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Dynamic miRNA–mRNA paradigms: New faces of miRNAs

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ABSTRACT

More and more evidences suggested that the flow of genetic information can be spatially and temporally regulated by non-coding RNAs (ncRNAs), such as microRNAs (miRNAs). Although biogenesis and function of miRNAs have been well detailed, elucidation of the dynamic interplays between miRNAs and mRNAs have just begun. Here, we highlighted that the miRNA–mRNA interactions which could take place in different cellular locations. During dynamic interactions, miRNA binding sites included not only 3′UTRs, but also 5′UTRs and CDSs. Under different physiological or pathological conditions, miRNAs could switch from translational inhibition to activation. Dynamic miRNA–mRNA paradigms which suggested a novel tip of the iceberg beneath the gene regulation network will provide clues for function studies of other ncRNAs.

Contents

1. Introduction

Eukaryotic genomes are nearly entirely transcribed, generating huge number of non-coding RNAs (ncRNAs) [1–4]. There are more than 100 unique classes of functional ncRNAs so far [5,6]. As important molecules, ncRNAs could function at different levels such as DNA transcription, RNA processing, protein translation and so on [7,8]. Among these ncRNAs, a distinctly different type named microRNAs (miRNAs), have attracted a great deal of global attention.

MiRNAs are small, single-stranded and regulatory RNA molecules, playing important roles in cells [9–11]. It is currently widely recognized that miRNAs are transcribed in the nucleus, being exported to cytoplasm as a post-transcriptional negative regulator. Firstly, most miRNAs are independently transcribed or generated from introns of host-genes [12,13]. After being transcribed, they are usually processed from primary-miRNAs (pri-miRNAs) into precursor-miRNA (pre-miRNA) in the nucleus [14–16]. After exported to the cytoplasm, pre-miRNAs are usually processed to mature, ~22 nt in length [9–11]. Finally, the mature miRNAs are incorporated into the RNA-induced silencing complex (RISC) for function [9–11]. Within RISC, Argonaute (AGO) proteins (AGO1–AGO4 in mammals) are core components that are directly associated with miRNAs [9–11]. And miRNA–mRNA duplex is required as miRNA seed region (nucleotides 2–7) interacts with the 3′UTR of target mRNA with perfect base-pair sequences [17,18]. Owing to short base-pairs within miRNA-3′UTR duplex, one miRNA can bind to several even hundreds target mRNAs or a single mRNA can be

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targeted by many different miRNAs [17,18]. Finally, target mRNAs are usually degraded or translationally repressed [9–11].

As a major regulator of gene expression at post-transcriptional level in the cytoplasm, expression of miRNA is physiologically or pathologically specific, leading to spatial and temporal specificity of mRNA expression [10]. Although biogenesis and functional patterns of miRNAs have been well documented, dynamic interactions between miRNAs and mRNAs are usually neglected. As crucial relationships, their interactions with different subcellular locations, distinct binding sites and cellular circumstances would shed flashlight for their biological function studies and provide paradigms for comprehending regulation and function of other ncRNAs.

2. MiRNAs acting in the nucleus, mitochondria and exosomes

It is generally recognized that mature miRNAs function in the cytoplasm. Increasing evidences suggest that mature miRNAs are found in the nucleus, mitochondria and exosomes, suggesting non-canonical roles of miRNA [19–26] (Fig. 1A). Here, we summarized some miRNAs with unexpected cellular locations in mammalians (Table. 1). Systematic studies of sub-cellular distribution of mature miRNAs reveal that miRNAs can shuttle from cytoplasm to nucleus in different mammals [27–32] (Table 1). Mature miRNAs discovered in the nucleus suggested that miRNAs can function in transcriptional silencing or activation, post-transcriptional silencing and alternative splicing [19]. Recent studies of RNAs in exosomes indicate that miRNAs can be transferred by exosomes, regulating inter-cellular communication [26,33–36] (Table 1). However, weather or/and how miRNAs interact with mRNAs in the nucleus and exosomes are still elusive. In this article, we emphasize on dynamic miRNA–mRNA interactions with cytoplasmic and mitochondria locations in the followed paragraphs.

As a central regulator of energy metabolism, the inter-organellar crosstalk is essential for the coordination or rapidly changed situations [37,38]. Previous studies indicate that many nuclear encoded proteins and RNAs can be imported to mitochondria for vitally cellular processes [39,40]. Through cellular fractionation, together with deep sequencing, microarray and qRT-PCR methods, many miRNAs in different mammals which are mitochondria located are systematically identified [23,24,41] (Table 1). More importantly, AGO2 protein which is directly associated with miRNAs is also found to be located in mitochondria by immunoblotting and confocal microscopy [22]. New evidences suggest that some miRNAs can regulate the function of mitochondria, even function in mitochondria [22–24,41–44].

Although there are lots of reports about miRNAs can interact with mRNAs that related to mitochondria function, the interactions occuring in the mitochondria are rare [25,45]. Up to now, *miR-181c* and *miR-1* are two miRNAs that can interact with mitochondria encoded mRNAs. Both miRNAs are nuclear encoded, after being processed to maturation in the cytoplasm, they can be imported to the mitochondria. When *miR-181c* is over-expressed, one of its target mRNA *mt-COX1* (cytochrome c oxidase subunit 1) is reduced, leading to cardiac dysfunction in rats [42,44]. As for *miR-1*, it is specifically expressed during myogenesis. Increasing levels of *miR-1* represses mRNA translation in the cytoplasm, while the translation of *mt-ND1* and *mt-COX1* in the mitochondria is stimulated unexpectedly [43]. These evidences provided new clues for functional studies of miRNA–mRNA interactions in mitochondria or other cellular localizations, suggesting highly coordinated inter-organellar crosstalk during rapidly physiological or pathological changes.

3. MiRNAs targeting 5′UTRs and CDSs

Beside different cellular localizations, miRNAs can target different regions of mRNAs during dynamic miRNA–mRNA interactions, changing the fates of different target mRNAs. Although it is well established that the mRNA 3′UTRs are usually targeted by miRNAs, un-conventional sites in the 5′UTRs or coding regions have also been reported [21,46,47] (Fig. 1B).

In vitro experiment, artificial *lin-4-like* miRNA can interact with the 5′UTR of *lin-28-like* mRNA which is consistent with *let-7a*:*lin-41* pairs, resulting in repression of translation of target mRNAs [47,48]. Further functional studies of *miR-103a-3p*, *miR-122* and

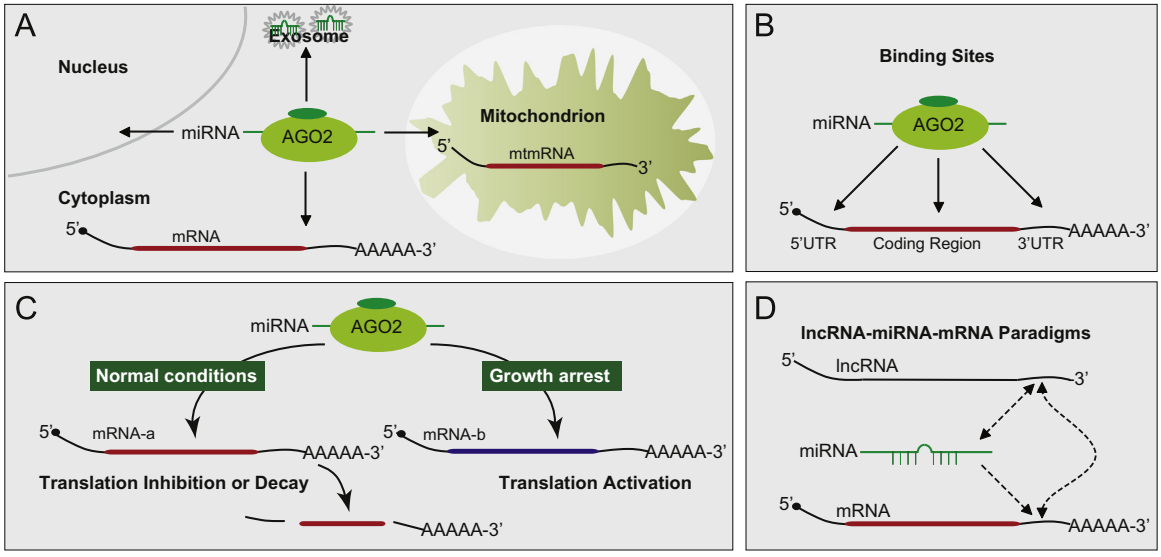

Fig. 1. Dynamic miRNA–mRNA paradigms. (A) miRNAs acting in different cellular locations. The cytoplasm, mitochondrion, nucleus and exosomes are indicated with drawings. Cellular location of miRNA–AGO2 complex are indicated with arrows. mtmRNA: mitochondrion mRNA. (B) Distinct binding sites of miRNAs. MiRNA targets are indicated with arrows pointed 5′UTR, coding region and 3′UTR of mRNA. (C) Dual faces of miRNA. During normal conditions, miRNA–AGO2 complex mediates target mRNAs for translational repression or decay. As cells are arrested, the translation of target mRNAs is activated. (D) Possible lncRNA-miRNA–mRNA interactions. MiRNA, mRNA and lncRNA constitute complex interactions. Among these interactions, miRNA can interact with both mRNA and lncRNA. Meanwhile, lncRNA can interact with miRNA and mRNA. RNA–RNA interactions are indicated with dotted line with arrows.

Table 1
Examples of miRNAs with unexpected cellular locations. miRNAs (column 1) with different cellular locations (column 2), functional description (column 3) and the corresponding references (column 4). Rno: *Rattus norvegicus*. Mmu: *Mus musculus*. Hsa: *Homo sapiens*.

miRNAs	Localizations	Functions	References
Hsa-mir-29b, *Hsa-mir-320*, *Hsa-mir-32*, *Hsa-mir-148a*, *Hsa-mir-148b*, *Hsa-mir-1285*, *Hsa-mir-29c*, *Hsa-mir-1*, *Hsa-mir-652*, *Hsa-mir-15b*, *Hsa-mir-135b*	Nucleus cytoplasm	Transcriptional regulation and alterantive splicing	[27–29]
Rno-mir-206, *Rno-mir-351*, *Rno-mir-494*, *Rno-mir-664*, *Rno-mir-1*, *Rno-let-7a*, *Rno-mir-21*, *Rno-mir-199a-3p*, *Rno-mir-125b-5p*			[30,31]
Mmu-mir-709, *Mmu-mir-805*, *Mmu-mir-690*, *Mmu-mir-122*, *Mmu-mir-30e*			[32]
Hsa-mir-365, *Hsa-mir-1*, *Hsa-mir-181c*, *Hsa-mir-720*, *let-7 familly*, *Hsa-mir-133a*, *Hsa-mir-206*, *Hsa-mir-195*, *Hsa-mir-181a*, *Hsa-mir-181b*	Mitochondria cytoplasm	Metabolism, development, apoptosis	[23,42,43]
Mmu-miR-1, *let-7*, *Mmu-miR-15*, *Mmu-miR-181*, *Mmu-miR-16*, *Mmu-miR-375*, *Mmu-miR-17*, *Mmu-miR-18*	Exosome cytoplasm	Cellular communication	[26]
let-7b, *Hsa-miR-150*, *Hsa-miR-27b*, *Hsa-miR-29b*, *Hsa-miR-29c*, *Hsa-miR-335*, *Hsa-miR-379*, *Hsa-miR-433*, *Hsa-miR-454*, *Hsa-miR-483-3p*, *Hsa-miR-584*, *Hsa-miR-621*, *Hsa-miR-652*, *Hsa-miR-760*, *Hsa-miR-888*, *Hsa-mir-292*, *Hsa-mir-103*, *Hsa-mir-15b*, *Hsa-mir-17*, *Hsa-mir-199a*, *Hsa-mir-20a*, *Hsa-mir-210*			[34,35]

miR-10a whose target sites are within 5′UTR regions confirmed that miRNAs can efficiently target 5′UTR sites in the cells [49–51]. MiRNAs which can target both 3′UTRs and 5′UTRs is found [48]. This kind of miRNA is sequences dependent when targeting both UTRs of mRNA. The function of endogenous miRNAs interacted with both UTRs such as *miR-34a*:*AXIN2*, *miR-605*:*SEC24D* pairs are also validated in vivo [48]. As both UTRs are targeted by miRNAs, the fold of target mRNA levels change is only modest, while the fold of corresponding protein levels change is significant [52].

Besides UTRs, CDSs can also be targeted by miRNAs. Through genome-wide screen, highly conserved target sequences within CDSs are found in the human genome [53]. Interestingly, conserved CDSs target sites are also widely observed in the *Drosophila* [54]. When miRNAs binding sites are in the CDSs of mRNAs, the translation of target mRNAs are usually inhibited [55]. As the target sites of *miR-199a* are cloned in the CDS of the luciferase, increasing levels of *miR-199a* can reduce its activity in vitro [55]. In vivo, *let-7* can target the CDS of Dicer, forming a negative feedback loop [53]. Meanwhile, *miR-148* targets the CDS of DNA methyltransferase 3b (*Dnmt3b*) is also confirmed in human cells [56]. As CDSs contain rich regulatory sequences, the miRNA-CDS patterns may influence gene architecture, alternative splicing and alternative poly-adenylation, tuning protein abundance with more flexible time-scale and magnitude [46].

A new algorithm (MinoTar-miRNA ORF Targets) is used to estimate preferentially conserved miRNA-target sites, suggesting the number of CDSs and 5′UTRs targets may exceed 3′UTRs in mammalians [54]. Systematic analysis of miRNA target sites located within 3′UTR and CDS between species indicate that CDS target sites are also functional [55,57]. MiRNAs whose center nucleotides 4–14 or 5–15 pair can target mRNAs are reported. They have extensive target sites, including UTRs and CDSs [58]. Crosslinking and immunoprecipitation (CLIP) experiments provide genome-wide miRNA target sites, indicating CDS target sites are frequent as 3′UTRs [59–61]. All these suggest that miRNA target sites within UTRs and CDSs are possibly functional. However, individual miRNA show different preferences in targeting the CDSs or the UTRs. RIP-Chip experiments in H4 cells suggest that *miR-107* prefers to target the CDSs while *miR-320* and *miR-124* tends to bind the 3′UTRs [62,63]. So, it is still challenging to study the function and mechanism of non-canonical miRNA target sites in the cells.

4. MiRNA-mediated activation of translation

Most (although not all) of miRNA-mRNA interactions showed negative regulation at the post-transcriptional level [52]. As dynamic interactions, dual function of miRNAs has been found under different cellular circumstances. On normal conditions, miRNA-mRNA interactions mediated target mRNAs for translational repression or decay. When cell growth was arrested, miRNA-AGO2 complex activated the translation of target mRNAs (Fig. 1C).

MiR-369 was the firstly reported miRNA that had double faces in regulating target mRNAs [64,65]. When HEK293 cells are grown with serum, target mRNAs (such as *TNF-α*) whose 3′ UTR contained the AU-rich elements (AREs) are subject to be translational inhibited or decayed, mediated by *miR-369*. But when the growth of cells are serum-starved, *miR-369* unexpectedly activated the translation of target mRNAs [64,65]. The mode of translational repression or activation requires the *FXR1* protein (fragile X mental retardation-related protein 1) whose presence can activate translation of proteins [64,65]. Further studies of *let-7* and the synthetic miRNA *miRcxcr4* suggest that dual roles of miRNPs are common during different cellular conditions [64,65]. However, when the same mRNA *TNF-α* is targeted within the 3′UTR (perhaps not the same binding site as *miR-369*) by *miR-16*, its translation is unexpectedly inhibited under changed cellular conditions [66].

Besides different physiological or pathological conditions, miRNAs can also translationally activate target mRNAs via binding different regions of target mRNAs or by distinctly cellular localizations. In the HCV (hepatitis C virus) life cycle, *miR-122* can positively activate the translation of HCV by targeting its 5′UTR in the cytoplasm [49]. During the early phase of liver regeneration, increased *miR-21* can accelerate the translation of *cyclin D1* by interacting with its 3′UTR in the cytoplasm [67]. During cellular stress, *miR-10a* can stimulate the translation of ribosomal proteins by binding their 5′UTRs in the cytoplasm [50]. Contrast to *miR-181c*, *miR-1* can activate the translation of *mt-COX1* in the mitochondria by binding its 3′UTR in the absence of GW182 which is a functional partner of AGO2 [42,43].

Under different cellular conditions, miRNA–mRNA interactions with different binding sites or/and cellular localizations make the interactions more complicated than we can anticipate. So, how many positive and novel miRNA–mRNA interactions in the cytoplasm and mitochondria are there still needs further studies.

5. Conclusions and perspectives

MiRNAs with different cellular locations and binding sites suggest possibly novel function in gene expression. At the post-transcriptional level, beyond translation repression or mRNA decay, miRNA can also active protein translation under different cellular circumstances.

In addition to mRNAs, lncRNAs can be the target of miRNAs, constituting complex circuits of gene regulatory network [68]

(Fig. 1D). The ceRNA (competing endogenous RNA) hypothesis suggests that lncRNAs sharing miRNA response elements could keep corresponding mRNAs from miRNAs mediated repression [69]. However, this hypothesis is challenged by quantitative study of abundance of miRNA and its binding site in vivo, suggesting this hypothesis is unlikely to cause significant effects on gene regulation through miRNA antagonist [70]. So, how mRNAs and lncRNAs harbored the same miRNA binding sites, communicating to each other still need further studies. Using novel experimental technology such as miR-CLIP would reveal more dynamic miRNA–mRNA, miRNA–lncRNA interactions under different physiological and pathological conditions [71]. Systematic and integrative analysis of miRNAs, lncRNAs, and mRNAs may unveil their regulatory relationships with different times and spaces [72]. Further studies of miRNA–mRNA interactions with distinct cellular locations and binding sites under differently physiological or pathological conditions will provide more discoveries before we can anticipate. And this will shed more lights on functional studies of other ncRNAs.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.bbrep.2015.10.011.

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