Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Chemical Biology

# The roles of microRNAs in epigenetic regulation

Qian Yao, Yuqi Chen and Xiang Zhou

MicroRNAs (miRNAs) are small noncoding RNAs, approximately 18–25 nucleotides in length, now recognized as one of the major regulatory gene families in eukaryotes. Recent advances have been made in understanding the complicated roles of miRNAs in epigenetic regulation. miRNAs, as epigenetic modulators, affect the protein levels of the target mRNAs without modifying the gene sequences. Moreover, miRNAs can also be regulated by epigenetic modifications, including DNA methylation, RNA modification, and histone modifications. The reciprocal actions of miRNAs and epigenetic pathway appear to form a miRNA-epigenetic feedback loop and have an extensive influence on gene expression proliferation. The dysregulation of the miRNA-epigenetic feedback loop interferes with the physiological and pathological processes and contributes to variety of diseases. In this review, we focus on the reciprocal interconnection of miRNAs in epigenetic regulation, with the aim of offering new insights into the epigenetic regulatory mechanism that can be used to combat diseases.

**Address**
College of Chemistry and Molecular Sciences, Key Laboratory of Biomedical Polymers of Ministry of Education, Hubei Province Key Laboratory of Allergy and Immunology, Wuhan University, Wuhan 430072, PR China

Corresponding author: Zhou, Xiang (xzhou@whu.edu.cn)

**Current Opinion in Chemical Biology** 2019, **51**:11–17

This review comes from a themed issue on **Chemical genetics and epigenetics**

Edited by **Xiaoguang Lei** and **Xiang David Li**

For a complete overview see the Issue and the Editorial

Available online 27th February 2019

**https://doi.org/10.1016/j.cbpa.2019.01.024**



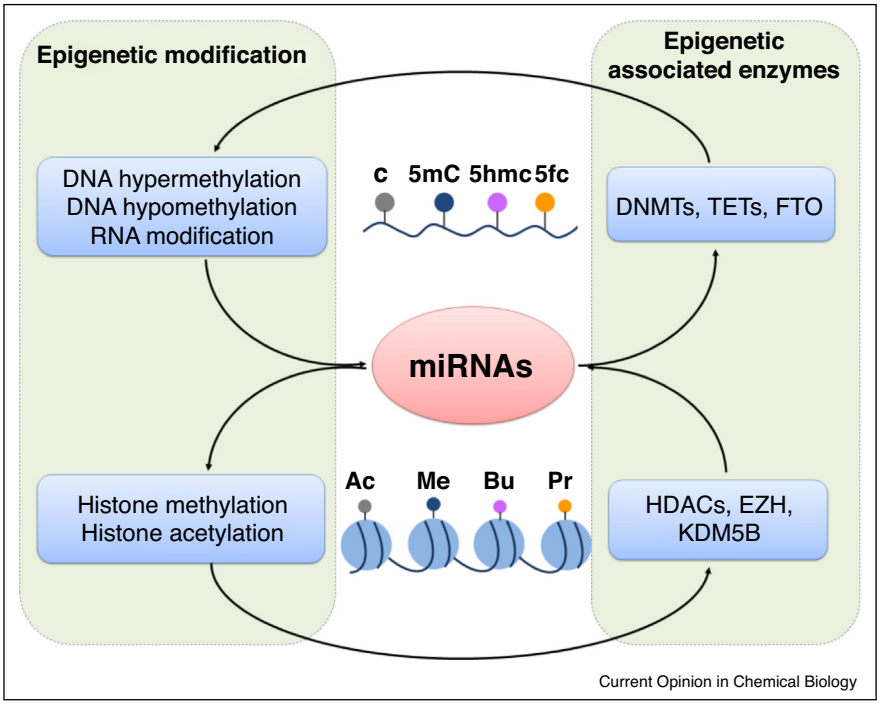
## Introduction

Epigenetics involves heritable changes in gene expression or cellular phenotype without changing the underlying DNA sequence. Epigenetics encompasses DNA methylation, chromatin variation, and noncoding RNAs, particularly miRNAs [1,2]. miRNAs are 18–25 nucleotides noncoding RNAs that post-transcriptionally regulate gene expression. miRNAs are involved in RNA interference (RNAi) machinery by binding to the untranslated regions (UTRs) of mRNA to suppress protein translation or decay mRNA [3]. It has been reported that each miRNA targets hundreds of mRNAs [4••]. More than 30% of human genes are thought to be the targeted of miRNAs, which means miRNAs have a global impact on transcriptomes and proteomes of eukaryotes [5,6]. miRNAs can act as epigenetic modulators by targeting key enzymes responsible for epigenetic reactions such as DNA methyltransferases (DNMTs), histone deacetylases (HDACs) and histone methyltransferases (EZH) [7–9]. Moreover, the expression of miRNAs is also regulated by epigenetic machinery, including DNA methylation, RNA modification and histone modification. The reciprocity relationship between miRNAs and epigenetic regulation forms the miRNA-epigenetic feedback loop (Figure 1). The modulation of miRNA-epigenetic feedback loop and its cellular function has emerged as a novel mechanism of regulating cell process, including cell proliferation [10•], apoptosis [11], and differentiation [12]. Further understanding of the dysregulation of miRNA-epigenetic feedback loop and its mechanism during the development of different diseases has great potential to lead to the discovery of novel therapeutic targets of strategies for these disorders.

## The biogenesis and RNAi mechanism of miRNAs

The biogenesis of miRNAs is initiated by RNA polymerase II, which transcribes miRNA genes as long, capped, polyadenylated RNA molecules named primary miRNAs (pri-miRNAs) (Figure 2) [3]. Pri-miRNAs are recognized by a microprocessor complex that contains the RNA-specific ribonuclease Drosha and its binding protein, DGCR8, in the nucleus. This complex cleaves the pri-miRNAs into hairpin RNAs of 60–100 nt, known as precursor miRNAs (pre-miRNAs) [13]. The pre-miRNAs are transported from the nucleus to the cytoplasm by the Exportin-5 transporter [14]. Once into the cytoplasm, the pre-miRNAs are processed by the RNase III endonuclease Dicer into a form of 18–25 nucleotides double strand RNA [15,16]. The duplex is loaded into the RNA-induced silencing complex (RISC), and one strand is degraded while the other is incorporated into the RISC and guides it to the mRNA target [17]. It has been reported that miRNAs can also be produced by a Dicer-independent pathway with Ago catalysis [18]. The specificity of miRNAs target sites is usually positioned in the 3′-UTR of mRNA. The hybridization of RISC mainly causes degradation or repression of target mRNA [3]. In addition, miRNAs can also bind to the 5′-UTR or coding region and active, rather than suppress, mRNA translation [19•,20]. miR-10a interacts with the 5′-UTR

Figure 1




Schematic illustration of the miRNA-epigenetic feedback loop. miRNAs are regulated by epigenetic regulators, including DNA methylation, RNA modification and histone modification. Epigenetics-associated enzymes are also under the control of miRNA regulation.

of many mRNAs encoding ribosomal proteins and enhanced mRNAs translation [19•].

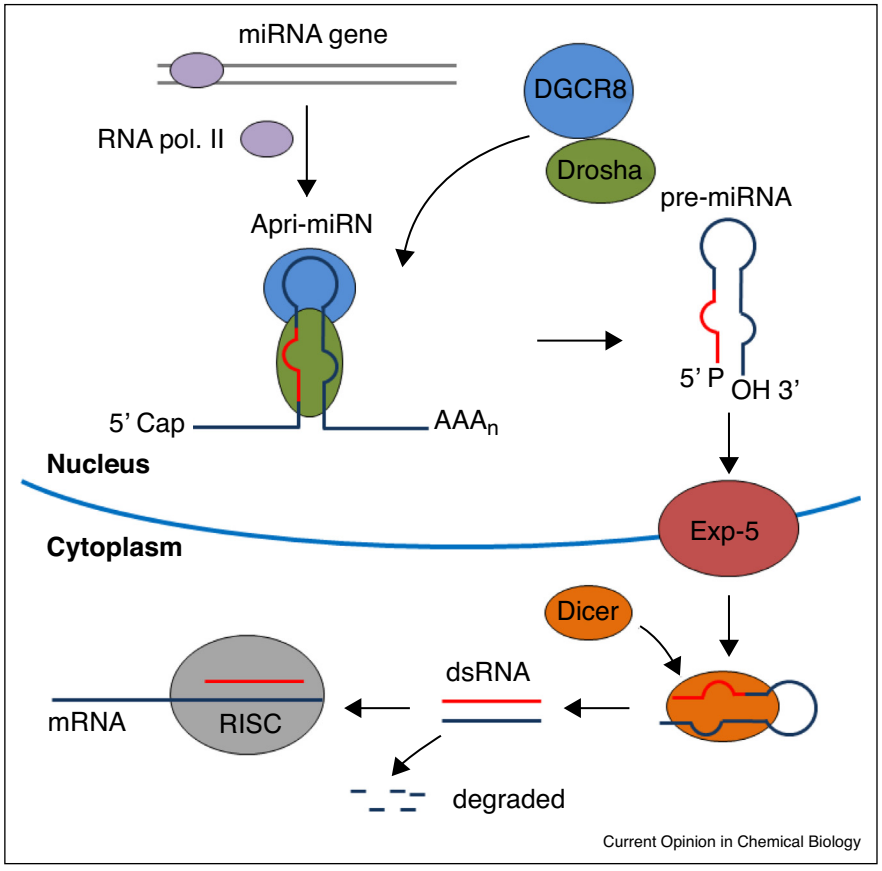
## Epigenetic regulation of miRNAs

Increasing evidence has indicated that miRNAs play an important role in a number of biological processes, including cell proliferation, differentiation, apoptosis, and hematopoiesis [21–24]. miRNAs expression profiles can function as biomarkers of various diseases. Aberrant miRNAs are known as epigenetic modulation. Increasing research has focused on exploring the mechanisms responsible for the dysregulation of miRNAs. Notably, a previous study has indicated that the expression of miRNAs is under the control of epigenetic regulation, including DNA methylation, RNA modification, and post-translational modification of histones [25••]. We summarized the epigenetic regulation of miRNAs in Table 1, including their target genes and function in corresponding cacinomas.

### DNA methylation-mediated regulation of miRNAs

DNA methylation is predominantly found in cytosine of the dinucleotide sequence of CpG islands. Hypermethylation of the CpG islands within the promoter of miRNA genes are responsible for the gene silencing potential and tumor suppressor properties. Typically, methylation of CpG islands within miRNAs promoters causes the methylation binding protein to bind to DNA and inhibits transcription factors and RNA polymerase from binding to the DNA, resulting in the repression of miRNA gene expression. Conversely, the hypomethylation of CpG islands actives gene expression and promotes cancer procession [26•]. Hypermethylation of the promoter CpG islands of miR-424 in glioma reduced miR-424 expression, which is associated with cell invasion and migration and promoted cell apoptosis. Moreover, when the promoter was treated a demethylating agent (5-aza-2′-dexycytidine, 5-AZA), the expression level of miR-424 was increased [27]. HOXA10 was overexpressed in gastric tumors and positively correlated with miR-196b-5p expression levels. When the promoter of HOXA10 was treated with 5-AZA, the demethylation of the HOXA10 promoter induced the overexpression of HOXA10 and miR-196b-5p, promoting gastric cancer proliferation and invasion *in vitro* [28]. Hypermethylation of the miR-10b promoter suppressed the expression of miR-10b and promoted the progression of clear-cell renal cell carcinoma (ccRCC). It was demonstrated that miR-10b played a tumor suppressive role in ccRCC [29]. A comprehensive analysis of miRNA genes found that approximately half of these genes are associated with CpG islands, suggesting that they could be subjected to regulation of DNA methylation [30].

**Figure 2**




miRNA biogenesis. miRNA genes are transcribed by RNA polymerase II into pri-miRNA transcripts. The Drosha and DGCR8 recognize and cleave the pri-miRNA into a hairpin structure pre-miRNA. Then, Exportin-5 binds to the pre-miRNA and helps their export into the cytoplasm, where Dicer cleaves the pre-miRNA into double strand RNA. Further processing leads to the incorporation of one strand miRNA into the RISC and guides it to target mRNA, while another strand degraded.

**Table 1**

**Examples of epigenetic regulation of miRNAs**

| miRNAs | Expression levels | Samples | Target gene | Function | Ref |
|---|---|---|---|---|---|
| miR-424 | ↓ | Giloma | – | Invasion, migration, apoptosis | [27] |
| miR-196b-5p | ↑ | Gastric | – | Proliferation, invasion | [28] |
| miR-10b | ↓ | ccRCC | – | Progression | [29] |
| miR-124 | ↓ | MDS | CDK4, CDK6, EZH2 | – | [33] |
| miR-663a<br>miR-4787-5p | ↓ | PDAC | TGFβ1 | – | [36] |
| miR-145<br>miR-132<br>miR-212 | ↓ | CRC | TCF4, SUZ12 | – | [37] |
| miR-106b-3p<br>miR-151a-3p | ↑ | Lung | PCDHB7, PTPN12, CHL1 | Adhesion, migration | [38] |
| miR-29 | ↓ | Bladder | DNMT3A, PETN | – | [43] |
| miR-377 | – | HSFs | DNMT1 | – | [45] |
| miR-34a | ↓ | Hcy-IA | HDAC1 | – | [48] |
| miR-137 | ↓ | Breast | KDM5B | Proliferation, migration | [49] |

Notes: ↑, upregulation expression of miRNAs; ↓, downregulation expression of miRNAs; ccRCC, clear-cell renal cell carcinoma; MDS, myelodysplastic syndrome; PDAC, human pancreatic ductal adenocarcinomas; CRC, colorectal cancer; HSFs, skin fibroblasts; Hcy-IA, Hcy-induced atherosclerosis.

### Histone modification-mediated regulation of miRNAs

In addition to DNA methylation, which is the most intensely studied epigenetic modification, histone modification may also lead to either activation or suppression of miRNAs expression. Histone amino-terminal regions can undergo diverse modification, such as methylation, acetylation, ubiquitylation, phosphorylation, sumoylation, biotinylation, and ADP-ribosylation [31]. Methylation and acetylation are the most well studied modification of histone residues. Acetylated lysine may relax chromatin structure and active gene-transcription, whereas histone deacetylation may lead to more compact chromatin state and gene-transcription suppression [32•]. By treating of HL60 leukemic cell line with a histone deacetylase (HDAC) inhibitor, panobinostat (LBH589), Liu *et al.* revealed the upregulation of miR-124, with the expression inhibition of downstream targets CDK4, CDK6 and EZH2 expression [33]. Inhibition or RNA interference against HDAC1 in chronic lymphocytic leukemia (CLL) can also induce the upregulation of the expression of miRNAs targeting Bruton tyrosine kinase (BTK), subsequently suppressing the downstream signaling and causing cell death [34]. Similarly, treating prostate cancer cell lines with another HDAC inhibitor, OBP-801, suppressed androgen receptor activity via a posttranscriptional upregulation of miRNA, resulting in repressed prostate tumorigenesis [8].

Lysine methylation at different positions causes different effects on gene expression, such as methylation at K36, H3K4, and K79, which is related with transcriptional activation, whereas methylation at H3K27, H3K9, and H4K20 is associated with gene suppression [32•,35]. By comparing the miRNAs expression before and after treatment with 3-deazaneplanocin-A (DZNep), an inhibitor of EZH2 histone lysine-*N*-methyltransferase, 52.3% of miRNAs were downregulated and the expression of more than 50 miRNAs was activated in MIA PaCa-2. Mody *et al.* demonstrated that DZNep could reprogram miRNAs expression [36]. By using another inhibitor, GSK-J4, which selectively targets the H3K27 demethylase subfamily to increase the trimethylation of H3K27, Wang *et al.* downregulated the expression of miR-145 in 293T cells [37]. By treating H1299 cells with BIX01294, an inhibitor of G9a methyltransferase which catalyzes the methylation of the lysine 9 residue of histone H3, the downregulation of miR-106b-3p and miR-151a-3p was observed in lung cancer development [38].

### RNA modification mediated regulation of miRNAs

RNA modification also found to play important roles in the expression of miRNAs, termed RNA epigenetics or epitranscriptomics. More than 140 different forms of RNA modification have been found in mammalian systems, such as m6A, m5C, m1A, pseudourylation ($\psi$) and deamination (A-to-I RNA editing). Among these modifications, m6A is the best understood and most frequent mark of mRNA. It has been reported that m6A is located in the pri-miRNAs and marking them for the recognition and processing by DGCR8 [39••]. Depletion of METTL3 reduced the binding of DGCR8 to pri-miRNAs leading to the reduction of mature miRNAs and accumulation of pri-miRNAs. Moreover, HNRBPA2B1, another m6A binding protein, has been reported to promote pri-miRNA processing interacted with DGCR8 [40]. Knockdown of m6A demethylase FTO results in altering of the steady state levels of several miRNAs [41]. These results indicated m6A acts as the key role of post-transcriptional modification in the expression of miRNAs.

## miRNAs affect epigenetic expression

In addition to being regulated by the epigenetic machinery, miRNAs can also affect the expressions of components of the epigenetic machinery by targeting epigenetics-associated enzymes. Epigenetic-related enzymes such as DNMTs, TETs, HDACs, and EZH can be epigenetically regulated by miRNAs and are called epi-miRNAs. The significant regulation of miRNAs on epigenetic expression, including DNA methylation, RNA modification, and histone modification, has been increasingly recognized in recent years.

### miRNAs regulate DNA methylation and RNA modification

DNA methylation and demethylation are mainly regulated by DNMTs and TETs. miRNAs can regulate the expression level of DNA methylation by influencing the expression of DNA methylation related enzymes, thereby affecting the whole genome methylation profile. miR-29b belongs to the miR-29 family, which targets DNMTs and TETs, thereby influencing DNA methylation. miR-29b inhibitor increased DNA methylation levels of global genome by upregulating DNMT3A/B and TET1 and downregulating TET2/3 during porcine early embryo development [42]. Similarly, suppression of miR-29 by ATDC led to the upregulation of DNMT3A and genome methylation, accompanied by the silencing of the tumor suppressor PTEN [43]. Bioinformatics has indicated that miR-101 is complementary to the 3′-UTR of DNMT3A mRNA. Overexpression of miR-101 could silence the expression of DNMT3A and suppress lung cell proliferation and S/G2 translation, eventually causing the apoptosis of the lung cells [44]. miRNAs can also target DNMT1. Xie *et al.* predicted that miR-377 targeted the 3′-UTR of DNMT1 mRNA. The promoter methylation levels of skin aging-associated genes, such as *FoxD3*, *p53*, and *UTF1* were regulated by DNMT1 in young human skin fibroblasts. These findings suggested that the miR-377-DNMT1-p53 axis plays a pivot role in skin senescence [45]. In contrast, it has been reported that m6A could be regulated by miRNAs via a sequence pairing mechanism which indicates the reciprocity relationship between miRNAs and m6A [46].

### miRNAs regulate histone modification

In addition to the DNA methyltransferases, miRNAs can also regulate the histone modification. Bioinformatics analyses have identified histone modifications, including H3K4me1, H3K27me3, H3K27ac, H3K9ac, H3K4me3, and H2AZ that are regulated by miRNAs during mammalian spermatogenesis [47]. Specifically, HDAC1 is regulated by miR-34a via binding to the 3′UTR of HDAC1 mRNA in the foam cells. Overexpression of miR-34a repressed the expression of HDAC1 and increased the acetylation levels of H3K9ac, eventually causing aberrant lipid accumulation in the foam cell [48]. Similarly, Denis *et al.* demonstrated that the histone demethylase KDM5B was regulated by miR-138 in breast cancer. Low-expression of miR-138 and overexpression of KDM5B were found in breast cancer cells. Restoring miR-138 resulted in reduced KDM5B and inhibited breast cancer cell proliferation and migration [49]. Comparing the gene expression profile of 4 hepatitis B virus-infected hepatocellular carcinoma (HCC) with the control group, 14 overexpressed miRNAs and 16 downregulated miRNAs were involved in the regulation of H3K9 methylation and related with the development of HCC [50].

## The crosstalk between miRNAs and epigenetic regulators

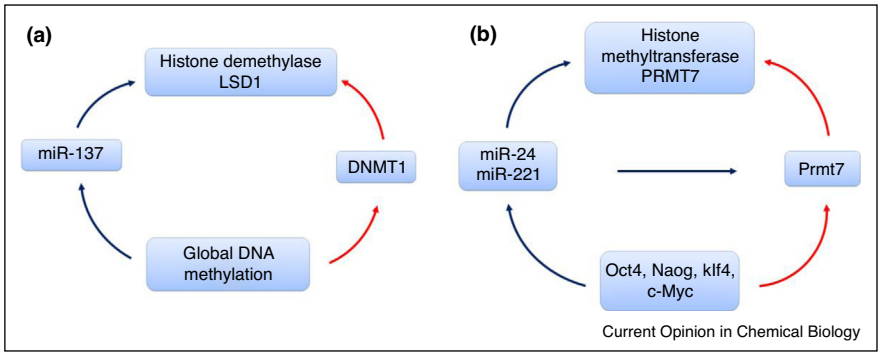
The same miRNAs that are influenced by epigenetic machinery can inversely provide epigenetic regulation. The crosstalk between miRNAs and epigenetic regulators forms closed epigenetic machinery loops. However, the crosstalk between the epigenetic regulators is not fully understood. As shown in Figure 3a, few miRNAs have been found to be regulated by epigenetic regulators and, in turn, affect the epigenetic machinery. miR-137 is commonly downregulated due to the hypermethylation of miR-137 CpG islands in colorectal cancer (CRC). Transfection of miR-137 precursor into CRC cell lines reduced cell proliferation, suggesting miR-137 is a tumor suppressor of in CRC. When treated with 5-aza-CdR, the demethylation of miR-137 CpG islands induced the upregulation of miR-137 in CRC cell lines. Using gene expression profiling and bioinformatics, Lysine (K)-specific demethylase 1A (LSD1) was discovered as the target of miR-137. LSD1, a histone demethylase, is extensively influenced the global DNA methylation through the demethylation of DNMT1 by increasing the stability of DNMT1 [51•]. The expression of miR-137 was inhibited by the hypermethylation of CpG islands and inversely correlated with the level of the global DNA methylation.

Both miR-24 and miR-221 were repressed by protein arginine methylation (PRMT-7) which upregulated the methylation level of histone marks at the miRNAs promoter in mouse embryonic stem cells (ESCs). An alkaline phosphatase staining analysis revealed that the spontaneous differentiation of mouse ESCs was induced by transfection of miR-24 and miR-221 mimics. However, the two miRNAs target the 3′-UTR of Oct4, Sox2, Nanog as well as Prmt7. The expression of PRMT7 was also repressed by miR-24 and miR-221. The two miRNAs and PRMT7 form a negative feedback loop (Figure 3b) [52,53•]. All these studies suggest that the reciprocal regulation of miRNAs and epigenetic regulators depict more complete profiles of miRNAs and epigenetic mechanisms.

## Conclusion and future prospective

The evidence discussed here indicates the reciprocal regulation between miRNAs and epigenetic machinery. miRNAs as a component of the epigenetic machinery are involved in epigenetic regulation. DNA methylation, RNA modification, and histone modification epigenetically regulated miRNAs expression. DNA methylation is commonly established at promoter CpG islands and inhibits the miRNAs expression. Histone modification gains the capability of enhancing and repressing translation activation of miRNAs. Additionally, epigenetic-related enzymes can be the target of miRNAs. miRNAs modulate

**Figure 3**




Schematic illustration for miR-137-mediated feedback loop **(a)** and miR-24 and miR-221 involved in the negative feedback loop of PRMT7 expression **(b)**. The blue and red arrows represent repression and activation, respectively.

the expression of DNA methylation and histone modification by regulating epigenetics-associated enzymes. Moreover, some miRNAs have been found to be regulated by epigenetic regulators and, therefore, affect the epigenetic machinery. These results have extended our understanding of the miRNA-epigenetic feedback loop.

As the dysregulation of miRNA-epigenetic feedback loop is associated with the initiation and development of various diseases, studies on the miRNA-epigenetic feedback loop in recent years have demonstrated the potential for application in clinical diagnosis and prognosis. To date, the regulators in the miRNA-epigenetic feedback loop, such as the methylation of the miRNA genes and the expression level of miRNA-associated epigenetic enzymes, can act as biomarkers for early diagnosis to distinct cancer types. The identification of miRNA genes methylation and the expression levels of miRNA-associated epigenetic enzymes is likely to become a potentially powerful approach for diseases diagnosis and prognosis. Epigenetic regulator drugs such as 5-AZA, LBH589, and GSK-J4, which can regulate the miRNA-epigenetic feedback loop, have become a potential powerful therapeutic strategy for various diseases. For example, 5-AZA, which can replace the cytosine of DNA during DNA replication, is used commonly for leukemia treatment. Additionally, utilizing synthetic miRNA mimics and miRNA sponges which contain complementary binding sites to the miRNA of interest to control the effector of epigenetic enzymes and further influence the expression of a broad range of proteins would provide a promising therapeutic strategy for associated diseases. However, to date, the application of miRNA-epigenetic feedback loops in clinical diagnosis and therapy is still in the research stage. In the future, the mechanism of miRNA-epigenetic feedback loops and the potential influence of global immunostimulatory properties need to be further studied in order to utilize miRNA-epigenetic regulators in real clinical applications.

## Conflict of interest statement

Nothing declared.

## Acknowledgement

This work was supported by the National Natural Science Foundation of China (21432008, 21721005, and 91753201).

## References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Goldberg AD, Allis CD, Bernstein E: **Epigenetics: a landscape takes shape**. *Cell* 2007, **128**:635-638.

2. Bird A: **Perceptions of epigenetics**. *Nature* 2007, **447**:396-398.

3. Lujambio A, Lowe SW: **The microcosmos of cancer**. *Nature* 2012, **482**:347-355.

4. •• Selbach M, Schwanhausser B, Thierfelder N, Fang Z, Khanin R, Rajewsky N: **Widespread changes in protein synthesis induced by microRNAs**. *Nature* 2008, **455**:58-63.
This out-standing paper describes that each miRNA can influence direct or indirect effect on hundreds or thousands of gene expression, which shows the important role of the miRNAs in the global mRNA expression levels.

5. Valinezhad Orang A, Safaralizadeh R, Kazemzadeh-Bavili M: **Mechanisms of miRNA-mediated gene regulation from common downregulation to mRNA-specific upregulation**. *Int J Genomics* 2014, **2014**:970607.

6. Vasudevan S, Tong YC, Steitz JA: **Switching from repression to activation: microRNAs can up-regulate translation**. *Science* 2007, **318**:1931-1934.

7. Kwa FAA, Jackson DE: **Manipulating the epigenome for the treatment of disorders with thrombotic complications**. *Drug Discov Today* 2018, **23**:719-726.

8. Sato S, Katsushima K, Shinjo K, Hatanaka A, Ohka F, Suzuki S, Naiki-Ito A, Soga N, Takahashi S, Kondo Y: **Histone deacetylase inhibition in prostate cancer triggers miR-320-mediated suppression of the androgen receptor**. *Cancer Res* 2016, **76**:4192-4204.

9. Li Y, He Q, Wen X, Hong X, Yang X, Tang X, Zhang P, Lei Y, Sun Y, Zhang J *et al.*: **EZH2-DNMT1-mediated epigenetic silencing of miR-142-143p promotes metastasis through targeting ZEB2 in nasopharyngeal carcinoma**. *Cell Death Differ* 2018 http://dx.doi.org/10.1038/s41418-018-0208-2.

10. • Kiga K, Mimuro H, Suzuki M, Shinozaki-Ushiku A, Kobayashi T, Sanada T, Kim M, Ogawa M, Iwasaki YW, Kayo H *et al.*: **Epigenetic silencing of miR-210 increases the proliferation of gastric epithelium during chronic Helicobacter pylori infection**. *Nat Commun* 2014, **5**:4497.
This paper indicates inhibition of miR-210 expression promotes cell proliferation by activating*STMN1* and *DIMT1*. The authors suggest the further understanding how miRNAs exhibit in tumor progression.

11. Matsushima K, Isomoto H, Yamaguchi N, Inoue N, Machida H, Nakayama T, Hayashi T, Kunizaki M, Hidaka S, Nagayasu T *et al.*: **MiRNA-205 modulates cellular invasion and migration via regulating zinc finger E-box binding homeobox 2 expression in esophageal squamous cell carcinoma cells**. *J Transl Med* 2011, **9**:30.

12. Chen JF, Mandel EM, Thomson JM, Wu Q, Callis TE, Hammond SM, Conlon FL, Wang DZ: **The role of microRNA-1 and microRNA-133 in skeletal muscle proliferation and differentiation**. *Nat Genet* 2006, **38**:228-233.

13. Denli AM, Tops BB, Plasterk RH, Ketting RF, Hannon GJ: **Processing of primary microRNAs by the microprocessor complex**. *Nature* 2004, **432**:231-235.

14. Bohnsack MT: **Exportin 5 is a RanGTP-dependent dsRNA-binding protein that mediates nuclear export of pre-miRNAs**. *RNA* 2004, **10**:185-191.

15. Yi R, Qin Y, Macara IG, Cullen BR: **Exportin-5 mediates the nuclear export of pre-microRNAs and short hairpin RNAs**. *Genes Dev* 2003, **17**:3011-3016.

16. Lund E, Guttinger S, Calado A, Dahlberg JE, Kutay U: **Nuclear export of microRNA precursors**. *Science* 2004, **303**:95-98.

17. Martinez J, Patkaniowska A, Urlaub H, Luhrmann R, Tuschl T: **Single-stranded antisense siRNAs guide target RNA cleavage in RNAi**. *Cell* 2002, **110**:563-574.

18. Cheloufi S, Dos Santos CO, Chong MM, Hannon GJ: **A dicer-independent miRNA biogenesis pathway that requires Ago catalysis**. *Nature* 2010, **465**:584-589.

19. • Orom UA, Nielsen FC, Lund AH: **MicroRNA-10a binds the 5′UTR of ribosomal protein mRNAs and enhances their translation**. *Mol Cell* 2008, **30**:460-471.
This paper offers a new sight into miRNAs regulating mRNA expression. It has the opposite effect on the mRNA translation compared to the common opinion that miRNAs suppress the translation of mRNAs.

20. Brummer A, Hausser J: **MicroRNA binding sites in the coding region of mRNAs: extending the repertoire of post-transcriptional gene regulation**. *Bioessays* 2014, **36**:617-626.

21. Dostie J: **Numerous microRNPs in neuronal cells containing novel microRNAs**. *RNA* 2003, **9**:180-186.

22. Wang Y, Keys DN, Au-Young JK, Chen C: **MicroRNAs in embryonic stem cells**. *J Cell Physiol* 2009, **218**:251-255.

23. Xu P, Vernooy SY, Guo M, Hay BA: **The Drosophila microRNA Mir-14 suppresses cell death and is required for normal fat metabolism**. *Curr Biol* 2003, **13**:790-795.

24. Chen CZ, Li L, Lodish HF, Bartel DP: **MicroRNAs modulate hematopoietic lineage differentiation**. *Science* 2004, **303**:83-86.

25. •• Seven M, Karatas OF, Duz MB, Ozen M: **The role of miRNAs in cancer: from pathogenesis to therapeutic implications**. *Future Oncol* 2014, **10**:1027-1048.

An excellent review on the role of miRNAs in cancer. miRNAs play a pivot role in the epigenetic machinery of cancer pathogenesis.

26. • Jaenisch R, Bird A: **Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals**. *Nat Genet* 2003, **33(Suppl)**:245-254.

The review indicates the mechanism of DNA methylation regulating gene expression and how DNA methylation influences biological processes.

27. Jin C, Li M, Ouyang Y, Tan Z, Jiang Y: **MiR-424 functions as a tumor suppressor in glioma cells and is down-regulated by DNA methylation**. *J Neurooncol* 2017, **133**:247-255.

28. Shao L, Chen Z, Peng D, Soutto M, Zhu S, Bates A, Zhang S, El-Rifai W: **Methylation of the HOXA10 promoter directs miR-196b-5p-dependent cell proliferation and invasion of gastric cancer cells**. *Mol Cancer Res* 2018, **16**:696-706.

29. He C, Zhao X, Jiang H, Zhong Z, Xu R: **Demethylation of miR-10b plays a suppressive role in ccRCC cells**. *Int J Clin Exp Pathol* 2015, **8**:10595-10604.

30. Weber B, Stresemann C, Brueckner B, Lyko F: **Methylation of human microRNA genes in normal and neoplastic cells**. *Cell Cycle* 2007, **6**:1001-1005.

31. Falkenberg KJ, Johnstone RW: **Histone deacetylases and their inhibitors in cancer, neurological diseases and immune disorders**. *Nat Rev Drug Discov* 2014, **13**:673-691.

32. • Tessarz P, Kouzarides T: **Histone core modifications regulating nucleosome structure and dynamics**. *Nat Rev Mol Cell Biol* 2014, **15**:703-708.

The review indicates the mechanism of histone modification regulating all DNA-templated processes.

33. Liu H, Pattie P, Chandrasekara S, Spencer A, Dear AE: **Epigenetic regulation of miRNA-124 and multiple downstream targets is associated with treatment response in myeloid malignancies**. *Oncol Lett* 2016, **12**:2175-2180.

34. Bottoni A, Rizzotto L, Lai TH, Liu C, Smith LL, Mantel R, Reiff S, El-Gamal D, Larkin K, Johnson AJ *et al.*: **Targeting BTK through microRNA in chronic lymphocytic leukemia**. *Blood* 2016, **128**:3101-3112.

35. Zhou VW, Goren A, Bernstein BE: **Charting histone modifications and the functional organization of mammalian genomes**. *Nat Rev Genet* 2010, **12**:7-18.

36. Mody HR, Hung SW, AlSaggar M, Griffin J, Govindarajan R: **Inhibition of S-adenosylmethionine-dependent methyltransferase attenuates TGFbeta1-induced EMT and metastasis in pancreatic cancer: putative roles of miR-663a and miR-4787-5p**. *Mol Cancer Res* 2016, **14**:1124-1135.

37. Wang W, Xiao X, Chen X, Huo Y, Xi WJ, Lin ZF, Zhang D, Li YF, Yang F, Wen WH *et al.*: **Tumor-suppressive miR-145 co-repressed by TCF4-beta-catenin and PRC2 complexes forms double-negative regulation loops with its negative regulators in colorectal cancer**. *Int J Cancer* 2018, **142**:308-321.

38. Pang AL, Title AC, Rennert OM: **Modulation of microRNA expression in human lung cancer cells by the G9a histone methyltransferase inhibitor BIX01294**. *Oncol Lett* 2014, **7**:1819-1825.

39. •• Alarcon CR, Lee H, Goodarzi H, Halberg N, Tavazoie SF: **N6-methyladenosine marks primary microRNAs for processing**. *Nature* 2015, **519**:482-485.

Out-standing paper describes the mechanism of how DGCR8 recognizes and binds to pri-miRNA. $m^6A$ mark on pri-miRNA sequences promotes the recognition of DGCR8 to the pri-miRNA and initiates the biogenesis of mature miRNA.

40. Alarcon CR, Goodarzi H, Lee H, Liu X, Tavazoie S, Tavazoie SF: **HNRNPA2B1 is a mediator of m(6)A-dependent nuclear RNA processing events**. *Cell* 2015, **162**:1299-1308.

41. Berulava T, Rahmann S, Rademacher K, Klein-Hitpass L, Horsthemke B: **N6-adenosine methylation in MiRNAs**. *PLoS One* 2015, **10**:e0118438.

42. Zhang Z, Cao Y, Zhai Y, Ma X, An X, Zhang S, Li Z: **MicroRNA-29b regulates DNA methylation by targeting Dnmt3a/3b and Tet1/2/3 in porcine early embryo development**. *Dev Growth Differ* 2018, **60**:197-204.

43. Palmbos PL, Wang L, Yang H, Wang Y, Leflein J, Ahmet ML, Wilkinson JE, Kumar-Sinha C, Ney GM, Tomlins SA *et al.*: **ATDC/TRIM29 drives invasive bladder cancer formation through miRNA-mediated and epigenetic mechanisms**. *Cancer Res* 2015, **75**:5155-5166.

44. Wang L, Yao J, Sun H, He K, Tong D, Song T, Huang C: **MicroRNA-101 suppresses progression of lung cancer through the PTEN/AKT signaling pathway by targeting DNA methyltransferase 3A**. *Oncol Lett* 2017, **13**:329-338.

45. Xie HF, Liu YZ, Du R, Wang B, Chen MT, Zhang YY, Deng ZL, Li J: **miR-377 induces senescence in human skin fibroblasts by targeting DNA methyltransferase 1**. *Cell Death Dis* 2017, **8**:e2663.

46. Chen T, Hao YJ, Zhang Y, Li MM, Wang M, Han W, Wu Y, Lv Y, Hao J, Wang L *et al.*: **m(6)A RNA methylation is regulated by microRNAs and promotes reprogramming to pluripotency**. *Cell Stem Cell* 2015, **16**:289-301.

47. Taguchi YH: **Apparent microRNA-target-specific histone modification in mammalian spermatogenesis**. *Evol Bioinform Online* 2015, **11**:13-26.

48. Zhao Q, Li S, Li N, Yang X, Ma S, Yang A, Zhang H, Yang S, Mao C, Xu L *et al.*: **miR-34a targets HDAC1-regulated H3K9 acetylation on lipid accumulation induced by homocysteine in foam cells**. *J Cell Biochem* 2017, **118**:4617-4627.

49. Denis H, Van Grembergen O, Delatte B, Dedeurwaerder S, Putmans P, Calonne E, Rothe F, Sotiriou C, Fuks F, Deplus R: **MicroRNAs regulate KDM5 histone demethylases in breast cancer cells**. *Mol Biosyst* 2016, **12**:404-413.

50. Ding W, Yang H, Gong S, Shi W, Xiao J, Gu J, Wang Y, He B: **Candidate miRNAs and pathogenesis investigation for hepatocellular carcinoma based on bioinformatics analysis**. *Oncol Lett* 2017, **13**:3409-3414.

51. • Balaguer F, Link A, Lozano JJ, Cuatrecasas M, Nagasaka T, Boland CR, Goel A: **Epigenetic silencing of miR-137 is an early event in colorectal carcinogenesis**. *Cancer Res* 2010, **70**:6609-6618.

It is shown that the expression of miR-137 is influenced by DNA methylation inversely correlated with the stability of DNMT1. The example indicates compelling evidence of the reciprocal regulation between miRNAs and epigenetic regulators.

52. Chen TY, Lee SH, Dhar SS, Lee MG: **Protein arginine methyltransferase 7-mediated microRNA-221 repression maintains Oct4, Nanog, and Sox2 levels in mouse embryonic stem cells**. *J Biol Chem* 2018, **293**:3925-3936.

53. • Lee SH, Chen TY, Dhar SS, Gu B, Chen K, Kim YZ, Li W, Lee MG: **A feedback loop comprising PRMT7 and miR-24-2 interplays with Oct4, Nanog, Klf4 and c-Myc to regulate stemness**. *Nucleic Acids Res* 2016, **44**:10603-10618.

Another example of miRNA-epigenetic feedback loop. MiR-24 and miR-221 are involved in the negative feedback loop of PRMT7 expression.