Nuclear miRNAs as transcriptional regulators in processes related to various cancers (Review)

ZIQIANG WANG[1,2*], YU ZHANG[2*] and KUN LI[1]

[1]Department of Nuclear Medicine, The First Affiliated Hospital of Shandong First Medical University & Shandong Provincial Qianfoshan Hospital, Jinan, Shandong 250014, P.R. China; [2]Biomedical Sciences College & Shandong Medicinal Biotechnology Centre, Shandong First Medical University & Shandong Academy of Medical Sciences, Jinan, Shandong 250117, P.R. China

Received December 13, 2023; Accepted March 29, 2024

DOI: 10.3892/ijo.2024.5644

Abstract. MicroRNAs (miRNAs) are noncoding small nucleic acids that contain ~22 nucleotides and are considered to promote the degradation or inhibit the translation of mRNA by targeting its 3'-untranslated region. However, growing evidence has revealed that nuclear miRNAs, combined with gene promoters or enhancers, are able to directly mediate gene transcription. These miRNAs exert a critical influence on cancer progression by affecting cell growth, migration and invasion. In this review, the direct regulation of gene expression by nuclear miRNAs at the transcriptional level was discussed and summarized, and their mechanisms of action in cancers were highlighted with reference to the various body systems.

Contents

Correspondence to: Dr Ziqiang Wang, Biomedical Sciences College & Shandong Medicinal Biotechnology Centre, Shandong First Medical University & Shandong Academy of Medical Sciences, 6699 Qingdao Road, Huaiyin, Jinan, Shandong 250117, P.R. China
E-mail: wangziqiang@sdfmu.edu.cn

Dr Kun Li, Department of Nuclear Medicine, The First Affiliated Hospital of Shandong First Medical University & Shandong Provincial Qianfoshan Hospital, 16766 Jingshi Road, Lixia, Jinan, Shandong 250014, P.R. China
E-mail: 2143@sdhospital.com.cn

*Contributed equally

Key words: cancer, nuclear miRNA, transcription, promoter, enhancer, therapeutic target

1. Introduction

MicroRNAs (miRNAs/miRs) are small, single-stranded, non-coding RNAs comprising ~22 nucleotides. miRNAs typically bind to the 3'-untranslated region (UTR) of genes by recruiting Argonaute (AGO) protein complexes of messenger RNA (mRNA), resulting in the downregulation of gene expression (1-3). Growing evidence indicates that miRNAs have critical roles in the progression of various disorders, such as viral infections, cancers and neurodegenerative diseases (4-10).

Mature miRNAs are thought to localize in multiple subcellular sites in the cytoplasm, such as the mitochondria, rough endoplasmic reticulum, lysosomes and endosomes, and are secreted outside cells via vesicles, such as exosomes (11). Furthermore, miRNAs have been found in the nucleus, where they exert biological functions in regulating gene transcription (12). Molecular mechanisms underlying miRNA-mediated transcriptional gene silencing or activation are complex. Gene activation requires an intact transcript for recognition and a small RNA with complementary pairing to its own sequence, which is capable of recruiting AGO2 to the target (13). In addition, miRNAs and their premature hairpins promote gene transcription by targeting specific sites that are highly complementary to miRNAs in their promoters (14). Nuclear activating miRNAs facilitate gene transcription by binding and activating targeted enhancers (15).

In the present review, the roles of nuclear miRNAs in the progression of different types of tumor were discussed. It focused on the function of these nuclear miRNAs as transcriptional regulators through targeting promoters or enhancers, which results in the alteration of tumor cell proliferation, invasion, metastasis, migration, apoptosis and angiogenesis. This review provides insight into the potential clinical utility of nuclear miRNAs in cancer treatment.

2. miRNAs in urinary system cancers

In this section, the roles of nuclear miRNAs that influence gene transcription in cancers of the urinary system, including prostate cancer (PCa), bladder cancer (BCa), renal cell carcinoma (RCC) and Wilms' tumor (WT), are discussed (Table I).

PCa. PCa is the most common malignancy in males and one of the leading causes of cancer-related mortality worldwide (16). In a study investigating the underlying mechanisms of miRNAs in the development of PCa, miRNAs were found to affect the viability, migration and invasiveness of PCa cells by downregulating and potentially upregulating target genes. Cyclin B1 (CCNB1) overexpression is associated with an aggressive phenotype and functions as an independent prognostic factor in various cancers (17,18). miRNA target prediction analysis and chromatin immunoprecipitation (ChIP) assay revealed that miRNAs, including miR-744 and miR-1186, regulate the transcription of CCNB1 by interacting with distinct binding sites in the CCNB1 promoter and increasing the enrichment of RNA polymerase II (PolII) and trimethylation of histone 3 at lysine 4, thus enhancing the proliferation of PCa cells (19). However, prolonged overexpression of miR-744 and miR-1186 negatively regulates tumor growth in PCa cells as the chromosome composition is altered, consequently leading to chromosomal instability (19). Majid *et al* (20) reported that miR-205 inhibited PCa cell proliferation and impaired cell viability, at least in part by binding to the promoters of interleukin (IL)24 and IL32 and inducing their gene expression, as determined through sequence scanning analysis and luciferase reporter assay. Furthermore, a ChIP assay with biotinylated miRNA confirmed that miR-3619-5p enhanced cyclin-dependent kinase (CDK) inhibitor 1A transcription by interacting with its promoter, suppressing the growth of PCa cells (21). In addition, Zhang *et al* (22) reported that miR-1236-3p activates the expression of P21, a tumor suppressor or oncogene, by interacting with the promoter region, as determined with a sequence scanning analysis, consequently inhibiting the proliferation and metastasis of PCa cells.

BCa. BCa is the most common urinary tract malignancy and has a high incidence worldwide (23,24). Li *et al* (25) performed a luciferase reporter assay and revealed that miR-877-3p increased the expression of P16 by binding to its promoter and significantly suppressing the proliferation and tumorigenicity of BCa cells via inducing G1-phase arrest. This process was mediated by the inhibition of CDKs, such as CDK4 and CDK6 (26). Wang *et al* (27) performed a ChIP assay via biotinylated miRNAs and found that P21 was inhibited by three miRNAs (miR-370-5p, miR-1180-5p and miR-1236-3p) at diverse sites on its promoter to inhibit BCa cell migration and invasion and induce apoptosis. As a subclass of the cadherin family, epithelial cadherin (E-cadherin) has an essential role in maintaining epithelial cell-cell adhesion and intercellular junctions (28). In a ChIP assay with biotinylated miR-373, miR-373 was revealed to facilitate E-cadherin expression by interacting with its gene promoter, with the effect of inhibiting BCa cell proliferation (29). Taken together, these findings support the development of novel therapies based on potentially targeted genes for BCa.

RCC. RCC is a common kidney cancer and the most frequent renal neoplasm (30,31). Wang *et al* (32) investigated the mechanisms underlying the role of miR-1236-3p in RCC progression and found that miR-1236-3p directly targets the P21 promoter to regulate its gene expression by using a ChIP assay with biotinylated miR-1236-3p, with the ultimate effect to inhibit its function and leading to the suppression of RCC cell proliferation. The result of a luciferase reporter assay showed that miR-24-1 overexpression enhanced fructose-1,6-bisphosphatase transcription by increasing its enhancer activity to attenuate RCC proliferation and metastasis (33).

WT. WT is the most common pediatric renal tumor and is associated with nephrogenesis, which may lead to malformations or overgrowth (34). Liu *et al* (35) showed that nuclear miR-483, which is overexpressed in WT, enhanced insulin-like growth factor 2 (IGF2) transcription through interaction with the 5'-UTR of IGF2, as indicated using a biotinylated miRNA-RNA affinity pulldown assay.

3. miRNAs in reproductive system cancers

In this section, the roles of miRNAs via their nuclear functions to influence gene transcription in diseases of the reproductive system were summarized, including breast cancer (BC) and ovarian cancer (OC) (Table II).

BC. BC is one of the most lethal and widespread cancers among females worldwide. It occurs in the epithelial tissue of the mammary gland and comprises diverse morphological characteristics (36,37). In three studies on the role of miRNAs in human BC, the authors performed a luciferase assay to investigate the roles of nuclear miRNAs in gene transcription. Tan *et al* (38) revealed that miRNA-10a mediates the repression of target promoters on homeobox D4 by interfering with promoter-associated transcripts to impact the development of BC. Liang *et al* (39) demonstrated that miR-339 represses the proliferation of BC cells, leading to the upregulation of tumor suppressor gene G protein-coupled estrogen receptor 1 expression by enhancer switching, indicating that miR-339 is a potential target and novel approach for the treatment of BC, particularly for triple-negative BC. In addition, Seviour *et al* (40) verified that, by binding to the P27 promoter, miR-124 induced the transcription of the P27 gene, leading to a subsequent G1-phase arrest. As a tumor suppressor, miR-124 was able to impair the growth of BC and OC cells and sensitize cells to etoposide.

OC. OC is associated with the highest mortality rate among gynecological malignancies (41). Forkhead box (Fox)o3 regulates ovarian follicular development and atresia (42). A luciferase reporter assay and a ChIP assay indicated that the interaction between miR-195-5p and the Foxo3 promoter may be associated with AGO2 recruitment and histone modification, which affect follicular development (43). In addition, Chaluvally-Raghavan *et al* (44) found that miR-551b-3p interacted directly with a complementary sequence within the signal transducer and activator 3 (STAT3) promoter by recruiting PolII, thus facilitating STAT3 transcription. By contrast, silencing miR-551b-3p inhibited the growth of OC cells, as shown using luciferase reporter and DNA pull-down assays.

Table I. Roles of miRNAs in urinary system diseases.

miRNA	Target	Binding site	Transcriptional role	Cellular function	(Refs.)
miR-1186	CCNB1	Promoter (-699 to -678)	Promotion	Affecting the growth of prostate cancer cells	(19)
miR-744	CCNB1	Promoter (-192 to -171)	Promotion		
miR-205	IL24	Promoter (-127 to -107)	Promotion	Inhibiting the progression of prostate cancer cells	(20)
miR-205	IL32	Promoter (-631 to -610)	Promotion		
miR-3619-5p	CDKN1A	promoter (-193 to -176)	Promotion	Inhibiting the growth of prostate cancer cells	(21)
miR-1236-3p	P21	Promoter (-243 to -226)	Promotion	Inhibiting the proliferation and metastasis of prostate cancer cells	(22)
miR-877-3p	P16	Promoter (-320 to -299)	Promotion	Inhibiting the proliferation and tumorigenicity of bladder cancer	(25)
miR-370-5p	P21	Promoter (-552 to -537)	Inhibition	Inhibiting the proliferation, migration and invasion of bladder cancer cells	(27)
miR-1180-5p	P21	Promoter (-397 to -379)			
miR-1236-3p	P21	Promoter (-243 to -226)			
miR-373	E-cadherin	Promoter (-644 to -622)	Promotion	Inhibiting the proliferation, migration and invasion of bladder cancer cells	(29)
miR-1236-3p	P21	Promoter (-243 to -226)	Promotion	Inhibiting RCC cell proliferation	(32)
miR-24-1	FBP1	Enhancer	Promotion	Inhibiting the proliferation and migration of RCC cells	(33)
miR-483-5p	IGF2	/	Promotion	Promoting tumorigenesis of Wilms' tumor	(35)

miRNA/miR, microRNA; RCC, renal cell carcinoma; CCNB1, cyclin B1; CDKN1A, cyclin-dependent kinase inhibitor 1A; FBP1, fructose-1,6-bisphosphatase; IGF, insulin-like growth factor.

4. miRNAs in nervous system cancers

In this section, the roles of miRNAs in nervous system diseases, including glioma and neuroblastoma (NB), were summarized (Table III).

Glioma. Gliomas account for the majority of primary malignant and central nervous system tumors and are associated with high morbidity and mortality (45,46). Wang *et al* (47) reported that miR-215-5p increases the development of aggressive phenotypes, facilitates cell proliferation and migration, and represses apoptosis in gliomas at least in part by negatively regulating the expression of protocadherin 9 via targeting both its promoter and 3'-UTR, as determined by sequence scanning analysis and a luciferase reporter assay.

NB. NB is a common extracranial solid tumor in children, mostly under the age of 10 years (48), and is an embryonal neoplasm of the sympathetic nervous system (49,50). NB exhibits clinical heterogeneity in response to current monotherapies (51,52). Researchers have studied the mechanisms underlying the role of miRNAs in NB. Luciferase reporter and ChIP assays demonstrated that miR-584-5p (53) and miR-337-3p (54) are involved in repressing the transcription of matrix metalloproteinase (MMP-14) by binding to different binding sites of its promoter, recruiting AGO2 and attenuating the proliferation, invasion, metastasis and angiogenesis of NB (55). By contrast, using a sequence scanning analysis and luciferase reporter assay, Qu *et al* (56) found that miR-558 facilitates the transcription of heparinase (HPSE) by binding to the MMP-14 promoter, recruiting AGO1 to promote the proliferation, invasion, metastasis and angiogenesis of NB.

5. miRNAs in digestive system cancers

In this section, the roles of miRNAs via their nuclear functions that influence gene transcription in digestive system diseases,

Table II. miRNAs in reproductive system cancers.

miRNA	Target	Binding site	Transcriptional role	Cellular function	(Refs.)
miR-10a	HOXD4	Promoter	Inhibition	Affecting human breast cancer cell development	(38)
miR-339	GPER1	Enhancer	Promotion	Inhibiting the proliferation of breast cancer cells	(39)
miR-124	P27	Promoter (-545 to -533)	Promotion	Inhibiting breast and ovarian cancer growth	(40)
miR-551b-3p	STAT3	Promoter (-530 to -503)	Promotion	Promoting the growth of ovarian cancer cells	(44)

miRNA/miR, microRNA; HOX, homeobox; GPER1, G protein-coupled estrogen receptor 1.

Table III. Role of miRNAs in nervous system cancers.

miRNA	Target	Binding site	Transcriptional role	Cellular function	(Refs.)
miR-215-5p	PCDH9	Promoter	Inhibition	Promoting glioma cell proliferation	(47)
miR-584-5p	MMP-14	Promoter (-167 to -150)	Inhibition	Inhibiting the growth, metastasis, invasion and angiogenesis of NB cells	(53)
miR-337-3p	MMP-14	Promoter (-90 to -71)	Inhibition	Inhibiting the growth, metastasis, invasion and angiogenesis of NB cells	(54)
miR-558	HPSE	Promoter (-2332 to -2314)	Promotion	Promoting the growth, metastasis, invasion and angiogenesis of NB cells	(56)

miRNA/miR, microRNA; NB, neuroblastoma; PCDH9, protocadherin 9; MMP, matrix metalloproteinase; HPSE, heparinase.

including colon cancer and gastric cancer (GC), were summarized (Table IV).

Colon cancer. Colon cancer is a malignant tumor and a common cause of cancer-related death worldwide, which may spread to organs such as the lymph nodes, liver, lungs and ovaries (57). P21 is a CDK inhibitor that is frequently deregulated in cancers, depending on the cellular context (58). Kang *et al* (59) performed a ChIP assay and found that miR-6734 induced the transcription of P21 and attenuated the proliferation and survival of HCT-116 cells by facilitating cell cycle arrest and apoptosis.

GC. GC is a heterogeneous disease and the fifth most common cancer type worldwide (37). The pathogenesis of GC is multifactorial and is associated with smoking and *Helicobacter pylori* infection (60). MMP-14 has a pivotal role in activating MMP-2 and is elevated in most human cancers, including GC (61), where it promotes tumor invasion and metastasis (62). A luciferase reporter assay indicated that miR-337-3p interacts directly with the MMP-14 promoter within the -90 to -71 bp region to repress myeloid zinc finger 1-facilitated MMP-14 expression through inducing repressive chromatin remodeling and recruiting AGO2, thus suppressing the growth, metastasis, invasion and angiogenesis of GC cells (63).

HPSE is amplified and overexpressed in GC specimens (64). HSPE exerts a crucial role in extracellular matrix degradation, facilitating the growth, invasiveness, metastasis and angiogenesis of tumors (65). Luciferase reporter and ChIP assays found that miR-558, which is upregulated in GC, targets the complementary site within the HPSE promoter to induce its expression, facilitating GC progression, metastasis and angiogenesis (66).

6. miRNAs in respiratory system cancers

In this section, the roles of miRNAs in respiratory system diseases were summarized, including non-small-cell lung cancer (NSCLC) and nasopharyngeal carcinoma (NPC) (Table V).

NSCLC. Lung cancer is the leading cause of cancer-related morbidity and mortality in China, and NSCLC accounts for the overwhelming majority of lung cancer cases (67). miR-1236-3p and miR-370-5p negatively regulate the proliferation, migration and invasiveness of NSCLC cells at least in part by targeting the promoter of the P21 gene to upregulate its expression, as indicated using sequence scanning analysis (68). As a major component of the activator protein-1 complex, c-Fos has been implicated in cell differentiation, proliferation, motility,

Table IV. miRNAs in digestive system cancers.

miRNA	Target	Binding site	Transcriptional role	Cellular function	(Refs.)
miR-6734	P21	Promoter (-322 to -303)	Promotion	Inhibiting the growth of colon cancer cells	(59)
miR-337-3p	MMP-14	Promoter (-90 to -71)	Inhibition	Inhibiting the growth, invasion, metastasis and angiogenesis of gastric cancer cells	(63)
miR-558	HPSE	Promoter (-2332 to -2314)	Promotion	Promoting the tumorigenesis and aggressiveness of gastric cancer cells	(66)

miRNA/miR, microRNA; MMP, matrix metalloproteinase; HPSE, heparinase.

Table V. miRNAs in respiratory system cancers.

miRNA	Target	Binding site	Transcriptional role	Cellular function	(Refs.)
miR-1236-3p	P21	Promoter (-243 to -226)	Promotion	Inhibiting the growth of NSCLC cells	(68)
miR-370-5p	P21	Promoter (-552 to -537)			
miR-744	c-Fos	Promoter (-1195 to -1227, -298 to -323)	Promotion	Promoting the growth and metastasis of NSCLC cells	(70)
miR-26A1	VILL	Enhancer	Promotion	Inhibiting the proliferation and metastasis of NSCLC cells	(71)
miR-744	ARHGAP5	Promoter (-508 to -484, -200 to -176)	Promotion	Promoting nasopharyngeal carcinoma cell invasion and migration	(74)

miRNA/miR, microRNA; NSCLC, non-small cell lung cancer; VILL, villin 1-like; ARHGAP5, Rho GTPase activating protein 5.

cancer growth, angiogenesis, invasion and metastasis (69). The results of a luciferase reporter assay indicated that miR-744 acts as an oncogene in NSCLC cell growth and metastasis at least in part by directly binding to the promoter of c-Fos (70). Li *et al* (71) found that miR-26A1 is decreased in NSCLC and used luciferase reporter and ChIP assays to demonstrate that miR-26A1 acts as a key regulator in reactivating villin 1-like protein by targeting its enhancer, leading to the inhibition of the proliferation and metastasis of NSCLC cells.

NPC. NPC is a malignant tumor associated with a specific geographical distribution in Southeast Asia and North Africa (72,73). Rho GTPase activating protein 5 (ARHGAP5), a proto-oncogene, is a direct target of miR-744. Using a luciferase reporter assay, Fang *et al* (74) found that miR-744 facilitates expression at the transcriptional level by directly targeting the ARHGAP5 promoter, consequently enhancing the progression and metastasis of NPC.

7. Conclusion and perspectives

Cancers are devastating to all physiological systems. Growth, invasion, metastasis and angiogenesis of cancer cells affect all organ systems and subsequently, morbidity and mortality (75). The effects of miRNAs in cancer through their action on the 3'-UTRs of relevant genes at the post-transcriptional level have been well-established. However, nuclear miRNAs have been reported to be aberrantly expressed in various cancers and other diseases. The present review outlines the current understanding of the contribution of nuclear miRNAs to cancer progression of different organs at the transcriptional level, as they mostly interact with gene promoters or enhancers (Fig. 1), suggesting that nuclear miRNAs may serve as promising candidate biomarkers for predicting prognosis and enhancing therapeutic strategies for patients with cancer.

Over the past decade, non-coding RNAs, including long non-coding RNAs and miRNAs, have emerged as powerful regulatory molecules in human diseases (76-84). Among them, nuclear miRNAs have been reported to be upregulated or downregulated in cancers and promote or inhibit the transcription of cancer progression-related genes. However, the roles and underlying molecular mechanisms of a specific nuclear miRNA vary greatly from cancer to cancer. For instance, miR-744 expression has been shown to be upregulated in PCa, NSCLC and NPC. In PCa, miR-744 targets

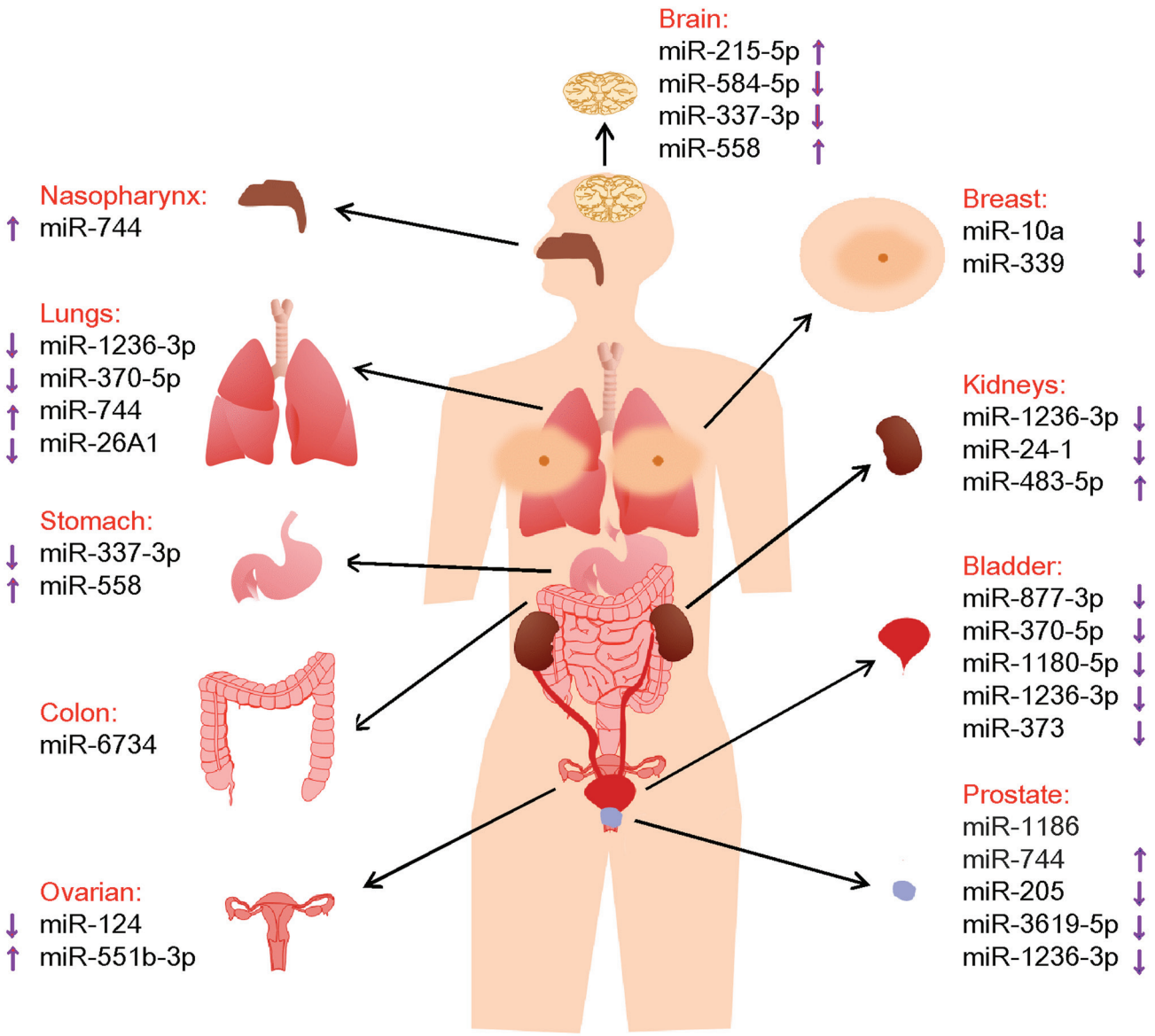

Figure 1. Schematic model showing the roles of nuclear miRs in the cancer progression of different organs. miR, microRNA.

the *CCNB1* gene promoter to initiate gene transcription by increasing the enrichment of PolII and trimethylation of histone 3 at lysine 4 at the *CCNB1* gene transcription start site (19). In NSCLC, miR-744 promoted the growth, invasion and metastasis of NSCLC cells at least in part by binding to the *c-FOS* gene promoter and induce gene transcription (70). In NPC, miR-744 was observed to be associated with TNM stage, cancer progression and metastasis at least in part by targeting the *ARHGAP5* gene and activating gene transcription (74).

At present, several miRNA-targeted therapeutics are in clinical development for the treatment of diseases, including keloids, hepatitis C virus infection, nonalcoholic fatty liver disease, type II diabetes, Huntington's disease and cancer; however, none has been approved by the Food and Drug Administration or the European Medicines Agency to treat cancers (85). Key challenges faced by miRNA-based therapeutics are the hurdles of specific delivery, immune responses and low specificity. Therefore, technical advancements in pharmacology, molecular biology, immunology and nanotechnology are needed to improve specificity, tolerance and delivery. In addition, more studies are required to reveal the underlying mechanisms by which nuclear miRNAs regulate gene transcription, such as the mechanisms by which nuclear miRNAs can be recruited to and retained in the nucleus, whether AGO proteins are required to the effects of nuclear miRNAs on gene transcription, and whether the interaction between nuclear miRNAs and promoters or enhancers influences the transcription of surrounding genes.

In summary, the present review summarizes and discusses nuclear miRNAs' centric regulation of gene transcription and their roles in cancer of various bodily systems, indicating that nuclear miRNAs may be potent targets for the treatment of cancers and other pathological disorders.

Acknowledgements

Not applicable.

Funding

This work was supported by the Shandong Provincial Natural Science Foundation (grant nos. ZR2020LZL008 and ZR2021LSW017).

Availability of data and materials

Not applicable.

Authors' contributions

ZW: Conceptualization, writing-original draft, supervision, writing-review & editing. YZ: Writing-original draft. KL: Conceptualization, supervision, writing-review & editing. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Omer AD, Janas MM and Novina CD: The chicken or the egg: microRNA-mediated regulation of mRNA translation or mRNA stability. Mol Cell 35: 739-740, 2009.
2. Lee RC, Feinbaum RL and Ambros V: The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell 75: 843-854, 1993.
3. Wightman B, Ha I and Ruvkun G: Posttranscriptional regulation of the heterochronic gene lin-14 by lin-4 mediates temporal pattern formation in C. elegans. Cell 75: 855-862, 1993.
4. Wang Z, Lu Y, Zhang X, Ren X, Wang Y, Li Z, Xu C and Han J: Serum microRNA is a promising biomarker for osteogenesis imperfecta. Intractable Rare Dis Res 1: 81-85, 2012.
5. Wang ZQ, Lu YQ and Han JX: MicroRNAs: Important mediators of ossification. Chin Med J (Engl) 125: 4111-4116, 2012.
6. Wang Z, Li K, Wang X and Huang W: MiR-155-5p modulates HSV-1 replication via the epigenetic regulation of SRSF2 gene expression. Epigenetics 14: 494-503, 2019.
7. Li K, Yao T, Zhang Y, Li W and Wang Z: NEAT1 as a competing endogenous RNA in tumorigenesis of various cancers: Role, mechanism and therapeutic potential. Int J Biol Sci 17: 3428-3440, 2021.
8. Li K and Wang Z: Non-coding RNAs: Key players in T cell exhaustion. Front Immunol 13: 959729, 2022.
9. Li K, Yao T and Wang Z: lncRNA-mediated ceRNA network in bladder cancer. Noncoding RNA Res 8: 135-145, 2022.
10. Wang Z, Lu Y and Han J: Peripheral blood microRNAs: A novel tool for diagnosing disease? Intractable Rare Dis Res 1: 98-102, 2012.
11. O'Brien J, Hayder H, Zayed Y and Peng C: Overview of MicroRNA biogenesis, mechanisms of actions, and circulation. Front Endocrinol (Lausanne) 9: 402, 2018.
12. Taft RJ, Simons C, Nahkuri S, Oey H, Korbie DJ, Mercer TR, Holst J, Ritchie W, Wong JJL, Rasko JEJ, *et al*: Nuclear-localized tiny RNAs are associated with transcription initiation and splice sites in metazoans. Nat Struct Mol Biol 17: 1030-1034, 2010.
13. Matsui M, Chu Y, Zhang H, Gagnon KT, Shaikh S, Kuchimanchi S, Manoharan M, Corey DR and Janowski BA: Promoter RNA links transcriptional regulation of inflammatory pathway genes. Nucleic Acids Res 41: 10086-10109, 2013.
14. Place RF, Li LC, Pookot D, Noonan EJ and Dahiya R: MicroRNA-373 induces expression of genes with complementary promoter sequences. Proc Natl Acad Sci USA 105: 1608-1613, 2008.
15. Zou Q, Liang Y, Luo H and Yu W: miRNA-mediated RNAa by targeting enhancers. Adv Exp Med Biol 983: 113-125, 2017.
16. Siegel RL, Miller KD, Fuchs HE and Jemal A: Cancer statistics, 2022. CA Cancer J Clin 72: 7-33, 2022.
17. Aaltonen K, Amini RM, Heikkilä P, Aittomäki K, Tamminen A, Nevanlinna H and Blomqvist C: High cyclin B1 expression is associated with poor survival in breast cancer. Br J Cancer 100: 1055-1060, 2009.
18. Yuan J, Yan R, Krämer A, Eckerdt F, Roller M, Kaufmann M and Strebhardt K: Cyclin B1 depletion inhibits proliferation and induces apoptosis in human tumor cells. Oncogene 23: 5843-5852, 2004.
19. Huang V, Place RF, Portnoy V, Wang J, Qi Z, Jia Z, Yu A, Shuman M, Yu J and Li LC: Upregulation of cyclin B1 by miRNA and its implications in cancer. Nucleic Acids Res 40: 1695-1707, 2012.
20. Majid S, Dar AA, Saini S, Yamamura S, Hirata H, Tanaka Y, Deng G and Dahiya R: MicroRNA-205-directed transcriptional activation of tumor suppressor genes in prostate cancer. Cancer 116: 5637-5649, 2010.
21. Li S, Wang C, Yu X, Wu H, Hu J, Wang S and Ye Z: miR-3619-5p inhibits prostate cancer cell growth by activating CDKN1A expression. Oncol Rep 37: 241-248, 2017.
22. Zhang Q, Yang X, Luo L, Ma X, Jiao W, Li B, Zhang M, Zhao K and Niu H: Targeted p21 activation by a new double stranded RNA suppresses human prostate cancer cells growth and metastasis. Am J Transl Res 12: 4175-4188, 2020.
23. Dobruch J and Oszczudłowski M: Bladder cancer: Current challenges and future directions. Medicina (Kaunas) 57: 749, 2021.
24. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global cancer statistics 2020: GLOBOCAN Estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71: 209-249, 2021.
25. Li S, Zhu Y, Liang Z, Wang X, Meng S, Xu X, Xu X, Wu J, Ji A, Hu Z, *et al*: Up-regulation of p16 by miR-877-3p inhibits proliferation of bladder cancer. Oncotarget 7: 51773-51783, 2016.
26. Liggett WH Jr and Sidransky D: Role of the p16 tumor suppressor gene in cancer. J Clin Oncol 16: 1197-1206, 1998.
27. Wang C, Chen Z, Ge Q, Hu J, Li F, Hu J, Xu H, Ye Z and Li LC: Up-regulation of p21(WAF1/CIP1) by miRNAs and its implications in bladder cancer cells. FEBS Lett 588: 4654-4664, 2014.
28. Oka H, Shiozaki H, Kobayashi K, Inoue M, Tahara H, Kobayashi T, Takatsuka Y, Matsuyoshi N, Hirano S, Takeichi M, *et al*: Expression of E-cadherin cell adhesion molecules in human breast cancer tissues and its relationship to metastasis. Cancer Res 53: 1696-1701, 1993.
29. Zhang Q, Wang C, Miao S, Li C, Chen Z and Li F: Enhancing E-cadherin expression via promoter-targeted miR-373 suppresses bladder cancer cells growth and metastasis. Oncotarget 8: 93969-93983, 2017.
30. Siddiqi A, Rani M, Bansal P and Rizvi MMA: Renal cell carcinoma management: A step to nano-chemoprevention. Life Sci 308: 120922, 2022.
31. Ljungberg B, Bensalah K, Canfield S, Dabestani S, Hofmann F, Hora M, Kuczyk MA, Lam T, Marconi L, Merseburger AS, *et al*: EAU guidelines on renal cell carcinoma: 2014 Update. Eur Urol 67: 913-924, 2015.
32. Wang C, Tang K, Li Z, Chen Z, Xu H and Ye Z: Targeted p21(WAF1/CIP1) activation by miR-1236 inhibits cell proliferation and correlates with favorable survival in renal cell carcinoma. Urol Oncol 34: 59.e23-e34, 2016.
33. Ju D, Liang Y, Hou G, Zheng W, Zhang G, Dun X, Wei D, Yan F, Zhang L, Lai D, *et al*: FBP1/miR-24-1/enhancer axis activation blocks renal cell carcinoma progression via Warburg effect. Front Oncol 12: 928373, 2022.
34. Treger TD, Chowdhury T, Pritchard-Jones K and Behjati S: The genetic changes of Wilms tumour. Nat Rev Nephrol 15: 240-251, 2019.
35. Liu M, Roth A, Yu M, Morris R, Bersani F, Rivera MN, Lu J, Shioda T, Vasudevan S, Ramaswamy S, *et al*: The IGF2 intronic miR-483 selectively enhances transcription from IGF2 fetal promoters and enhances tumorigenesis. Genes Dev 27: 2543-2548, 2013.
36. Giaquinto AN, Sung H, Miller KD, Kramer JL, Newman LA, Minihan A, Jemal A and Siegel RL: Breast cancer statistics, 2022. CA Cancer J Clin 72: 524-541, 2022.

37. Miller KD, Nogueira L, Mariotto AB, Rowland JH, Yabroff KR, Alfano CM, Jemal A, Kramer JL and Siegel RL: Cancer treatment and survivorship statistics, 2019. CA Cancer J Clin 69: 363-385, 2019.
38. Tan Y, Zhang B, Wu T, Skogerbø G, Zhu X, Guo X, He S and Chen R: Transcriptional inhibiton of Hoxd4 expression by miRNA-10a in human breast cancer cells. BMC Mol Biol 10: 12, 2009.
39. Liang Y, Lu Q, Li W, Zhang D, Zhang F, Zou Q, Chen L, Tong Y, Liu M, Wang S, *et al*: Reactivation of tumour suppressor in breast cancer by enhancer switching through NamiRNA network. Nucleic Acids Res 49: 8556-8572, 2021.
40. Seviour EG, Sehgal V, Lu Y, Luo Z, Moss T, Zhang F, Hill SM, Liu W, Maiti SN, Cooper L, *et al*: Functional proteomics identifies miRNAs to target a p27/Myc/phospho-Rb signature in breast and ovarian cancer. Oncogene 35: 691-701, 2016.
41. Coburn SB, Bray F, Sherman ME and Trabert B: International patterns and trends in ovarian cancer incidence, overall and by histologic subtype. Int J Cancer 140: 2451-2460, 2017.
42. Cui C, Han S, Yin H, Luo B, Shen X, Yang F, Liu Z, Zhu Q, Li D and Wang Y: FOXO3 is expressed in ovarian tissues and acts as an apoptosis initiator in granulosa cells of chickens. Biomed Res Int 2019: 6902906, 2019.
43. Bai Y, Pan B, Zhan X, Silver H and Li J: MicroRNA 195-5p targets Foxo3 promoter region to regulate its expression in granulosa cells. Int J Mol Sci 22: 6721, 2021.
44. Chaluvally-Raghavan P, Jeong KJ, Pradeep S, Silva AM, Yu S, Liu W, Moss T, Rodriguez-Aguayo C, Zhang D, Ram P, *et al*: Direct upregulation of STAT3 by MicroRNA-551b-3p deregulates growth and metastasis of ovarian cancer. Cell Rep 15: 1493-1504, 2016.
45. Miller KD, Ostrom QT, Kruchko C, Patil N, Tihan T, Cioffi G, Fuchs HE, Waite KA, Jemal A, Siegel RL and Barnholtz-Sloan JS: Brain and other central nervous system tumor statistics, 2021. CA Cancer J Clin 71: 381-406, 2021.
46. Fang Y, Zhang G, Bai Z, Yan Y, Song X, Zhao X, Yang P and Zhang Z: Low-intensity ultrasound: A novel technique for adjuvant treatment of gliomas. Biomed Pharmacother 153: 113394, 2022.
47. Wang C, Chen Q, Li S, Li S, Zhao Z, Gao H, Wang X, Li B, Zhang W, Yuan Y, *et al*: Dual inhibition of PCDH9 expression by miR-215-5p up-regulation in gliomas. Oncotarget 8: 10287-10297, 2017.
48. Cheung NK and Dyer MA: Neuroblastoma: Developmental biology, cancer genomics and immunotherapy. Nat Rev Cancer 13: 397-411, 2013.
49. Qiu B and Matthay KK: Advancing therapy for neuroblastoma. Nat Rev Clin Oncol 19: 515-533, 2022.
50. Gomez RL, Ibragimova S, Ramachandran R, Philpott A and Ali FR: Tumoral heterogeneity in neuroblastoma. Biochim Biophys Acta Rev Cancer 1877: 188805, 2022.
51. Johnsen JI, Dyberg C and Wickström M: Neuroblastoma-a neural crest derived embryonal malignancy. Front Mol Neurosci 12: 9, 2019.
52. Lin L, Miao L, Lin H, Cheng J, Li M, Zhuo Z and He J: Targeting RAS in neuroblastoma: Is it possible? Pharmacol Ther 236: 108054, 2022.
53. Xiang X, Mei H, Qu H, Zhao X, Li D, Song H, Jiao W, Pu J, Huang K, Zheng L and Tong Q: miRNA-584-5p exerts tumor suppressive functions in human neuroblastoma through repressing transcription of matrix metalloproteinase 14. Biochim Biophys Acta 1852: 1743-1754, 2015.
54. Xiang X, Mei H, Zhao X, Pu J, Li D, Qu H, Jiao W, Zhao J, Huang K, Zheng L and Tong Q: miRNA-337-3p suppresses neuroblastoma progression by repressing the transcription of matrix metalloproteinase 14. Oncotarget 6: 22452-22466, 2015.
55. Mei H, Lin ZY and Tong QS: The roles of microRNAs in neuroblastoma. World J Pediatr 10: 10-16, 2014.
56. Qu H, Zheng L, Pu J, Mei H, Xiang X, Zhao X, Li D, Li S, Mao L, Huang K and Tong Q: miRNA-558 promotes tumorigenesis and aggressiveness of neuroblastoma cells through activating the transcription of heparanase. Hum Mol Genet 24: 2539-2551, 2015.
57. PDQ Adult Treatment Editorial Board. Colon Cancer Treatment (PDQ®): Patient version. 2022 Apr 6. In: PDQ Cancer Information Summaries (Internet). Bethesda (MD): National Cancer Institute (US); 2002.
58. Abbas T and Dutta A: p21 in cancer: Intricate networks and multiple activities. Nat Rev Cancer 9: 400-414, 2009.
59. Kang MR, Park KH, Yang JO, Lee CW, Oh SJ, Yun J, Lee MY, Han SB and Kang JS: miR-6734 Up-regulates p21 gene expression and induces cell cycle arrest and apoptosis in colon cancer cells. PLoS One 11: e0160961, 2016.
60. Watari J, Chen N, Amenta PS, Fukui H, Oshima T, Tomita T, Miwa H, Lim KJ and Das KM: Helicobacter pylori associated chronic gastritis, clinical syndromes, precancerous lesions, and pathogenesis of gastric cancer development. World J Gastroenterol 20: 5461-5473, 2014.
61. He L, Chu D, Li X, Zheng J, Liu S, Li J, Zhao Q and Ji G: Matrix metalloproteinase-14 is a negative prognostic marker for patients with gastric cancer. Dig Dis Sci 58: 1264-1270, 2013.
62. Imanishi Y, Fujii M, Tokumaru Y, Tomita T, Kanke M, Kanzaki J, Kameyama K, Otani Y and Sato H: Clinical significance of expression of membrane type 1 matrix metalloproteinase and matrix metalloproteinase-2 in human head and neck squamous cell carcinoma. Hum Pathol 31: 895-904, 2000.
63. Zheng L, Jiao W, Mei H, Song H, Li D, Xiang X, Chen Y, Yang F, Li H, Huang K and Tong Q: miRNA-337-3p inhibits gastric cancer progression through repressing myeloid zinc finger 1-facilitated expression of matrix metalloproteinase 14. Oncotarget 7: 40314-40328, 2016.
64. Takaoka M, Naomoto Y, Ohkawa T, Uetsuka H, Shirakawa Y, Uno F, Fujiwara T, Gunduz M, Nagatsuka H, Nakajima M, *et al*: Heparanase expression correlates with invasion and poor prognosis in gastric cancers. Lab Invest 83: 613-622, 2003.
65. Hulett MD, Freeman C, Hamdorf BJ, Baker RT, Harris MJ and Parish CR: Cloning of mammalian heparanase, an important enzyme in tumor invasion and metastasis. Nat Med 5: 803-809, 1999.
66. Zheng L, Jiao W, Song H, Qu H, Li D, Mei H, Chen Y, Yang F, Li H, Huang K and Tong Q: miRNA-558 promotes gastric cancer progression through attenuating Smad4-mediated repression of heparanase expression. Cell Death Dis 7: e2382, 2016.
67. Gao S, Li N, Wang S, Zhang F, Wei W, Li N, Bi N, Wang Z and He J: Lung cancer in People's Republic of China. J Thorac Oncol 15: 1567-1576, 2020.
68. Li C, Ge Q, Liu J, Zhang Q, Wang C, Cui K and Chen Z: Effects of miR-1236-3p and miR-370-5p on activation of p21 in various tumors and its inhibition on the growth of lung cancer cells. Tumour Biol 39: 1010428317710824, 2017.
69. Liu ZG, Jiang G, Tang J, Wang H, Feng G, Chen F, Tu Z, Liu G, Zhao Y, Peng MJ, *et al*: c-Fos over-expression promotes radioresistance and predicts poor prognosis in malignant glioma. Oncotarget 7: 65946-65956, 2016.
70. Li S, Qiao S, Li N and Zhu X: MiR-744 functions as an oncogene through direct binding to c-Fos promoter and facilitates non-small cell lung cancer progression. Ann Surg Oncol 29: 1465-1475, 2022.
71. Li H, Da D, Yu W, Chen L, Yang S, Zhang B, Wang Y, Li L and Dang C: Tumor suppressor genes are reactivated by miR-26A1 via enhancer reprogramming in NSCLC. Hum Mol Genet 32: 79-92, 2023.
72. Chen YP, Chan ATC, Le QT, Blanchard P, Sun Y and Ma J: Nasopharyngeal carcinoma. Lancet 394: 64-80, 2019.
73. McDermott AL, Dutt SN and Watkinson JC: The aetiology of nasopharyngeal carcinoma. Clin Otolaryngol Allied Sci 26: 82-92, 2001.
74. Fang Y, Zhu X, Wang J, Li N, Li D, Sakib N, Sha Z and Song W: MiR-744 functions as a proto-oncogene in nasopharyngeal carcinoma progression and metastasis via transcriptional control of ARHGAP5. Oncotarget 6: 13164-13175, 2015.
75. Fares J, Fares MY, Khachfe HH, Salhab HA and Fares Y: Molecular principles of metastasis: A hallmark of cancer revisited. Signal Transduct Target Ther 5: 28, 2020.
76. Li K and Wang Z: lncRNA NEAT1: Key player in neurodegenerative diseases. Ageing Res Rev 86: 101878, 2023.
77. Yang T, Wang Y, Liao W, Zhang S, Wang S, Xu N, Xie W, Luo C, Wang Y, Wang Z and Zhang Y: Down-regulation of EPB41L4A-AS1 mediated the brain aging and neurodegenerative diseases via damaging synthesis of NAD^+ and ATP. Cell Biosci 11: 192, 2021.
78. Li K and Wang Z: Speckles and paraspeckles coordinate to regulate HSV-1 genes transcription. Commun Biol 4: 1207, 2021.
79. Wang Z, Zhang S and Li K: LncRNA NEAT1 induces autophagy through epigenetic regulation of autophagy-related gene expression in neuroglial cells. J Cell Physiol 237: 824-832, 2022.

80. Zhao Y, Wang Z, Mao Y, Li B, Zhu Y, Zhang S, Wang S, Jiang Y, Xu N, Xie Y, *et al*: NEAT1 regulates microtubule stabilization via FZD3/GSK3β/P-tau pathway in SH-SY5Y cells and APP/PS1 mice. Aging (Albany NY) 12: 23233-23250, 2020.
81. Wang Z, Zhao Y, Xu N, Zhang S, Wang S, Mao Y, Zhu Y, Li B, Jiang Y, Tan Y, *et al*: NEAT1 regulates neuroglial cell mediating Aβ clearance via the epigenetic regulation of endocytosis-related genes expression. Cell Mol Life Sci 76: 3005-3018, 2019.
82. Wang Z, Zhao Y and Zhang Y: Viral lncRNA: A regulatory molecule for controlling virus life cycle. Noncoding RNA Res 2: 38-44, 2017.
83. Wang Z, Fan P, Zhao Y, Zhang S, Lu J, Xie W, Jiang Y, Lei F, Xu N and Zhang Y: NEAT1 modulates herpes simplex virus-1 replication by regulating viral gene transcription. Cell Mol Life Sci 74: 1117-1131, 2017.
84. Wang Z, Li K and Huang W: Long non-coding RNA NEAT1-centric gene regulation. Cell Mol Life Sci 77: 3769-3779, 2020.
85. Winkle M, El-Daly SM, Fabbri M and Calin GA: Noncoding RNA therapeutics-challenges and potential solutions. Nat Rev Drug Discov 20: 629-651, 2021.