miRNA and mRNA are reciprocal and shows different level of sensitivity, either ultrasensitive or subsensitive.

Third, ultrasensitivity from the miRNA-mRNA mutual regulation can also contribute to the generation of bistability. ceRNA with stronger binding affinity further enhances the ultrasensitivity of miRNA regulation on mRNA.

Fourth, several kinds of response curves exist when considering two binding sites, including inhibitory subsensitivity, inhibitory ultrasensitivity, protective subsensitivity, duality, and especially bistability. The bistability generated from mRNA-miRNA reciprocal interaction in the absence of any imposed feedback regulation are never reported theoretically or experimentally.

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