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Small but influential: the role of microRNAs on gene regulatory network and 3′UTR evolution

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Abstract

MicroRNAs (miRNAs) are endogenous ~22 nucleotide noncoding RNAs that regulate the expression of complementary messenger RNAs (mRNAs). Thousands of miRNA genes have been found in diverse species, and many of them are highly conserved. With the miRNA roles identified in nearly all aspects of biological processes, evidence is mounting that miRNAs could represent a new layer of regulatory network, and their regulatory effect might be much more pervasive than previously suspected. Here we focus on the post-transcriptional level gene regulation of miRNAs in animals and review how the miRNAs act to sustain and shape up the expression profiles of specific cell types; how the miRNAs integrate into the existing gene regulatory networks; and how the miRNAs influence the evolution of 3′UTR of mammalian mRNAs.

Keywords: miRNA; gene expression; regulatory network; 3′UTR evolution

Introduction

MicroRNAs (miRNAs) have been identified as a large class of small noncoding RNAs important for a diverse range of biological functions, such as developmental timing, cell death, cell proliferation, haematopoiesis, patterning of the nervous system and tumorigenesis (Bartel, 2004; He and Hannon, 2004; Esquela-Kerscher and Slack, 2006). Thousands of miRNAs have been found in animals, and an individual miRNA could act posttranscriptionally to target hundreds of mRNAs for translational repression, cleavage or destabilization (Lim et al., 2005; Giraldez et al., 2006; Wu et al., 2006). Recent estimate reveals that ~30% of all genes are miRNA targets in animals (Lewis et al., 2005). Together, these discoveries suggest that the miRNAs might represent a new layer controlling transcriptional regulatory system.

Mature miRNA is ~22 nt short RNA molecule, which is produced from a ~70 nt hairpin-like structure named precursor miRNA (pre-miRNA) (He and Hannon, 2004). Because of its relative simple structure, it is suggested that the miRNA genes could have more rapid turnover rate than protein-coding genes. However, one miRNA normally regulates the expression of hundreds of its target genes. Once a miRNA has been integrated into the gene regulatory network, the sequential miRNA sequence change might be constrained by this pleiotropy. As a result, most miRNAs verified with important function are highly conserved among species. However, adaptive evolution of lineage specific miRNAs is also identified in diverse species (Zhang et al., 2007; Lu et al., 2008; Zhang et al., 2008), indicating the active role of miRNA on lineage specific functional novelty.

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In this review, we summarize recent findings of miRNA-mediated mRNA level regulation in animals. We also discuss how the miRNAs function on cell type specific expression profiles; how the miRNAs can be integrated into the existing regulatory networks, and the impact of miRNAs on mRNA 3′UTR evolution.

Repression of target gene expression by miRNAs

It has been well known that the animal miRNAs could downregulate their target genes by translational repression, cleavage, or destabilization. However, at the beginning of the miRNA studies, we believed that the animal miRNAs mostly function in the way of translational repression whereas the plant miRNAs function as posttranscriptional gene silencing (He and Hannon, 2004). This hypothesis sounds reasonable because of the different levels of complementarity between the miRNA and its target in animals and plants. In plants, miRNAs are normally complimentary to the entire target site on the mRNA of the gene they are regulating (Rhoades et al., 2002). In other words, ~22 nucleotides of the miRNA match a sequence of similar length in the target mRNA. But in animals, only about seven nucleotides of the miRNA complementing its target are sufficient to trigger miRNA-mRNA interaction (Brennecke et al., 2005). However, the concept changed due to a seminal paper in 2005 by Lim and colleagues. They found that an individual miRNA (miR-1 or miR-124) could downregulate expression of hundreds of its target genes directly when it is overexpressed in HeLa cell line (Lim et al., 2005). Fig. 1 shows that the predicted targets of miR-1 or miR-124 are downregulated compared with the overall gene expression when the HeLa cell was transfected with single miRNA. Combined with the other papers working on specific miRNA-mRNA pairs, it has been suggested that the animal miRNAs can directly lead to target mRNA downregulation by mRNA cleavage (Yekta et al., 2004) or accelerated deadenylation of mRNAs (Giraldez et al., 2006; Wu et al., 2006). In addition, with the technical advance of proteomics, the global impact of miRNA on protein output has been examined recently. And it was suggested that individual miRNA could directly repress the protein level of hundreds of genes (Baek et al., 2008; Selbach et al., 2008). In fact, the truth is always unexpected. Recent studies revealed that animal miRNAs could induce translation upregulation of target mRNAs on cell cycle arrest (Vasudevan et al., 2007) or bind the 5′UTR of ribosomal protein mRNAs and enhance their translation (Orom et al., 2008). Whereas the plant miRNAs could alternatively function in the way of translational inhibition (Brodersen et al., 2008).

Contribution of miRNAs to the expression profiles of specific cell types

Back to the Lim's experiment, one of the interesting results is that delivering miR-124 causes the expression profile of HeLa cell to shift towards that of brain, the organ in which miR-124 is preferentially expressed, whereas delivering miR-1 causes the profile to shift towards that of muscle, where miR-1 preferentially expressed. Consequently, it raises the possibility that the individual miRNA might provide a crucial context in shaping up gene expression profiles of specific cell types.

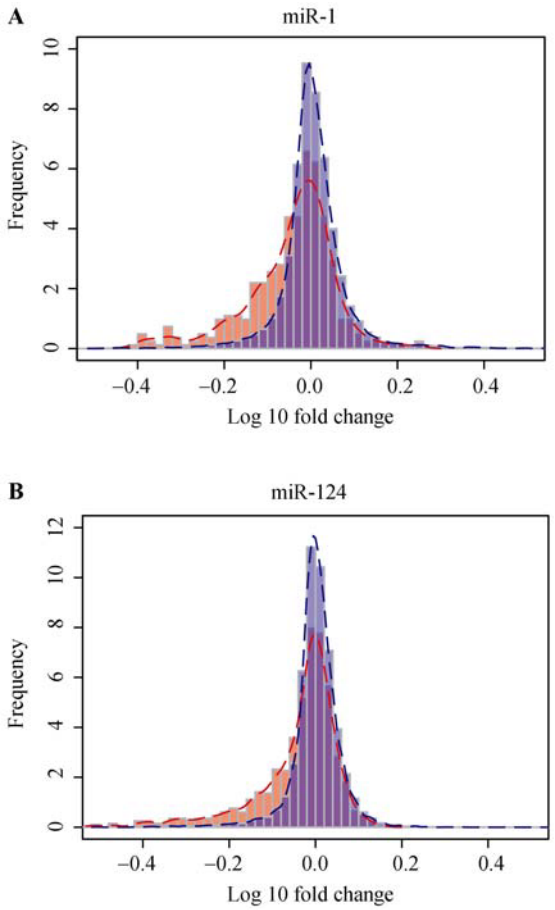

Fig. 1. A miRNA downregulates hundreds of genes. **A:** histogram of mRNA changes in HeLa cell after miR-1 overexpression. The expression changes of predicted miRNA targets are marked by red. The expression changes of all genes in the array are marked by blue. **B:** histogram of mRNA changes in HeLa cell after miR-124 overexpression. Symbols are as A. Data are adopted from Lim's paper (Lim et al., 2005).