*Review Article*

# Epi-miRNAs: Regulators of the Histone Modification Machinery in Human Cancer

**Deniz Mortazavi,[1] Behnoush Sohrabi,[2] Meysam Mosallaei,[3] Ziba Nariman-Saleh-Fam,[4] Milad Bastami,[5] Yaser Mansoori,[5] Abdolreza Daraei,[6] Sepideh Zununi Vahed,[7] Shadan Navid,[8] Zahra Saadatian [ID],[9] Tannaz Jamialahmadi,[10] Yong Teng [ID],[11] and Amirhossein Sahebkar [ID][12,13,14,15]**

[1]*Koç University Research Center for Translational Medicine, Istanbul, Turkey*
[2]*Department of Biology, Faculty of Sciences, Arak University, Arak, Iran*
[3]*Department of Genetics and Molecular Biology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran*
[4]*Women's Reproductive Health Research Center, Tabriz University of Medical Sciences, Tabriz, Iran*
[5]*Non Communicable Diseases Research Center, Fasa University of Medical Sciences, Fasa, Iran*
[6]*Department of Medical Genetics, School of Medicine, Babol University of Medical Sciences, Babol, Iran*
[7]*Kidney Research Center, Tabriz University of Medical Sciences, Tabriz, Iran*
[8]*Department of Anatomy, Faculty of Medicine, Social Determinants of Health Research Center, Gonabad University of Medical Science, Gonabad, Iran*
[9]*Department of Physiology, Faculty of Medicine, Infectious Diseases Research Center, Gonabad University of Medical Sciences, Gonabad, Iran*
[10]*Department of Nutrition, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*
[11]*Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA 30322, USA*
[12]*Applied Biomedical Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran*
[13]*Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran*
[14]*Department of Medical Biotechnology and Nanotechnology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*
[15]*Department of Biotechnology, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran*

Correspondence should be addressed to Zahra Saadatian; z.saadatian@yahoo.com and Amirhossein Sahebkar; amir_saheb2000@yahoo.com

Cancer is a leading cause of death and disability worldwide. Epigenetic deregulation is one of the most critical mechanisms in carcinogenesis and can be classified into effects on DNA methylation and histone modification. MicroRNAs are small noncoding RNAs involved in fine-tuning their target genes after transcription. Various microRNAs control the expression of histone modifiers and are involved in a variety of cancers. Therefore, overexpression or downregulation of microRNAs can alter cell fate and cause malignancies. In this review, we discuss the role of microRNAs in regulating the histone modification machinery in various cancers, with a focus on the histone-modifying enzymes such as acetylases, deacetylases, methyltransferases, demethylases, kinases, phosphatases, desumoylases, ubiquitinases, and deubiquitinases. Understanding of microRNA-related aberrations underlying histone modifiers in pathogenesis of different cancers can help identify novel therapeutic targets or early detection approaches that allow better management of patients or monitoring of treatment response.

## 1. Introduction

Epigenetics is defined as stable and heritable alterations in gene expression and cellular function without changes to the original DNA sequence and can still be passed on from generation to generation [1]. This term was first used to describe gene-environment interactions that lead to manifestations of various phenotypes during development. Epigenetic changes are perceived to be key contributors to cell differentiation and acquisition of different cell fates with the background of the same genome. DNA methylation, histone modification, and RNA modifications are crucial components of epigenetics [2–4].

DNA methylation is defined as the addition of methyl groups ($CH_3$) on cytosine residues of CpG islands, especially those located in the gene promoter region [2, 5]. For instance, the promoter regions of microRNA (miR) 101-2, miR-126, miR-148a, miR-152, and miR-185-5p are hypomethylated in prostate cancer [6], and the promoter region of miR-200b is hypermethylated in the metastatic phase of the same disease, leading to increased and decreased gene expression [7].

Histone modification is a post-translational rearrangement of histone proteins driven by methylation, acetylation, phosphorylation, ubiquitylation, and sumoylation [8]. RNA modification and noncoding RNA-associated gene silencing are involved in epigenetics by DNA methylation and/or histone modifications in two ways: (1) changing the structure of RNA and interference with RNA and proteins interactions and (2) inciting subsequent events by altered RNA-binding proteins (RBPs) [4].

These regulatory mechanisms can cause gene expression to be turned on or off [8]. Several studies have suggested that such modifications may play a role in inducing various disorders, most notably cancer [9]. Aberrant regulation of proteins or enzymes that regulate these modifications is a common feature in most cancers [9]. Among the multiple gene expression events regulated by these enzymes, the most pivotal genes controlling the cell cycle are refined into oncogenes or tumor suppressors [10].

MicroRNAs (miRNAs and miRs) are small noncoding RNAs with a length of approximately 22 nucleotides [11]. In the nucleus, they are first transcribed as 70 base-pair long double-stranded pri-miRNAs containing stem-loop structures [11]. Then, they undergo a cascade of processes in which they are converted to pre-miRNAs and transmitted to the cytoplasm, where they are cleaved to form single-stranded mature miRNAs [11]. With the cooperation of the RNA-induced silencing complex (RISC), mature miRNAs can seek and bind to complementary sequences in the target mRNA [11]. Depending on the exact or imprecise miRNA-mRNA interactions, mRNA eradication or translational hindrance will occur [11].

Cancer development is a multistep process, and genetic alterations in every step are manifested by significant dysregulation of proteins involved in cell cycle regulation, which may have been triggered by miRNAs [11, 12].

miRNAs can accomplish this by not only directly blocking the expression of the targeted genes but also by regulating the expression of epigenetic modifiers as well as histone methylases that play role in chromosomal structural changes [12, 13]. Hence, microRNAs can also participate in regulating epigenetic mechanisms in cancer, and their abnormal expression profiles have been frequently indicated in malignancies.

This review will discuss histone modifications and the microRNA-mediated regulation of the histone modification machinery in cancer.

## 2. Alterations of Histone Modification in Cancer

Histones are lysine–arginine abundant proteins involved in chromosome condensation, consisting of four core types (H2A, H2B, H3, and H4) located in the bead of the nucleosome, along with two linker histones (H1/H5). The amino and carboxy termini of these proteins may undergo modifications, such as methylation, acetylation, phosphorylation, sumoylation, ubiquitination, and ADP-ribosylation, which are pivotal for transcriptional regulation. The addition of acetyl group on lysine residues of the H3 and H4 classes of histones results in a lightly packed chromosome structure and transcription activation [14]. Lysine residues can be mono-, di-, or trimethylated although arginine residues can only be mono- or dimethylated. Functioning like a double-edged sword, histone methylation may lead to the development of either heterochromatin or euchromatin structures depending on factors such as the number of methyl groups, type of histone, and amino acid residues [15]. The heterochromatin formation that is followed by H3 three methylation at lysine 9 (i.e., H3K9me3) inclines towards transcriptional inactivation. However, histone H3 Lys-4 methylation (i.e., H3K4me) may lead to a transcriptional activation change [14]. Moreover, phosphorylation that occurs on serine residues, especially on H1 and H3 histones, can lead to gene expression induction. Ubiquitination usually takes place on H2A and H2B proteins and is correlated with activation although ADP-ribosylation is associated with chromosomal condensation [16]. The outcome of the ubiquitin-like modifier (SUMO) has been termed histone sumoylation and is related to transcription inactivation. Table 1 summarizes the above effects of different histone modifications and their impact on transcriptional regulation.

Given that histone modification affects gene transcription and appears early in tumorigenesis, considerable research has been carried out on the role of these alterations in malignancies. H4K16 hypoacetylation has been identified in breast, colon, lung, and liver cancers as well as in medulloblastomas [17, 18]. This abatement in acetylation, together with H4K20me3 loss and co-occurrence in repetitive sequences with decreased DNA methylation and H4k20 trimethylation, has been reported in many cancers such as breast and lung cancer [17, 18]. Besides lysine 20 and 16 H4,

alterations of other lysine residues of this histone are prominent in malignancies. For instance, H4k5 and H4K8 hyperacetylation along with H4K12 deacetylation has been demonstrated in lung cancer [15]. As stated in a meta-analysis study, elevated levels of H3K4me3 and decreased levels of H3K4me2 are indicators of a poor outcome in cancer patients [19]. Other lysine residues of the H3 shift have been found to be elevated in tumorigenesis. For example, loss of H3K4me2, H3K18ac, H3K9ac, and H3K9me3 is related to lung cancer recurrence and poor prognosis [15]. These modifications are located in promoters of transcribed genes and are essential for transcriptional suppression [20]. Moreover, H3K9me3 could serve as prognostic and staging estimation biomarkers in gastric cancer [21]. Loss of H2Bub1 is found in the development of numerous cancers as well as breast, lung, and colorectal cancer [22]. In addition, extensive phosphorylation of H2Bser32 has been shown in skin cancer cells [23].

All of these modifications are involved in malignancy induction by revising tumor suppressors or oncogene expression. H3 and H4 hypoacetylation and hypermethylation lead to p21WAF1 tumor suppressor inactivation [17]. Loss of H3K9ac, H3K4me2, and H3K9me3 has been linked to an increase in oncogene levels, such as MEIS1 and HOXA9 [21]. Increased and decreased methylation of H3K9 and H3K4, respectively, have been associated with p16INKA and p14ARF tumor suppressor gene reductions in some neoplasia [21].

Furthermore, dysregulation of histone-modifying enzymes in cancer and their distinct expression profile in tumor cells compared to normal cells have been identified in some studies [24]. For example, histone deacetylase (HDAC) reduction may be correlated with lung cancer promotion. However, HDAC overexpression in colon, prostate, and gastric cancers can result in blockage of tumor suppressor genes [15, 25]. EZH2, an H3K27 trimethylation enzyme, raises in breast carcinoma [15]. A histone methyltransferase upregulation along with histone demethylase downregulation has been found in prostate tissues. Moreover, HDM (histone demethylase) high expression levels have been reported in the liver, while HDM and HMT are largely decreased in the brain. By contrast, elevated levels of HDMs have been found in prostate and brain malignant cells [26].

## 3. Regulation of miRNA Expression by Histone Modifiers

miRNAs are involved in the regulation of biological processes such as development, growth, differentiation, proliferation, and apoptosis [27]. Alterations in miRNA function have been reported in all diseases and conditions, markedly in cancer [27]. Furthermore, miRNA expression profiling can provide prognostic and treatment monitoring biomarkers, as well as indicators of recurrence [27]. They can target cellular checkpoint genes and genes involved in mitosis division and apoptosis. For this reason, they are typically divided into two classes, onco MIRs and tumor suppressor MIRs [28].

*3.1. Onco MIRs.* Onco MiRs (oncomir) switch tumor-linked operations, such as unlimited cell growth, transformation, and metastasis. miR-21 is an oncomir known to be elevated in many cancers and drives cell proliferation. A sort of H3K4 demethylase, known as RBP2, can decrease miR-21 levels followed by decreased H3K4 trimethylation of its promoter and could act as a novel treatment in chronic myeloid leukemia cells [29]. Overexpression of miR-224 oncomir is regulated by H3K9 and H3K14 acetylation in hepatocellular carcinoma [30]. The miR-155 promoter will alter heterochromatin as a result of H2A and H3 deacetylation carried out by BRCA1 and HDAC2, resulting in increased cell growth and proliferation [31].

*3.2. Tumor Suppressor miRs.* miR-29 is known as a tumor suppressor gene because of its function in preventing cell growth and proliferation. H3K27 trimethylation is accomplished by recruiting YY1 and Ezh2. This change is related to the miR-29 promoter and could repress its expression in skeletal muscle cells. Aberrant downregulation of miR-29 by raised H3K27me3 is found in rhabdomyosarcoma [32]. Furthermore, induction of H3K27me3 and histone acetylation results in reduced levels of miR-31 [20]. miR-34a, a tumor suppressor gene governing apoptosis and cell cycle obstruction, can be arrested due to H3K27 trimethylation of its promoter by EZH2 in pancreatic ductal adenocarcinoma [33]. miR-125b has a tumor suppressor function in breast cancer, and its expression can be silenced through H3K9 and H3K27 trimethylation in breast cancer cell lines since miR-125b-1 promoter is located in a CpG island [34]. miR-30 family members classified as tumor suppressors are downregulated in a variety of malignancies. In esophageal squamous cell carcinoma cells, miR-30c expression is inactivated as a result of H2B and H4 histone deacetylation at the promoter region of miR-30c [35]. Downregulation of miR-15a, miR-16, and miR-29b in chronic lymphocytic leukemia is mediated by HDACs [36]. Other examples of these miRNAs are given in Table 2.

## 4. Epi-miRNAs and Histone Modification Machinery in Cancer

The epigenetic profile in numerous cancers is altered by the action of miRNAs [49, 50]. These small noncoding RNAs can target different enzymes involved in histone modifications. In the following sections, we discuss these miRNAs in more detail according to their enzyme targets.

*4.1. miRNA-Mediated Regulation of Histone Acetyltransferases.* There are numerous studies demonstrating miRNA-mediated regulation of different histone acetyltransferases including EP300, PCAF, TIP60, and hCLOCK (Table 3). The polycistronic miR-106b-25 cluster, which consists of miR-106b, miR-93, and miR-25, is associated with proto-oncogenic functions and uncontrolled growth. As Zhou et al. suggested in their research, this oncoMIR cluster can target EP300, a histone acetyltransferase that modifies chromatin remodeling, cellular

Table 1: Modified residues of histones, different histone modifications, and their impact on transcriptional regulation.

| Modified residues of histones | Histone modification | Transcription regulation |
| --- | --- | --- |
| Lysine | Acetylation | Activation |
| Lysine me1, me2, and me3 | Methylation (lysine) | Repression/activation |
| Arginine me1, arginine me2a, and arginine me2s | Methylation (arginine) | Repression/activation |
| Serine, threonine, and tyrosine | Phosphorylation | Activation |
| Lysine | Ubiquitination | Activation |
| Glutamic | ADP-ribosylation | Repression |
| Lysine | Sumoylation | Repression |

Table 2: Regulation of miRNA expression by histone modifiers.

| miRNAs | Cancer type | Decrease/increase | Type of histone modification | Reference |
| --- | --- | --- | --- | --- |
| miR-127 | Primary human tumors | Decrease | Increased histone H3 acetylation and H3-K4 methylation | [37] |
| miRNA-1260b | Prostate cancer cells | Increase | Increased H3K9-me2, H3K9me3 and H3K27me3 | [38] |
| miR-124a | Acute lymphoblastic leukemia | Decrease | Decreased levels of 3mk4H3 and AcH3 and increased levels of 2mK9H3, 3mK9H3, and 3mK27H3 | [39] |
| let-7e, miR-1246, miR-1826, and miR-361-5p | Breast cancer | Decrease | Decreased H3K4me3 | [40] |
| miR-615 | Prostate cancer | Increase | Increased H3K9 acetylation | [41] |
| miR-29 | B-cell lymphomas | Decrease | Increased histone deacetylation and trimethylation | [42] |
| miR-15a, miR-16, and miR-29b | Chronic lymphocytic leukemia | Decrease | Increased histone deacetylation | [36] |
| miR-15a and miR-16 | Non-Hodgkin B-cell lymphomas | Decrease | Increased histone deacetylation (HDAC3) | [43] |
| miR-31 | Breast cancer | Decrease | Increased methylation | [44] |
| miR-31 | Adult T-cell leukemia | Decrease | Increased H3K9 and H3K27 methylation | [45] |
| miR-23a | Human leukemic Jurkat cells | Decrease | Increased deacetylation (HDAC4) | [46] |
| miR-139-5p, miR-125b, miR-101, let-7c, and miR-200b | Hepatocellular carcinoma | Decrease | Increased histone H3 lysine 27 (H3K27) trimethylating (EZH2) | [47] |
| miR-449 | Hepatocellular carcinoma | Decrease | Increased histone deacetylation (HDAC1–3) | [48] |
| miR-224 | Hepatocellular carcinoma | Increase | Increased histone acetyltation (Ep300) | [30] |
| miR-155 | Breast cancer | Increase | Decreased H2A and H3 deacetylation (HDAC) | [31] |

Table 3: miRNA-mediated regulation of histone acetyltransferases.

| Target gene | miRNAs | Cancer tissue or cell line | Reference |
| --- | --- | --- | --- |
| EP300 | miR-106b, miR-93, and miR-25 | Breast cancer | [51] |
| PCAF | miR-17-5p | Prostate cancer | [52] |
| TIP60 | miR-22 | Breast cancer cell lines | [53] |
| hCLOCK | miR-124 | Colorectal cancer cell line | [54] |

growth, and differentiation processes. Upregulation of the miR-106b-25 cluster in breast cancer leads to metastatic alterations by EP300 blockage [51]. PCAF or p300/CBP-associated factor is another histone acetyltransferase upregulated in prostate cancer cells, and its expression level is decreased through miR-17-5p binding [52]. miR-22, elevated in most cancers, can target and repress a lysine acetyltransferase named TIP60 [53]. Accordingly, miR-22 suppression may influence treatment in breast cancer cell lines by reducing metastasis [53]. hCLOCK, a target of miR-124, is significantly decreased in response to the elevated levels of miR-124 in a human colorectal cancer cell line known as LOVO cells [54].

### 4.2. miRNA-Mediated Regulation of Histone Deacetylases.
HDACs are classified into four classes including classes I–IV [55]. There has been accumulating evidence of miRNA-mediated regulation of these enzymes (Table 4), and the following section describes these according to their classifications.

TABLE 4: miRNA-mediated regulation of histone deacetylases.

| Classification | Target gene | miRNAs | Cancer tissue or cancer cell line | Reference |
|---|---|---|---|---|
| | HDAC1 | miR-34a | Ovarian cancer | [56] |
| Class I Rpd3-like proteins | HDAC2 | miR-145 | Liver cancer | [57] |
| | HDAC3 | miR-326 | Hepatoma and melanoma-related cell lines | [58] |
| | HDAC4 | miR-29b | Multiple myeloma | [59] |
| | HDAC4 | miR-10b | Breast cancer cells | [60] |
| | HDAC4 | miR-22 | Breast cancer cells | [61] |
| | HDAC4 | miR-125a-5p | Breast cancer | [62] |
| | HDAC5 | miR-125a-5p | Breast cancer | [63] |
| Class II Hda1-like proteins | HDAC5 | miR-589-5p | Non-small-cell lung cancer cells | [64] |
| | HDAC6 | miR-221 and miR-221 | Liver cancer cells | [65] |
| | HDAC7 | miR-489 | Gastric cancer cells | [66] |
| | HDAC7 | miR-34a | Breast cancer | [67] |
| | HDAC8 | miR-216b | Gastric adenocarcinoma | [68] |
| | HDAC9 | miR-377 | Oral squamous cell carcinoma | [69] |
| | SIRT1 | miR-34a | Breast cancer | [70] |
| | SIRT1 | miR-34a | Breast cancer stem cell | [71] |
| | SIRT1 | miR-200a | Breast cancer | [72] |
| | SIRT1 | miR-590-3p | Breast cancer cells | [73] |
| | SIRT1 | miR-22 | Breast cancer tissues | [74] |
| Class III Sir2-like proteins | SIRT2 | miR-150 | Non-small-cell lung cancer (NSCLC) cells | [75] |
| | SIRT3 | miR-708-5p and miR-708-5p | Pancreatic ductal adenocarcinoma | [76] |
| | SIRT5 | miR-299-3p | Hepatocellular carcinoma (HCC) cells | [77] |
| | SIRT6 | miR-186 | Lung cancer | [78] |
| | SIRT7 | miR-3666 | NSCLC | [79] |
| | SIRT7 | miR-3666 | Breast cancer cell | [64] |

*4.2.1. Class I Rpd3-Like Proteins (HDAC1, HDAC2, HDAC3, and HDAC8).* The upregulation of HDAC1 results in uncontrolled growth and cisplatin-resistant in ovarian cancer cells. miR-34a suppresses this process by targeting HDAC1 [56]. Moreover, an HDAC1 decrease through the action of miR-34a can overcome treatment resistance in breast cancer [67]. miR-145 is a tumor suppressor, and its inactivation can increase HDAC2 levels and lead to the development of hepatocellular carcinoma [57]. Kim et al. demonstrated that miR-326 inhibition may give rise to HDAC3 upregulation followed by a response to anticancer drugs in hepatoma and melanoma-related cell lines [58]. As demonstrated by Wang et al., the expression of miR-216b, which controls HDAC8, is downregulated in gastric adenocarcinoma [68].

*4.2.2. Class II Hda1-Like Proteins (HDAC4, HDAC5, HDAC6, HDAC7, and HDAC9).* Alterations in HDAC4 expression occur via several miRNAs and vary based on cancer type. Amodio et al. found that miR-29b/HDAC4 serves as an epigenetic loop in multiple myeloma and the induction of miR-29b expression could repress HDAC4 and result in cell survival and reduced malignancy in myeloma [59]. However, Ahmad et al. reported that induction in miR-10b levels leads to the tamoxifen-resistance phenotype due to loss of HDAC4 expression in ER-positive breast cancer cells [60]. Moreover, in another study carried out on fulvestrant-resistant breast cancer cells, it was found that miR-22 overexpression inhibits HDAC4 and promotes cell proliferation [61]. One observation has already drawn attention to the paradox in HDAC4 function in breast tumorigenesis since its suppression through miR-125a-5p

inhibits tumor progression [62]. The downregulation of this miRNA, which targets HDAC5 in breast cancer cells, is related to the blockade of cancer progression [63]. Liu et al. found that the expression level of HDAC5 was reduced by binding of miR-589-5p to the 3' untranslated region (UTR) of HDAC5 in non-small-cell lung cancer (NSCLC) cells [64]. HDAC6 is downregulated via miR-221, which is upregulated in liver cancer cells [65]. Diminished levels of miR-489 induce metastatic processes of gastric cancer cells and block HDAC7 expression [66]. The levels of miR-34a may reflect the tumor-suppressive effect, and its transcription is abolished in cancer stem cells [67]. miR-34a targets HDAC7 and thereby contributes to the regulation of therapy resistance in breast cancer [67]. It has been shown that HDAC7-mediated deacetylation of a specific lysine residue of a heat shock protein, namely HSP70 K246, contributes to the augmentation of treatment resistance, in which miR-34a may exert a suppressive role through its downstream effectors HDAC7 [67]. miR-377 depression is found in oral squamous cell carcinoma, influencing the expression of HDAC9 and tumor invasion [69].

*4.2.3. Class III Sir2-Like Proteins (SIRT1, SIRT2, SIRT3, SIRT5, SIRT6, and SIRT7).* SIRT is a family of histone deacetylase compromised seven proteins and divided into four classes. Class I includes SIRT1, SIRT2, and SIRT3. Class II consists of SIRT4. SIRT5 belongs to class III, and SIRT6 and SIRT7 are class IV members [80]. Being elevated in breast cancer, SIRT1 plays a significant role in this disorder [62]. Several miRNAs interact with SIRT1. miR-34a, a direct regulator of SIRT1, is decreased in breast cancer [62]. As

suggested by Li et al., induction of miR-34a along with 5-FU therapy has significant antitumor effects in breast malignancies [70]. In addition, Eades et al. demonstrated a diminished level of miR-34a and an increased level of SIRT1 in CD44+/CD24− breast cancer stem cells [71]. Moreover, SIRT1 forms a negative feedback loop with miR-200a, with overexpression of SIRT1 being related to decreased levels of miR-200a in patients suffering from breast cancer [72]. Reduced levels of miR-590-3p are associated with upregulation of SIRT1 followed by hyperacetylation of p53 and increased levels of BAX and p21, leading to malignant characteristics in breast cancer cells [73]. It has been shown that downregulation of miR-22 is accompanied by overexpression of SIRT1 in breast cancer tissues [74]. Downregulation of SIRT2 as a result of miR-150 augmentation has been observed in NSCLC cells, potentially serving as a survival element through blocking the AKT signaling pathway in this cell line [75]. SIRT3 is fine-tuned by miR-708-5p that is upregulated in pancreatic ductal adenocarcinoma [76]. Dang et al. confirmed that miR-299-3p, downregulated in hepatocellular carcinoma cells [77], exerts tumor-suppressive roles by modifying growth and metastasis through SIRT5 inactivation [77]. SIRT6 is a direct target of miR-186, and Ruan and colleagues demonstrated that miR-186 upregulation could serve as a treatment target in lung cancer [78]. miR-3666 inhibits breast cancer cell proliferation by targeting SIRT7. Also, overexpression of SIRT7 in response to downregulation of miR-3666 has been observed in NSCLC and breast cancer cells [79, 81].

### 4.3. miRNA-Mediated Regulation of Histone Methyltransferases.
There are two major types of histone methyltranferases termed histone lysine N-methyltransferases and histone arginine N-methyltransferases. The following sections discuss the miRNA-mediated regulation of both types.

### 4.3.1. miRNA-Mediated Regulation of Histone Lysine Methyltransferases.
Lysine methyletransferases (KMTs) are divided into groups based on the site of methyl group addition [82]. In this section, we discuss miRNA-mediated regulation of histone lysine methyltransferases considering their classification. The data summary is given in Table 5.

*(1) Suv39H1, Suv39H2, SETDB1, and G9A/EHMT2 (H3K9).* miR-125a-5p, a recognized prognostic factor in gastric cancer, regulates SUV39H1 (KMT1A) and prevents angiogenesis [83]. The downregulation of this miRNA has been correlated to SUV39H1 upregulation in hepatocellular carcinoma cells [84]. In addition, miR-122 is another regulator of SUV39H1 in hepatocellular carcinoma cells [85]. miR-675 along with PKM2 leads to decreased levels of SUV39H2 and cancer progression in liver stem cells via c-myc upregulation [86]. Low levels of miR-212 have been linked to lung cancer and can target G9a/KMT1C [87]. Wu et al. identified SETDB1 upregulation as a target of miR-381-3p in breast malignancies [88].

*(2) KMT2A (MLL1).* KMT2A is a direct target of hsa-miR-22-3p, and hsa-miR-22-3p upregulation has been found in the metastatic form of prostatic cancer [89].

*(3) NSD1 and ASH1L (H3K36).* miR-142 could inhibit ASH1L (KMT2H), and its downregulation leads to increased levels of ASH1L in leukemia [90]. Moreover, Colamaio et al. described the same finding in thyroid tumors [91]. KMT3B (NSD1) is one of the miR-181a targets, and the oncogenic role of hsa-miR-181a suggests it could be a prognostic biomarker in endometrial cancer [92].

*(4) SMYD3 (H4K5).* miR-124 acts as a SMYD3 (KMT3E) expression modifier, and its decreased levels that result in cellular invasive criteria have been shown in intrahepatic cholangiocarcinoma cells [93]. miR-346 downregulation induces SMYD3 upregulation in hepatocellular carcinoma and could be a poor prognostic factor [94].

*(5) hDOT1L (H3K79).* DOT1L (KMT4) is blocked by miR-133b. miR-133b is a tumor suppressor, and low levels cause chemoresistance in colorectal cancers [95].

*(6) SET8 (H4K20).* SET8 is a histone methyltransferase that adds one methyl group on lysine 20 of H4. Its expression can be switched by miR-502, and it has oncogenic effects and contributes to cell growth and migration. This oncogene expression can be increased due to reduced levels of miR-502 in many malignancies including breast cancer, ovarian cancer, small-cell lung cancer, colorectal cancer, non-Hodgkin's lymphoma, esophageal squamous cell carcinoma, clear cell renal cell carcinoma, and hepatocellular carcinoma [96, 98, 102, 103]. For these reasons, it has been considered as a potential target for cancer therapy. Also, a single nucleotide polymorphism (SNP; rs16917496) located at the binding sequences of miR-502 may affect SET8 expression and has been associated with the risk of these malignancies [97, 99–101, 104, 124]. Moreover, this histone methyltransferase could be regulated with miR-7, and its suppression prevents cell invasion in breast cancer [105].

*(7) EZH1 and EZH2 (H3K27).* Elevation of KMT6B (EZH1) caused by miR-17-5p downregulation is related to erlotinib resistance in NSCLC [106]. miR-765 is another regulating element of EZH1, and its downregulation is associated with aggravation of breast cancer [107]. Additionally, a study by Hu J. et al. showed that miR-93 is a key regulator of EZH1 as well as JAK1, STAT3, AKT3, SOX4, and HMGA2 in breast cancer stem cells [108]. In a study of prostate cancer stem cells, Lai et al. reported miR-574-5p depletion along with EZH1 and REL increased levels [109].

Multiple microRNAs can alter EZH2 expression. Effects of miR-101 on EZH2 have been observed in various cancers [125], and downregulation of this microRNA and elevation of EZH2 have been found in NSCLC tumor tissues, prostate cancer, and renal cancer [110–112]. According to a study by Konno et al., the microRNA-101-EZH2/MCL-1/FOS axis may be a target for endometrial cancer treatment [113]. miR-26a as an apoptosis inducer is another regulator of EZH2,

TABLE 5: miRNA-mediated regulation of histone lysine methyltransferases.

| Site of methyl group addition | Target gene | miRNAs | Cancer tissue or cancer cell line | Reference |
|---|---|---|---|---|
| | SUV39H1 (KMT1A) | miR-125a-5p | Gastric cancer | [83] |
| | SUV39H1 (KMT1A) | miR-125b | Hepatocellular carcinoma cells | [84] |
| | SUV39H1 (KMT1A) | miR-122 | Hepatocellular carcinoma cells | [85] |
| H3K9 | SUV39H2 (KMT1B) | miR-675 | Liver stem cells | [86] |
| | G9a (KMT1C) | miR-212 | Lung cancer (NSCLC) | [87] |
| | SETDB1 (KMT1E) | miR-381-3p | Breast cancer | [88] |
| H3K4 (MLL1) | Mll1 (KMT2A) | miR-22-3p | Prostatic cancer | [89] |
| | ASH1L (KMT2H) | miR-142 | Leukemia | [90] |
| H3K36 | ASH1L (KMT2H) | miR-142 | Thyroid tumors | [91] |
| | KMT3B (NSD1) | miR-181a | Endometrial cancer | [92] |
| H4K5 | SMYD3 (KMT3E) | miR-124 | Cholangiocarcinoma | [93] |
| | SMYD3 (KMT3E) | miR-346 | Hepatocellular carcinoma | [94] |
| H3K79 | DOT1L (KMT4) | miR-133b | Colorectal cancer | [95] |
| | SET8 (KMT5A) | miR-502 | Breast cancer | [96] |
| | SET8 (KMT5A) | miR-502 | Ovarian cancer | [97] |
| | SET8 (KMT5A) | miR-502 | Non-small-cell lung cancer | [98, 99] |
| | SET8 (KMT5A) | miR-502 | Colorectal cancer | [100] |
| H4K20 | SET8 (KMT5A) | miR-502 | Non-Hodgkin's lymphoma | [101] |
| | SET8 (KMT5A) | miR-502 | Esophageal squamous cell carcinoma | [102] |
| | SET8 (KMT5A) | miR-502 | Clear cell renal cell carcinoma | [103] |
| | SET8 (KMT5A) | miR-502 | Hepatocellular carcinoma | [104] |
| | SET8 (KMT5A) | miR-7 | Breast cancer | [105] |
| | KMT6B (EZH1) | miR-17-5p | NSCLC | [106] |
| | KMT6B (EZH1) | miR-765 | Breast cancer | [107] |
| | KMT6B (EZH1) | miR-93 | Breast cancer stem cells | [108] |
| | KMT6B (EZH1) | miR-574-5p | Prostate cancer stem cells | [109] |
| | KMT6 (EZH2) | miR-101 | NSCLC | [110] |
| | KMT6 (EZH2) | miR-101 | Prostate cancer | [111] |
| | KMT6 (EZH2) | miR-101 | renal cancer | [112] |
| | KMT6 (EZH2) | miR-101 | Endometrial cancer | [113] |
| | KMT6 (EZH2) | miR-26a | Lung cancer | [114] |
| | KMT6 (EZH2) | miR-26a | Burkitt lymphoma | [115] |
| H3K27 | KMT6 (EZH2) | miR-26a | Rhabdomyosarcoma | [116] |
| | KMT6 (EZH2) | miR-26a | Prostate cancer | [117] |
| | KMT6 (EZH2) | miR-26a | Nasopharyngeal carcinoma | [118] |
| | KMT6 (EZH2) | miR-137 | Liver cancer | [119] |
| | KMT6 (EZH2) | miR-124 | Hepatocellular cell carcinoma | [120] |
| | KMT6 (EZH2) | miR-138 | Squamous cell carcinoma cell lines | [121] |
| | KMT6 (EZH2) and HDAC3 | miR-31 | Esophageal cancer | [125] |
| | KMT6 (EZH2) | miR-98 | Ovarian cancer stem cells | [126] |

and its diminished levels of this miRNA have been found in lung cancer, rhabdomyosarcoma, and prostate cancer [114, 116, 117]. It plays a role in Burkitt lymphoma and prostate cancer prevention by targeting c-myc, a transcription factor of EZH2 [115, 117], and is involved in nasopharyngeal carcinoma inhibition by mitigating cyclin D3, E2, CDK4, and CDK6 along with overexpression of the CDK inhibitors p14ARF and p21CIP1 [118]. miR-137 downregulation is related to EZH2 upregulation in hepatocellular cell carcinoma and miR-137 inhibits hepatocellular cell carcinoma progression by EZH2 suppression [119]. In addition, miR-124 manifests the same action on EZH2 in cancer cell lines [120]. Liu and co-workers demonstrated miR-138 deficiency can give rise to cellular metastasis via targeting VIM, ZEB2, and EZH2 in squamous cell carcinoma cell lines [121]. A study by Koumangoye et al. implicated EZH2 and HDAC3 as indirect targets of miR-31 in esophageal cancer cells as their upregulation was associated

with raised levels of miR-31 by directly regulating SOX4, which then acts on EZH2 and HDAC3 [125]. miR-98 is a key regulator of EZH2 and, according to the investigation of Liu et al., treatment of ovarian cancer stem cells with an expression plasmid containing EZH2-targeted miR-98 blocked cell growth, and ameliorated cell cycle status via increasing p21CIPI/WAF1 and E2F1 tumor suppressors and downregulating c-Myc and CDK2/cyclin E complex proto-oncogenes [126].

4.3.2. miRNA-Mediated Regulation of Histone Arginine Methyltransferases. Protein arginine methyltransferases (PRMTs) are involved in histone post-translational methylation [126], and multiple investigations have found miRNA-mediated regulation of these enzymes in various cancers (Table 6). For example, an investigation by Li et al. found that diminished miR-503 levels were associated with

TABLE 6: miRNA-mediated regulation of histone arginine methyltransferases.

| Target gene | miRNAs | Cancer tissue or cancer cell line | Reference |
|---|---|---|---|
| PRMT1 | miR-503 | Hepatocellular carcinoma | [127] |
| PRMT4 (CARM1) | miR-195 | Colorectal cancer cells | [128, 129] |
| PRMT4 (CARM1) | miR-424-5p | NSCLC | [130] |
| PRMT5 | miR-92b and miR-96 | Lymphoid cancer cell lines | [131] |
| PRMT5 | miR-1266 | Prostate cancer cell lines | [132] |
| PRMT9 | miR-543 | Osteosarcoma | [133] |

PRMT1 elevation in hepatocellular carcinoma [127]. CARM1 elevation improves cell growth in colorectal malignancies. miR-195 is an antitumor element and increases radiosensitivity in colorectal cancer cells as a result of PRMT4/CARM1 targeting [128, 129]. miR-424-5p is another regulator of CARM1. Wang and his colleagues indicated its low levels in NSCLC tissues. Also, they stated that high levels of miR-424-5p could suppress CARM1 followed by decreasing tumor development [130]. Upregulation of PRMT5 is related to the impaired expression of miR-92b and miR-96 in lymphoid cancer cell lines and leads to ST7 inactivation by H3R8 and H4R3 methylation [131]. miR-1266 overexpression appears to decrease PRMT5 levels and modify cellular growth and proliferation, thus suggesting its use as a novel therapeutic target in prostate cancer [132]. PRMT9 expression is shifted by direct binding of miR-543 to its 3′-UTR and increased levels of this miRNA have been associated with downregulation of PRMT9 and osteosarcoma cell growth [133].

## 4.4. miRNA-Mediated Regulation of Histone Demethylases.
There are multiple histone demethylase enzymes divided into lysine and arginine methyltransferase groups. Histone lysine demethylases are classified into KDM1-8 families [134]. miRNA-mediated regulation of histone demethylases in cancer is described in the following sections and summaries shown in Table 7.

### 4.4.1. KDM1 (LSD1).
LSD1 is a histone demethylase, controlled by miR-137 in a negative feedback loop in endometrial cancer [135]. miR-302 has been shown to be downregulated in hepatocellular carcinoma cells, and this miRNA could decrease LSD1 (AOF2) levels resulting in drug sensitivity improvement and c-myc suppression [136]. By contrast, Bourguignon et al. reported miR-302a and miR-302b upregulation and AOF2 suppression in mouse tumors and human head and neck squamous cell carcinomas [137]. Likewise, miR-302a overexpression along with AOF2, BCRP, and permeability glycoprotein 1 decrease has been found in prostate cancer [138].

### 4.4.2. KDM2 (FBXL10 and KDM2B).
FBXL10 is a direct target of miR-146b, and downregulation of this miRNA in later stages of epithelial ovarian cancer has been linked to FBXL10 increase that, in turn, induces metastasis. However, in the early stage of the disease, miR-146b reduction results in overexpression of cyclin D1 and cell proliferation [139]. Hong and co-authors reported miR-448 overexpression in

gastric cancer. This miRNA binds to KDM2B and suppresses its expression that results in myc induction [140]. KDM2B is upregulated in cervical cancer cell lines and downregulates miR-146a-5p expression that, in turn, increases c-myc levels [141].

### 4.4.3. KDM3 (JMJD1A).
JMJD1A is a direct target of miR-627, and its low expression is related to growth and differentiation inhibition [142]. LMP1 and LMP2A induce miR-155 upregulation followed by JMJD1A suppression in nasopharyngeal carcinoma cases with poor prognosis [143]. There is a loop between JMJD1A, EZH2, and let-7c in NSCLC cells, and inhibition of JMJD1A can downregulate EZH2. EZH2 depletion causes the let-7c increase. However, let-7c binds to the 3′-UTR of JMJD1A and EZH2 and shifts their expression in a feedback loop, predisposing them to cancer phenotype amelioration [144]. EWS/Fli1 oncoprotein participates in miR-22 suppression that can regulate KDM3A (JMJD1A/JHDM2A) expression. Downregulation of KDM3A results in tumorigenic profile reduction in Ewing sarcoma [145].

### 4.4.4. KDM4 (JMJD2B and JMJD2C).
JMJD2B can be regulated by miR-491-5p, and its overexpression via miR-491-5p downregulation has been observed in ERα-positive breast cancers and cell lines. miR-491-5p upregulation results in cell cycle arrest and attenuates growth through inhibition of JMJD2B in the same cancer [146]. miR-491-5p carries out the same function in gastric cancer by binding to the 3′UTR of JMJD2B. This miRNA is a tumor suppressor, and its downregulation has been used as a biomarker in this disease [147]. Yong et al. illustrated that circZMYM2 inhibits miR-335-5p expression in prostate cancer cells and tissues and induces prostate cancer development. Overexpression of miR-335-5p as a treatment can block JMJD2C expression and reduce prostate cancer progression [148].

### 4.4.5. KDM5 (JARID1B and RBP2).
Studies have shown that JARID1B levels are ameliorated by miR-137 [152]. Thus, increased levels of JARID1B and reduced levels of miR-137 have been found in acute lymphoblastic leukemia cell lines, and increased miR-137 can prevent uncontrolled cell proliferation [152]. miR-363-3p is expressed as a result of HIF-2a induction, followed by p21 suppression and resulting in JARID1B elevation in melanoma [151]. JARID1B/KDM5B is also known to be regulated by miR-138, miR-381-3p, and miR-486-5p as observed in breast cancer [153]. Reference [154] RBP2 is a direct target of miR-212, and its

TABLE 7: miRNA-mediated regulation of histone demethylases.

| Demethylase groups | Target gene | miRNAs | Cancer tissue or cancer cell line | Reference |
|---|---|---|---|---|
| KDM1 | AOF2 (LSD1) | miR-137 | Endometrial cancer | [135] |
| | AOF2 (LSD1) | miR-302 | Hepatocellular carcinoma cells | [136] |
| | AOF2 (LSD1) | miR-302a and miR-302b | Human head and neck squamous cell carcinomas | [137] |
| | AOF2 (LSD1) | miR-302 | Prostate cancer | [138] |
| KDM2 | FBXL10 (KDM2B) | miR-146b | Ovarian cancer | [139] |
| | FBXL10 (KDM2B) | miR-448 | Gastric cancer | [140] |
| | FBXL10 (KDM2B) | miR-146a-5p | Cervical cancer cell lines | [141] |
| KDM3 | JMJD1A | miR-627 | Colorectal tumors | [142] |
| | JMJD1A | miR-155 | Nasopharyngeal carcinoma | [143] |
| | JMJD1A | let-7c | NSCLC | [144] |
| | KDM3A (JMJD1A/ JHDM2A) | miR-22 | Ewing sarcoma | [145] |
| KDM4 | JMJD2B (KDM4B) | miR-491-5p | Breast cancer | [146] |
| | JMJD2B (KDM4B) | miR-491-5p | Gastric cancer | [147] |
| | JMJD2C | miR-335-5p | Prostate cancer | [148] |
| KDM5 | JARID1A (RBP2) | miR-212 | Hepatocellular carcinoma | [149] |
| | JARID1A (RBP2) | miR-212 | Gastric cancer | [150] |
| | JARID1B (KDM5B) | miR-363-3p | Melanoma | [151] |
| | JARID1B (KDM5B) | miR-137 | Acute lymphoblastic leukemia cell lines | [152] |
| | JARID1B (KDM5B) | miR-138, miR-381-3p, and miR-486-5p | Breast cancer | [153, 154] |
| KDM7 | PHF2 | miR-221 | Hepatocellular carcinoma | [155] |
| Arginine demethylase | JMJD6 | miR-770 | Non-small-cell lung cancer | [156] |
| | JMJD6 | miR-146a and miR-193a | Melanoma | [157] |

overexpression in response to downregulation of miR-212 has been found in gastric carcinogenesis and hepatocellular carcinoma [149, 150]. miR-212 acts as a tumor suppressor, and its aberrant expression participates in the augmentation of a cell proliferation phenotype through induction of impaired RBP2 expression and downregulation of P21CIP1/ P27kip1 [149, 150].

*4.4.6. KDM7 (PHF2).* miR-221 can target PHF2, and its upregulation along with PHF2 decrease has been shown in hepatocellular carcinoma cells [155].

*4.4.7. JMJD6 (Arginine Demethylase).* JMJD6 is a miR-770 direct target, and its overexpression due to miR-770 downregulation followed by WNT/$\beta$-catenin pathway activation has been found in NSCLC [156]. Furthermore, miR-146a and miR-193a target JMJD6 overexpression has been described in melanoma progression [157].

*4.5. miRNA-Mediated Regulation of Histone Kinases.* There are several clusters of kinases classified by kinase domain sequences similarity, biological function, and other criteria [158]. miRNA-mediated regulation of histone kinases is described below and summarized in Table 8.

*4.5.1. AGC (RPS6KA4/MSK2, PRKCD, PRKCB, RSK2, and PRKDC).* Reduction of miR-517a is found in bladder cancer cell lines. It has a tumor-suppressive effect and can target RPS6KA4/MSK2 [159]. The PRKCD kinase can be regulated by many kinds of miRNAs. miR-181a acts as an oncogene, and its upregulation decreases the chemosensitivity of cervical squamous cell carcinoma via PRKCD inhibition [160, 161]. In ovarian cancer tissues, miR-181c was found to be decreased and caused a PRKCD increase via binding to its 3'UTR [162]. As reported by Yao et al., PRKCD knockdown in A2780 cells resulted in cell cycle arrest in the G1 phase and metastasis inhibition [162]. However, in another study carried out by Zhao et al., miR-224 functioned as an oncogene targeting PRKCD and enhanced chemoresistance in ovarian papillary serous carcinoma [163]. The downregulation of miR-197-3p along with PRKCB overexpression in gastric cancer has been reported [164]. Low levels of miR-634 increase RSK2 in relation to cisplatin resistance in ovarian cancer [165]. miR-488-3p represses PRKDC and increases malignant melanoma cell sensitivity to cisplatin [166].

*4.5.2. Nonreceptor Tyrosine Kinase (JAK2).* JAK2 is one of the most important kinases involved in histone regulation and the key member of the JAK2/STAT3 signaling pathway recruited in inflammation and apoptosis [218]. The level of JAK2 is regulated by a variety of miRNAs. The miR-543 expression serves as a tumor suppressor and prevents cell proliferation by targeting JAK2 and STAT3 in hepatocellular carcinoma [167]. Low levels of miR-216a and high levels of JAK2 in pancreatic cancer were reported in two distinct studies [168, 169]. JAK2, BCl-2, and surviving are direct targets of miR-204 in breast cancer, and the opposite expression pattern of miR-204-JAK2 has been reported in

TABLE 8: miRNA-mediated regulation of histone kinases.

| Kinase groups | Target gene | miRNAs | Cancer tissue or cancer cell line | Reference |
|---|---|---|---|---|
| AGC | RPS6KA4 (MSK2) | miR-517a | Bladder cancer cell lines | [159] |
| | PRKCD | miR-181a | Cervical squamous cells | [160, 161] |
| | PRKCD | miR-181c | Ovarian cancer tissues | [162] |
| | PRKCD | miR-224 | Ovarian papillary serous carcinoma | [163] |
| | PRKCB | miR-197-3p | Gastric cancer | [164] |
| | RSK2 | miR-634 | Ovarian cancer | [165] |
| | PRKDC | miR-488-3p | Malignant melanoma | [166] |
| Nonreceptor tyrosine kinase families | JAK2 | mR-543 | Hepatocellular carcinoma | [167] |
| | JAK2 | miR-216a | Pancreatic cancer | [168, 169] |
| | JAK2 | miR-204 | Breast cancer | [170] |
| | JAK2 | miR-204 | Non-small lung cancer cell lines | [171] |
| | JAK2 | miR-375 | Gastric cancer | [172, 173] |
| | JAK2 | miR-135a | Hodgkin lymphoma | [174] |
| | JAK2 | miR-135a | Renal cancer | [175] |
| | JAK2 | miR-135a | Gastric carcinoma | [176] |
| CMGC | CDK3 | miR-873 | Breast cancer | [177] |
| | CDK3 | miR-4469 | Primary breast tumors | [178] |
| | MAP3K8 | miR-589-5p | Hepatocellular carcinoma | [179] |
| | MAP3K8 | miR-144-3p | Renal cell carcinoma | [180] |
| | MAP3K8 | miR-509-3p | Renal cell carcinoma | [181] |
| | GSK3B | miR-769 | Melanoma | [182] |
| Tyrosine kinase-like (TKL) | LIMK2 | miR-135a | Bladder cancer | [183] |
| Other kinases family | NEK6 | miR-23 | Hepatocellular carcinoma | [184] |
| | NEK6 | miR-26 | Marek's disease lymphoma | [185] |
| | NEK6 | miR-506-3p | Retinoblastoma | [186] |
| | AURKA | miR-124-3p | Bladder cancer | [187] |
| | AURKA | miR-124-3p | Glioblastoma | [188] |
| | AURKA | miR-32 | Non-small-cell lung cancer | [189] |
| | AURKA | miR-137 | Multiple myeloma | [190] |
| | AURKA | let-7 | Hepatocellular cancer | [191] |
| | AURKA | miR-490 | Hepatocellular carcinoma | [192] |
| | AURKA | miR-4715-3p | Gastrointestinal cancers | [193] |
| | BUB1 | miR-490-5p | Hepatocellular carcinoma | [194] |
| | BUB1 | miR-145-3p | Prostate cancer | [195] |
| CAMK | CHEK2 (Chk2) | miR-191 | Osteosarcoma | [196] |
| | CHEK2 (Chk2) | miR-182-5p | Breast cancer | [197] |
| | CHEK1 (Chk1) | miR-195 | Non-small-cell lung cancer | [198] |
| | CHEK1 (Chk1) | miR-195 | Colon cancer | [199] |
| | CHEK1 (Chk1) | miR-497 | Hepatocellular carcinoma | [200] |
| | CHEK1 (Chk1) | miR-145 | Bladder cancer | [201] |
| | CHEK1 (Chk1) | miR-424 | Cervical cancer | [202] |
| | CHEK1 (Chk1) | miR-15 | Breast cancer cells | [203] |
| | CHEK1 (Chk1) | miR-26a | Prostate cancer | [204] |
| | DAPK3 | miR-1307 | Ovarian cancer cell lines | [205] |
| | AMPK | miR-451 | Colorectal cancer | [206] |
| | AMPK | miR-25-5p | Colorectal cancer | [207] |
| | AMPK | miR-101 | Breast cancer | [208] |
| | AMPK | miR-34 | Prostate cancer | [209] |
| STE | STK4 | miR-18a | Prostate cancer | [210] |
| | PAK2 | miR-4779 | Colon cancer | [211] |
| | PAK2 | miR-216a-5p | Breast cancer | [212] |
| | PAK2 | miR-137 | Melanoma | [213] |
| | PAK2 | miR-75p | Non-small-cell lung cancer | [214] |
| | PAK2 | miR-134 | Human ovarian cancer cells | [215] |
| | PAK2 | miR-922 | Oral squamous cell carcinoma | [216] |
| | PAK2 | miR-26a | Hepatocellular carcinoma | [217] |

NSCLC [170, 171]. Furthermore, miR-204 can be used as a prognostic marker in these cancers [170, 171]. Several studies reported the downregulation of miR-375 in gastric cancer and its function in inhibiting tumor development by suppressing JAK2 [172, 173]. miR-135a is another regulator of JAK2 in different cancers such as lymphoma and renal and gastric carcinoma and can influence apoptotic genes as well as Bcl-x and Bcl-2 [174–176].

*4.5.3. Tyrosine Kinase-Like (LIMK2).* LIMK2 plays an oncogenic role in bladder cancer and can be decreased by miR-135a [183].

*4.5.4. Other Kinases Family (NEK6, AURKA, and BUB1).* miR-23 can target NEK6, the enzyme that negatively regulates p53. The natural substance berberine plays a role in hepatocellular carcinoma treatment by activating this signal [184]. In another study, miR-26 was documented as a modulator of NEK6 in Marek's disease lymphoma and suppressed cell proliferation [185]. NEK6 is an oncogene and a direct target of miR-506-3p in retinoblastoma [186]. miR-124-3p was found to be decreased in bladder cancer tissues and cell lines and glioblastoma, and its downregulation led to AURKA increase [187, 188]. In NSCLC, miR-32 targets AURKA and causes p53 inhibition [189]. miR-137 can suppress AURKA expression and prevent drug resistance in multiple myeloma [190]. let-7 is another modulator of AURKA that is downregulated in hepatocellular cancer [191]. Diminished levels of miR-490 have been found in hepatocellular carcinoma, and AURKA as an established target of miR-490 was elevated [192]. Gomaa and colleagues found a relationship between miR-4715-3p downregulation caused by methylation and AURKA overexpression in gastrointestinal cancers that were attenuated by 5-Aza-2'-deoxycytidine, a demethylation element [193]. Downregulation of miR-490-5p and miR-145-3p along with an increase in BUB1 was found in hepatocellular carcinoma and prostate cancer, respectively, leading to cancer cell invasion [194, 195].

*(1) CAMK (DAPK3, CHEK1, CHEK2, and AMPK).* DAPK3 is a p53-activating kinase and a direct target of miR-1307, which is overexpressed in chemoresistant ovarian cancer cell lines [205]. CHEK2 can be regulated by miR-191 in osteosarcoma, and miR-191 provokes cell growth [196]. miR-182-5p overexpression promotes CHEK2 suppression and is involved in breast cancer [197]. CHEK1 is controlled by several miRNAs, and its alteration functions a double-edged sword in different malignancies. Downregulation of miR-195 in NSCLC is correlated with augmentation of CHEK1, which is an indication of poor survival [198]. However, downregulation of miR-195 in colon cancer cell lines can suppress the viability of cancer 5-FU-resistant cells by increasing CHEK1 and might be considered as a treatment in colon cancer [199]. miR-497 is another regulator of CHEK1 in hepatocellular carcinoma [200]. miR-145 and miR-424 downregulation together with CHEK1 upregulation were found in bladder cancer and cervical cancer, respectively [201, 202]. miR-15 can increase breast cancer cells irradiation by targeting CHEK1 [203]. p53 induces miR-16 and

miR-26a expression, and they inhibit CHEK1 expression leading to enhanced apoptosis and better survival in breast and prostate cancers [204]. miR-451 overexpression hampers AMPK and promotes mTOR and FCN1 expression in colorectal cancers leading to proliferation induction [206]. A similar result was found with exogenous expression of miR-25-5p [207]. miR-101 and miR-34 are other regulators of AMPK, and an increase in their expression is associated with proliferation arrest and initiation of apoptosis in breast and prostate cancer, respectively [208, 209].

*(2) STE (STK4 and PAK2).* miR-18a elevation motivates prostate cancer development through STK4 suppression [210]. PAK2 is modulated by various microRNAs in different cancers. miR-4779, miR-216a-5p, miR-137, and miR-7-5p are tumor suppressors that regulate PAK2 in colon cancer, breast cancer, melanoma, and NSCLC. Downregulation of these miRNAs has been associated with tumor growth and proliferation [211–214]. Moreover, Shuang et al. showed that miR-134 suppression led to augmentation of PAK2 followed by paclitaxel resistance in human ovarian cancer cells [215]. In addition, CCHE1 inhibited miR-922, which, in turn, leads to an incline in PAK2 and participates in tumorigenesis of oral squamous cell carcinoma development [216], and miR-26a halted cancer invasion by restricting PAK2 in hepatocellular carcinomas [217].

*(3) CMGC (MAP3K8, GSK3B, and CDK3).* miR-589-5p limits MAP3K8 expression and causes suppression of CD90+ cancer stem cells in hepatocellular carcinoma [179]. miR-144-3p and miR-509-3p participate in the inhibition of cancer cell proliferation by inactivating MAP3K8 in renal cell carcinoma [180, 181]. miR-769 promotes melanoma improvement by modulating GSK3B expression [182]. CDK3 is also modulated by numerous miRNAs. miR-873 controls CDK3 activity, and decreased levels of this miRNA have been described in breast cancer [177]. miR-873 shifts tamoxifen resistance by targeting CDK3 and inducing ER phosphorylation [219]. miR-4469 is another noncoding RNA that targets CDK3 elevation in primary breast tumors compared to metastatic ones [178].

*4.6. miRNA-Mediated Regulation of Histone Phosphatases.* The main groups of protein phosphatases are sorted considering the structural fold of the catalytic domain [220], and miRNA-mediated regulations of these are summarized in Table 9.

*4.6.1. PPM (PPM1D).* PPM1D has been found to be modulated by miR-499a-5p and miR-499a-5p downregulation followed by PPM1D upregulation in osteosarcoma [221].

*4.6.2. PPPL (PPP2CA and PPP2CB).* PPP2CA is a direct target of miR-155, and its overexpression leads to PPP2CA low levels in colon cancer [222]. miR-650 acts as an oncogene, and its upregulation causes a PPP2CA decrease in

TABLE 9: miRNA-mediated regulation of histone phosphatases.

| Phosphatase groups | Target gene | miRNAs | Cancer tissue or cell line | Reference |
|---|---|---|---|---|
| PPM | PPM1D | miR-499a-5p | Osteosarcoma | [221] |
| | PPP2CA | miR-155 | Colon cancer | [222] |
| | PPP2CA | miR-650 | Thyroid cancer | [223] |
| PPL | PPP2CA | miR-130b | Glioma | [224] |
| | PPP2CB | miR-1246 | Breast cancer | [225] |
| | PPP2CB | miR-129-5P | Papillary thyroid carcinoma | [226] |
| | EYA1 | miR-101 | Breast cancer | [227] |
| | EYA1 | miR-562 | Sporadic Wilms' tumor | [228] |
| | EYA2 | miR-338 | Breast cancer | [229] |
| HAD | EYA2 | miR-30a | Breast cancer | [230] |
| | EYA2 | miR-30a | Lung adenocarcinoma | [231] |
| | EYA2 | miR-219a-5p | Osteosarcoma | [232] |
| | EYA2 | miR-338-3p | Cervical cancer | [233] |
| | EYA3 | miR-708 | Ewing sarcoma | [234] |
| | DUSP1 | miR-34a | Osteosarcoma | [235] |
| CC1 | DUSP1 | miR-202-3p | Gastric neuroendocrine neoplasm | [236] |
| | DUSP1 | miR-324 | Hepatocellular carcinoma | [237] |
| | DUSP1 | miR-101 | Hepatocellular carcinoma | [238] |

thyroid cancer [223]. miR-130b overexpression provides invasion through PPP2CA targeting in glioma [224]. Upregulation of miR-1246 induces inflammatory element expression by targeting PPP2CB in breast cancer [225]. However, decreased levels of miR-129-5P have been found in papillary thyroid carcinoma, and PPP2CB expression was induced as its target [226].

### 4.6.3. HAD (EYA1 and EYA2).

The apoptosis activator miR-101 can repress EYA1 and is diminished in breast cancer [227]. miR-562 is another modulator of EYA1, and its downregulation has been found in sporadic Wilms' tumor [228]. miR-338 and miR-30a are EYA2 regulators, and their downregulation increases EYA2 expression in breast cancer, and its reduction and epidermal growth factor receptor (EGFR) downregulation have been associated with lung metastasis [229, 230]. Furthermore, miR-30a overexpression was found to reduce EYA2 and attenuate cell metastasis in lung adenocarcinoma [231]. The expression of miR-219a-5p and miR-338-3p were shown to be diminished in osteosarcoma and cervical cancer, respectively, both targeting EYA2 [232, 233]. EYA3, a direct target of miR-708, was upregulated in Ewing sarcoma, promoting chemoresistance [234].

### 4.6.4. CC1 (DUSP1).

DUSP1 is controlled by various miRNAs. In osteosarcoma, miR-34a targets DUSP1, and its repression is related to elevated levels of Bax and E-cadherin, along with diminished levels of Bcl-2, cyclin E, cyclin D1, and $\beta$-catenin [235]. Upregulation of miR-202-3p downregulates DUSP1 and provokes tumor development in gastric neuroendocrine neoplasms [236]. Various studies revealed that miR-324 and miR-101 function in DUSP1 targeting in hepatocellular carcinoma, and their upregulation impedes metastasis and promotes apoptosis, suggesting these as potential novel treatment targets [237, 238].

### 4.7. miRNA-Mediated Regulation of Histone Desumoylation.

SENP1 is one of the most important desumoylation proteins modulated by various miRNAs (Table 10). SENP1 can be inactivated by multiple miRNAs. In lung cancer samples and cell lines, reduction of miR-138 along with SENP1 increase has been identified. miR-138 overexpression can elevate radiosensitivity by SENP1 blockage leading to increased apoptosis [239]. miR-133-3p and miR-186 are the regulators of SENP1 in colorectal and renal cell carcinoma, respectively. Their downregulation raises expression of the SENP1 oncogene in these cancers followed by accelerated proliferation [240, 241]. In prostate cancer, miR-145 loses its tumor suppressor activity, and this leads to increased SENP1expression. In addition, CDX2 can target miR-145-5p and decrease metastasis [242, 243].

### 4.8. miRNA-Mediated Regulation of Histone Ubiquitinations.

RBX1, RNF8, HUWE1, and UHRF1 are histone ubiquitinating enzymes involved in different malignancies. Below, we summarize the miRNA-mediated effects on the regulation of these enzymes (Table 11). RBX1 has been shown to be decreased by miR-378 and miR-194 in lung and gastric cancer, and this suppresses proliferation and metastasis [244, 245]. Cheng et al. revealed that miR-542-5p targets HUWE1 and impedes osteosarcoma development [246]. RNF8 is another histone lysine ubiquitinase. miR-214 upregulation has been associated with RNF8 downregulation and provokes chromosomal instability in ovarian cancer cells [247]. Overexpression of miR-214 and miR-622 in breast cancer prevents cell proliferation by targeting RNF8 [248, 249]. Several miRNAs can control UHRF1 expression in different neoplasia. For example, low levels of miR-145 and miR-124 have been linked to increased levels of UHRF1 in bladder cancer cell lines and accelerated cell aggressiveness [201, 250, 251]. miR-9 and miR-202 serve as tumor suppressors and attenuate cell migration through UHRF1 blockage [252, 253]. Moreover, Goto et al.

TABLE 10: miRNA-mediated regulation of histone desumoylation.

| Target gene | miRNAs | Cancer tissue or cell line | Reference |
| --- | --- | --- | --- |
| SENP1 | miR-138 | Lung cancer | [239] |
| SENP1 | miR-133-3p | Colorectal cancer | [240] |
| SENP1 | miR-186 | Renal cell carcinoma | [241] |
| SENP1 | miR-145-5p | Prostate cancer | [242, 243] |

TABLE 11: miRNA-mediated regulation of histone ubiquitination.

| Target gene | miRNAs | Cancer tissue or cancer cell line | Reference |
| --- | --- | --- | --- |
| RBX1 | miR-378 | Lung cancer | [244] |
| RBX1 | miR-194 | Gastric cancer | [245] |
| HUWE1 | miR-542-5p | Osteosarcoma | [246] |
| RNF8 | miR-214 | Ovarian cancer | [247] |
| RNF8 | miR-214 | Breast cancer | [248] |
| RNF8 | miR-622 | Breast cancer | [249] |
| UHRF1 | miR-145 | Bladder cancer cell lines | [201, 250] |
| UHRF1 | miR-124 | Bladder cancer | [251] |
| UHRF1 | miR-9 | Colorectal cancer | [252] |
| UHRF1 | miR-202 | Colorectal cancer | [253] |
| UHRF1 | miR-101 | Renal cell carcinoma | [254] |

TABLE 12: miRNA-mediated regulation of histone deubiquitination.

| Target gene | miRNAs | Cancer tissue or cancer cell line | Reference |
| --- | --- | --- | --- |
| USP3 | miR-224 | Colorectal cancer | [255] |
| USP3 | miR-224 | Gastric cancer | [256] |
| USP7 | miR-205 | Hepatocellular carcinoma | [257] |
| USP7 | miR-34a | Hepatocellular carcinoma | [258] |
| USP22 | miR-30-5p | Non-small lung cancer cell | [259] |
| USP22 | miR-30-5p | Colorectal cancer | [260] |
| USP22 | miR-30-5p | Nasopharyngeal carcinoma | [261] |
| USP22 | miR-29c | Pancreatic cancer | [262] |
| USP22 | miR-6886-3p | Hepatocellular carcinoma | [263] |
| USP22 | miR-4490 | Gastric cancer | [264] |
| USP22 | miR-101 | Papillary thyroid carcinoma | [265] |

demonstrated the antitumor function of miR-101 in renal cell carcinoma through the inactivation of UHRF1 [254].

*4.9. miRNA-Mediated Regulation of Histone Deubiquitination.* USP3, USP7, and USP22 are three deubiquitination enzymes studied in cancers, and these are controlled by various miRNAs (Table 12). USP3 that is targeted by miR-224 is reduced in colorectal cancer and induces its progression [255]. Conversely, USP3 overexpression and miR-224 underexpression lead to an increase in the proliferation of gastric cancer cells [256]. Two separate investigations demonstrated that USP7 serves as a tumor suppressor, and an increase in miR-205 and miR-34a causes an alleviation in hepatocellular carcinoma [257, 258]. miR-30-5p may represent a novel therapeutic target in NSCLC, colorectal cancer, and nasopharyngeal carcinoma since it

can mitigate tumorigenesis through USP22 suppression, leading to Wnt/$\beta$-catenin signaling target genes (Axin2 and MYC) and Sirt1/JAK/STAT3 signaling modulation [259–261]. miR-29c enhances the chemosensitivity of pancreatic cancer cells by inhibition of USP22 (264). LncRNA HULC attenuates miR-6825-5p, miR-6845-5p, and miR-6886-3p levels that target USP22 in hepatocellular carcinoma [263]. In gastric cancer, POU2F1 can target miR-4490 and increase USP22 levels [264]. Additionally, miR-101 overexpression leads to USP22 depletion and reduces tumor progression in papillary thyroid carcinoma [265].

## 5. Conclusions and Future Prospects

With due attention to the high cancer mortality rate, early diagnosis and initiation of appropriate therapeutics are urgently needed. To further these objectives, it is crucial to increase our understanding of the mechanisms and pathways involved in malignancy progression and improvement. The histone-modifying enzymes that catalyze the remodeling of chromatin structures play a major role in cancer biology. In this review, we discussed miRNAs that interact with a complex array of histone modifiers and reviewed the effects of their aberrant expression in various cancers. These alterations impact the fluctuation of multiple cancer cell properties such as drug sensitivity, drug resistance, proliferation, apoptosis, and malignancy trajectories. Hence, recognition of these small noncoding RNAs is imperative for the early diagnosis of cancer and may lead to the identification of new biomarker tests to facilitate earlier diagnosis and treatment than is currently possible for the best outcomes.

## Abbreviations

miR: microRNA
HDAC: Histone deacetylase
HDM: Histone demethylase
HMT: Histone methyltransferases
SNP: Single nucleotide polymorphism
NSCLC: Non-small-cell lung cancer
USP: Ubiquitin-specific protease.

## Data Availability

There are no raw data associated with this review article.

## Ethical Approval

Not applicable.

## Consent

Not applicable.

## Disclosure

Deniz Mortazavi and Behnoush Sohrabi are co-first authors.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

## Authors' Contributions

The authors Deniz Mortazavi and Behnoush Sohrab were contributed equally to this work.

## Acknowledgments

## References

[1] J. Gayon, "From Mendel to epigenetics: history of genetics," *Comptes Rendus Biologies*, vol. 339, no. 7-8, pp. 225–230, 2016.

[2] S. Sharma, T. K. Kelly, and P. A. Jones, "Epigenetics in cancer," *Carcinogenesis*, vol. 31, no. 1, pp. 27–36, 2010.

[3] A. Miremadi, M. Z. Oestergaard, P. D. P. Pharoah, and C. Caldas, "Cancer genetics of epigenetic genes," *Human Molecular Genetics*, vol. 16, no. R1, pp. R28–R49, 2007.

[4] D. Rong, G. Sun, F. Wu et al., "Epigenetics: roles and therapeutic implications of non-coding RNA modifications in human cancers," *Molecular Therapy-Nucleic Acids*, vol. 25, pp. 67–82, 2021.

[5] M. R. Karimzadeh, P. Pourdavoud, N. Ehtesham et al., "Regulation of DNA methylation machinery by epi-miRNAs in human cancer: emerging new targets in cancer therapy," *Cancer Gene Therapy*, vol. 28, no. 3-4, pp. 157–174, 2020.

[6] V. Gurbuz, I. Kiliccioglu, A. U. Dikmen, C. Y. Bilen, S. Sozen, and E. Konac, "Comparative analysis of epi-miRNA expression levels in local/locally advanced and metastatic prostate cancer patients," *Gene*, vol. 758, Article ID 144963, 2020.

[7] V. Gurbuz, S. Sozen, C. Bilen, and E. Konac, "miR-148a, miR-152 and miR-200b promote prostate cancer metastasis by targeting DNMT1 and PTEN expression," *Oncology Letters*, vol. 22, no. 5, Article ID 805, 2021.

[8] A. J. Bannister and T. Kouzarides, "Regulation of chromatin by histone modifications," *Cell Research*, vol. 21, no. 3, pp. 381–395, 2011.

[9] S. K. Kurdistani, "Histone modifications as markers of cancer prognosis: a cellular view," *British Journal of Cancer*, vol. 97, no. 1, pp. 1–5, 2007.

[10] J. E. Audia and R. M. Campbell, "Histone modifications and cancer," *Cold Spring Harbor Perspectives in Biology*, vol. 8, no. 4, Article ID a019521, 2016.

[11] L.-A. Macfarlane and P. Murphy, "MicroRNA: biogenesis, function and role in cancer," *Current Genomics*, vol. 11, no. 7, pp. 537–561, 2010.

[12] N. Varol, E. Konac, O. S. Gurocak, and S. Sozen, "The realm of microRNAs in cancers," *Molecular Biology Reports*, vol. 38, no. 2, pp. 1079–1089, 2011.

[13] J. C. Chuang and P. A. Jones, "Epigenetics and microRNAs," *Pediatric Research*, vol. 61, no. 5, pp. 24R–29R, 2007.

[14] Y. Kondo, L. Shen, and J.-P. J. Issa, "Critical role of histone methylation in tumor suppressor gene silencing in colorectal cancer," *Molecular and Cellular Biology*, vol. 23, no. 1, pp. 206–215, 2003.

[15] Y. Chervona and M. Costa, "Histone modifications and cancer: biomarkers of prognosis?" *American Journal of Cancer Researc.*vol. 2, no. 5, pp. 589–597, 2012.

[16] R. Kristeleit, L. Stimson, P. Workman, and W. Aherne, "Histone modification enzymes: novel targets for cancer drugs," *Expert Opinion on Emerging Drugs*, vol. 9, no. 1, pp. 135–154, 2004.

[17] M. Esteller, "Cancer epigenomics: DNA methylomes and histone-modification maps," *Nature Reviews Genetics*, vol. 8, no. 4, pp. 286–298, 2007.

[18] M. F. Fraga, E. Ballestar, A. Villar-Garea et al., "Loss of acetylation at Lys16 and trimethylation at Lys20 of histone H4 is a common hallmark of human cancer," *Nature Genetics*, vol. 37, no. 4, pp. 391–400, 2005.

[19] S. Li, L. Shen, and K.-N. Chen, "Association between H3K4 methylation and cancer prognosis: a meta-analysis," *Thoracic Cancer*, vol. 9, no. 7, pp. 794–799, 2018.

[20] J. Füllgrabe, E. Kavanagh, and B. Joseph, "Histone onco-modifications," *Oncogene*, vol. 30, no. 31, pp. 3391–3403, 2011.

[21] A. Lennartsson and K. Ekwall, "Histone modification patterns and epigenetic codes," *Biochimica et Biophysica Acta (BBA)-General Subjects*, vol. 1790, no. 9, pp. 863–868, 2009.

[22] A. J. Cole, R. Clifton-Bligh, and D. J. Marsh, "Histone H2B monoubiquitination: roles to play in human malignancy," *Endocrine-related Cancer*, vol. 22, no. 1, pp. T19–T33, 2015.

[23] M. K. Shanmugam, F. Arfuso, S. Arumugam et al., "Role of novel histone modifications in cancer," *Oncotarget*, vol. 9, no. 13, pp. 11414–11426, 2018.

[24] K. Zhang and S. Y. R. Dent, "Histone modifying enzymes and cancer: going beyond histones," *Journal of Cellular Biochemistry*, vol. 96, no. 6, pp. 1137–1148, 2005.

[25] Q. W. Chen, X. Y. Zhu, Y. Y. Li, and Z. Q. Meng, "Epigenetic regulation and cancer (review)," *Oncology Reports*, vol. 31, no. 2, pp. 523–532, 2014.

[26] A. B. M. M. K. Islam, W. F. Richter, L. A. Jacobs, N. Lopez-Bigas, and E. V. Benevolenskaya, "Co-regulation of histone-modifying enzymes in cancer," *PLoS one*, vol. 6, no. 8, Article ID e24023, 2011.

[27] W. C. S. Cho, "MicroRNAs: potential biomarkers for cancer diagnosis, prognosis and targets for therapy," *The International Journal of Biochemistry & Cell Biology*, vol. 42, no. 8, pp. 1273–1281, 2010.

[28] B. Zhang, X. Pan, G. P. Cobb, and T. A. Anderson, "microRNAs as oncogenes and tumor suppressors," *Developmental Biology*, vol. 302, no. 1, pp. 1–12, 2007.

[29] M. Zhou, J. Zeng, X. Wang et al., "Histone demethylase RBP2 decreases miR-21 in blast crisis of chronic myeloid leukemia," *Oncotarget*, vol. 6, no. 2, pp. 1249–1261, 2015.

[30] Y. Wang, H. C. Toh, P. Chow et al., "MicroRNA-224 is up-regulated in hepatocellular carcinoma through epigenetic mechanisms," *FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology*, vol. 26, no. 7, pp. 3032–3041, 2012.

[31] S. Chang, R. H. Wang, .K Akagi et al., "Tumor suppressor BRCA1 epigenetically controls oncogenic microRNA-155," *Nature Medicine*, vol. 17, no. 10, pp. 1275–1282, 2011.

[32] H. Wang, R. Garzon, H. Sun et al., "NF-$\kappa$B-YY1-miR-29 regulatory circuitry in skeletal myogenesis and rhabdomyosarcoma," *Cancer Cell*, vol. 14, no. 5, pp. 369–381, 2008.

[33] S. Morales, M. Monzo, and A. Navarro, "Epigenetic regulation mechanisms of microRNA expression," *Biomolecular Concepts*, vol. 8, no. 5-6, pp. 203–212, 2017.

[34] F. Cisneros-Soberanis, M. A. Andonegui, and L. A. Herrera, "miR-125b-1 is repressed by histone modifications in breast cancer cell lines," *SpringerPlus*, vol. 5, no. 1, Article ID 959, 2016.

[35] Y. Xiao, M. Su, W. Ou et al., "Involvement of noncoding RNAs in epigenetic modifications of esophageal cancer," *Biomedicine & Pharmacotherapy*, vol. 117, Article ID 109192, 2019.

[36] D. Sampath, C. Liu, K. Vasan et al., "Histone deacetylases mediate the silencing of miR-15a, miR-16, and miR-29b in chronic lymphocytic leukemia," *Blood*, vol. 119, no. 5, pp. 1162–1172, 2012.

[37] Y. Saito, G. Liang, G. Egger et al., "Specific activation of microRNA-127 with downregulation of the proto-oncogene BCL6 by chromatin-modifying drugs in human cancer cells," *Cancer Cell*, vol. 9, no. 6, pp. 435–443, 2006.

[38] H. Hirata, Y. Hinoda, V. Shahryari et al., "Genistein downregulates onco-miR-1260b and upregulates sFRP1 and Smad4 via demethylation and histone modification in prostate cancer cells," *British Journal of Cancer*, vol. 110, no. 6, pp. 1645–1654, 2014.

[39] X. Agirre, A. Vilas-Zornoza, A. Jiménez-Velasco et al., "Epigenetic silencing of the tumor suppressor MicroRNA hsa-miR-124a regulates CDK6 expression and confers a poor prognosis in acute lymphoblastic leukemia," *Cancer Research*, vol. 69, no. 10, pp. 4443–4453, 2009.

[40] D. Mitra, P. M. Das, F. C. Huynh, and F. E. Jones, "Jumonji/ARID1 B (JARID1B) protein promotes breast tumor cell cycle progression through epigenetic repression of microRNA let-7e," *Journal of Biological Chemistry*, vol. 286, no. 47, pp. 40531–40535, 2011.

[41] T. Hulf, T. Sibbritt, E. D. Wiklund et al., "Discovery pipeline for epigenetically deregulated miRNAs in cancer: integration of primary miRNA transcription," *BMC Genomics*, vol. 12, no. 1, Article ID 54, 2011.

[42] X. Zhang, X. Zhao, W. Fiskus et al., "Coordinated silencing of MYC-mediated miR-29 by HDAC3 and EZH2 as a therapeutic target of histone modification in aggressive B-cell lymphomas," *Cancer Cell*, vol. 22, no. 4, pp. 506–523, 2012.

[43] X. Zhang, X. Chen, J. Lin et al., "Myc represses miR-15a/miR-16-1 expression through recruitment of HDAC3 in mantle cell and other non-Hodgkin B-cell lymphomas," *Oncogene*, vol. 31, no. 24, pp. 3002–3008, 2012.

[44] K. Augoff, B. McCue, E. F. Plow, and K. Sossey-Alaoui, "miR-31 and its host gene lncRNA LOC554202 are regulated by promoter hypermethylation in triple-negative breast cancer," *Molecular Cancer*, vol. 11, no. 1, p. 5, 2012.

[45] M. Yamagishi, K. Nakano, A. Miyake et al., "Polycomb-mediated loss of miR-31 activates NIK-dependent NF-κB pathway in adult T cell leukemia and other cancers," *Cancer Cell*, vol. 21, no. 1, pp. 121–135, 2012.

[46] M. G. Rathore, A. Saumet, J.-F. Rossi et al., "The NF-κB member p65 controls glutamine metabolism through miR-23a," *The International Journal of Biochemistry & Cell Biology*, vol. 44, no. 9, pp. 1448–1456, 2012.

[47] S. L.-K. Au, C. C.-L. Wong, J. M.-F. Lee et al., "Enhancer of zeste homolog 2 epigenetically silences multiple tumor suppressor microRNAs to promote liver cancer metastasis," *Hepatology*, vol. 56, no. 2, pp. 622–631, 2012.

[48] R. Buurman, E. Gürlevik, V. Schäffer et al., "Histone deacetylases activate hepatocyte growth factor signaling by repressing MicroRNA-449 in hepatocellular carcinoma cells," *Gastroenterology*, vol. 143, no. 3, pp. 811–820, 2012.

[49] K. M. T. Arif, E. K. Elliott, L. M. Haupt, and L. R. Griffiths, "Regulatory mechanisms of epigenetic miRNA relationships in human cancer and potential as therapeutic targets," *Cancers (Basel)*, vol. 12, no. 10, p. 2922, 2020.

[50] R. Salarinia, A. Sahebkar, M. Peyvandi et al., "Epi-drugs and epi-mirs: moving beyond current cancer therapies," *Current Cancer Drug Targets*, vol. 16, no. 9, pp. 773–788, 2016.

[51] Y. Zhou, Y. Hu, M. Yang et al., "The miR-106b~25 cluster promotes bypass of doxorubicin-induced senescence and increase in motility and invasion by targeting the E-cadherin transcriptional activator EP300," *Cell Death & Differentiation*, vol. 21, no. 3, pp. 462–474, 2014.

[52] A.-Y. Gong, A. N. Eischeid, J. Xiao et al., "miR-17-5p targets the p300/CBP-associated factor and modulates androgen receptor transcriptional activity in cultured prostate cancer cells," *BMC Cancer*, vol. 12, no. 1, p. 492, 2012.

[53] A. K. Pandey, Y. Zhang, S. Zhang et al., "TIP60-miR-22 axis as a prognostic marker of breast cancer progression," *Oncotarget*, vol. 6, no. 38, pp. 41290–41306, 2015.

[54] J.-Z. Yu, N. Sun, Y.-B. Bei, X.-B. Li, C. Lu, and L.-C. Hua, "Circadian gene hCLOCK contributes to progression of colorectal carcinoma and is directly regulated by tumor-suppressive microRNA-124," *Molecular Medicine Reports*, vol. 16, no. 6, pp. 7923–7930, 2017.

[55] D. D. Leipe and D. Landsman, "Histone deacetylases, acetoin utilization proteins and acetylpolyamine amidohydrolases are members of an ancient protein superfamily," *Nucleic Acids Research*, vol. 25, no. 18, pp. 3693–3697, 1997.

[56] T. Lv, K. Song, L. Zhang et al., "miRNA-34a decreases ovarian cancer cell proliferation and chemoresistance by targeting HDAC1," *Biochemistry and Cell Biology*, vol. 96, no. 5, pp. 663–671, 2018.

[57] J. H. Noh, Y. G. Chang, M. G. Kim et al., "MiR-145 functions as a tumor suppressor by directly targeting histone deacetylase 2 in liver cancer," *Cancer Letters*, vol. 335, no. 2, pp. 455–462, 2013.

[58] Y. Kim, H. Kim, H. Park et al., "miR-326-histone deacetylase-3 feedback loop regulates the invasion and tumorigenic and angiogenic response to anti-cancer drugs," *Journal of Biological Chemistry*, vol. 289, no. 40, pp. 28019–28039, 2014.

[59] N. Amodio, M. A. Stamato, A. M. Gullà et al., "Therapeutic targeting of miR-29b/HDAC4 epigenetic loop in multiple myeloma," *Molecular Cancer Therapeutics*, vol. 15, no. 6, pp. 1364–1375, 2016.

[60] A. Ahmad, K. R. Ginnebaugh, S. Yin, A. Bollig-Fischer, K. B. Reddy, and F. H. Sarkar, "Functional role of miR-10b in tamoxifen resistance of ER-positive breast cancer cells through down-regulation of HDAC4," *BMC Cancer*, vol. 15, no. 1, Article ID 540, 2015.

[61] B. Wang, D. Li, J. Filkowski et al., "A dual role of miR-22 modulated by RelA/p65 in resensitizing fulvestrant-resistant breast cancer cells to fulvestrant by targeting FOXP1 and HDAC4 and constitutive acetylation of p53 at Lys382," *Oncogenesis*, vol. 7, no. 7, p. 54, 2018.

[62] T.-H. Hsieh, C.-Y. Hsu, C.-F. Tsai et al., "miR-125a-5p is a prognostic biomarker that targets HDAC4 to suppress breast tumorigenesis," *Oncotarget*, vol. 6, no. 1, pp. 494–509, 2015.

[63] T.-H. Hsieh, C.-Y. Hsu, C.-F. Tsai et al., "HDAC inhibitors target HDAC5, upregulate MicroRNA-125a-5p, and induce apoptosis in breast cancer cells," *Molecular Therapy*, vol. 23, no. 4, pp. 656–666, 2015.

[64] C. Liu, D. Lv, M. Li et al., "Hypermethylation of miRNA-589 promoter leads to upregulation of HDAC5 which promotes

malignancy in non-small cell lung cancer," *International Journal of Oncology*, vol. 50, no. 6, pp. 2079–2090, 2017.

[65] H. J. Bae, K. H. Jung, J. W. Eun et al., "MicroRNA-221 governs tumor suppressor HDAC6 to potentiate malignant progression of liver cancer," *Journal of Hepatology*, vol. 63, no. 2, pp. 408–419, 2015.

[66] H. Zhang, L. Li, C. Yuan, C. Wang, T. Gao, and Z. Zheng, "MiR-489 inhibited the development of gastric cancer via regulating HDAC7 and PI3K/AKT pathway," *World Journal of Surgical Oncology*, vol. 18, no. 1, p. 73, 2020.

[67] M.-Y. Wu, J. Fu, X. Xiao, J. Wu, and R.-C. Wu, "MiR-34a regulates therapy resistance by targeting HDAC1 and HDAC7 in breast cancer," *Cancer Letters*, vol. 354, no. 2, pp. 311–319, 2014.

[68] Y. Wang, P. Xu, J. Yao et al., "Retracted article: MicroRNA-216b is down-regulated in human gastric adenocarcinoma and inhibits proliferation and cell cycle progression by targeting oncogene HDAC8," *Targeted Oncology*, vol. 11, no. 2, pp. 197–207, 2016.

[69] B. Rastogi, A. Kumar, S. K. Raut et al., "Downregulation of miR-377 promotes oral squamous cell carcinoma growth and migration by targeting HDAC9," *Cancer Investigation*, vol. 35, no. 3, pp. 152–162, 2017.

[70] L. Li, L. Yuan, J. Luo, J. Gao, J. Guo, and X. Xie, "MiR-34a inhibits proliferation and migration of breast cancer through down-regulation of Bcl-2 and SIRT1," *Clinical and Experimental Medicine*, vol. 13, no. 2, pp. 109–117, 2013.

[71] W. Ma, G. G. Xiao, J. Mao et al., "Dysregulation of the miR-34a-SIRT1 axis inhibits breast cancer stemness," *Oncotarget*, vol. 6, no. 12, pp. 10432–10444, 2015.

[72] G. Eades, Y. Yao, M. Yang, Y. Zhang, S. Chumsri, and Q. Zhou, "miR-200a regulates SIRT1 expression and epithelial to mesenchymal transition (EMT)-like transformation in mammary epithelial cells," *Journal of Biological Chemistry*, vol. 286, no. 29, pp. 25992–26002, 2011.

[73] Z. Abdolvahabi, M. Nourbakhsh, S. Hosseinkhani et al., "MicroRNA-590-3P suppresses cell survival and triggers breast cancer cell apoptosis via targeting sirtuin-1 and deacetylation of p53," *Journal of Cellular Biochemistry*, vol. 120, no. 6, pp. 9356–9368, 2019.

[74] Q. Zou, Q. Tang, Y. Pan et al., "MicroRNA-22 inhibits cell growth and metastasis in breast cancer via targeting of SIRT1," *Experimental and Therapeutic Medicine*, vol. 14, no. 2, pp. 1009–1016, 2017.

[75] K. Jiang, M. Shen, Y. Chen, and W. Xu, "miR150 promotes the proliferation and migration of nonsmall cell lung cancer cells by regulating the SIRT2/JMJD2A signaling pathway," *Oncology Reports*, vol. 40, no. 2, pp. 943–951, 2018.

[76] S. Huang, H. Guo, Y. Cao, and J. Xiong, "MiR-708-5p inhibits the progression of pancreatic ductal adenocarcinoma by targeting Sirt3," *Pathology-Research and Practice*, vol. 215, no. 4, pp. 794–800, 2019.

[77] S. Dang, J. Zhou, Z. Wang, K. Wang, S. Dai, and S. He, "MiR-299-3p functions as a tumor suppressor via targeting Sirtuin 5 in hepatocellular carcinoma," *Biomedicine & Pharmacotherapy*, vol. 106, pp. 966–975, 2018.

[78] L. Ruan, J. Chen, L. Ruan, T. Yang, and P. Wang, "MicroRNA-186 suppresses lung cancer progression by targeting SIRT6," *Cancer Biomarkers: Section A of Disease Markers*, vol. 21, no. 2, pp. 415–423, 2018.

[79] H. Shi, Y. Ji, D. Zhang, Y. Liu, and P. Fang, "MicroRNA-3666-induced suppression of SIRT7 inhibits the growth of non-small cell lung cancer cells," *Oncology Reports*, vol. 36, no. 5, pp. 3051–3057, 2016.

[80] S. C. Dryden, F. A. Nahhas, J. E. Nowak, A.-S. Goustin, and M. A. Tainsky, "Role for human SIRT2 NAD-dependent deacetylase activity in control of mitotic exit in the cell cycle," *Molecular and Cellular Biology*, vol. 23, no. 9, pp. 3173–3185, 2003.

[81] D. Li and L. Li, "MicroRNA-3666 inhibits breast cancer cell proliferation by targeting sirtuin 7," *Molecular Medicine Reports*, vol. 16, no. 6, pp. 8493–8500, 2017.

[82] D. Husmann and O. Gozani, "Histone lysine methyltransferases in biology and disease," *Nature Structural & Molecular Biology*, vol. 26, no. 10, pp. 880–889, 2019.

[83] M. Cai, Q. Chen, J. Shen, C. Lv, and L. Cai, "Retracted: epigenetic silenced miR-125a-5p could be self-activated through targeting Suv39H1 in gastric cancer," *Journal of Cellular and Molecular Medicine*, vol. 22, no. 10, pp. 4721–4731, 2018.

[84] D. N. Y. Fan, F. H. C. Tsang, S. L. K. Au, L. L. Wei, A. H. K. Tam, and C. M. Wong, "Abstract 1059: SUV39H1 promotes HCC tumorigenesis and is targeted by tumor suppressive miRNA-125b," *Cancer Research*, vol. 72, no. 8, p. 1059, 2012.

[85] K. Song, C. Han, J. Zhang et al., "Epigenetic regulation of MicroRNA-122 by peroxisome proliferator activated receptor-gamma and hepatitis b virus X protein in hepatocellular carcinoma cells," *Hepatology*, vol. 58, no. 5, pp. 1681–1692, 2013.

[86] Y. Yang, Q. Meng, C. Wang et al., "MicroRNA 675 cooperates PKM2 to aggravate progression of human liver cancer stem cells induced from embryonic stem cells," *Journal of Molecular Medicine (Berlin, Germany)*, vol. 96, no. 10, pp. 1119–1130, 2018.

[87] M. Incoronato, L. Urso, A. Portela et al., "Epigenetic regulation of miR-212 expression in lung cancer," *PLoS One*, vol. 6, no. 11, Article ID e27722, 2011.

[88] M. Wu, B. Fan, Q. Guo et al., "Knockdown of SETDB1 inhibits breast cancer progression by miR-381-3p-related regulation," *Biological Research*, vol. 51, no. 1, p. 39, 2018.

[89] E. N. Knyazev, T. R. Samatov, K. A. Fomicheva, K. M. Nyushko, B. Y. Alekseev, and M. Y. Shkurnikov, "MicroRNA hsa-miR-4674 in hemolysis-free blood plasma is associated with distant metastases of prostatic cancer," *Bulletin of Experimental Biology and Medicine*, vol. 161, no. 1, pp. 112–115, 2016.

[90] M. C. Trissal, T. N. Wong, J.-C. Yao et al., "MIR142 loss-of-function mutations derepress ASH1L to increase HOXA gene expression and promote leukemogenesis," *Cancer Research*, vol. 78, no. 13, pp. 3510–3521, 2018.

[91] M. Colamaio, F. Puca, E. Ragozzino et al., "miR-142-3p down-regulation contributes to thyroid follicular tumorigenesis by targeting ASH1L and MLL1," *The Journal of Clinical Endocrinology & Metabolism*, vol. 100, no. 1, pp. E59–E69, 2015.

[92] S. He, S. Zeng, Z. W. Zhou, Z. X. He, and S. F. Zhou, "Hsa-microRNA-181a is a regulator of a number of cancer genes and a biomarker for endometrial carcinoma in patients: a bioinformatic and clinical study and the therapeutic implication," *Drug Design, Development and Therapy*, vol. 9, pp. 1103–1175, 2015.

[93] B. Zeng, Z. Li, R. Chen et al., "Epigenetic regulation of miR-124 by hepatitis C virus core protein promotes migration and invasion of intrahepatic cholangiocarcinoma cells by targeting SMYD3," *FEBS Letters*, vol. 586, no. 19, pp. 3271–3278, 2012.

[94] W. Zhu, J. Qian, L. Ma, P. Ma, F. Yang, and Y. Shu, "MiR-346 suppresses cell proliferation through SMYD3 dependent approach in hepatocellular carcinoma," *Oncotarget*, vol. 8, no. 39, pp. 65218–65229, 2017.

[95] L. Lv, Q. Li, S. Chen et al., "miR-133b suppresses colorectal cancer cell stemness and chemoresistance by targeting methyltransferase DOT1L," *Experimental Cell Research*, vol. 385, no. 1, Article ID 111597, 2019.

[96] B. Liu, X. Zhang, F. Song et al., "MiR-502/SET8 regulatory circuit in pathobiology of breast cancer," *Cancer Letters*, vol. 376, no. 2, pp. 259–267, 2016.

[97] C. Wang, Z. Guo, C. Wu, Y. Li, and S. Kang, "A polymorphism at the miR-502 binding site in the 3' untranslated region of the SET8 gene is associated with the risk of epithelial ovarian cancer," *Cancer Genetics*, vol. 205, no. 7, pp. 373–376, 2012.

[98] S. Yang, H. Guo, B. Wei et al., "Association of miR-502-binding site single nucleotide polymorphism in the 3'-untranslated region of SET8 and TP53 codon 72 polymorphism with non-small cell lung cancer in Chinese population," *Acta biochimica et biophysica Sinica*, vol. 46, no. 2, pp. 149–154, 2014.

[99] C. Ding, R. Li, J. Peng, S. Li, and Z. Guo, "A polymorphism at the miR-502 binding site in the 3' untranslated region of the SET8 gene is associated with the outcome of small-cell lung cancer," *Experimental and Therapeutic Medicine*, vol. 3, no. 4, pp. 689–692, 2012.

[100] S. Liu, H. Dong, J. Wu, and C. Wang, "Association of an miR-502-binding site polymorphism in the 3'-untranslated region of SET8 with colorectal cancer," *Oncology Letters*, vol. 17, no. 4, pp. 3960–3964, 2019.

[101] L. Diao, H. Su, G. Wei et al., "Prognostic value of microRNA 502 binding site SNP in the 3'-untranslated region of the SET8 gene in patients with non-hodgkin's lymphoma," *Tumori Journal*, vol. 100, no. 5, pp. 553–558, 2014.

[102] C. Wang, J. Wu, Y. Zhao, and Z. Guo, "miR-502 medaited histone methyltransferase SET8 expression is associated with outcome of esophageal squamous cell carcinoma," *Scientific Reports*, vol. 6, no. 1, p. 32921, 2016.

[103] S. Zhang, Z. Guo, J. Xu et al., "miR-502-mediated histone methyltransferase SET8 expression is associated with clear cell renal cell carcinoma risk," *Oncology Letters*, vol. 14, no. 6, pp. 7131–7138, 2017.

[104] Z. Guo, C. Wu, X. Wang, C. Wang, R. Zhang, and B. Shan, "A polymorphism at the miR-502 binding site in the 3'-untranslated region of the histone methyltransferase SET8 is associated with hepatocellular carcinoma outcome," *International Journal of Cancer*, vol. 131, no. 6, pp. 1318–1322, 2012.

[105] N. Yu, P. Huangyang, X. Yang et al., "microRNA-7 suppresses the invasive potential of breast cancer cells and sensitizes cells to DNA damages by targeting histone methyltransferase SET8," *Journal of Biological Chemistry*, vol. 288, no. 27, pp. 19633–19642, 2013.

[106] W. Zhang, J. Lin, P. Wang, and J. Sun, "miR-17-5p downregulation contributes to erlotinib resistance in non-small cell lung cancer cells," *Journal of Drug Targeting*, vol. 25, no. 2, pp. 125–131, 2017.

[107] Z. Zeng, Y. Yang, and H. Wu, "MicroRNA-765 alleviates the malignant progression of breast cancer via interacting with EZH1," *American Journal of Translational Research*, vol. 11, no. 7, pp. 4500–4507, 2019.

[108] S. Liu, S. H. Patel, C. Ginestier et al., "MicroRNA93 regulates proliferation and differentiation of normal and malignant breast stem cells," *PLoS Genetics*, vol. 8, no. 6, Article ID e1002751, 2012.

[109] X. Lai, Y. Guo, Z. Guo, R. Liu, X. Wang, and F. Wang, "Downregulation of microRNA-574 in cancer stem cells causes recurrence of prostate cancer via targeting REL," *Oncology Reports*, vol. 36, no. 6, pp. 3651–3656, 2016.

[110] J.-g. Zhang, J.-F. Guo, D.-L. Liu, Q. Liu, and J.-J. Wang, "MicroRNA-101 exerts tumor-suppressive functions in non-small cell lung cancer through directly targeting enhancer of zeste homolog 2," *Journal of Thoracic Oncology*, vol. 6, no. 4, pp. 671–678, 2011.

[111] P. Cao, Z. Deng, M. Wan et al., "MicroRNA-101 negatively regulates Ezh2 and its expression is modulated by androgen receptor and HIF-1α/HIF-1β," *Molecular Cancer*, vol. 9, no. 1, p. 108, 2010.

[112] T. Sakurai, V. N. Bilim, A. V. Ugolkov et al., "The enhancer of zeste homolog 2 (EZH2), a potential therapeutic target, is regulated by miR-101 in renal cancer cells," *Biochemical and Biophysical Research Communications*, vol. 422, no. 4, pp. 607–614, 2012.

[113] Y. Konno, P. Dong, Y. Xiong et al., "MicroRNA-101 targets EZH2, MCL-1 and FOS to suppress proliferation, invasion and stem cell-like phenotype of aggressive endometrial cancer cells," *Oncotarget*, vol. 5, no. 15, pp. 6049–6062, 2014.

[114] X. Dang, A. Ma, L. Yang et al., "MicroRNA-26a regulates tumorigenic properties of EZH2 in human lung carcinoma cells," *Cancer Genetics*, vol. 205, no. 3, pp. 113–123, 2012.

[115] S. Sander, L. Bullinger, K. Klapproth et al., "MYC stimulates EZH2 expression by repression of its negative regulator miR-26a," *Blood*, vol. 112, no. 10, pp. 4202–4212, 2008.

[116] R. Ciarapica, G. Russo, F. Verginelli et al., "Deregulated expression of miR-26a and Ezh2 in rhabdomyosarcoma," *Cell Cycle*, vol. 8, no. 1, pp. 172–175, 2009.

[117] C. M. Koh, T. Iwata, Q. Zheng, C. Bethel, S. Yegnasubramanian, and A. M. De Marzo, "Myc enforces overexpression of EZH2 in early prostatic neoplasia via transcriptional and post-transcriptional mechanisms," *Oncotarget*, vol. 2, no. 9, pp. 669–683, 2011.

[118] J. Lu, M.-L. He, L. Wang et al., "MiR-26a inhibits cell growth and tumorigenesis of nasopharyngeal carcinoma through repression of EZH2," *Cancer Research*, vol. 71, no. 1, pp. 225–233, 2011.

[119] S. Cui, Y. Sun, Y. Liu et al., "MicroRNA-137 has a suppressive role in liver cancer via targeting EZH2," *Molecular Medicine Reports*, vol. 16, no. 6, pp. 9494–9502, 2017.

[120] F. Zheng, Y.-J. Liao, M.-Y. Cai et al., "The putative tumour suppressor microRNA-124 modulates hepatocellular carcinoma cell aggressiveness by repressing ROCK2 and EZH2," *Gut*, vol. 61, no. 2, pp. 278–289, 2012.

[121] X. Liu, C. Wang, Z. Chen et al., "MicroRNA-138 suppresses epithelial-mesenchymal transition in squamous cell carcinoma cell lines," *Biochemical Journal*, vol. 440, no. 1, pp. 23–31, 2011.

[122] R. B. Koumangoye, T. Andl, K. J. Taubenslag et al., "SOX4 interacts with EZH2 and HDAC3 to suppress microRNA-31 in invasive esophageal cancer cells," *Molecular Cancer*, vol. 14, no. 1, p. 24, 2015.

[123] T. Liu, L. Hou, and Y. Huang, "EZH2-specific microRNA-98 inhibits human ovarian cancer stem cell proliferation via regulating the pRb-E2F pathway," *Tumour Biology: The Journal of the International Society for Oncodevelopmental Biology and Medicine*, vol. 35, no. 7, pp. 7239–7247, 2014.

[124] J. Xu, Z. Yin, W. Gao et al., "Genetic variation in a MicroRNA-502 minding site in SET8 gene confers clinical

outcome of non-small cell lung cancer in a Chinese population," *PLoS One*, vol. 8, no. 10, Article ID e77024, 2013.

[125] S. Varambally, Q. Cao, R.-S. Mani et al., "Genomic loss of microRNA-101 leads to overexpression of histone methyltransferase EZH2 in cancer," *Science*, vol. 322, no. 5908, pp. 1695–1699, 2008.

[126] A. Di Lorenzo and M. T. Bedford, "Histone arginine methylation," *FEBS Letters*, vol. 585, no. 13, pp. 2024–2031, 2011.

[127] B. Li, L. Liu, X. Li, and L. Wu, "miR-503 suppresses metastasis of hepatocellular carcinoma cell by targeting PRMT1," *Biochemical and Biophysical Research Communications*, vol. 464, no. 4, pp. 982–987, 2015.

[128] L. Zheng, J. Chen, Z. Zhou, and Z. He, "miR-195 enhances the radiosensitivity of colorectal cancer cells by suppressing CARM1," *OncoTargets and Therapy*, vol. 10, pp. 1027–1038, 2017.

[129] M. Zhang, W. Wu, M. Gao et al., "Coactivator-associated arginine methyltransferase 1 promotes cell growth and is targeted by microRNA-195-5p in human colorectal cancer. Tumour biology," *Tumour Biology: The Journal of the International Society for Oncodevelopmental Biology and Medicine*, vol. 39, no. 3, 2017.

[130] D. Wang and Y. Hu, "Long non-coding RNA PVT1 competitively binds MicroRNA-424-5p to regulate CARM1 in radiosensitivity of non-small-cell lung cancer," *Molecular Therapy-Nucleic Acids*, vol. 16, pp. 130–140, 2019.

[131] S. Pal, R. A. Baiocchi, J. C. Byrd, M. R. Grever, S. T. Jacob, and S. Sif, "Low levels of miR-92b/96 induce PRMT5 translation and H3R8/H4R3 methylation in mantle cell lymphoma," *The EMBO Journal*, vol. 26, no. 15, pp. 3558–3569, 2007.

[132] C. M. Sun, G. M. Zhang, H. N. Qian et al., "MiR-1266 suppresses the growth and metastasis of prostate cancer via targeting PRMT5," *European Review for Medical and Pharmacological Sciences*, vol. 23, no. 15, pp. 6436–6444, 2019.

[133] H. Zhang, X. Guo, X. Feng et al., "MiRNA-543 promotes osteosarcoma cell proliferation and glycolysis by partially suppressing PRMT9 and stabilizing HIF-1$\alpha$ protein," *Oncotarget*, vol. 8, no. 2, 2016.

[134] L. Verrier, M. Vandromme, and D. Trouche, "Histone demethylases in chromatin cross-talks," *Biology of the Cell*, vol. 103, no. 8, pp. 381–401, 2011.

[135] W. Zhang, J.-H. Chen, T. Shan et al., "miR-137 is a tumor suppressor in endometrial cancer and is repressed by DNA hypermethylation," *Laboratory Investigation; A Journal of Technical Methods and Pathology*, vol. 98, no. 11, pp. 1397–1407, 2018.

[136] C. Koga, S. Kobayashi, H. Nagano et al., "Reprogramming using microRNA-302 improves drug sensitivity in hepatocellular carcinoma cells," *Annals of Surgical Oncology*, vol. 21, no. 4, pp. S591–S600, 2014.

[137] L. Y. W. Bourguignon, G. Wong, C. Earle, and L. Chen, "Hyaluronan-CD44v3 interaction with Oct4-Sox2-Nanog promotes miR-302 expression leading to self-renewal, clonal formation, and cisplatin resistance in cancer stem cells from head and neck squamous cell carcinoma," *Journal of Biological Chemistry*, vol. 287, no. 39, pp. 32800–32824, 2012.

[138] A. Razdan, P. de Souza, and T. L. Roberts, "Role of MicroRNAs in treatment response in prostate cancer," *Current Cancer Drug Targets*, vol. 18, no. 10, pp. 929–944, 2018.

[139] M. Yan, X. Yang, R. Shen et al., "miR-146b promotes cell proliferation and increases chemosensitivity, but attenuates cell migration and invasion via FBXL10 in ovarian cancer," *Cell Death & Disease*, vol. 9, no. 11, p. 1123, 2018.

[140] X. Hong, Y. Xu, X. Qiu et al., "MiR-448 promotes glycolytic metabolism of gastric cancer by downregulating KDM2B," *Oncotarget*, vol. 7, no. 16, pp. 22092–22102, 2016.

[141] E. Peta, A. Sinigaglia, G. Masi et al., "HPV16 E6 and E7 upregulate the histone lysine demethylase KDM2B through the c-MYC/miR-146a-5p axys," *Oncogene*, vol. 37, no. 12, pp. 1654–1668, 2018.

[142] S. K. R. Padi, Q. Zhang, Y. M. Rustum, C. Morrison, and B. Guo, "MicroRNA-627 mediates the epigenetic mechanisms of vitamin D to suppress proliferation of human colorectal cancer cells and growth of xenograft tumors in mice," *Gastroenterology*, vol. 145, no. 2, pp. 437–446, 2013.

[143] Z.-M. Du, L.-F. Hu, H.-Y. Wang et al., "Upregulation of MiR-155 in nasopharyngeal carcinoma is partly driven by LMP1 and LMP2A and downregulates a negative prognostic marker JMJD1A," *PLoS One*, vol. 6, no. 4, Article ID e19137, 2011.

[144] M. Zhan, F. Wen, L. Liu, Z. Chen, H. Wei, and H. Zhou, "JMJD1A promotes tumorigenesis and forms a feedback loop with EZH2/let-7c in NSCLC cells," *Tumor Biology*, vol. 37, no. 8, pp. 11237–11247, 2016.

[145] J. K. Parrish, M. Sechler, R. A. Winn, and P. Jedlicka, "The histone demethylase KDM3A is a microRNA-22-regulated tumor promoter in Ewing Sarcoma," *Oncogene*, vol. 34, no. 2, pp. 257–262, 2015.

[146] Z. Hui, C. Yiling, Y. Wenting, H. XuQun, Z. ChuanYi, and L. Hui, "miR-491-5p functions as a tumor suppressor by targeting JMJD2B in ER$\alpha$-positive breast cancer," *FEBS Letters*, vol. 589, no. 7, pp. 812–821, 2015.

[147] J. Zhang, J. Ren, S. Hao et al., "MiRNA-491-5p inhibits cell proliferation, invasion and migration via targeting JMJD2B and serves as a potential biomarker in gastric cancer," *American Journal of Translational Research*, vol. 10, no. 2, pp. 525–534, 2018.

[148] S. F. Chen, Z. Liu, S. Chaurasiya et al., "Identification of core aberrantly expressed microRNAs in serous ovarian carcinoma," *Oncotarget*, vol. 9, no. 29, pp. 20451–20466, 2018.

[149] X. Liang, J. Zeng, L. Wang et al., "Histone demethylase retinoblastoma binding protein 2 is overexpressed in hepatocellular carcinoma and negatively regulated by hsa-miR-212," *PloS One*, vol. 8, no. 7, Article ID e69784, 2013.

[150] Z. Jiping, F. Ming, W. Lixiang et al., "MicroRNA-212 inhibits proliferation of gastric cancer by directly repressing retinoblastoma binding protein 2," *Journal of Cellular Biochemistry*, vol. 114, no. 12, pp. 2666–2672, 2013.

[151] T. Hao, C. X. Li, X. Y. Ding, and X. J. Xing, "MicroRNA-363-3p/p21(Cip1/Waf1) axis is regulated by HIF-2$\alpha$ in mediating stemness of melanoma cells," *Neoplasma*, vol. 66, no. 3, pp. 427–436, 2019.

[152] Y. Huang, Y. Zou, R. Zheng, and X. Ma, "MiR-137 inhibits cell proliferation in acute lymphoblastic leukemia by targeting JARID1B," *European Journal of Haematology*, vol. 103, no. 3, pp. 215–224, 2019.

[153] H. Denis, O. Van Grembergen, B. Delatte et al., "MicroRNAs regulate KDM5 histone demethylases in breast cancer cells," *Molecular BioSystems*, vol. 12, no. 2, pp. 404–413, 2016.

[154] I. Mocavini, S. Pippa, V. Licursi et al., "JARID 1B expression and its function in DNA damage repair are tightly regulated by mi RNA s in breast cancer," *Cancer Science*, vol. 110, no. 4, pp. 1232–1243, 2019.

[155] Y. Fu, M. Liu, F. Li et al., "MiR-221 promotes hepatocellular carcinoma cells migration via targeting PHF2," *BioMed Research International*, vol. 2019, Article ID 4371405, 11 pages, 2019.

[156] Z. Zhang, Y. Yang, and X. Zhang, "MiR-770 inhibits tumorigenesis and EMT by targeting JMJD6 and regulating WNT/β-catenin pathway in non-small cell lung cancer," *Life Sciences*, vol. 188, pp. 163–171, 2017.

[157] V. Anelli, A. Ordas, S. Kneitz et al., "Ras-induced miR-146a and 193a target Jmjd6 to regulate melanoma progression," *Frontiers in Genetics*, vol. 9, p. 675, 2018.

[158] G. Manning, D. B. Whyte, R. Martinez, T. Hunter, and S. Sudarsanam, "The protein kinase complement of the human genome," *Science (New York, NY)*, vol. 298, no. 5600, pp. 1912–1934, 2002.

[159] T. Yoshitomi, K. Kawakami, H. Enokida et al., "Restoration of miR-517a expression induces cell apoptosis in bladder cancer cell lines," *Oncology Reports*, vol. 25, no. 6, pp. 1661–1668, 2011.

[160] Y. Chen, G. Ke, D. Han, S. Liang, G. Yang, and X. Wu, "MicroRNA-181a enhances the chemoresistance of human cervical squamous cell carcinoma to cisplatin by targeting PRKCD," *Experimental Cell Research*, vol. 320, no. 1, pp. 12–20, 2014.

[161] G. Ke, L. Liang, J. M. Yang et al., "MiR-181a confers resistance of cervical cancer to radiation therapy through targeting the pro-apoptotic PRKCD gene," *Oncogene*, vol. 32, no. 25, pp. 3019–3027, 2013.

[162] L. Yao, L. Wang, F. Li, X. Gao, X. Wei, and Z. Liu, "MiR181c inhibits ovarian cancer metastasis and progression by targeting PRKCD expression," *International Journal of Clinical and Experimental Medicine*, vol. 8, no. 9, pp. 15198–15205, 2015.

[163] H. Zhao, T. Bi, Z. Qu, J. Jiang, S. Cui, and Y. Wang, "Expression of miR-224-5p is associated with the original cisplatin resistance of ovarian papillary serous carcinoma," *Oncology Reports*, vol. 32, no. 3, pp. 1003–1012, 2014.

[164] Z. Chen, H. Ju, T. Zhao et al., "hsa_circ_0092306 targeting miR-197-3p promotes gastric cancer development by regulating PRKCB in MKN-45 cells," *Molecular Therapy-Nucleic Acids*, vol. 18, pp. 617–626, 2019.

[165] M. T. M. van Jaarsveld, P. F. van Kuijk, A. W. M. Boersma et al., "miR-634 restores drug sensitivity in resistant ovarian cancer cells by targeting the Ras-MAPK pathway," *Molecular Cancer*, vol. 14, no. 1, p. 196, 2015.

[166] N. Li, Y. Ma, L. Ma, Y. Guan, L. Ma, and D. Yang, "MicroRNA-488-3p sensitizes malignant melanoma cells to cisplatin by targeting PRKDC," *Cell Biology International*, vol. 41, no. 6, pp. 622–629, 2017.

[167] D. Xiu, D. Wang, J. Wang, F. Ji, and W. Zhang, "MicroRNA-543 suppresses liver cancer growth and induces apoptosis via the JAK2/STAT3 signaling pathway," *Oncology Letters*, vol. 17, no. 2, pp. 2451–2456, 2019.

[168] B.-h. Hou, Z.-X. Jian, P. Cui, S.-J. Li, R.-Q. Tian, and J.-R. Ou, "miR-216a may inhibit pancreatic tumor growth by targeting JAK2," *FEBS Letters*, vol. 589, no. 17, pp. 2224–2232, 2015.

[169] S. Wang, X. Chen, and M. Tang, "MicroRNA-216a inhibits pancreatic cancer by directly targeting Janus kinase 2," *Oncology Reports*, vol. 32, no. 6, pp. 2824–2830, 2014.

[170] X. Wang, W. Qiu, G. Zhang, S. Xu, Q. Gao, and Z. Yang, "MicroRNA-204 targets JAK2 in breast cancer and induces cell apoptosis through the STAT3/BCl-2/survivin pathway," *International Journal of Clinical and Experimental Pathology*, vol. 8, no. 5, pp. 5017–5025, 2015.

[171] S. Zhang, L. Gao, A. Thakur et al., "miRNA-204 suppresses human non-small cell lung cancer by targeting ATF2," *Tumor Biology*, vol. 37, no. 8, 2016.

[172] L. Ding, Y. Xu, W. Zhang et al., "MiR-375 frequently downregulated in gastric cancer inhibits cell proliferation by targeting JAK2," *Cell Research*, vol. 20, no. 7, pp. 784–793, 2010.

[173] Y. Xu, J. Jin, Y. Liu et al., "Snail-regulated MiR-375 inhibits migration and invasion of gastric cancer cells by targeting JAK2," *PLoS one*, vol. 9, Article ID e99516, 2014.

[174] A. Navarro, T. Diaz, A. Martinez et al., "Regulation of JAK2 by miR-135a: prognostic impact in classic Hodgkin lymphoma," *Blood*, vol. 114, no. 14, pp. 2945–2951, 2009.

[175] W. Zhou, X. Bi, G. Gao, and L. Sun, "miRNA-133b and miRNA-135a induce apoptosis via the JAK2/STAT3 signaling pathway in human renal carcinoma cells," *Biomedicine & Pharmacotherapy*, vol. 84, 2016.

[176] H. Wu, M. Huang, P. Cao, T. Wang, Y. Shu, and P. Liu, "MiR-135a targetsJAK2and inhibits gastric cancer cell proliferation," *Cancer Biology & Therapy*, vol. 13, no. 5, pp. 281–288, 2012.

[177] J. Cui, Y. Yang, H. Li et al., "MiR-873 regulates ERα transcriptional activity and tamoxifen resistance via targeting CDK3 in breast cancer cells," *Oncogene*, vol. 34, no. 30, pp. 3895–3907, 2015.

[178] T. Cao, T. Xiao, G Huang et al., "CDK3, target of miR-4469, suppresses breast cancer metastasis via inhibiting Wnt/β-catenin pathway," *Oncotarget*, vol. 8, no. 49, pp. 84917–84927, 2017.

[179] X. Zhang, P. Jiang, L. Shuai et al., "miR-589-5p inhibits MAP3K8 and suppresses CD90+ cancer stem cells in hepatocellular carcinoma," *Journal of Experimental & Clinical Cancer Research*, vol. 35, no. 1, p. 176, 2016.

[180] F. Liu, N. Chen, R. Xiao, W. Wang, and Z. Pan, "miR-144-3p serves as a tumor suppressor for renal cell carcinoma and inhibits its invasion and metastasis by targeting MAP3K8," *Biochemical and Biophysical Research Communications*, vol. 480, no. 1, pp. 87–93, 2016.

[181] Z. Su, D. Chen, E. Zhang et al., "MicroRNA-509-3p inhibits cancer cell proliferation and migration by targeting the mitogen-activated protein kinase kinase kinase 8 oncogene in renal cell carcinoma," *Molecular Medicine Reports*, vol. 12, no. 1, pp. 1535–1543, 2015.

[182] H.-J. Qiu, X.-H. Lu, S.-S. Yang, C.-Y. Weng, E.-K. Zhang, and F.-C. Chen, "MiR-769 promoted cell proliferation in human melanoma by suppressing GSK3B expression," *Biomedicine & Pharmacotherapy*, vol. 82, pp. 117–123, 2016.

[183] W. Wang, C. Yang, H. Nie et al., "LIMK2 acts as an oncogene in bladder cancer and its functional SNP in the microRNA-135a binding site affects bladder cancer risk," *International Journal of Cancer*, vol. 144, no. 6, pp. 1345–1355, 2019.

[184] N. Wang, M. Zhu, X. Wang, H.-Y. Tan, S.-W. Tsao, and Y. Feng, "Berberine-induced tumor suppressor p53 up-regulation gets involved in the regulatory network of MIR-23a in hepatocellular carcinoma," *Biochimica et Biophysica Acta (BBA)-Gene Regulatory Mechanisms*, vol. 1839, no. 9, pp. 849–857, 2014.

[185] X. Li, L. Lian, D. Zhang, L. Qu, and N. Yang, "gga-miR-26a targets NEK6 and suppresses Marek's disease lymphoma cell proliferation," *Poultry Science*, vol. 93, no. 5, pp. 1097–1105, 2014.

[186] L. Wu, Z. Chen, and Y. Xing, "MiR-506-3p inhibits cell proliferation, induces cell cycle arrest and apoptosis in

retinoblastoma by directly targeting NEK6," *Cell Biology International*, vol. 43, no. 12, 2018.

[187] Q. Yuan, T. Sun, F. Ye, W. Kong, and H. Jin, "MicroRNA-124-3p affects proliferation, migration and apoptosis of bladder cancer cells through targeting AURKA," *Cancer Biomarkers: Section A of Disease Markers*, vol. 19, no. 1, pp. 93–101, 2017.

[188] W. Qiao, B. Guo, H. Zhou et al., "miR-124 suppresses glioblastoma growth and potentiates chemosensitivity by inhibiting AURKA," *Biochemical and Biophysical Research Communications*, vol. 486, no. 1, pp. 43–48, 2017.

[189] Z.-L. Ma, B.-J. Zhang, D.-T. Wang et al., "Tanshinones suppress AURKA through up-regulation of miR-32 expression in non-small cell lung cancer," *Oncotarget*, vol. 6, no. 24, pp. 20111–20120, 2015.

[190] Y. Qin, S. Zhang, S. Deng et al., "Epigenetic silencing of miR-137 induces drug resistance and chromosomal instability by targeting AURKA in multiple myeloma," *Leukemia*, vol. 31, no. 5, pp. 1123–1135, 2017.

[191] C. D. Johnson, A. Esquela-Kerscher, G. Stefani et al., "The let-7 microRNA represses cell proliferation pathways in human cells," *Cancer Research*, vol. 67, no. 16, pp. 7713–7722, 2007.

[192] H. Zhang, J. Bao, S. Zhao, Z. Huo, and B. Li, "MicroRNA-490-3p suppresses hepatocellular carcinoma cell proliferation and migration by targeting the aurora kinase A gene (AURKA)," *Archives of Medical Science*, vol. 16, no. 2, pp. 395–406, 2020.

[193] A. Gomaa, D. Peng, Z. Chen et al., "Epigenetic regulation of AURKA by miR-4715-3p in upper gastrointestinal cancers," *Scientific Reports*, vol. 9, no. 1, Article ID 16970, 2019.

[194] B. Xu, T. Xu, H. Liu, Q. Min, S. Wang, and Q. Song, "MiR-490-5p suppresses cell proliferation and invasion by targeting BUB1 in hepatocellular carcinoma cells," *Pharmacology*, vol. 100, no. 5-6, pp. 269–282, 2017.

[195] Y. Goto, A. Kurozumi, T. Arai et al., "Impact of novel miR-145-3p regulatory networks on survival in patients with castration-resistant prostate cancer," *British Journal of Cancer*, vol. 117, no. 3, pp. 409–420, 2017.

[196] Y.-Z. Huang, J. Zhang, H.-Y. Shao, J.-P. Chen, and H.-Y. Zhao, "MicroRNA-191 promotes osteosarcoma cells proliferation by targeting checkpoint kinase 2," *Tumor Biology*, vol. 36, no. 8, pp. 6095–6101, 2015.

[197] K. Krishnan, A. L. Steptoe, H. C. Martin et al., "MicroRNA-182-5p targets a network of genes involved in DNA repair," *RNA*, vol. 19, no. 2, pp. 230–242, 2013.

[198] B. Liu, J. Qu, F. Xu et al., "MiR-195 suppresses non-small cell lung cancer by targeting CHEK1," *Oncotarget*, vol. 6, no. 11, 2015.

[199] C. Kim, Y. Hong, H. Lee, H. Kang, and E. K. Lee, "MicroRNA-195 desensitizes HCT116 human colon cancer cells to 5-fluorouracil," *Cancer Letters*, vol. 412, pp. 264–271, 2018.

[200] Y. Xie, R.-R. Wei, G.-L. Huang, M.-Y. Zhang, Y.-F. Yuan, and H.-Y. Wang, "Checkpoint kinase 1 is negatively regulated by miR-497 in hepatocellular carcinoma," *Medical Oncology*, vol. 31, no. 3, p. 844, 2014.

[201] R. Matsushita, H. Yoshino, H. Enokida et al., "Regulation of UHRF1 by dual-strand tumor-suppressor microRNA-145 (miR-145-5p and miR-145-3p): inhibition of bladder cancer cell aggressiveness," *Oncotarget*, vol. 7, no. 19, pp. 28460–28487, 2016.

[202] J. Xu, Y. Li, F. Wang et al., "Suppressed miR-424 expression via upregulation of target gene Chk1 contributes to the progression of cervical cancer," *Oncogene*, vol. 32, no. 8, pp. 976–987, 2013.

[203] Z. Mei, T. Su, J. Ye, C. Yang, S. Zhang, and C. Xie, "The miR-15 family enhances the radiosensitivity of breast cancer cells by targeting G2Checkpoints," *Radiation Research*, vol. 183, no. 2, pp. 196–207, 2015.

[204] L. Lezina, N. Purmessur, A. V. Antonov et al., "miR-16 and miR-26a target checkpoint kinases Wee1 and Chk1 in response to p53 activation by genotoxic stress," *Cell Death & Disease*, vol. 4, no. 12, p. e953, 2013.

[205] Y. Zhou, M. Wang, J. Wu, Z. Jie, S. Chang, and T. Shuang, "The clinicopathological significance of miR-1307 in chemotherapy resistant epithelial ovarian cancer," *Journal of Ovarian Research*, vol. 8, no. 1, p. 23, 2015.

[206] M.-B. Chen, M.-X. Wei, H. Junyi et al., "MicroRNA-451 regulates AMPK/mTORC1 signaling and fascin1 expression in HT-29 colorectal cancer," *Cellular Signalling*, vol. 26, no. 1, pp. 102–109, 2013.

[207] S. Zhang, Y. Zhang, Q. Cheng et al., "Silencing protein kinase C ζ by microRNA-25-5p activates AMPK signaling and inhibits colorectal cancer cell proliferation," *Oncotarget*, vol. 8, no. 39, pp. 65329–65338, 2017.

[208] P. Liu, F. Ye, X. Xie et al., "mir-101-3p is a key regulator of tumor metabolism in triple negative breast cancer targeting AMPK," *Oncotarget*, vol. 7, no. 23, pp. 35188–35198, 2016.

[209] H. Liao, Y. Xiao, Y. Hu et al., "Methylation-induced silencing of miR-34a enhances chemoresistance by directly upregulating ATG4B-induced autophagy through AMPK/mTOR pathway in prostate cancer," *Oncology Reports*, vol. 35, no. 1, pp. 64–72, 2016.

[210] T.-I. Hsu, C.-H. Hsu, K.-H. Lee et al., "MicroRNA-18a is elevated in prostate cancer and promotes tumorigenesis through suppressing STK4 in vitro and in vivo," *Oncogenesis*, vol. 3, no. 4, p. e99, 2014.

[211] K. H. Koo and H. Kwon, "MicroRNA miR-4779 suppresses tumor growth by inducing apoptosis and cell cycle arrest through direct targeting of PAK2 and CCND3," *Cell Death & Disease*, vol. 9, no. 2, p. 77, 2018.

[212] Y. Zhang, P. Lin, J. Y Zou et al., "MiR-216a-5p act as a tumor suppressor, regulating the cell proliferation and metastasis by targeting PAK2 in breast cancer," *European Review for Medical and Pharmacological Sciences*, vol. 23, no. 6, pp. 2469–2475, 2019.

[213] S. Hao, C. Luo, A. Abukiwan et al., "miR-137 inhibits proliferation of melanoma cells by targeting PAK2," *Experimental Dermatology*, vol. 24, no. 12, pp. 947–952, 2015.

[214] Q. Li, X. Wu, L. Guo, J. Shi, and J. Li, "MicroRNA-7-5p induces cell growth inhibition, cell cycle arrest and apoptosis by targeting PAK2 in non-small cell lung cancer," *FEBS Open Bio*, vol. 9, no. 11, pp. 1983–1993, 2019.

[215] T. Shuang, M. Wang, C. Shi, Y. Zhou, and D. Wang, "Down-regulated expression of miR-134 contributes to paclitaxel resistance in human ovarian cancer cells," *FEBS Letters*, vol. 589, no. 20, pp. 3154–3164, 2015.

[216] Y. Wang, J. Tong, H. Lin, L. Ma, and Y. Xu, "CCHE1 accelerated the initiation of oral squamous cell carcinoma through enhancing PAK2 expression by sponging miR-922," *Journal of Oral Pathology & Medicine*, vol. 49, no. 7, pp. 636–644, 2020.

[217] X. Zhang, X. Zhang, T. Wang et al., "MicroRNA-26a is a key regulon that inhibits progression and metastasis of c-Myc/EZH2 double high advanced hepatocellular carcinoma," *Cancer Letters*, vol. 426, pp. 98–108, 2018.

[218] J. S. Rawlings, K. M. Rosler, and D. A. Harrison, "The JAK/STAT signaling pathway," *Journal of Cell Science*, vol. 117, no. 8, pp. 1281–1283, 2004.

[219] X. Zhang, B. Zhang, P. Zhang et al., "Norcantharidin regulates ERα signaling and tamoxifen resistance via targeting miR-873/CDK3 in breast cancer cells," *PLoS One*, vol. 14, no. 5, Article ID e0217181, 2019.

[220] M. J. Chen, J. E. Dixon, and G. Manning, "Genomics and evolution of protein phosphatases," *Science Signaling*, vol. 10, no. 474, Article ID eaag1796, 2017.

[221] J. Liu, L. Huang, P. Su et al., "MicroRNA-499a-5p inhibits osteosarcoma cell proliferation and differentiation by targeting protein phosphatase 1D through protein kinase B/glycogen synthase kinase 3β signaling," *Oncology Letters*, vol. 15, no. 4, pp. 4113–4120, 2018.

[222] C. Bossard, F. Souazé, A. Jarry et al., "Over-expression of neurotensin high-affinity receptor 1 (NTS1) in relation with its ligand neurotensin (NT) and nuclear β-catenin in inflammatory bowel disease-related oncogenesis," *Peptides*, vol. 28, no. 10, pp. 2030–2035, 2007.

[223] F. M. Orlandella, R. M. Mariniello, P. L. C. Iervolino et al., "miR-650 promotes motility of anaplastic thyroid cancer cells by targeting PPP2CA," *Endocrine*, vol. 65, no. 3, pp. 582–594, 2019.

[224] L. Tong, M. Chu, B. Yan et al., "MTDH promotes glioma invasion through regulating miR-130b-ceRNAs," *Oncotarget*, vol. 8, no. 11, pp. 17738–17749, 2017.

[225] A. Bott, N. Erdem, S Lerrer et al., "miRNA-1246 induces pro-inflammatory responses in mesenchymal stem/stromal cells by regulating PKA and PP2A," *Oncotarget*, vol. 8, no. 27, pp. 43897–43914, 2017.

[226] L. Liang, Y. Luo, X. Yang et al., "Lowered levels of microRNA-129 and potential signaling pathways in papillary thyroid carcinoma: a determination of microRNA sequencing in 507 patients and bioinformatics analysis," *International Journal of Clinical and Experimental Pathology*, vol. 10, no. 7, pp. 7511–7527, 2017.

[227] H. Guan, Z. Dai, Y. Ma, Z. Wang, X. Liu, and X. Wang, "MicroRNA-101 inhibits cell proliferation and induces apoptosis by targeting EYA1 in breast cancer," *International Journal of Molecular Medicine*, vol. 37, no. 6, pp. 1643–1651, 2016.

[228] K. M. Drake, E. C. Ruteshouser, R. Natrajan et al., "Loss of heterozygosity at 2q37 in sporadic Wilms' tumor: putative role for miR-562," *Clinical Cancer Research*, vol. 15, no. 19, pp. 5985–5992, 2009.

[229] Y. Liang, X. Xu, T. Wang et al., "The EGFR/miR-338-3p/EYA2 axis controls breast tumor growth and lung metastasis," *Cell Death & Disease*, vol. 8, no. 7, Article ID e2928, 2017.

[230] J. Fu, X. Xu, L. Kang et al., "miR-30a suppresses breast cancer cell proliferation and migration by targeting Eya2," *Biochemical and Biophysical Research Communications*, vol. 445, no. 2, pp. 314–319, 2014.

[231] Y. Yuan, S. Zheng, Q. Li et al., "Overexpression of miR-30a in lung adenocarcinoma A549 cell line inhibits migration and invasion via targetingEYA2," *Acta biochimica et biophysica Sinica*, vol. 48, no. 3, pp. 220–228, 2016.

[232] X. Zhu, L. Chen, and J. Lin, "miR-219a-5p represses migration and invasion of osteosarcoma cells via targeting EYA2," *Artificial Cells, Nanomedicine, and Biotechnology*, vol. 46, no. 3, pp. S1004–S1010, 2018.

[233] X. Luan and Y. Wang, "LncRNA XLOC_006390 facilitates cervical cancer tumorigenesis and metastasis as a ceRNA against miR-331-3p and miR-338-3p," *Journal of Gynecologic Oncology*, vol. 29, no. 6, p. e95, 2018.

[234] T. P. Robin, A. Smith, E. McKinsey, L. Reaves, P. Jedlicka, and H. L. Ford, "EWS/FLI1 regulates EYA3 in Ewing sarcoma via modulation of miRNA-708, resulting in increased cell survival and chemoresistance," *Molecular Cancer Research*, vol. 10, no. 8, pp. 1098–1108, 2012.

[235] L. Gang, L. Qun, W. D. Liu, Y. S. Li, Y. Z. Xu, and D. T. Yuan, "MicroRNA-34a promotes cell cycle arrest and apoptosis and suppresses cell adhesion by targeting DUSP1 in osteosarcoma," *American Journal of Translational Research*, vol. 9, no. 12, pp. 5388–5399, 2017.

[236] D. Dou, Y.-F. Shi, Q. Liu et al., "Hsa-miR-202-3p, up-regulated in type 1 gastric neuroendocrine neoplasms, may targetDUSP1," *World Journal of Gastroenterology*, vol. 24, no. 5, pp. 573–582, 2018.

[237] W. L. Xiao, H. L. Zeng, Y. Z. Wang, Q. Gou, Z. J. Zhou, and R. D. Xu, "Up-regulation of miR-324 suppresses cell apoptosis by targeting DUSP1 in hepatocellular carcinoma," *International Journal of Clinical and Experimental Pathology*, vol. 10, pp. 1243–1252, 2017.

[238] X. Wei, C. Tang, X. Lu et al., "MiR-101 targets DUSP1 to regulate the TGF-β secretion in sorafenib inhibits macrophage-induced growth of hepatocarcinoma," *Oncotarget*, vol. 6, no. 21, pp. 18389–18405, 2015.

[239] H. Yang, Y. Tang, W. Guo et al., "Up-regulation of microRNA-138 induce radiosensitization in lung cancer cells," *Tumor Biology*, vol. 35, no. 7, pp. 6557–6565, 2014.

[240] G.-Q. Zhou, F. Han, Z.-L. Shi et al., "MiR-133a-3p targets SUMO-specific protease 1 to inhibit cell proliferation and cell cycle progress in colorectal cancer," *Oncology Research Featuring Preclinical and Clinical Cancer Therapeutics*, vol. 26, no. 5, pp. 795–800, 2017.

[241] D. Jiao, M. Wu, L. Ji, F. Liu, and Y. Liu, "MicroRNA-186 suppresses cell proliferation and metastasis through targeting sentrin-specific protease 1 in renal cell carcinoma," *Oncology Research Featuring Preclinical and Clinical Cancer Therapeutics*, vol. 26, no. 2, pp. 249–259, 2018.

[242] C. Wang, W. Tao, S. Ni et al., "Tumor-suppressive micro RNA -145 induces growth arrest by targeting SENP 1 in human prostate cancer cells," *Cancer Science*, vol. 106, no. 4, pp. 375–382, 2015.

[243] J. H. He, Z. P. Han, M. X. Zou, M. L. He, Y. G. Li, and L. Zheng, "CDX2/mir-145-5p/SENP1 pathways affect LNCaP cells invasion and migration," *Frontiers in Oncology*, vol. 9, p. 477, 2019.

[244] C. S. Ho, S. M. Noor, and N. H. Nagoor, "MiR-378 and MiR-1827 regulate tumor invasion, migration and angiogenesis in human lung adenocarcinoma by targeting RBX1 and CRKL, respectively," *Journal of Cancer*, vol. 9, no. 2, pp. 331–345, 2018.

[245] X. Chen, Y. Wang, W. Zang, Y. Du, M. Li, and G. Zhao, "miR-194 targets RBX1 gene to modulate proliferation and migration of gastric cancer cells," *Tumor Biology*, vol. 36, no. 4, pp. 2393–2401, 2015.

[246] D.-d. Cheng, T. Yu, T. Hu, M. Yao, C.-y. Fan, and Q.-c. Yang, "MiR-542-5p is a negative prognostic factor and promotes osteosarcoma tumorigenesis by targeting HUWE1," *Oncotarget*, vol. 6, no. 40, pp. 42761–42772, 2015.

[247] Z. Wang, H. Yin, Y. Zhang et al., "miR-214-mediated downregulation of RNF8 induces chromosomal instability in ovarian cancer cells," *Cell Cycle*, vol. 13, no. 22, pp. 3519–3528, 2014.

[248] L. Min, C. Liu, J. Kuang, X. Wu, and L. Zhu, "miR-214 inhibits epithelial-mesenchymal transition of breast cancer cells via downregulation of RNF8," *Acta biochimica et biophysica Sinica*, vol. 51, no. 8, pp. 791–798, 2019.

[249] C. Liu, L. Min, J. Kuang, C. Zhu, X. Y. Qiu, and L. Zhu, "Bioinformatic identification of miR-622 key target genes and experimental validation of the miR-622-RNF8 Axis in breast cancer," *Frontiers in Oncology*, vol. 9, p. 1114, 2019.

[250] R. Matsushita, N. Seki, H. Yoshino, Y. Goto, K. Miyamoto, and M. Yonemori, "Abstract B15: MicroRNA-145/145∗ as a dual tumor-suppressor targeting UHRF1 in bladder cancer," *Cancer Research*, vol. 76, p. B15, 2016.

[251] X. Wang, Q. Wu, B. Xu et al., "MiR-124 exerts tumor suppressive functions on the cell proliferation, motility and angiogenesis of bladder cancer by fine-tuning UHRF1," *FEBS Journal*, vol. 282, no. 22, pp. 4376–4388, 2015.

[252] M. Zhu, Y. Xu, M. Ge, Z. Gui, and F. Yan, "Regulation of UHRF 1 by micro RNA -9 modulates colorectal cancer cell proliferation and apoptosis," *Cancer Science*, vol. 106, no. 7, pp. 833–839, 2015.

[253] Y. Lin, Z. Chen, S. Lin et al., "MiR-202 inhibits the proliferation and invasion of colorectal cancer by targeting UHRF1," *Acta biochimica et biophysica Sinica*, vol. 51, no. 6, pp. 598–606, 2019.

[254] Y. Goto, A. Kurozumi, N. Nohata et al., "The microRNA signature of patients with sunitinib failure: regulation of UHRF1 pathways by microRNA-101 in renal cell carcinoma," *Oncotarget*, vol. 7, no. 37, pp. 59070–59086, 2016.

[255] Z. Wang, J. Yang, J. Di et al., "Downregulated USP3 mRNA functions as a competitive endogenous RNA of SMAD4 by sponging miR-224 and promotes metastasis in colorectal cancer," *Scientific Reports*, vol. 7, no. 1, Article ID 4281, 2017.

[256] B. Li, M. Jin, F. Cao et al., "Hsa_circ_0017639 expression promotes gastric cancer proliferation and metastasis by sponging miR-224-5p and upregulating USP3," *Gene*, vol. 750, Article ID 144753, 2020.

[257] L. Zhu, R. Liu, W. Zhang, S. Qian, and J.-H. Wang, "MicroRNA-205 regulates ubiquitin specific peptidase 7 protein expression in hepatocellular carcinoma cells," *Molecular Medicine Reports*, vol. 12, no. 3, pp. 4652–4656, 2015.

[258] H. Zhang, T. Deng, S. Ge et al., "Exosome circRNA secreted from adipocytes promotes the growth of hepatocellular carcinoma by targeting deubiquitination-related USP7," *Oncogene*, vol. 38, no. 15, pp. 2844–2859, 2019.

[259] G. Xu, J. Cai, L. Wang et al., "MicroRNA-30e-5p suppresses non-small cell lung cancer tumorigenesis by regulating USP22-mediated Sirt1/JAK/STAT3 signaling," *Experimental Cell Research*, vol. 362, no. 2, pp. 268–278, 2018.

[260] S. Jiang, D. Miao, M. Wang, J. Lv, Y. Wang, and J. Tong, "MiR-30-5p suppresses cell chemoresistance and stemness in colorectal cancer through USP22/Wnt/$\beta$-catenin signaling axis," *Journal of Cellular and Molecular Medicine*, vol. 23, no. 1, pp. 630–640, 2019.

[261] Y. X. Ma, H. Zhang, X. H. Li, and Y. H. Liu, "MiR-30e-5p inhibits proliferation and metastasis of nasopharyngeal carcinoma cells by target-ing USP22," *European Review for Medical and Pharmacological Sciences*, vol. 22, no. 19, pp. 6342–6349, 2018.

[262] L. Huang, C. Hu, H. Cao et al., "MicroRNA-29c increases the chemosensitivity of pancreatic cancer cells by inhibiting USP22 mediated autophagy," *Cellular Physiology and Biochemistry*, vol. 47, no. 2, pp. 747–758, 2018.

[263] H. Xiong, Z. Ni, J. He et al., "LncRNA HULC triggers autophagy via stabilizing Sirt1 and attenuates the chemosensitivity of HCC cells," *Oncogene*, vol. 36, no. 25, pp. 3528–3540, 2017.

[264] Y. Xiao, S. Liu, J. Li et al., "The POU2F1/miR-4490/USP22 axis regulates cell proliferation and metastasis in gastric cancer," *Cellular Oncology*, vol. 43, no. 6, pp. 1017–1033, 2020.

[265] H. Zhao, H. Tang, Q Huang et al., "MiR-101 targets USP22 to inhibit the tumorigenesis of papillary thyroid carcinoma," *American Journal of Cancer Research*, vol. 6, no. 11, pp. 2575–2586, 2016.