Abstract: The ability to reprogram the transcriptional circuitry by remodeling the three-dimensional structure of the genome is exploited by cancer cells to promote tumorigenesis. This reprogramming occurs because of hereditable chromatin chemical modifications and the consequent formation of RNA-protein-DNA complexes that represent the principal actors of the epigenetic phenomena. In this regard, the deregulation of a transcribed non-coding RNA may be both cause and consequence of a cancer-related epigenetic alteration. This review summarizes recent findings that implicate microRNAs in the aberrant epigenetic regulation of cancer cells.

Keywords: microRNAs; epigenetics; human cancer

1. Introduction

In 1942, Conrad Waddington (1905–1975) introduced for the first time the term “epigenetics” in a paper entitled “The Epigenotype,” defining it as “the branch of biology which studies the causal interactions between genes and their products which bring the phenotype into being” [1]. The meaning of this word has gradually evolved since the exponential growth of genetics and in-depth knowledge of this phenomenon. At present, the definition of “epigenetics” as “the study of changes in gene function that are mitotically and/or meiotically heritable and that do not entail a change in DNA sequence” is generally accepted [2–5].

The most common mammalian epigenetic modifications are (i) DNA methylation at the 5-carbon of the cytosine and (ii) histone acetylation and methylation [6,7]. However, it has become evident that (iii) non-coding RNAs have an important role in the molecular mechanisms that sustain epigenetics [8]. Alterations of these factors can cause abnormal epigenetic patterns at canonical promoter boxes or distant regulatory elements and may contribute to deregulate critical genes involved in proliferation, programmed cell death, and cell differentiation [9–11].

The initiation and progression of human cancer is thought to be driven by combinations of epigenetic and genetic alterations that activate multistep programs of carcinogenesis [12,13]. Recent evidence shows that epigenetic reprogramming of cancer stem cell (CSC) is a key step in the earliest phases of neoplastic progression. This promotes the clonal expansion of aberrant cells prone to subsequent genetic and epigenetic alterations associated with neoplastic evolution [13–15].

Compared to aberrant DNA methylation, little is known about abnormal histone modifications in carcinogenesis, but this is an area of great interest given its importance for chromosome remodeling and, therefore, for transcription regulation, DNA repair, chromosome condensation, and segregation [16–21]. Non-coding RNAs can be distinguished in long non-coding RNAs (lncRNAs) and small RNAs including microRNAs, focus of this review. While a role as new epigenetic factors has been assigned to lncRNAs [22,23], microRNAs need a more in-depth discussion.
MicroRNAs (miRNAs or miRs) are small, noncoding RNAs that directly modulate gene expression at the post-transcriptional level binding predominantly to 3′-untranslated region (3′UTR) of target messenger RNAs (mRNAs) in a sequence-specific manner \[24,25\].

Through this regulation, miRNAs play a pivotal role in several cellular processes, including proliferation, cell cycle control, programmed cell death, differentiation, invasiveness, and tissue specific functions such as immune responses, hormone secretions, and angiogenesis. All these processes are implicated in the development and evolution of cancer \[26–29\]. Genome-wide analysis has demonstrated that miRNAs expression is deregulated in most cancer types through various mechanisms, including defects in the miRNA biogenesis machinery, amplification/deletion of the region encompassing the miRNA, or aberrant transcriptional control \[26\]. Compelling evidence demonstrated that miRNAs can also be deregulated in cancer by abnormal CpGs methylation and/or histone modifications \[30\]. On the other hand, several miRNAs are not only regulated by epigenetic mechanisms, but themselves have an active role on the epigenetic machinery, creating highly-controlled feedback circuits that finely tune gene expression. These subgroups of miRNAs, called “epi-miRNAs”, are often deregulated in human cancer and target specific epigenetic regulators, such as components of the polycomb repressive complexes 1 and 2 (PRC1 and PRC2), DNA methyl-transferases (DNMTs) and histone deacetylases (HDACs) enzymes, and the Retinoblastoma-Like protein 2 (RBL2) \[31–36\]. Moreover, it was shown that miRNAs are also present in the nucleus \[37,38\], where they regulate gene expression via distinct mechanisms.

This review summarizes the state-of-the-art of an intimate but still largely unknown networking between epigenetics and microRNAs in human cancer.

2. Epigenetic Alterations of miRNAs in Cancer

2.1. By DNA Methylation

DNA methylation occurs in vertebrate cells at carbon-5 of the cytosine ring in CpG di-nucleotides. The reaction is catalyzed by DNMTs using S-adenosyl-methionine as methyl-donor. It is a normal process used by cells to maintain the physiological expression of genes and to maintain mono-allelic expression of imprinted genes \[39\]. About 70% of the promoters in the human genome are associated with regions characterized by a high frequency of CpGs (CpG islands, CGIs) that can be methylated by the DNA methylation machinery \[40\]. In 2007, Weber et al. found that 155 out of 332 human miRNA investigated (47%) were associated with CGIs, suggesting that miRNAs were subject to transcriptional regulation by DNA methylation \[41\].

The first evidence of regulation of miRNAs by DNA methylation came from a profiling of miRNA expression of the T24 bladder cancer cell line after treatment with the DNA de-methylating agent 5-Aza-2′-deoxycytidine (5-AZA), in combination with an HDAC inhibitor (4-phenylbutyric acid; 4-PBA). Seventeen out of 313 miRNAs were deregulated after treatment. Among these, miR-127 was up-regulated, with consequent down-regulation of its target, the proto-oncogene B-cell lymphoma 6 (BCL6) \[42\].

In another study, after stable depletion of DNMT1 and DNMT3B in the HCT116 colorectal cancer cell line, the miR-124a, miR-373, and miR-517c were demonstrated to be transcriptionally inactivated by CGI methylation \[43\]. The same authors also found a signature of microRNA hyper-methylated in metastatic cell lines from colon (SW620), melanoma (IGR37) and head and neck (SIHN-011B) cancers. Hyper-methylation-associated silencing of miR-9, miR-34b/c, and miR-148a observed in those metastatic cell lines was also evident in primary colon, breast, lung, head, and neck carcinomas and melanomas \[44\].

After these general approaches to identify miRNAs aberrantly expressed by DNA methylation in cancer cells \[41–43\], several tumor specific studies were performed to obtain exploitable data in cancer research.
MiR-9, miR-34b/c, miR-124a, and miR-148a hyper-methylation was confirmed in breast cancer cells [45–47], together with let-7a, miR-10b, miR-125b, miR126, miR-152, miR-195/497, miR-200 family, and miRs at the imprinted locus DLK1-DIO3 region [48–56]. Moreover, down-regulation by methylation of the miR-149 was reported in clinical cases of chemoresistant breast cancer [57].

In pancreatic ductal adenocarcinoma (PDAC) were found hyper-methylated the miR-9-1, miR-124s, miR-192, miR-615-5p, and miR-1247, suggesting tumor suppressor roles in this type of cancer [58–62]. Differently from breast and other cancers, miR-200a and miR-200b were reported to be expressed and de-methylated in PDAC [63].

In gastric cancer (GC) cell lines and in about 70% of primary GCs the miR-34b/c and the miR-181c genes were found to be epigenetically silenced by CGI hyper-methylation [64]. This was postulated to contribute to the activation of notch 4 (NOTCH4) and KRAS proto-oncogene, GTPase (KRAS), targets of these miRs [65]. Aberrant methylation of the miR-1, miR-9, miR-129, miR-10a/b, of the miR-200a/b/429 locus, and of miR-33b was observed in GC [66–72]. Of note is the analysis of the methylation status of miR-124 in the normal gastric mucosa of GC patients and healthy volunteers with or without Helicobacter pylori infection. Among the healthy volunteers, the cases with H. pylori infection showed higher levels of methylation of miR-124 than in samples without infection, and among the non-infected samples, gastric mucosa from gastric cancer patients show higher levels of methylation of miR-124 than in the mucosa from healthy donors. These data suggest that the aberrant methylation of miR-124 is an early event in the pathogenesis of GC [73].

In hepatocellular carcinoma (HCC), several miRs were confirmed to be aberrantly methylated such as miR-1, miR-9, miR-34b, miR-124, miR-148a and, miR-200b [74–78]. A microRNA host gene involved in HCC, the insulin like growth factor 2 (IGF2), shows hyper-methylation of 3 CpGs at the intron 2, immediately upstream the miR-483, associated with strong expression of this miR. When methylated, those CpGs cannot bind the transcriptional repressor CCCTC-binding factor (CTCF), permitting microRNA transcription [79]. In the same tumor type, miR-221 is up-regulated [80]. Hypo-methylation of the region upstream miR-221 in a cellular context holding the wild type tumor protein p53 (TP53) seems to enable its expression [81]. A recent study shows a global, cancer-specific microRNA cluster hypo-methylation in HCCs that do not harbor hepatitis C virus (HCV) or hepatitis B virus (HBV) infections [82].

Aberrant methylation of several miRs is a recurrent theme in cancer, which underlines their biological importance in general tumorigenic processes. The miR-9 has been reported aberrantly methylated in ovarian, renal, liver, lung, colorectal cancer, and multiple myeloma. Its silencing allows up-regulation of important oncogenic products, such as cyclin G1 (CCNG1) and epidermal growth factor (EGF) [83]. miR-34s are similarly methylated in several type of cancers, and their silencing affects cellular stemness by targeting CD44 molecule (CD44) and notch 1 (NOTCH1), cell cycle by targeting MYC proto-oncogene, bHLH transcription factor (MYC) and cyclin dependent kinase 6 (CDK6), and apoptosis by targeting BCL2 apoptosis regulator (BCL2) protein[84–88]. Of note is miR-124, whose expression was found to be deregulated by hyper-methylation in 14 different tumor types (Table 1). MiR-124 targets four lncRNAs (metastasis associated lung adenocarcinoma transcript 1 (MALAT1); HOX transcript antisense RNA (HOTAIR); HOXA11 antisense RNA (HOXA11-AS) and long intergenic non-protein coding RNA, regulator of reprogramming (LINC-ROR)) [89–92] that act as sponges for the miRs, as the miR-124, inhibiting its oncosuppressor functions [93–96]. MiR-137 was also hyper-methylated in nine different tumor types, which is consistent with the fact that this microRNA controls many cellular processes deregulated in cancer, such as cell cycle progression by targeting CDK6 [97], tumor glutamine metabolism by targeting solute carrier family 1 (neutral amino acid transporter), member 5 (ASCT2) [98], and chromosome remodeling by targeting the enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2) [99].

MiR-200a/b-429 and miR-200c-141 play a pivotal role in the epithelial to mesenchymal transition (EMT) by targeting the transcription factors zinc finger E-box binding homeobox 1 and 2 (ZEB1; ZEB2) [100–103], and in cell proliferation by targeting phosphatase and tensin homolog (PTEN)
and KRAS [104,105]. These targets play a role also in cellular stemness. Indeed, the stem-like cell fractions isolated from metastatic breast cancers displayed loss of miR-200. Moreover, it has been demonstrated that in the stem-like phenotype, the miR-200c-141 cluster was repressed by promoter CpG hyper-methylation, whereas the miR-200b-200a-429 cluster was silenced through polycomb group-mediated histone modifications [106].

2.2. By Histone Modifications

Histone post-translational modifications include methylation, phosphorylation, acetylation, ubiquitination, and sumoylation. Histone methylation and histone acetylation are covalent post-translational modifications by which methyl or acetyl groups are transferred to amino acids on the histone tails, modifying gene accessibility and hence expression by alteration of the chromatin structure. Specifically, acetylation is associated with an open chromatin state marking active region of transcription, while methylation can be present both in actively transcribed and in repressed regions [107].

The first evidence of deregulation of miRNA due to histone modification in cancer cells was reported by Scott et al. in 2006. These authors demonstrated the aberrant expression of 27 miRNAs after treatment of SKBr3 breast cancer cells with an HDACs inhibitor [108]. In chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL), miR-15a and miR-16 are epigenetically silenced due to overexpression of HDACs. Indeed, treatment with a deacetylase inhibitor restored the expression of these miRNAs in CLL cells, with associated down-regulation of MCL-1 levels and decreased CLL cell survival [109,110]. In 2006, Merens et al. demonstrated that genes at the 13q14.3 region, which harbors miR-15a and miR-16-1, shows mono-allelic expression in B-CLL cells independently of the chromosome copy number. Mono-allelic expression was due to different chromatin packaging of the two copies of 13q14.3; indeed, treatment with 5-aza-CdR or trichostatin A (TSA) induced bi-allelic expression at 13q14.3 [111]. In line with these evidences, we have recently found in CLL a double allele-specific transcriptional regulation of the miR-15a/16-1 cluster involving both the RNA polymerase II and the RNA polymerase III. If either the epigenetic silencing of the 13q14.3 region or the 13q14 deletion affects the allele transcribed by the RNA polymerase II, the allele transcribed by the RNA polymerase III can be un-masked [112]. The oncogenic miR-155 has been found to be epigenetically repressed in breast cancer by BRCA1, DNA repair associated (BRCA1), which recruits HDAC2 on the miR-155 promoter. MiR-155 is up-regulated only in breast cancer cells with loss of wild-type BRCA1 or mutant-BRCA1, since HDCA2 cannot be recruited on the miR promoter [113]. Recent evidence indicates that in prostate cancer, the mocetinostat, a class I selective inhibitor of the HDACs, up-regulates miR-31 with consequent loss of expression of its target E2F transcription factor 6 (E2F6), induction of apoptosis, and reduction in cancer growth [114]. MiR-449 was repressed by HDACI-3 in HCC cell line [115].

Wang et al. in 2012 demonstrated in HCC that HDAC1 and HDAC3 act as negative regulators of miR-224 expression, whereas the histone acetyl-transferase EP300 is a positive regulator. They suggest that in normal cells, the miR-224 locus is maintained transcriptionally quiescent by HDAC1 and HDAC3, while during cellular transformation, miR-224 expression is activated by overexpression of EP300. Finally, they propose that EP300 could represent a potential drug target to reverse miR-224 overexpression in HCC patients [116].

In 2009, Yang et al. demonstrated that miR-449a/b expression in an osteosarcoma cell line was epigenetically repressed through tri-methylation of the lysine 27 on the histone H3 (H3K27me3), reversible by epigenetic drug treatment [117]. Multiple miRNAs are down-regulated in HCC by EZH2, which mediates H3K27me3, such as miR-139-5p, miR-125b, miR-101, let-7c, and miR-200b [118]. In prostate cancer, miR-181a, miR-181b, miR-200b, miR-200c, and miR-203 were found epigenetically repressed by EZH2 [119]. Recently, miR-31 was also identified to be repressed by EZH2 in prostate cancer [120].

MicroRNAs epigenetically regulated in cancer are reported in Table 1.
Table 1. Epigenetically regulated miRNAs in human cancer.

| miRNA   | Cancer Type                                                                 | Epigenetic Modification | Target                                      | Reference                  |
|---------|------------------------------------------------------------------------------|-------------------------|--------------------------------------------|----------------------------|
| miR-1   | Hepatocellular, liver, colorectal, lung                                        | DM<sub>hyper</sub>      | FOXP1, MET, HDAC4, Pim1                     | [74,121,122]               |
| miR-9   | Breast, ovarian, pancreatic, multiple myeloma, renal, gastric, hepatocellular, colorectal, melanoma, head and neck, multiple myeloma, lung | DM<sub>hyper</sub>      | CCNG1, IL-6, AP3B1, TC10, ONECUT2, IGF2BP1, MYO1D, ANXA2 | [44,47,58,67,75,123–125]   |
| miR-10a | Gastric, bladder, hepatocellular                                              | DM<sub>hyper</sub>      | HOXA1                                       | [69,126,127]               |
| miR-10b | Gastric, hepatocellular                                                       | DM<sub>hyper</sub>      |                                            | [70,127]                   |
| miR-15a/16 | Chronic lymphocytic leukemia, mantle cell lymphoma                           | HDA                     | BCL2, MCL1                                  | [109,110]                  |
| miR-17-92 | Colorectal                                                                 | HDA                     | PTEN, BCL2L11, CDKN1A                       | [128]                      |
| miR-21  | Ovarian, prostate, colorectal                                                 | DM<sub>hyper</sub>, DM<sub>hyper</sub>, HMT | ITGB4                                      | [129–131]                  |
| miR-23a-27a | Hepatocellular                                                              | DM<sub>hypo</sub>       |                                            | [78]                       |
| miR-24  | Nasopharyngeal                                                              | DM<sub>hyper</sub>      |                                            | [132]                      |
| miR-29a/b | B-cell Lymphoma, chronic lymphocytic leukemia, acute myeloid leukemia, lung | HMT, HDA                | MCL1, DNMT3A-B                              | [31,32,109,133,134]        |
| miR-31  | Melanoma, prostate, breast                                                   | HMT, DM<sub>hyper</sub>, HDA | SRC, RAB27A, MAP3K14, MET, E2F1, E2F2, EXO1, FOXM1, MCM2, E2F6, BMI-1 | [120,135–139]              |
| miR-33b | Gastric                                                                     | DM<sub>hyper</sub>      |                                            | [72]                       |
| miR-34a | Lung, breast, colon, kidney, bladder, pancreatic cancer cells, melanoma     | DM<sub>hypo</sub>       | CDK6                                       | [76,140,141]               |
| miR-34b/c | Gastric, ovarian, lung, colon, melanoma, head and neck, breast, non-small cell lung, neuroblastoma, hepatocellular, pleural mesothelioma, oral | DM<sub>hyper</sub>      | MYC, CDK6, E2F3                             | [45,68,76,141–145]         |
| miR-101 | Hepatocellular                                                              | HMT                     |                                            | [118]                      |
| miR-106b-25-93 | Hepatocellular                             | DM<sub>hypo</sub>       |                                            | [78]                       |
| miR-107 | Pancreate                                                                   | DM<sub>hypo</sub>       | CDK6                                       | [146]                      |
| miR-124 | Colon, gastric, hematological, cervical, glioblastoma cells, breast, prostate, neuroblastoma, pancreatic, colorectal, non-small cell lung, acute lymphoblastic leukemia, hepatocellular, renal | DM<sub>hyper</sub>      | BCL2, CDK6, VIM, SMYD3, IQGAP1, RAC1       | [45,59,73,77,142,144,147–152] |
| miR-125b | Breast, hepatocellular                                                      | HMT, DM<sub>hypo</sub> | PGF                                         | [45,118,153]               |
| miR-126 | Bladder, malignant pleural mesothelioma, colorectal, non-small cell lung    | DM<sub>hypo</sub>, HDA  | VEGF                                        | [154–157]                  |
| miR-127 | Prostate, bladder, colon, breast, clear renal cell carcinoma                | DM<sub>hypo</sub>, HDA  | DAPK1, BCL6                                 | [42,45,158]                |
| miR-129 | Gastric, endometrial, colorectal, hepatocellular, hematological             | DM<sub>hypo</sub>       | SOX4                                        | [68,159–163]               |
| miRNA     | Cancer Type                                                                 | Epigenetic Modification | Target                                      | Reference                  |
|-----------|------------------------------------------------------------------------------|-------------------------|---------------------------------------------|----------------------------|
| miR-132   | Pancreas, prostate, breast                                                   | DM<sub>hyper</sub>, HDA  | TALIN2, HB-EGF                              | [45,164,165]               |
| miR-133b  | Colorectal                                                                   | DM<sub>hyper</sub>      |                                             | [166]                      |
| miR-137   | Head and neck squamous cells, colorectal, glioblastoma cells, prostate,      | DM<sub>hyper</sub>      | CDK6, E2F6, LSD-1, ASCT2, AURKA            | [98,145,151,167–171]       |
|           | multiple myeloma, gastric, oral, hepatocellular cells                        |                         |                                             |                           |
| miR-139   | Hepatocellular, non-small cell lung                                          | HMT                     | ROCK2                                      | [172,173]                  |
| miR-141   | Clear cell renal cell carcinoma                                              | DM<sub>hyper</sub>, HDA | TET1, TET3, ZEB1                            | [158,174]                  |
| miR-143   | Leukemia                                                                     | DM<sub>hyper</sub>      | MLL-AF4                                    | [175]                      |
| miR-145   | Prostate, lung adenocarcinoma, non-small cell carcinoma, clear cell renal    | DM<sub>hyper</sub>, HDA | TNFSF10, MUCIN1                            | [158,176–179]              |
|           | cell carcinoma                                                               |                         |                                             |                           |
| miR-148a  | Colorectal, melanoma, head and neck, breast, pancreas, hepatocellular       | DM<sub>hyper</sub>      | TGF2                                       | [44,78]                    |
| miR-149   | Breast                                                                       | DM<sub>hyper</sub>      | NDST1                                      | [57]                       |
| miR-152   | Endometrium, bladder cancer cells, prostate, breast cancer cells             | DM<sub>hyper</sub>      | DNMT1, E2F3, MET, RICTOR                   | [34,126,171,180,181]       |
| miR-155   | Breast, prostate                                                            | HDA, DM<sub>hyper</sub> |                                             | [113,171]                  |
| miR-181a/b| Prostate                                                                     | HMT, DM<sub>hyper</sub>, HDA | RING2                                      | [119]                      |
| miR-181c  | Gastric, prostate, glioblastoma cells                                        | DM<sub>hyper</sub>      | NOTCH4, KRAS, NOTCH2                       | [65,182]                   |
| miR-191   | Breast, hepatocellular                                                       | DM<sub>hypo</sub>       | TIMP3                                      | [45,183]                   |
| miR-192   | Pancreatic ductal adenocarcinoma                                             | DM<sub>hypo</sub>       | SERPINE1                                   | [61]                       |
| miR-193a  | Hepatocellular, acute myeloid leukemia, bladder, breast, oral                | DM<sub>hypo</sub>, DM<sub>hypo</sub> | E2F6, SRSF2, PLAU, HIC2                   | [45,145,184–186]          |
| miR-193b  | Prostate                                                                     | DM<sub>hypo</sub>, HDA  |                                             | [187,188]                  |
| miR-195/497| Hepatocellular                                                               | DM<sub>hypo</sub>       |                                             | [78]                       |
| miR-196b  | Gastric, prostate, hepatocellular                                             | DM<sub>hypo</sub>, DM<sub>hypo</sub> |                                             | [127,131,189]             |
| miR-196a  | Testicular, ovarian                                                          | DM<sub>hypo</sub>       | PODXL, DDR1                                | [190,191]                  |
| miR-200a/h| Hepatocellular, prostate, gastric, glioblastoma, pancreatic, bladder         | HMT, DM<sub>hypo</sub>, HDA, DM<sub>hypo</sub> | BMI1, RING2                              | [63,71,118,119,126,192]    |
| miR-200c/141| Colon, breast, lung, prostate, non-small cell lung                          | HMT, DM<sub>hypo</sub>, HDA | DNMT3A TET1, TET3, BMI1, RING2, SOX2, ZEB1, DNMT3A | [119,174,193–195]         |
| miR-203   | Hematological, hepatocellular, endometrial, ovarian, prostate, oral          | DM<sub>hypo</sub>, DM<sub>hypo</sub>, HMT, HDA | ABCE1, BMI1, SOX4                    | [77,119,129,145,196,197]  |
| miRNA      | Cancer Type                      | Epigenetic Modification | Target                  | Reference                        |
|------------|----------------------------------|-------------------------|-------------------------|----------------------------------|
| miR-205    | Bladder, prostate, ovarian       | DM<sub>hyper</sub>, DM<sub>hypo</sub> | BCL2L2                  | [129,131,139,198]               |
| miR-218    | Oral squamous cell carcinoma     | DM<sub>hypo</sub>       | RICTOR                  | [199]                           |
| miR-219a   | Gastric, endometrial             | DM<sub>hypo</sub>       |                         | [196,200]                      |
| miR-221    | Hepatocellular                   | DM<sub>hypo</sub>       | MDM2                    | [61]                            |
| miR-224    | Hepatocellular                   |                         | HDA, HAT                | [116]                           |
| miR-335    | Breast, hepatocellular, gastric   | DM<sub>hypo</sub>       | RASA1, CRKL             | [201–204]                      |
| miR-342    | Colorectal                       | DM<sub>hypo</sub>       |                         | [205]                           |
| miR-345    | Colorectal                       | DM<sub>hypo</sub>       | BAG3                    | [206]                           |
| miR-370    | Cholangiocarcinoma, oral squamous cells | DM<sub>hypo</sub> | IRS1                    | [207,208]                      |
| miR-373    | Cholangiocarcinoma               | DM<sub>hypo</sub>, HDA  |                         | [209]                           |
| miR-375    | Esophagus, melanoma, prostate, hepatocellular, breast | DM<sub>hypo</sub> | RASFF1(A), PDK1         | [45,78,210–212]                |
| miR-376c   | Cholangiocarcinoma               | DM<sub>hypo</sub>       |                         | [207]                           |
| miR-378    | Hepatocellular                   | DM<sub>hypo</sub>       |                         | [78]                            |
| miR-449a/b | Osteosarcoma cell line, breast cell line, hepatocellular | DM<sub>hypo</sub> | CDK6, CDC25A, C-MET    | [115,117]                      |
| miR-512    | Gastric                          | DM<sub>hypo</sub>, HDA  |                         | [42]                            |
| miR-514    | Clear cell renal cell carcinoma  | DM<sub>hypo</sub>, HDA  |                         | [158]                           |
| miR-585    | Oral squamous cell carcinoma     | DM<sub>hypo</sub>       |                         | [199]                           |
| miR-597    | Endometrial                      | DM<sub>hypo</sub>       |                         | [196]                           |
| miR-615    | Pancreatic ductal adenocarcinoma | DM<sub>hypo</sub> | IGF2                    | [60,131]                       |
| miR-618    | Endometrial                      | DM<sub>hypo</sub>       |                         | [196]                           |
| miR-874    | Breast                           | DM<sub>hypo</sub>       |                         | [213]                           |
| miR-941    | Colorectal cells                 | DM<sub>hypo</sub>       |                         | [214,215]                      |
| miR-1224   | Bladder                          | DM<sub>hypo</sub>       |                         | [214,216]                      |
| miR-1237   | Colorectal cells                 | DM<sub>hypo</sub>       |                         | [214]                           |
| miR-1247   | Colorectal and gastric cells, pancreatic, non-small cell lung | DM<sub>hypo</sub> | RARA, STX1B, RCC2      | [62,214,215,217]               |
| Let-7a     | Ovarian, acute myeloid leukemia, lung, nasopharyngeal carcinoma cells | DM<sub>hypo</sub>, DM<sub>hypo</sub> | C-MYC                  | [218–221]                      |
| Let-7c     | Hepatocellular                   | HMT                     |                         | [118]                           |

DM<sub>hypo</sub>: DNA hypo-methylation; DM<sub>hypo</sub>: DNA hyper-methylation; HMT: histone methyl-transferase; HDA: histone de-acetilase; HAT: histone acetyl-transferase. Targets are referred to epigenetically modified miRNAs.
3. MiRNAs as Epigenetic Regulators

Although miRNAs are mitotically and meiotically hereditable factors [222–224] able to regulate gene expression without involving changes in the DNA sequence, their classification as epigenetic factors is still debated [225]. However, growing evidence shows their substantial role in the control of several canonical epigenetic mechanisms. Specifically, miRNAs regulate at the post-transcriptional level many epigenetic-related-genes (Figure 1). Nevertheless, miRNAs can also act in the nucleus by stimulating or repressing genes transcription in a manner strictly correlated to the chromatin state (Figure 2).

3.1. Post-Transcriptional Gene Silencing by miRNAs

MiRNAs regulate at the post-transcriptional level several epigenetic factors involved in transcriptional regulation, such as DNMTs, PRC1 and PRC2, heterochromatin protein 1 (HP1), and HDACs. Deregulation of these proteins induced by aberrant expression of miRNAs could lead to the epigenetic silencing of tumor suppressor genes, believed to be an early driver of oncogenesis [226].

![Figure 1. Feedback circuit between microRNAs and epigenetic machinery](image)

The epigenetic modification, such as promoter CpG island hyper- or hypo-methylation and/or histone modifications, affect miRNAs and genes transcription. MiRNAs can themselves regulate the epigenetic machinery by post-transcriptional gene silencing (PTGS), targeting DNMTs, HDACs, and the histone methyl-transferases (HMTs), establishing epigenetic pathway loops. In the figure, black lines represent the pathway starting from the epigenetic modifications and ending with the miRNAs maturation, while blue lines represent the pathway from the mature miRNA to the post transcriptional gene silencing of the epigenetic machinery.

Deregulation of DNMTs was observed in cancer [227]. The miR-29 family, down-regulated in lung cancer, targets DNA methyl-transferase 3 alpha and 3 beta (DNMT3A-B) [31]. Exogenous expression of miR-29s results in a decrease of global DNA methylation and in the re-expression of tumor suppressor genes in lung cancer and in acute myeloid leukemia [31,32]. Moreover, in hepatocellular carcinoma, miR-29a modulates both the DNA methyl-transferase 1 (DNMT1) and DNMT3B [228]. A DNMT3B splice variant is regulated by miR-148 through the binding to the coding region in cancer cell lines [229]. In cholangiocarcinoma, miR-148a and miR-152 target DNMT1; reduced expression of these miRNAs contributes to increased DNMT1 activity, which affects transcription of the tumor suppressor genes Ras association domain family member 1 (RASSF1A) and cyclin-dependent kinase inhibitor 2A (p16INK4a) [34].
The DNMT family was also found to be regulated by miR-K12-4-5p, which is encoded by Kaposi’s sarcoma-associated herpesvirus (KSHV). miR-K12-4-5p directly down-regulates RBL2, a repressor of DNMT3A-B mRNA transcription [230]. Thus, enforced expression of this viral miRNA reduces RBL2 protein level and increases DNMT and DNMT3A-B mRNA levels, leading to global hypo-methylation [33].

PRC2, one of the two classes of Polycomb group proteins was found to cooperate with DNMTs in silencing of target genes [231]. PRC2 mediates the di- and tri-methylation of H3K27 (H3K27me2 and H3K27me3) through the SUZ12 polycomb repressive complex 2 subunit (SUZ12) and EZH2 [232,233], each of which is regulated by miRNAs. For instance, miR-200b negatively regulates the expression of SUZ12 in breast cancer stem cells (BCSC). Loss of miR-200b results in an increase of SUZ12 binding at the E-cadherin (CDH1) promoter, leading to the aberrant H3K27me3 and CDH1 repression. The pathway involving miR-200b, SUZ12, and the CDH1 is important for BCSC growth: induced expression of miR-200b or SUZ12 silencing block tumor formation in vivo models [234]. In glioma stem-like cells, a tumor subpopulation with self-renewal capacity, down-regulation of SUZ12 depends on miR-128 expression. The restoration of miR-128 affects SUZ12 levels and reduces cell proliferation [235].

EZH2, another member of the PRC2 complex, is over-expressed in cancer, enhancing cell growth and transformation [236,237]. It was found to be regulated by miR-26a and miR-101. miR-26a influences cell cycle progression in Burkitt’ lymphoma cell lines by targeting EZH2 [238], while miR-101 attenuates cell proliferation in bladder transitional carcinoma and prostate cancer cell lines [239,240].

A stable gene silencing is maintained by PRC1, which recognizes H3K27me3, catalyses histone H2A ubiquitylation, and promotes chromatin compaction [241]. It contains several subunits, among which is BMI1 proto-oncogene, polycomb ring finger (BMI1). BMI1 is up-regulated in cancer and promotes stem cell self-renewal [242]. BMI1 expression is controlled by different miRNAs in cancer. In glioma, the miR-128 targets BMI1 leading to reduced self-renewal capacity [243]. In ovarian cancer, BMI1 is regulated by miR-15a and miR-16-1 and induced expression of these miRNAs decreases BMI1 protein levels, reducing ovarian cancer cell proliferation [244]. In endometrial cancer cells, miR-194...
negatively regulates BMI1 and reduces cell invasion [245]. By targeting BMI1, miR-218 affects the migration, invasion, and proliferation of glioma cells and blocks self-renewal ability [246]. In multiple myeloma, miR-203 is down-regulated, and its restoration suppresses BMI1 expression and inhibits myeloma cell growth [247].

HDACs interact with PRC2 [248] and are up-regulated in various type of cancer [249]. miR-449a is down-regulated in prostate cancer and its expression negatively correlates with the expression of its direct target, the histone deacetylase 1 (HDAC1); introduction of miR-449a in prostate cancer cells affects cell growth and viability, in part by targeting HDAC1 [250]. However, in different cancer cell models, HDAC1 was demonstrated to act as a repressor of this miR, suggesting a loop that regulates the expression of these genes [115]. In hepatocellular carcinoma, miR-145 is down-regulated and negatively regulates the histone deacetylase 2 (HDAC2) expression. Overexpression of miR-145 reduces the tumorigenic potential of hepatocellular carcinoma cells in vitro and in vivo, recapitulating the effects of HDAC2 inhibition [251]. In B-lymphoma cells the histone deacetylase 4 (HDAC4) is down-regulated by miR-155. In this context, HDAC4 acts as tumor suppressor, reducing proliferation and promoting apoptosis [252].

The HP1 family is involved in several functions, including heterochromatin spread and chromatin condensation [253]. The HP1 family is deregulated in cancer [254]. In colorectal cancer, the HP1γ protein encoded by chromobox 3 gene (CBX3), is overexpressed and associated with poor prognosis, while miR-30a is down-regulated. It was demonstrated that miR-30a targets HP1γ in colon cancer cells inhibiting cell growth and tumour progression in vitro and in vivo [255].

Epigenetic protein factors targeted by miRNAs are shown in Table 2.

Table 2. MicroRNAs target epigenetic complex at post-transcriptional level.

| MicroRNAs      | Target   | Cancer Type                                      | Reference                        |
|----------------|----------|-------------------------------------------------|-----------------------------------|
| miR-15a/16-1   | BMI      | Ovarian                                         | [244]                             |
| miR-26a        | EZH2     | Burkitt lymphoma                                | [238]                             |
| miR-29a/b      | DNMT3A-B, DNMT1 | Lung, acute myeloid leukemia, hepatocellular | [31,32,228]                      |
| miR-30a        | HP1γ     | Colorectal                                      | [255]                             |
| miR-101        | EZH2     | Prostate, bladder transitional cell carcinoma   | [239,240]                         |
| miR-128        | BMI, SUZ12 | Gloma                                          | [235,243]                         |
| miR-137        | EZH2     | Cervical                                       | [256]                             |
| miR-140        | DNMT1, HDAC4 | Hepatocellular, osteosarcoma, colorectal    | [257,258]                         |
| miR-143        | DNMT3A   | Colorectal                                      | [259]                             |
| miR-145        | HDAC2    | Hepatocellular                                  | [260]                             |
| miR-148        | DNMT3B   | Cervical cancer cells                          | [229]                             |
| miR-148a       | DNMT1    | Cholangiocarcinoma, gastric                    | [34,261]                          |
| miR-152        | DNMT1    | Cholangiocarcinoma, breast                     | [34,181]                          |
| miR-155        | HDAC4    | B-cells lymphoma                               | [252]                             |
| miR-185        | DNMT1    | Gloma                                          | [262]                             |
| miR-194        | BMI      | Endometrial                                    | [245]                             |
| miR-200b       | SUZ12, BMI | Breast, hepatocellular                         | [192,234]                         |
| miR-200c       | BMI      | Breast                                         | [263]                             |
| miR-203        | BMI      | Multiple myeloma                               | [247]                             |
| miR-218        | BMI      | Gloma                                          | [246]                             |
| miR-221        | HDAC6    | Liver                                          | [264]                             |
| miR-449a       | HDAC1    | Prostate                                       | [250]                             |
| miR-K12-4-5p   | RBL2     | Kaposi’s sarcoma-associated herpesvirus         | [33]                              |

3.2. miRNAs Regulate Gene Transcription

Several miRNAs were identified in the nuclear compartment [38]. miR-29b, which is localized in the nucleus, shows in the 3′ end a hexanucleotide motif that drives nuclear localization [265]. In this, compartment, miRNAs act on gene promoters, both activating and repressing gene expression (Table 3). Interestingly, the argonaute 1, RISC catalytic component (AGO1), which interacts with miRNAs, was
also found to drive transcriptional gene silencing in the nucleus [266,267] or to bind and cooperate with RNA Polymerase II on actively transcribed promoters [268].

| Table 3. MicroRNAs acting as transcriptional regulator. |
|---------------------------------|
| MicroRNA | Target | TGS/TGA | Reference |
|---------|--------|--------|-----------|
| miR-10a | HOXD4  | TGS    | [269]     |
| miR-205 | IL24   | TGA    | [270]     |
| miR-205 | IL32   | TGA    | [270]     |
| miR-223 | NFI-A  | TGS    | [271]     |
| miR-320 | POLR3D | TGS    | [272]     |
| miR-373 | CDH1   | TGA    | [273]     |
| miR-373 | CSDC2  | TGA    | [273]     |
| miR-423 (synthetic) | PR | TGS    | [274]     |
| miR-483 | IGF2   | TGA    | [275]     |
| miR-589 | COX2   | TGA    | [260]     |
| miR-774 | Cnnb1  | TGA    | [276]     |
| miR-1186 | Cnnb1 | TGA    | [276]     |

3.2.1. MiRNAs Transcriptional Gene Silencing (TGS)

The TGS mechanism mediated by small RNAs was identified in human cells [277]; it involves both AGO1-2 and small interfering RNAs that recognize the target promoter region by sequence complementarity [266,267]. Furthermore, the target region exhibits chromatin markers associated with an inactive state, such as methylation of lysines 27 and 9 of histone H3 (H3K27 and H3K9) [266,278]. Recent studies demonstrated that miRNAs could influence the expression of target genes with similar mechanisms.

MiR-320 was the first identified miRNA able to repress gene transcription. It is located within the RNA polymerase III subunit D (POLR3D) promoter region in antisense orientation. It acts as cis-regulatory element for transcriptional silencing of the POLR3D gene by recruiting AGO1 and EZH2 and causing tri-methylation of the H3K27 on the POLR3D promoter [272]. This epigenetic mechanism could be relevant in cancer since the POLR3D gene product is a component of the RNA polymerase III, whose abnormal activity is characteristic of cancer cells [279].

MiR-10a recognizes a complementary region within the homebox D4 (HOXD4) promoter and reduces HOXD4 gene expression in breast cancer cells. This mechanism requires the presence of the dicer 1, ribonuclease III protein (DICER) and AGO1-3 and is accompanied by tri-methylation of H3K27 and de novo DNA methylation at target regions [269]. In breast cancer cells, overexpression of a synthetic miR-423-5p inhibits the expression of the Progesterone Receptor (PGR) gene, a prognostic marker of breast cancer [280], by reducing RNA polymerase II binding and enriching silent chromatin markers on PGR gene promoter [274]. In patients with acute myeloid leukemia, miR-223 expression shows an inverse correlation with the expression of NFI-A, a transcription factor whose expression impacts on erythroid or granulocytic lineage commitment [281]. During granulopoiesis induced by retinoic acid, miR-223 represses transcription of nuclear factor I A (NFI-A) by recruiting DICER and the Polycomb group proteins YY1 transcription factor (YY1) and SUZ12 on its promoter to induce a silent chromatin state with the increase of H3K27me3 [271].

3.2.2. MiRNAs Transcriptional Gene Activation (TGA)

MiRNAs are also able to induce gene expression by activating the target gene promoter. This is accompanied by an active chromatin state that includes an increase of di-methylation and tri-methylation of histone H3K4 (H3K4me2 and H3K4me3) and acetylation of histone H3 and H4 (H3ac and H4ac) [282]. MiR-373 is the first discovered miRNA involved in the TGA. In prostate cancer cells, it induces the expression of the tumor suppressor gene CDH1 by complementary binding to its promoter with consequent enrichment of RNA polymerase II on the target promoter [273].
MiR-205 is down-regulated in prostate cancer, and its restoration reduces cell proliferation by activating the interleukin 24 and interleukin 32 (IL24 and IL32) genes. Indeed, miR-205 induces expression of IL24 and IL32 by targeting their promoters, thus leading to an enrichment of RNA polymerase II and of H3ac, H4ac, and H3K4me2 [270]. The miR-483 is encoded within an intron of the IGF2 gene, and overexpression of both IGF2 and miR-483 was observed in Wilms’ tumor [275,283]. MiR-483 up-regulates IGF2 transcription by interacting with the 5’UTR of the transcript and by enhancing the interaction with the RNA helicase DExH-Box Helicase 9 (DHX9) [275], a transcriptional co-activator [284]. The cytochrome c oxidase II (COX2) is a pro-inflammatory gene that shows two complementary sequences for the miR-589 on its promoter: by using an anti-miR-589-5p in lung cancer cells, a reduction of the basal expression of COX2 was observed, while enforced expression of miR-589 results in an increased COX2 protein level [260].

Transcriptional gene activation mediated by miRNAs was also observed in mice: miR-774 and miR-1186 binding sites were identified in the promoter of the cyclin B1 (Ccnb1). The miR-774 recruits AGO1 and promotes the enrichment of the RNA Polymerase II and of the histone H3K4 tri-methylation on Ccnb1 promoter in prostate adenocarcinoma cells [276].

4. Others

With the non-coding RNA world, other areas of research involving the epigenetic phenomena are growing. Recently, the findings of ribonucleoside modifications at RNA-expressed sequences (epi-transcriptome) [285,286] opened a new field of research in cancer biology. Those changes can affect microRNAs maturation influencing expression and downstream targets. A modification able to affect microRNAs processing is methylation of the ribonucleoside adenine (N6-methyladenosine, m6A): the methylated pri-let-7e was processed in pre-let-7e more efficiently than the un-methylated pri-let-7e [287]. Then, it was shown that Adenosine (A) to Inosine (I) editing on miR-200b RNA influences the downstream targeting of the microRNA and, more importantly, correlates with cancer patient prognosis [288].

Another field of research that should be explored is the microRNA targeting the non-coding RNAs involved in chromatin remodeling. It was shown that IncRNAs as H19, imprinted maternally expressed transcript (non-protein coding) (H19) and HOTAIR can act as decoy for microRNAs [89,289–292], however they also affect chromosome state by binding the epigenetic complex PRC2 [290,293]. It could be possible that the lncRNA-miRNA complexes, other than work as miRNAs decoys, have a functional role in the chromosome remodeling.

5. Conclusions

This review underlines the importance of microRNAs in the complex regulatory mechanisms that control cancer epigenetics. MicroRNAs are tightly regulated by epigenetic modifications such as DNA methylation and histone modifications. However, microRNAs themselves strictly regulate the epigenetic machinery at the post-transcriptional level by establishing epigenetic pathway loops. For instance, overexpression of DNMT1 causes hyper-methylation of miR-148a that, in turn, targets DNMT1 [34,52,261].

As reported, microRNAs can also modulate transcription by binding the promoter of target genes, functioning as a scaffold for chromatin modifiers and transcriptional regulators. The finely-tuned epigenetic network that is unveiling highlights a new level of complexity in the regulation mediated by microRNAs, which modulate at several levels the cellular transcriptome.

Epigenetics changing are reversible, and RNAs are targetable. The possibilities to find useful therapeutic targets in the cancer treatment will increase with future research progress in this area.

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References

1. Waddington, C.H. The epigenotype. *Endeavour* **1942**, *1*, 18–20. [CrossRef] [PubMed]
2. Holliday, R. The inheritance of epigenetic defects. *Science* **1987**, *238*, 163–170. [CrossRef] [PubMed]
3. Holliday, R. Epigenetics: An overview. *Dev. Genet.* **1994**, *15*, 453–457. [CrossRef] [PubMed]
4. Russo, V.E.A.; Martienssen, R.A.; Riggs, A.D. *Epigenetic Mechanisms of Gene Regulation*; Cold Spring Harbor Laboratory Press: Woodbury, NY, USA, 1996.
5. Wu, C.; Morris, J.R. Genes, genetics, and epigenetics: A correspondence. *Science* **2001**, *293*, 1103–1105. [CrossRef] [PubMed]
6. Bannister, A.J.; Kouzarides, T. Regulation of chromatin by histone modifications. *Cell Res.* **2011**, *21*, 381–395. [CrossRef] [PubMed]
7. Mersfelder, E.L.; Parthun, M.R. The tale beyond the tail: Histone core domain modifications and the regulation of chromatin structure. *Nucleic Acids Res.* **2006**, *34*, 2653–2662. [CrossRef] [PubMed]
8. Bernstein, E.; Allis, C.D. RNA meets chromatin. *Genes Dev.* **2005**, *19*, 1635–1655. [CrossRef] [PubMed]
9. Murtha, M.; Esteller, M. Extraordinary cancer epigenomics: Thinking outside the classical coding and promoter box. *Trends Cancer* **2016**, *2*, 572–584. [CrossRef] [PubMed]
10. Esteller, M. Epigenetics in cancer. *N. Engl. J. Med.* **2008**, *358*, 1148–1159. [CrossRef] [PubMed]
11. Esteller, M. Aberrant DNA methylation as a cancer-inducing mechanism. *Annu. Rev. Pharmacol. Toxicol.* **2005**, *45*, 629–656. [CrossRef] [PubMed]
12. Jones, P.A.; Baylin, S.B. The epigenomics of cancer. *Cell* **2007**, *128*, 683–692. [CrossRef] [PubMed]
13. Easwaran, H.; Tsai, H.C.; Baylin, S.B. Cancer epigenetics: Tumor heterogeneity, plasticity of stem-like states, and drug resistance. *Mol. Cell* **2014**, *54*, 716–727. [CrossRef] [PubMed]
14. Wainwright, E.N.; Scaffidi, P. Epigenetics and cancer stem cells: Unleashing, hijacking, and restricting cellular plasticity. *Trends Cancer* **2017**, *3*, 372–386. [CrossRef] [PubMed]
15. Feinberg, A.P.; Ohlsson, R.; Henikoff, S. The epigenetic progenitor origin of human cancer. *Nat. Rev. Genet.* **2006**, *7*, 21–33. [CrossRef] [PubMed]
16. Cairns, B.R. The logic of chromatin architecture and remodelling at promoters. *Nature* **2009**, *461*, 193–198. [CrossRef] [PubMed]
17. Comet, I.; Riising, E.M.; Leblanc, B.; Helin, K. Maintaining cell identity: PRC2-mediated regulation of transcription and cancer. *Nat. Rev. Cancer* **2016**, *16*, 803–810. [CrossRef] [PubMed]
18. Wilson, B.G.; Roberts, C.W. SWI/SNF nucleosome remodelers and cancer. *Nat. Rev. Cancer* **2011**, *11*, 481–492. [CrossRef] [PubMed]
19. Lai, A.Y.; Wade, P.A. Cancer biology and nurd: A multifaceted chromatin remodelling complex. *Nat. Rev. Cancer* **2011**, *11*, 588–596. [CrossRef] [PubMed]
20. Beck, D.B.; Oda, H.; Shen, S.S.; Reinberg, D. Pr-Set7 and H4K20me1: At the crossroads of genome integrity, cell cycle, chromosome condensation, and transcription. *Genes Dev.* **2012**, *26*, 325–337. [CrossRef] [PubMed]
21. Thiagalingam, S.; Cheng, K.H.; Lee, H.J.; Mineva, N.; Thiagalingam, A.; Ponte, J.F. Histone deacetylases: Unique players in shaping the epigenetic histone code. *Ann. N. Y. Acad. Sci.* **2003**, *983*, 984–100. [CrossRef] [PubMed]
22. Saxena, A.; Carninci, P. Long non-coding RNA modifies chromatin: Epigenetic silencing by long non-coding RNAs. *Bioessays* **2011**, *33*, 830–839. [CrossRef] [PubMed]
23. Forrest, M.E.; Khalil, A.M. Review: Regulation of the cancer epigenome by long non-coding RNAs. *Cancer Lett.* **2017**, *407*, 106–112. [CrossRef] [PubMed]
24. Ha, M.; Kim, V.N. Regulation of microRNA biogenesis. *Nat. Rev. Mol. Cell Biol.* **2014**, *15*, 509–524. [CrossRef] [PubMed]
25. He, L.; Hannon, G.J. MicroRNAs: Small RNAs with a big role in gene regulation. *Nat. Rev. Genet.* **2004**, *5*, 522–531. [CrossRef] [PubMed]
26. Peng, Y.; Croce, C.M. The role of microRNAs in human cancer. *Signal Transduct. Target. Ther.* **2016**, *1*, 15004. [CrossRef] [PubMed]
27. Lovat, F.; Valeri, N.; Croce, C.M. MicroRNAs in the pathogenesis of cancer. *Semin. Oncol.* **2011**, *38*, 724–733. [CrossRef] [PubMed]
28. Di Leva, G.; Garofalo, M.; Croce, C.M. MicroRNAs in cancer. *Annu. Rev. Pathol.* **2014**, *9*, 287–314. [CrossRef] [PubMed]
Garzon, R.; Calin, G.A.; Croce, C.M. MicroRNAs in cancer. *Annu. Rev. Med.* **2009**, *60*, 167–179. [CrossRef] [PubMed]

Suzuki, H.; Maruyama, R.; Yamamoto, E.; Kai, M. DNA methylation and microRNA dysregulation in cancer. *Mol. Oncol.* **2012**, *6*, 567–578. [CrossRef] [PubMed]

Fabbri, M.; Garzon, R.; Cimmino, A.; Liu, Z.; Zanesi, N.; Callegari, E.; Liu, S.; Alder, H.; Costinean, S.; Fernandez-Cymering, C.; et al. MicroRNA-29 family reverses aberrant methylation in lung cancer by targeting DNA methyltransferases 3a and 3b. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 15805–15810. [CrossRef] [PubMed]

Garzon, R.; Liu, S.; Fabbri, M.; Liu, Z.; Heaphy, C.E.; Callegari, E.; Schwind, S.; Pang, J.; Yu, J.; Muthusamy, N.; et al. MicroRNA-29b induces global DNA hypomethylation and tumor suppressor gene reexpression in acute myeloid leukemia by targeting directly *DNMT3A* and 3B and indirectly *DNMT1*. *Blood* **2009**, *113*, 6411–6418. [CrossRef] [PubMed]

Lu, F.; Stedman, W.; Yousef, M.; Renne, R.; Lieberman, P.M. Epigenetic regulation of kaposi’s sarcoma-associated herpesvirus latency by virus-encoded microRNAs that target Rta and the cellular Rbl2-DNMT pathway. *J. Virol.* **2010**, *84*, 2697–2706. [CrossRef] [PubMed]

Baconi, C.; Huang, N.; Patel, T. MicroRNA-dependent regulation of DNA methyltransferase-1 and tumor suppressor gene expression by interleukin-6 in human malignant cholangiocytes. *Hepatology* **2010**, *51*, 881–890. [CrossRef] [PubMed]

Wellner, U.; Schubert, J.; Burk, U.C.; Schmalhofer, O.; Zhu, F.; Sonntag, A.; Waldvogel, B.; Vannier, C.; Darling, D.; zur Hausen, A.; et al. The emt-activator ZEB1 promotes tumorigenicity by repressing stemness-inhibiting microRNAs. *Nat. Cell Biol.* **2009**, *11*, 1487–1495. [CrossRef] [PubMed]

Lei, Q.; Liu, X.; Fu, H.; Sun, Y.; Wang, L.; Xu, G.; Wang, W.; Yu, Z.; Liu, C.; Li, P.; et al. miR-101 reverses hypomethylation of the PRDM16 promoter to disrupt mitochondrial function in astrocytoma cells. *OncoTarget* **2016**, *7*, 5007–5022. [CrossRef] [PubMed]

Park, C.W.; Zeng, Y.; Zhang, X.; Subramanian, S.; Steer, C.J. Mature microRNAs identified in highly purified nuclei from HCT116 colon cancer cells. *RNA Biol.* **2010**, *7*, 606–614. [CrossRef] [PubMed]

Liao, J.Y.; Ma, L.M.; Guo, Y.H.; Zhang, Y.C.; Zhou, H.; Shao, P.; Chen, Y.Q.; Qu, L.H. Deep sequencing of human nuclear and cytoplasmic small RNAs reveals an unexpectedly complex subcellular distribution of miRNAs and tRNA 3′ trailers. *PLoS ONE* **2010**, *5*, e10563. [CrossRef] [PubMed]

Klose, R.J.; Bird, A.P. Genomic DNA methylation: The mark and its mediators. *Trends Biochem. Sci.* **2006**, *31*, 89–97. [CrossRef] [PubMed]

Saxonov, S.; Berg, P.; Brutlag, D.L. A genome-wide analysis of CpG dinucleotides in the human genome distinguishes two distinct classes of promoters. *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 1412–1417. [CrossRef] [PubMed]

Weber, B.; Stremensam, C.; Brueckner, B.; Lyko, F. Methylation of human microRNA genes in normal and neoplastic cells. *Cell Cycle* **2007**, *6*, 1001–1005. [CrossRef] [PubMed]

Saito, Y.; Liang, G.; Egger, G.; Friedman, J.M.; Chuang, J.C.; Coetzee, G.A.; Jones, P.A. Specific activation of microRNA-127 with downregulation of the proto-oncogene BCL6 by chromatin-modifying drugs in human cancer cells. *Cancer Cell* **2006**, *9*, 435–443. [CrossRef] [PubMed]

Lujambio, A.; Ropero, S.; Ballestar, E.; Fraga, M.F.; Cerrato, C.; Setien, F.; Casado, S.; Suarez-Gauthier, A.; Sanchez-Cespedes, M.; Git, A.; et al. Genetic unmasking of an epigenetically silenced microRNA in human cancer cells. *Cancer Res.* **2007**, *67*, 1424–1429. [CrossRef] [PubMed]

Lujambio, A.; Calin, G.A.; Villanueva, A.; Ropero, S.; Sanchez-Cespedes, M.; Blanco, D.; Montuenga, L.M.; Rossi, S.; Nicoloso, M.S.; Faller, W.J.; et al. A microRNA DNA methylation signature for human cancer metastasis. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 13556–13561. [CrossRef] [PubMed]

Pronina, I.V.; Loginov, V.I.; Burdennyy, A.M.; Fridman, M.V.; Senchenko, V.N.; Kazubskaya, T.P.; Kushlinskii, N.E.; Dmitriev, A.A.; et al. DNA methylation contributes to deregulation of 12 cancer-associated microRNAs and breast cancer progression. *Gene* **2017**, *604*, 1–8. [CrossRef] [PubMed]

Hsu, P.Y.; Deathage, D.E.; Rodriguez, B.A.; Liyanarachchi, S.; Weng, Y.I.; Zuo, T.; Liu, J.; Cheng, A.S.; Huang, T.H. Xenoestrogen-induced epigenetic repression of microRNA gene *hsa-mir-9-1* in human breast cancer. *J. Pathol.* **2008**, *214*, 17–24. [CrossRef] [PubMed]
48. Lu, L.; Katsaros, D.; Zhu, Y.; Hoffman, A.; Luca, S.; Marion, C.E.; Mu, L.; Risch, H.; Yu, H. Let-7a regulation of insulin-like growth factors in breast cancer. *Breast Cancer Res. Treat.* 2011, 126, 687–694. [CrossRef] [PubMed]

49. Biagioni, F.; Bossel Ben-Moshe, N.; Fontemaggi, G.; Canu, V.; Mori, F.; Antoniani, B.; Di Benedetto, A.; Santoro, R.; Germoni, S.; De Angelis, F.; et al. miR-10b*, a master inhibitor of the cell cycle, is down-regulated in human breast tumours. *EMBO Mol. Med.* 2012, 4, 1214–1229. [CrossRef] [PubMed]

50. Zhang, Y.; Yan, L.X.; Wu, Q.N.; Du, Z.M.; Chen, J.; Liao, D.Z.; Huang, M.Y.; Hou, J.H.; Wu, Q.L.; Zeng, M.S.; et al. miR-125b is methylated and functions as a tumor suppressor by regulating the ETS1 proto-oncogene in human invasive breast cancer. *Cancer Res.* 2011, 71, 3552–3562. [CrossRef] [PubMed]

51. Zhang, Y.; Yang, P.; Sun, T.; Li, D.; Xu, X.; Rui, Y.; Li, C.; Chong, M.; Ibrahim, T.; Mercatali, L.; et al. miR-126 and miR-126* repress recruitment of mesenchymal stem cells and inflammatory monocytes to inhibit breast cancer metastasis. *Nat. Cell Biol.* 2013, 15, 284–294. [CrossRef] [PubMed]

52. Xu, Q.; Jiang, Y.; Yin, Y.; Li, Q.; He, J.; Jing, Y.; Qi, Y.T.; Xu, Q.; Li, W.; Lu, B.; et al. A regulatory circuit of miR-148a/152 and DNMT1 in modulating cell transformation and tumor angiogenesis through IGF-IR and IRS1. *J. Mol. Cell Biol.* 2013, 5, 3–13. [CrossRef] [PubMed]

53. Li, D.; Zhao, Y.; Liu, C.; Chen, X.; Qi, Y.; Jiang, Y.; Zou, C.; Zhang, X.; Liu, S.; Wang, X.; et al. Analysis of miR-195 and miR-497 expression, regulation and role in breast cancer. *Clin. Cancer Res.* 2011, 17, 1722–1730. [CrossRef] [PubMed]

54. Castilla, M.A.; Diaz-Martin, J.; Sarrio, D.; Romero-Perez, L.; Lopez-Garcia, M.A.; Vieites, B.; Biscuola, M.; Rami-Ro-Fuentes, S.; Isache, C.M.; Palacios, J. MicroRNA-200 family modulation in distinct breast cancer phenotypes. *PLoS ONE* 2012, 7, e47709. [CrossRef] [PubMed]

55. Haga, C.L.; Phinney, D.G. MicroRNAs in the imprinted DLK1-DIO3 region repress the epithelial-to-mesenchymal transition by targeting the TWIST1 protein signaling network. *J. Biol. Chem.* 2012, 287, 42695–42707. [CrossRef] [PubMed]

56. Lehmann, U. Aberrant DNA methylation of microRNA genes in human breast cancer—A critical appraisal. *Cell Tissue Res.* 2014, 356, 657–664. [CrossRef] [PubMed]

57. He, D.X.; Gu, X.T.; Li, Y.R.; Jin, J.; Ma, X. Methylation-regulated miR-149 modulates chemoresistance by targeting glucan N-deacetylase/N-sulfotransferase-1 in human breast cancer. *FEBS J.* 2014, 281, 4718–4730. [CrossRef] [PubMed]

58. Omura, N.; Li, C.P.; Li, A.; Hong, S.M.; Walter, K.; Jimeno, A.; Hidalgo, M.; Goggins, M. Genome-wide profiling of methylated promoters in pancreatic adenocarcinoma. *Cancer Biol. Ther.* 2008, 7, 1146–1156. [CrossRef] [PubMed]

59. Wang, P.; Chen, L.; Zhang, J.; Chen, H.; Fan, J.; Wang, K.; Luo, J.; Chen, Z.; Meng, Z.; Liu, L. Methylation-mediated silencing of the miR-124 genes facilitates pancreatic cancer progression and metastasis by targeting Rac1. *Oncogene* 2013, 34, 514–524. [CrossRef] [PubMed]

60. Gao, W.; Gu, Y.; Li, Z.; Cai, H.; Peng, Q.; Tu, M.; Kondo, Y.; Shinjo, K.; Zhu, Y.; Zhang, J.; et al. miR-615-5p is epigenetically inactivated and functions as a tumor suppressor in pancreatic ductal adenocarcinoma. *Oncogene* 2015, 34, 1629–1640. [CrossRef] [PubMed]

61. Botla, S.K.; Savant, S.; Jandaghi, P.; Bauer, A.S.; Muckle, O.; Moskalev, E.A.; Neoptolemos, J.P.; Costello, E.; Greenhalf, W.; Scarpa, A.; et al. Early epigenetic downregulation of microRNA-192 expression promotes pancreatic cancer progression. *Cancer Res.* 2016, 76, 4149–4159. [CrossRef] [PubMed]

62. Yi, J.M.; Kang, E.J.; Kwon, H.M.; Bae, J.H.; Kang, K.; Ahuja, N.; Yang, K. Epigenetically altered miR-1247 functions as a tumor suppressor in pancreatic cancer. *Oncotarget* 2017, 8, 26600–26612. [CrossRef] [PubMed]

63. Li, A.; Omura, N.; Hong, S.M.; Vincent, A.; Walter, K.; Griffith, M.; Borges, M.; Goggins, M. Pancreatic cancers epigenetically silence SIP1 and hypomethylate and overexpress miR-200a/200b in association with elevated circulating miR-200a and miR-200b levels. *Cancer Res.* 2010, 70, 5226–5237. [CrossRef] [PubMed]

64. Suzuki, H.; Yamamoto, E.; Nojima, M.; KI, M.; Yamano, H.O.; Yoshikawa, K.; Kimura, T.; Kudo, T.; Harada, E.; Sugai, T.; et al. Methylation-associated silencing of microRNA-34b/c in gastric cancer and its involvement in an epigenetic field defect. *Carcinogenesis* 2010, 31, 2066–2073. [CrossRef] [PubMed]

65. Hashimoto, Y.; Akiyama, Y.; Otsubo, T.; Shimada, S.; Yuasa, Y. Involvement of epigenetically silenced microRNA-181c in gastric carcinogenesis. *Carcinogenesis* 2010, 31, 777–784. [CrossRef] [PubMed]

66. Tsai, K.W.; Hu, L.Y.; Chen, T.W.; Li, S.C.; Ho, M.R.; Yu, S.Y.; Tu, Y.T.; Chen, W.S.; Lam, H.C. Emerging role of microRNAs in modulating endothelin-1 expression in gastric cancer. *Oncol. Rep.* 2015, 33, 485–493. [CrossRef] [PubMed]
67. Tsai, K.W.; Liao, Y.L.; Wu, C.W.; Hu, L.Y.; Li, S.C.; Chan, W.C.; Ho, M.R.; Lai, C.H.; Kao, H.W.; Fang, W.L.; et al. Aberrant hypermethylation of miR-9 genes in gastric cancer. *Epigenetics* **2011**, *6*, 1189–1197. [CrossRef] [PubMed]

68. Tsai, K.W.; Wu, C.W.; Hu, L.Y.; Li, S.C.; Liao, Y.L.; Lai, C.H.; Kao, H.W.; Fang, W.L.; Huang, K.H.; Chan, W.C.; et al. Epigenetic regulation of miR-34b and miR-129 expression in gastric cancer. *Int. J. Cancer* **2011**, *129*, 2600–2610. [CrossRef] [PubMed]

69. Jia, H.; Zhang, Z.; Zou, D.; Wang, B.; Yan, Y.; Luo, M.; Dong, L.; Yin, H.; Gong, B.; Li, Z.; et al. DNA methylation downregulated miR-10a acts as a tumor suppressor in gastric cancer. *Gastric Cancer* **2015**, *18*, 43–54. [CrossRef] [PubMed]

70. Li, Z.; Lei, H.; Luo, M.; Wang, Y.; Dong, L.; Ma, Y.; Liu, C.; Song, W.; Wang, F.; Zhang, J.; et al. DNA methylation downregulated miR-10b acts as a tumor suppressor in gastric cancer. *Gastric Cancer* **2015**, *18*, 43–54. [CrossRef] [PubMed]

71. Ning, X.; Shi, Z.; Liu, X.; Zhang, A.; Han, L.; Jiang, K.; Kang, C.; Zhang, Q. DNMT1 and EZH2 mediated methylation silences the microRNA-200b/a/429 gene and promotes tumor progression. *Cancer Lett.* **2015**, *359*, 198–205. [CrossRef] [PubMed]

72. Yin, H.; Song, P.; Su, R.; Yang, G.; Dong, L.; Luo, M.; Wang, B.; Gong, B.; Li, C.; Song, W.; et al. DNA methylation mediated down-regulating of microRNA-33b and its role in gastric cancer. *Sci. Rep.* **2016**, *6*, 18824. [CrossRef] [PubMed]

73. Ando, T.; Yoshida, T.; Enomoto, S.; Asada, K.; Tatematsu, M.; Ichinose, M.; Sugiyama, T.; Ushijima, T. DNA methylation of microRNA genes in gastric mucosae of gastric cancer patients: Its possible involvement in the formation of epigenetic field defect. *Int. J. Cancer* **2009**, *124*, 2367–2374. [CrossRef] [PubMed]

74. Datta, J.; Kutay, H.; Nasser, M.W.; Nuovo, G.J.; Wang, B.; Majumder, S.; Liu, C.G.; Volinia, S.; Croce, C.M.; Schmittgen, T.D.; et al. Methylation mediated silencing of microRNA-1 gene and its role in hepatocellular carcinogenesis. *Cancer Res.* **2008**, *68*, 5049–5058. [CrossRef] [PubMed]

75. Zhang, J.; Cheng, J.; Zeng, Z.; Wang, Y.; Li, X.; Xie, Q.; Jia, J.; Yan, Y.; Guo, Z.; Gao, J.; et al. Comprehensive profiling of novel microRNA-9 targets and a tumor suppressor role of microRNA-9 via targeting IGF2BP1 in hepatocellular carcinoma. *Onco Targets Ther.* **2015**, *6*, 42040–42052. [CrossRef] [PubMed]

76. Xie, K.; Liu, J.; Chen, J.; Dong, J.; Ma, H.; Liu, Y.; Hu, Z. Methylation-associated silencing of microRNA-34b in hepatocellular carcinoma. *Gene* **2014**, *543*, 101–107. [CrossRef] [PubMed]

77. Furuta, M.; Kozaki, K.I.; Tanaka, S.; Arii, S.; Imoto, I.; Inazawa, J. miR-124 and miR-203 are epigenetically silenced tumor-suppressive microRNAs in hepatocellular carcinoma. *Carcinogenesis* **2010**, *31*, 766–776. [CrossRef] [PubMed]

78. Veronese, A.; Visone, R.; Consiglio, J.; Acunzo, M.; Lupini, L.; Kim, T.; Ferracin, M.; Lovat, F.; Miotto, E.; Balatti, V.; et al. Mutated beta-catenin evades a microRNA-dependent regulatory loop. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 4840–4845. [CrossRef] [PubMed]

79. Callegari, E.; Elamin, B.K.; Giannone, F.; Milazzo, M.; Altavilla, G.; Fornari, F.; Giacomelli, L.; D’Abundo, L.; Ferracin, M.; Bassi, C.; et al. Liver tumorigenicity promoted by microRNA-221 in a mouse transgenic model. *Hepatology* **2012**, *56*, 1025–1033. [CrossRef] [PubMed]

80. Fornari, F.; Milazzo, M.; Galassi, M.; Callegari, E.; Veronese, A.; Miyaaki, H.; Sabbioni, S.; Mantovani, V.; Marasco, E.; Chieco, P.; et al. P53/mdm2 feedback loop sustains miR-221 expression and dictates the response to anticancer treatments in hepatocellular carcinoma. *Mol. Cancer Res. MCR* **2014**, *12*, 203–216. [CrossRef] [PubMed]

81. Nojima, M.; Matsui, T.; Tamori, A.; Kubo, S.; Shirabe, K.; Kimura, K.; Shimada, M.; Utsumomiya, T.; Kondo, Y.; Iio, E.; et al. Global, cancer-specific microRNA cluster hypomethylation was functionally associated with the development of non-b non-c hepatocellular carcinoma. *Mol. Cancer Res. MCR* **2014**, *12*, 203–216. [CrossRef] [PubMed]

82. Selcuklu, S.D.; Donoghue, M.T.; Rehmet, K.; de Souza Gomes, M.; Fort, A.; Kovvuru, P.; Muniyappa, M.K.; Kerin, M.J.; Enright, A.J.; Spillane, C. MicroRNA-9 inhibition of cell proliferation and identification of novel miR-9 targets by transcriptome profiling in breast cancer cells. *J. Biol. Chem.* **2012**, *287*, 29516–29528. [CrossRef] [PubMed]
101. Park, S.M.; Gaur, A.B.; Lengyel, E.; Peter, M.E. The miR-200 family determines the epithelial phenotype of cancer cells by targeting the e-cadherin repressors ZEB1 and ZEB2.

102. Gregory, P.A.; Bert, A.G.; Paterson, E.L.; Barry, S.C.; Tsykin, A.; Farshid, G.; Vadas, M.A.; Khew-Goodall, Y.; Goodall, G.J. The miR-200 family and miR-205 regulate epithelial to mesenchymal transition by targeting ZEB1 and SIP1.

84. Liu, C.; Kelnar, K.; Liu, B.; Chen, X.; Calhoun-Davis, T.; Li, H.; Patrawala, L.; Yan, H.; Jeter, C.; Honorio, S.; et al. The microRNA miR-34a inhibits prostate cancer stem cells and metastasis by directly repressing CD44.

85. Park, E.Y.; Chang, E.; Lee, E.J.; Lee, H.W.; Kang, H.G.; Chun, K.H.; Woo, Y.M.; Kong, H.K.; Ko, J.Y.; Suzuki, H.; et al. Targeting of miR34a-NOTCH1 axis reduced breast cancer stemness and chemoresistance.

99. Sun, J.; Zheng, G.; Gu, Z.; Guo, Z. miR-137 inhibits proliferation and angiogenesis of human glioblastoma cells by targeting the miR-137/NOTCH1 axis.

94. Sun, M.; Nie, F.; Wang, Y.; Zhang, Z.; Hou, J.; He, D.; Xie, M.; Xu, L.; De, W.; Wang, Z.; et al. LncRNA HOXA11-AS exerts oncogenic functions by repressing p21 and miR-124 in uveal melanoma.

92. Li, C.; Zhao, Z.; Zhou, Z.; Liu, R. LncRNA HOTAIR functions as a competing endogenous RNA to regulate HER2 expression by sponging miR-331-3p in gastric cancer.

88. Hermeking, H. The miR-34 family in cancer and apoptosis. Cell Death Differ. 2010, 17, 193–199. [CrossRef] [PubMed]
103. Kim, T.; Veronese, A.; Pichiorri, F.; Lee, T.J.; Jeon, Y.J.; Volinia, S.; Pineau, P.; Marchio, A.; Palatini, J.; Suh, S.S.; et al. P53 regulates epithelial-mesenchymal transition through microRNAs targeting ZEB1 and ZEB2. *J. Exp. Med.* 2011, 208, 875–883. [CrossRef] [PubMed]

104. Li, H.; Tang, J.; Lei, H.; Cai, P.; Zhu, H.; Li, B.; Xu, X.; Xia, Y.; Tang, W. Decreased miR-200a/141 suppress cell migration and proliferation by targeting pten in hirschsprung’s disease. *Cell Physiol. Biochem.* 2014, 34, 543–553. [CrossRef] [PubMed]

105. Scott, G.K.; Mattie, M.D.; Berger, C.E.; Benz, S.C.; Benz, C.C. Rapid alteration of microRNA levels by histone deacytelase inhibition. *Cancer Res.* 2006, 66, 1277–1281. [CrossRef] [PubMed]

106. Wang, Y.; Toh, H.C.; Chow, P.; Chung, A.Y.; Meyers, D.J.; Cole, P.A.; Ooi, L.L.; Lee, C.G. MicroRNA-224 is up-regulated in hepatocellular carcinoma through epigenetic mechanisms. *FASEB J.* 2012, 26, 3032–3041. [CrossRef] [PubMed]

107. Zhang, Q.; Padi, S.K.; Tindall, D.J.; Guo, B. Polycomb protein EZH2 suppresses apoptosis by silencing the proapoptotic miR-31. *Cell Death Dis.* 2014, 5, e1486. [CrossRef] [PubMed]

108. Chang, S.; Wang, R.H.; Akagi, K.; Kim, K.A.; Martin, B.K.; Cavallone, L.; Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer (kConFab); Haines, D.C.; Basik, M.; Mai, P.; et al. Tumor suppressor BRCA1 epigenetically controls oncogenic microRNA-155. *Nat. Med.* 2011, 17, 1275–1282. [CrossRef] [PubMed]

109. Scott, G.K.; Mattie, M.D.; Berger, C.E.; Benz, S.C.; Benz, C.C. Rapid alteration of microRNA levels by histone deacytelase inhibition. *Cancer Res.* 2006, 66, 1277–1281. [CrossRef] [PubMed]

110. Kopp, F.; Wagner, E.; Roidl, A. The proto-oncogene kras is targeted by miR-200c. *Oncotarget* 2014, 5, 185–195. [CrossRef] [PubMed]

111. Scott, G.K.; Mattie, M.D.; Berger, C.E.; Benz, S.C.; Benz, C.C. Rapid alteration of microRNA levels by histone deacytelase inhibition. *Cancer Res.* 2006, 66, 1277–1281. [CrossRef] [PubMed]

112. Lim, Y.Y.; Wright, J.A.; Attema, J.L.; Gregory, P.A.; Lee, T.J.; Pichiorri, F.; Marchio, A.; Palatini, J.; Kawao, T.; et al. Allelic silencing at the tumor-suppressor locus 13q14.3 suggests an epigenetic tumor-suppressor mechanism. *Proc. Natl. Acad. Sci. USA* 2006, 103, 7741–7746. [CrossRef] [PubMed]

113. Kopp, F.; Wagner, E.; Roidl, A. The proto-oncogene kras is targeted by miR-200c. *Oncotarget* 2014, 5, 185–195. [CrossRef] [PubMed]

114. Zhang, Q.; Sun, M.; Zhou, S.; Guo, B. Class I HDAC inhibitor mocetinostat induces apoptosis by activation of miR-31 expression and suppression of E2F6. *Cell Death Discov.* 2016, 2, 16036. [CrossRef] [PubMed]

115. Mertens, D.; Wolf, S.; Tschuch, C.; Mund, C.; Kienle, D.; Ohil, S.; Schroeter, P.; Lyko, F.; Dohner, H.; Stilgenbauer, S.; et al. Allelic silencing at the tumor-suppressor locus 13q14.3 suggests an epigenetic tumor-suppressor mechanism. *Proc. Natl. Acad. Sci. USA* 2006, 103, 7741–7746. [CrossRef] [PubMed]

116. Chen, W.S.; Leung, C.M.; Pan, H.W.; Hu, L.Y.; Li, S.C.; Ho, M.R.; Tsai, K.W. Silencing of miR-1-1 and miR-133a-2 cluster expression by DNA hypermethylation in colorectal cancer. *Oncol. Rep.* 2012, 28, 1069–1076. [CrossRef] [PubMed]

117. Yang, X.; Feng, M.; Jiang, X.; Wu, Z.; Li, Z.; Aau, M.; Yu, Q. miR-449a and miR-449b are direct transcriptional targets of E2F1 and negatively regulate PRB-E2F1 activity through a feedback loop by targeting CDK6 and CDC25a. *Genes Dev.* 2009, 23, 2388–2393. [CrossRef] [PubMed]

118. Au, S.L.; Wong, C.C.; Lee, J.M.; Fan, D.N.; Tsang, F.H.; Ng, I.O.; Wong, C.M. Enhancer of zeste homolog 2 (EZH2) is epigenetically silenced multiple tumor suppressor microRNAs to promote liver cancer metastasis. *Hepatology* 2012, 56, 622–631. [CrossRef] [PubMed]

119. Cao, Q.; Mani, R.S.; Ateeq, B.; Dhanasekaran, S.M.; Asangani, I.A.; Prensner, J.R.; Kim, J.H.; Brenner, J.C.; Vannata, B.; et al. Allele-specific loss and transcription of the miR-15a/16-1 cluster in chronic lymphocytic leukemia. *Blood* 2012, 119, 1162–1172. [CrossRef] [PubMed]

120. Zhang, Q.; Sun, M.; Zhou, S.; Guo, B. Class I HDAC inhibitor mocetinostat induces apoptosis by activation of miR-31 expression and suppression of E2F6. *Cell Death Discov.* 2016, 2, 16036. [CrossRef] [PubMed]

121. Chen, W.S.; Leung, C.M.; Pan, H.W.; Hu, L.Y.; Li, S.C.; Ho, M.R.; Tsai, K.W. Silencing of miR-1-1 and miR-133a-2 cluster expression by DNA hypermethylation in colorectal cancer. *Oncol. Rep.* 2012, 28, 1069–1076. [CrossRef] [PubMed]
122. Nasser, M.W.; Datta, J.; Nuovo, G.; Kutay, H.; Motiwala, T.; Majumder, S.; Wang, B.; Suster, S.; Jacob, S.T.; Ghoshal, K. Down-regulation of micro-RNA-1 (miR-1) in lung cancer. Suppression of tumorigenic property of lung cancer cells and their sensitization to doxorubicin-induced apoptosis by miR-1. *J. Biol. Chem.* 2008, 283, 33394–33405. [CrossRef] [PubMed]

123. Li, X.; Pan, Q.; Wan, X.; Mao, Y.; Lu, W.; Xie, X.; Cheng, X. Methylation-associated has-miR-9 deregulation in paclitaxel-resistant epithelial ovarian carcinoma. *BMC Cancer* 2015, 15, 509. [CrossRef] [PubMed]

124. Zhang, Q.; Wang, L.Q.; Wong, K.Y.; Li, Z.Y.; Chim, C.S. Infrequent DNA methylation of miR-9-1 and miR-9-3 in multiple myeloma. *J. Clin. Pathol.* 2015, 68, 557–561. [CrossRef] [PubMed]

125. Hildebrandt, M.A.; Gu, J.; Lin, J.; Ye, Y.; Tan, W.; Tamboli, P.; Wood, C.G.; Wu, X. Hsa-miR-9 methylation status is associated with cancer development and metastatic recurrence in patients with clear cell renal cell carcinoma. *Oncogene* 2010, 29, 5724–5728. [CrossRef] [PubMed]

126. Kohler, C.U.; Bryk, O.; Meier, S.; Lang, K.; Rozynek, P.; Brunsing, T.; Kafferlein, H.U. Analyses in human urothelial cells identify methylation of miR-152, miR-200b and miR-10a genes as candidate bladder cancer biomarkers. *Biochem. Biophys. Res. Commun.* 2013, 438, 48–53. [CrossRef] [PubMed]

127. Shen, J.; Wang, S.; Zhang, Y.J.; Kappil, M.A.; Wu, H.C.; Kibriya, M.G.; Wang, Q.; Jasmine, F.; Ahsan, H.; Lee, P.H.; et al. Genome-wide aberrant DNA methylation of microRNA host genes in hepatocellular carcinoma. *Epigenetics* 2012, 7, 1230–1237. [CrossRef] [PubMed]

128. Humphreys, K.J.; Cobi, L.; Le Leu, R.K.; Van der Hoek, M.B.; Michael, M.Z. Histone deacetylase inhibition in colorectal cancer cells reveals competing roles for members of the oncogenic miR-17-92 cluster. *Mol. Carcinog.* 2013, 52, 459–474. [CrossRef] [PubMed]

129. Iorio, M.V.; Visone, R.; Di Leva, G.; Donati, V.; Petrocca, F.; Casalini, P.; Taccioli, C.; Volinia, S.; Liu, C.G.; Alder, H.; et al. MicroRNA signatures in human ovarian cancer. *Cancer Res.* 2007, 67, 8699–8707. [CrossRef] [PubMed]

130. Ferrari, A.; Kontos, C.K.; Boni, T.; Bantounas, I.; Siakouli, D.; Kosmidou, V.; Vlassi, M.; Spyridakis, Y.; Tsipras, I.; Zogoras, G.; et al. Epigenetic regulation of miR-21 in colorectal cancer: ITGB4 as a novel miR-21 target and a three-gene network (miR-21-ITGBETA4-PDCD4) as predictor of metastatic tumor potential. *Epigenetics* 2014, 9, 129–141. [CrossRef] [PubMed]

131. Hulf, T.; Sibbritt, T.; Wiklund, E.D.; Bert, S.; Statham, A.L.; Robinson, M.D.; Clark, S.J. Discovery pipeline for epigenetically deregulated miRNAs in cancer: Integration of primary miRNA transcription. *BMC Genom.* 2011, 12, 54. [CrossRef] [PubMed]

132. Wang, S.; Zhang, R.; Clare, F.X.; Yang, H. Involvement of microRNA-24 and DNA methylation in resistance of nasopharyngeal carcinoma to ionizing radiation. *Mol. Cancer Ther.* 2014, 13, 3163–3174. [CrossRef] [PubMed]

133. Zhang, X.; Zhao, X.; Fiskus, W.; Lin, J.; Lwin, T.; Rao, R.; Zhang, Y.; Chan, J.C.; Fu, K.; Marquez, V.E.; 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* 2012, 22, 506–523. [CrossRef] [PubMed]

134. Liu, S.; Wu, L.C.; Pang, J.; Santhanam, R.; Schwind, S.; Wu, Y.Z.; Hickey, C.J.; Yu, J.; Becker, H.; Maharry, K.; et al. Sp1/NFκB/HDAC/miR-29b regulatory network in kit-driven myeloid leukemia. *Cancer Cell* 2010, 17, 333–347. [CrossRef] [PubMed]

135. Cho, J.H.; Dimri, M.; Dimri, G.P. MicroRNA-31 is a transcriptional target of histone deacetylase inhibitors and a regulator of cellular senescence. *J. Biol. Chem.* 2015, 290, 10555–10567. [CrossRef] [PubMed]

136. Lin, P.C.; Chiu, Y.L.; Banerjee, S.; Park, K.; Mosquera, J.M.; Giannopoulou, E.; Alves, P.; Tewari, A.K.; Gerstein, M.B.; Beltran, H.; et al. Epigenetic repression of miR-31 disrupts androgen receptor homeostasis and contributes to prostate cancer progression. *Cancer Res.* 2013, 73, 1232–1244. [CrossRef] [PubMed]

137. Asangani, I.A.; Harms, P.W.; Dodson, L.; Pandhi, M.; Kunju, L.P.; Maher, C.A.; Fullen, D.R.; Johnson, T.M.; Giordano, T.J.; Palanisamy, N.; et al. Genetic and epigenetic loss of microRNA-31 leads to feed-forward expression of EZH2 in melanoma. *Oncotarget* 2012, 3, 1011–1025. [CrossRef] [PubMed]

138. Augoff, K.; McCue, B.; Plow, E.F.; Sossey-Alaoui, K. miR-31 and its host gene IncRNA LOC554202 are regulated by promoter hypermethylation in triple-negative breast cancer. *Mol. Cancer* 2012, 11. [CrossRef] [PubMed]

139. Bhatnagar, N.; Li, X.; Padi, S.K.; Zhang, Q.; Tang, M.S.; Guo, B. Downregulation of miR-205 and miR-31 confers resistance to chemotherapy-induced apoptosis in prostate cancer cells. *Cell Death Dis.* 2010, 1, e105. [CrossRef] [PubMed]
157. Watanabe, K.; Emoto, N.; Hamano, E.; Sunohara, M.; Kawakami, M.; Kage, H.; Kitano, K.; Nakajima, J.; Goto, A.; Fukayama, M.; et al. Genome structure-based screening identified epigenetically silenced microRNA associated with invasiveness in non-small-cell lung cancer. *Int. J. Cancer* **2012**, *130*, 2580–2590. [CrossRef] [PubMed]

158. Wotschofsky, Z.; Liep, J.; Meyer, H.A.; Jung, M.; Wagner, I.; Disch, A.C.; Schaser, K.D.; Melcher, I.; Kilić, E.; Busch, J.; et al. Identification of metastamiRs as metastasis-associated microRNAs in clear cell renal cell carcinomas. *Int. J. Biol. Sci.* **2012**, *8*, 1363–1374. [CrossRef] [PubMed]

159. Shen, R.; Pan, S.; Qi, S.; Lin, X.; Cheng, S. Epigenetic repression of microRNA-129-2 leads to overexpression of SOX4 oncogene in endometrial cancer. *Cancer Res.* **2009**, *69*, 9038–9046. [CrossRef] [PubMed]

160. Queen, Y.; Zhang, S.; Hao, J.; Xie, F.; Hu, X.; Liu, C.; Tong, J.; Zhou, J.; Wu, J.; Shao, C. Downregulation of miR-132 by promoter methylation contributes to pancreatic cancer development. *Carcinogenesis* **2011**, *32*, 1183–1189. [CrossRef] [PubMed]

161. Formosa, A.; Lena, A.M.; Markert, E.K.; Cortelli, S.; Miano, R.; Mauriello, A.; Croce, N.; Vandesompele, J.; Mestdagh, P.; Finaazzi-Agro, E.; et al. DNA methylation silences miR-132 in prostate cancer. *Oncogene* **2013**, *32*, 127–134. [CrossRef] [PubMed]

162. Lv, L.V.; Zhou, J.; Lin, C.; Hu, G.; Yi, L.U.; Du, J.; Gao, K.; Li, X. DNA methylation is involved in the aberrant expression of miR129-2 in colorectal cancer. *Int. J. Cancer* **2009**, *125*, 2737–2743. [CrossRef] [PubMed]

163. Zhang, S.; Hao, J.; Xie, F.; Hu, X.; Liu, C.; Tong, J.; Zhou, J.; Wu, J.; Shao, C. Downregulation of miR-132 by promoter methylation contributes to pancreatic cancer development. *Carcinogenesis* **2011**, *32*, 1183–1189. [CrossRef] [PubMed]

164. Formosa, A.; Lena, A.M.; Markert, E.K.; Cortelli, S.; Miano, R.; Mauriello, A.; Croce, N.; Vandesompele, J.; Mestdagh, P.; Finaazzi-Agro, E.; et al. DNA methylation silences miR-132 in prostate cancer. *Oncogene* **2013**, *32*, 127–134. [CrossRef] [PubMed]

165. Steponaitiene, R.; Kucinskas, J.; Langner, C.; Balaguér, F.; Vencluksas, L.; Pauzas, H.; Tamelis, A.; Škieceviciene, J.; Kucinskas, L.; Malfertheiner, P.; et al. Epigenetic silencing of miR-137 is a frequent event in gastric carcinogenesis. *Mol. Carcinog.* **2016**, *55*, 376–386. [CrossRef] [PubMed]

166. Balagué, F.; Link, A.; Deatherage, D.E.; Luo, J.; Mutch, D.G.; Goodfellow, P.J.; Miller, D.S.; Huang, T.H. Epigenetic repression of microRNA-129-2 leads to overexpression of SOX4 oncogene in endometrial cancer. *Cancer Res.* **2009**, *69*, 9038–9046. [CrossRef] [PubMed]

167. Shien, R.; Pan, S.; Qi, S.; Lin, X.; Cheng, S. Epigenetic repression of microRNA-129-2 leads to overexpression of SOX4 in gastric cancer. *Biochem. Biophys. Res. Commun.* **2010**, *394*, 1047–1052. [CrossRef] [PubMed]

168. Formosa, A.; Lena, A.M.; Markert, E.K.; Cortelli, S.; Miano, R.; Mauriello, A.; Croce, N.; Vandesompele, J.; Mestdagh, P.; Finazzi-Agro, E.; et al. DNA methylation silences miR-132 in prostate cancer. *Oncogene* **2013**, *32*, 127–134. [CrossRef] [PubMed]

169. Zhang, S.; Hao, J.; Xie, F.; Hu, X.; Liu, C.; Tong, J.; Zhou, J.; Wu, J.; Shao, C. Downregulation of miR-132 by promoter methylation contributes to pancreatic cancer development. *Carcinogenesis* **2011**, *32*, 1183–1189. [CrossRef] [PubMed]

170. Queen, Y.; Zhang, S.; Deng, S.; An, G.; Qin, X.; Li, F.; Xu, Y.; Hao, M.; Yang, Y.; Zhou, W.; et al. Epigenetic silencing of miR-137 induces drug resistance and chromosomal instability by targeting AURKA in multiple myeloma. *Leukemia* **2017**, *31*, 1123–1135. [CrossRef] [PubMed]

171. Langevin, S.M.; Stone, R.A.; Bunker, C.H.; Lyons-Weiler, M.A.; LaFramboise, W.A.; Kelly, L.; Seethala, R.R.; Grandis, J.R.; Solor, R.W.; Taioli, E. MicroRNA-137 promoter methylation is associated with poorer overall survival in patients with squamous cell carcinoma of the head and neck. *Cancer* **2011**, *117*, 1454–1462. [CrossRef] [PubMed]

172. Balagué, F.; Link, A.; Lozano, J.J.; Cuatrecasas, M.; Nagasaka, T.; Boland, C.R.; Goel, A. Epigenetic silencing of miR-137 is an early event in colorectal carcinogenesis. *Cancer Res.* **2010**, *70*, 6609–6618. [CrossRef] [PubMed]

173. Daniužaitė, K.; Dubikaitytė, M.; Gibas, P.; Bakavicius, A.; Rimantienė, J.; Ulys, A.; Jankevicius, F.; Jarmalaitė, S. Clinical significance of miRNA host gene promoter methylation in prostate cancer. *Hum. Mol. Genet.* **2017**, *26*, 2451–2461. [CrossRef] [PubMed]

174. Watanabe, K.; Amano, Y.; Ishikawa, R.; Sunohara, M.; Kage, H.; Ichinose, J.; Sano, A.; Nakajima, J.; Fukayama, M.; Yatomi, Y.; et al. Histone methylation-mediated silencing of miR-139 enhances invasion of non-small-cell lung cancer. *Cancer Med.* **2015**, *4*, 1573–1582. [CrossRef] [PubMed]

175. Lynch, S.M.; O’Neill, K.M.; McKenna, M.M.; Walsh, C.P.; McKenna, D.J. Regulation of miR-200c and miR-141 by methylation in prostate cancer. *Prostate* **2016**, *76*, 1146–1159. [CrossRef] [PubMed]
175. Dou, L.; Zheng, D.; Li, J.; Li, Y.; Gao, L.; Wang, L.; Yu, L. Methylation-mediated repression of microRNA-143 enhances MLL-AF4 oncogene expression. *Oncogene* **2012**, *31*, 507–517. [CrossRef] [PubMed]

176. Xia, W.; Chen, Q.; Wang, J.; Mao, Q.; Dong, G.; Shi, R.; Zheng, Y.; Xu, L.; Jiang, F. DNA methylation mediated silencing of microRNA-145 is a potential prognostic marker in patients with lung adenocarcinoma. *Sci. Rep.* **2015**, *5*, 16901. [CrossRef] [PubMed]

177. Ye, Z.; Shen, N.; Weng, Y.; Li, K.; Hu, L.; Liao, H.; An, J.; Liu, L.; Lao, S.; Cai, S. Low miR-145 silenced by DNA methylation promotes NSCLC cell proliferation, migration and invasion by targeting mucin 1. *Cancer Biol. Ther.* **2015**, *16*, 1071–1079. [CrossRef] [PubMed]

178. Suh, S.O.; Chen, Y.; Zaman, M.S.; Hirata, H.; Yamamura, S.; Shahryari, V.; Liu, J.; Tabatabai, Z.L.; Kakar, S.; Deng, G.; et al. MicroRNA-145 is regulated by DNA methylation and p53 gene mutation in prostate cancer. *Carcinogenesis* **2011**, *32*, 772–778. [CrossRef] [PubMed]

179. Zaman, M.S.; Chen, Y.; Deng, G.; Shahryari, V.; Suh, S.O.; Saini, S.; Majid, S.; Liu, J.; Khatri, G.; Tanaka, Y.; et al. The functional significance of microRNA-145 in prostate cancer. *Br. J. Cancer* **2010**, *103*, 256–264. [CrossRef] [PubMed]

180. Tsuruta, T.; Kozaki, K.; Uesugi, A.; Furuta, M.; Hirasa, A.; Iimoto, I.; Susumu, N.; Aoki, D.; Inazawa, J. miR-152 is a tumor suppressor microRNA that is silenced by DNA hypermethylation in endometrial cancer. *Cancer Res.* **2011**, *71*, 6450–6462. [CrossRef] [PubMed]

181. Sengupta, D.; Deb, M.; Rath, S.K.; Kar, S.; Parbin, S.; Pradhan, N.; Patra, S.K. DNA methylation and not H3K4 trimethylation dictates the expression status of miR-152 gene which inhibits migration of breast cancer cells via DNMT1/CDH1 loop. *Exp. Cell Res.* **2016**, *346*, 176–187. [CrossRef] [PubMed]

182. Ayala-Ortega, E.; Arzate-Mejia, R.; Perez-Molina, R.; Gonzalez-Buendia, E.; Meier, K.; Guerrero, G.; Recillas-Targa, F. Epigenetic silencing of miR-181c by DNA methylation in glioblastoma cell lines. *BMC Cancer* **2016**, *16*, 226. [CrossRef] [PubMed]

183. He, Y.; Cui, Y.; Wang, W.; Gu, J.; Guo, S.; Ma, K.; Luo, X. Hypomethylation of the hsa-miR-191 locus causes high expression of hsa-miR-191 and promotes the epithelial-to-mesenchymal transition in hepatocellular carcinoma. *Neoplasia* **2011**, *13*, 841–853. [CrossRef] [PubMed]

184. Ma, K.; He, Y.; Zhang, H.; Fei, Q.; Niu, D.; Wang, D.; Ding, X.; Xu, H.; Chen, X.; Zhu, J. DNA methylation-regulated miR-193a-3p dictates resistance of hepatocellular carcinoma to 5-fluorouracil via repression of SRSF2 expression. *J. Biol. Chem.* **2012**, *287*, 5639–5649. [CrossRef] [PubMed]

185. Lv, L.; Deng, H.; Li, Y.; Zhang, C.; Liu, X.; Liu, Q.; Zhang, D.; Wang, L.; Pu, Y.; Zhang, H.; et al. The DNA methylation-regulated miR-193a-3p dictates the multi-chemoresistance of bladder cancer via repression of SRSF2/PLAU/HIC2 expression. *Cell Death Dis.* **2014**, *5*, e1402. [CrossRef] [PubMed]

186. Gao, X.N.; Lin, J.; Li, Y.H.; Gao, L.; Wang, X.R.; Wang, W.; Kang, H.Y.; Yan, G.T.; Wang, L.L.; Yu, L. MicroRNA-193a represses c-kit expression and functions as a methylation-silenced tumor suppressor in acute myeloid leukemia. *Oncogene* **2011**, *30*, 3416–3428. [CrossRef] [PubMed]

187. Torres-Ferreira, J.; Ramalho-Carvalho, J.; Gomez, A.; Menezes, F.D.; Freitas, R.; Oliveira, J.; Antunes, L.; Bento, M.J.; Esteller, M.; Henrique, R.; et al. miR-193b promoter methylation accurately detects prostate cancer in urine sediments and miR-34b/c or miR-129-2 promoter methylation define subsets of clinically aggressive tumors. *Mol. Cancer* **2017**, *16*, 26. [CrossRef] [PubMed]

188. Rauhala, H.E.; Jalava, S.E.; Isotalo, J.; Bracken, H.; Lehmusvaara, S.; Tammela, T.L.; Oja, H.; Visakorpi, T. MLL-AF4 is an epigenetically regulated putative tumor suppressor in prostate cancer. *Int. J. Cancer* **2010**, *127*, 1363–1372. [CrossRef] [PubMed]

189. Tsai, K.W.; Hu, L.Y.; Wu, C.W.; Li, S.C.; Lai, C.H.; Kao, H.W.; Fang, W.L.; Lin, W.C. Epigenic regulation of miR-196b expression in gastric cancer. *Genes Chromosom. Cancer* **2010**, *49*, 969–980. [CrossRef] [PubMed]

190. Cheung, H.H.; Davis, A.J.; Lee, T.L.; Pang, A.L.; Nagrani, S.; Rennert, O.M.; Chan, W.Y. Methylation of an intronic region regulates miR-199a in testicular tumor malignancy. *Oncogene* **2011**, *30*, 3404–3415. [CrossRef] [PubMed]

191. Deng, Y.; Zhao, F.; Hui, L.; Li, X.; Zhang, D.; Lin, W.; Chen, Z.; Ning, Y. Suppressing miR-199a-3p by promoter methylation contributes to tumor aggressiveness and cisplatin resistance of ovarian cancer through promoting DDR1 expression. *J. Ovarian Res.* **2017**, *10*, 50. [CrossRef] [PubMed]

192. Wu, W.R.; Sun, H.; Zhang, R.; Yu, X.H.; Shi, X.D.; Zhu, M.S.; Zeng, H.; Yan, L.X.; Xu, L.B.; Liu, C. Methylation-associated silencing of miR-200b facilitates human hepatocellular carcinoma progression by directly targeting BMI1. *Oncotarget* **2016**, *7*, 18684–18693. [CrossRef] [PubMed]
193. Neves, R.; Scheel, C.; Weinhold, S.; Honisch, E.; Iwaniuk, K.M.; Trompeter, H.I.; Niederacher, D.; Wernet, P.; Santourlidis, S.; Uhrberg, M. Role of DNA methylation in miR-200c/141 cluster silencing in invasive breast cancer cells. BMC Res. Notes 2010, 3, 219. [CrossRef] [PubMed]

194. Ceppi, P.; Mudduluru, G.; Kumarswamy, R.; Rapa, I.; Scagliotti, G.V.; Papotti, M.; Allgayer, H. Loss of Neves, R.; Scheel, C.; Weinhold, S.; Honisch, E.; Iwaniuk, K.M.; Trompeter, H.I.; Niederacher, D.; Wernet, P.; Santourlidis, S.; Uhrberg, M. Role of DNA methylation in miR-200c/141 cluster silencing in invasive breast cancer cells. BMC Res. Notes 2010, 3, 219. [CrossRef] [PubMed]

195. Davalos, V.; Moutinho, C.; Villanueva, A.; Boque, R.; Silva, P.; Carneiro, F.; Esteller, M. Dynamic epigenetic regulation of the microRNA-200 family mediates epithelial and mesenchymal transitions in human tumorigenesis. Oncogene 2012, 31, 2062–2074. [CrossRef] [PubMed]

196. Huang, Y.W.; Kuo, C.T.; Chen, J.H.; Goodfellow, P.J.; Huang, T.H.; Rader, J.S.; Uyar, D.S. Hypermethylation of miR-200 expression induces an aggressive, invasive, and chemoresistant phenotype in non-small cell lung cancer. Mol. Cancer Res. MCR 2010, 8, 1207–1216. [CrossRef] [PubMed]

197. Chim, C.S.; Wong, K.Y.; Leung, C.Y.; Chung, L.P.; Hui, P.K.; Chan, S.Y.; Yu, L. Epigenetic inactivation of the hsa-miR-203 in haematological malignancies. J. Cell Mol. Med. 2011, 15, 2760–2767. [CrossRef] [PubMed]

198. Wiklund, E.D.; Branssen, J.B.; Hulf, T.; Dyrskjo, L.; Ramanathan, R.; Hansen, T.B.; Villadsen, S.B.; Gao, S.; Ostenfeld, M.S.; Borre, M.; et al. Coordinated epigenetic repression of the miR-200 family and miR-205 in invasive bladder cancer. Int. J. Cancer 2011, 128, 1327–1334. [CrossRef] [PubMed]

199. Uesugi, A.; Kozaki, K.; Tsuruta, T.; Furuta, M.; Morita, K.; Imoto, I.; Omura, K.; Inazawa, J. The tumor suppressive microRNA miR-218 targets the mtor component rictor and inhibits AKT phosphorylation in oral cancer. Cancer Res. 2011, 71, 5765–5778. [CrossRef] [PubMed]

200. Lei, H.; Zou, D.; Li, Z.; Luo, M.; Dong, L.; Wang, B.; Yin, H.; Ma, Y.; Liu, C.; Wang, F.; et al. MicroRNA-219-2-3p functions as a tumor suppressor in gastric cancer and is regulated by DNA methylation. PLoS ONE 2013, 8, e60369. [CrossRef] [PubMed]

201. Png, K.J.; Yoshida, M.; Zhang, X.H.; Shen, W.; Lee, H.; Rimner, A.; Chan, T.A.; Comen, E.; Andrade, V.P.; Kim, S.W.; et al. MicroRNA-335 inhibits tumor reinitiation and is silenced through genetic and epigenetic mechanisms in human breast cancer. Genes Dev. 2011, 25, 226–231. [CrossRef] [PubMed]

202. Zhang, J.K.; Li, Y.S.; Zhang, C.D.; Dai, D.Q. Up-regulation of ckr1 by microRNA-335 methylation is associated with poor prognosis in gastric cancer. Cancer Cell Int. 2017, 17, 28. [CrossRef] [PubMed]

203. Grady, W.M.; Parkin, R.K.; Mitchell, P.S.; Lee, J.H.; Kim, Y.H.; Tsuchiya, K.D.; Washington, M.K.; Paraskeva, C.; Willson, J.K.; Kaz, A.M.; et al. Epigenetic silencing of the intrinsic microRNA hsa-miR-342 and its host gene evl in colorectal cancer. Oncogene 2008, 27, 3880–3888. [CrossRef] [PubMed]

204. Tang, J.T.; Wang, J.L.; Du, W.; Hong, J.; Zhao, S.L.; Wang, Y.C.; Xiong, H.; Chen, H.M.; Fang, J.Y. MicroRNA 345, a methylation-sensitive microRNA is involved in cell proliferation and invasion in human colorectal cancer. Carcinogenesis 2011, 32, 1207–1215. [CrossRef] [PubMed]

205. Nakaoka, T.; Saito, Y.; Saito, H. Aberrant DNA methylation as a biomarker and a therapeutic target of cholangiocarcinoma. Int. J. Mol. Sci. 2017, 18, 1111. [CrossRef] [PubMed]

206. Chen, Y.; Gao, W.; Luo, J.; Tian, R.; Sun, H.; Zou, S. Methyl-CpG binding protein MBD2 is implicated in methylation-mediated suppression of miR-373 in hilar cholangiocarcinoma. Oncol. Rep. 2011, 25, 443–451. [CrossRef] [PubMed]

207. Chu, M.; Chang, Y.; Li, P.; Guo, Y.; Zhang, K.; Gao, W. Androgen receptor is negatively correlated with the methylation-mediated transcriptional repression of miR-375 in human prostate cancer cells. Oncol. Rep. 2014, 31, 34–40. [CrossRef] [PubMed]

208. Li, X.; Lin, R.; Li, J. Epigenetic silencing of microRNA-375 regulates pdk1 expression in esophageal cancer. Dig. Dis. Sci. 2011, 56, 2849–2856. [CrossRef] [PubMed]
212. Mazar, J.; DeBlasio, D.; Govindarajan, S.S.; Zhang, S.; Perera, R.J. Epigenetic regulation of microRNA-375 and its role in melanoma development in humans. FEBS Lett. 2011, 585, 2467–2476. [CrossRef] [PubMed]

213. Zhang, L.; Yan, D.L.; Yang, F.; Wang, D.D.; Chen, X.; Wu, J.Z.; Tang, J.H.; Xia, W.J. DNA methylation mediated silencing of microRNA-874 is a promising diagnosis and prognostic marker in breast cancer. Oncotarget 2017, 8, 45496–45505. [CrossRef] [PubMed]

214. Yan, H.; Choi, A.J.; Lee, B.H.; Ting, A.H. Identification and functional analysis of epigenetically silenced microRNAs in colorectal cancer cells. PLoS ONE 2011, 6, e20628. [CrossRef] [PubMed]

215. Ko, Y.C.; Fang, W.H.; Lin, T.C.; Hou, H.A.; Chen, C.Y.; Tien, H.F.; Lin, L.I. MicroRNA let-7a-3 gene methylation is associated with the phenotype and presence of bladder cancer. Clin. Cancer Res. 2011, 17, 1287–1296. [CrossRef] [PubMed]

216. Zhang, X.; Liu, H.; Xie, Z.; Deng, W.; Wu, C.; Qin, B.; Hou, J.; Lu, M. Epigenetically regulated miR-449a enhances hepatitis B virus replication by targeting cAMP-responsive element binding protein 5 and modulating hepatocytes phenotype. Sci. Rep. 2016, 6, 25389. [CrossRef] [PubMed]

217. Yan, H.; Choi, A.J.; Lee, B.H.; Ting, A.H. Identification and functional analysis of epigenetically silenced microRNAs in colorectal cancer cells. PLoS ONE 2011, 6, e20628. [CrossRef] [PubMed]

218. Dudziec, E.; Miah, S.; Choudhry, H.M.; Owen, H.C.; Blizard, S.; Glover, M.; Hamdy, F.C.; Croce, C.M.; Kazanets, A.; Shorstova, T.; Hilmi, K.; Marques, M.; Witcher, M. Epigenetic silencing of tumor suppressor genes: Paradigms, puzzles, and potential. Biochim. Biophys. Acta 2016, 1865, 275–288. [PubMed]

219. Lu, L.; Katsaros, D.; de la Longrais, I.A.; Sochirca, O.; Yu, H. Hypermethylation of let-7a-3 in epithelial ovarian cancer is associated with low insulin-like growth factor-II expression and favorable prognosis. Cancer Res. 2007, 67, 10117–10122. [CrossRef] [PubMed]

220. Brueckner, B.; Stresemann, C.; Kuner, R.; Mund, C.; Musch, T.; Meister, M.; Sultmann, H.; Lyko, F. The human let-7a-3 locus contains an epigenetically regulated microRNA gene with oncogenic function. Cancer Res. 2007, 67, 1419–1423. [CrossRef] [PubMed]

221. Wong, T.S.; Man, O.Y.; Tsang, C.M.; Tsao, S.W.; Tsang, R.K.; Chan, J.Y.; Ho, W.K.; Wei, W.I.; To, V.S. MicroRNA MIR1247 in hepatocellular cancer. Gene 2008, 415, 1419–1423. [CrossRef] [PubMed]

222. Klatt, P.; et al. A mammalian microRNA cluster controls DNA methylation and telomere recombination via Rbl2-dependent regulation of DNA methyltransferases. Nat. Struct. Mol. Biol. 2008, 15, 998. [CrossRef] [PubMed]

223. Vire, E.; Brenner, C.; Deplus, R.; Blanchon, L.; Fraga, M.; Didelot, C.; Morey, L.; Van Eynde, A.; Bernard, D.; Vanderwinden, J.M.; et al. The polycomb group protein EZH2 directly controls DNA methylation. Nature 2006, 439, 871–874. [CrossRef] [PubMed]
232. Cao, R.; Wang, L.; Wang, H.; Xia, L.; Erdjument-Bromage, H.; Tempst, P.; Jones, R.S.; Zhang, Y. Role of histone H3 lysine 27 methylation in polycomb-group silencing. *Science* **2002**, 298, 1039–1043. [CrossRef] [PubMed]

233. Iliopoulos, D.; Lindahl-Allen, M.; Polytaichou, C.; Hirsch, H.A.; Tsichlis, P.N.; Struhl, K. Loss of miR-200 inhibition of SUZ12 leads to polycomb-mediated repression required for the formation and maintenance of cancer stem cells. *Mol. Cell* **2010**, 39, 761–772. [CrossRef] [PubMed]

234. Cao, R.; Wang, L.; Wang, H.; Xia, L.; Erdjument-Bromage, H.; Tempst, P.; Jones, R.S.; Zhang, Y. Role of histone H3 lysine 27 methylation in polycomb-group silencing. *Science* **2002**, 298, 1039–1043. [CrossRef] [PubMed]

235. Peruzzi, P.; Bronisz, A.; Nowicki, M.O.; Wang, Y.; Ogawa, D.; Price, R.; Nakano, I.; Kwon, C.H.; Hayes, J.; Lawler, S.E.; et al. MicroRNA-128 coordinately targets polycomb repressor complexes in glioma stem cells. *Neuro Oncol.* **2013**, 15, 1212–1224. [CrossRef] [PubMed]

236. Jiang, L.; Li, J.; Song, L. Bmi-1, stem cells and cancer. *Acta Biochim. Biophys. Sin. (Shanghai)* **2013**, 45, 761–772. [CrossRef] [PubMed]

237. Bachmann, I.M.; Halvorsen, O.J.; Collett, K.; Stefansson, I.M.; Straume, O.; Haukaas, S.A.; Salvesen, H.B.; Otte, A.P.; Akslen, L.A. EZH2 expression is associated with high proliferation rate and aggressive tumor subgroups in cutaneous melanoma and cancers of the endometrium, prostate, and breast. *J. Clin. Oncol.* **2006**, 24, 268–273. [CrossRef] [PubMed]

238. Sander, S.; Bullinger, L.; Klapproth, K.; Fiedler, K.; Kestler, H.A.; Barth, T.F.; Moller, P.; Stilgenbauer, S.; Pollack, J.R.; Wirth, T. MYC stimulates EZH2 expression by repression of its negative regulator miR-26a. *Blood* **2008**, 112, 4202–4212. [CrossRef] [PubMed]

239. Friedman, J.M.; Liang, G.; Liu, C.C.; Wolff, E.M.; Tsai, Y.C.; Ye, W.; Zhou, H.; Jones, P.A. The putative tumor suppressor microRNA-101 modulates the cancer epigenome by repressing the polycomb group protein EZH2. *Cancer Res.* **2009**, 69, 2623–2629. [CrossRef] [PubMed]

240. Varambally, S.; Cao, Q.; Varambally, S.; Shen, R.; Ota, I.; Tomlins, S.A.; Ghosh, D.; Sewalt, R.G.; Otte, A.P.; Hayes, J.; et al. Genomic loss of microRNA-101 leads to overexpression of histone methyltransferase EZH2 in cancer. *Science* **2008**, 322, 1695–1699. [CrossRef] [PubMed]

241. Di Croce, L.; Helin, K. Transcriptional regulation by polycomb group proteins. *Nat. Struct. Mol. Biol.* **2013**, 20, 1147–1155. [CrossRef] [PubMed]

242. Jiang, L.; Li, J.; Song, L. Bmi-1, stem cells and cancer. *Acta Biochim. Biophys. Sin. (Shanghai)* **2009**, 41, 527–534. [CrossRef] [PubMed]

243. Godlewski, J.; Nowicki, M.O.; Bronisz, A.; Williams, S.; Otsuki, A.; Nuovo, G.; Raychaudhury, A.; Newton, H.B.; Chiocca, E.A.; Lawler, S. Targeting of the Bmi-1 oncogene/stem cell renewal factor by microRNA-128 inhibits glioma proliferation and self-renewal. *Cancer Res.* **2008**, 68, 9125–9130. [CrossRef] [PubMed]

244. Bhattacharyya, R.; Nicoloso, M.; Arvizo, R.; Wang, E.; Cortez, A.; Rossi, S.; Calin, G.A.; Mukherjee, P. miR-15a and miR-16 control Bmi-1 expression in ovarian cancer. *Cancer Res.* **2009**, 69, 9090–9095. [CrossRef] [PubMed]

245. Dong, P.; Kaneuchi, M.; Watarai, H.; Hamada, J.; Sudo, S.; Ju, J.; Sakuragi, N. MicroRNA-194 inhibits epithelial to mesenchymal transition of endometrial cancer cells by targeting oncogene BMI-1. *Mol. Cancer* **2011**, 10, 1–10. [CrossRef] [PubMed]

246. Tu, Y.; Gao, X.; Li, G.; Fu, H.; Cui, D.; Liu, H.; Jin, W.; Zhang, Y. MicroRNA-218 inhibits glioma invasion, migration, proliferation, and cancer stem-like cell self-renewal by targeting the polycomb group gene Bmi1. *Cancer Res.* **2013**, 73, 6046–6055. [CrossRef] [PubMed]

247. Wu, S.Q.; Niu, W.Y.; Li, Y.P.; Huang, H.B.; Zhan, R. miR-203 inhibits cell growth and regulates G1/S transition by targeting Bmi-1 in myeloma cells. *Mol. Med. Rep.* **2016**, 14, 4795–4801. [CrossRef] [PubMed]

248. Van der Vlag, J.; Otte, A.P. Transcriptional repression mediated by the human polycomb-group protein eed involves histone deacetylation. *Nat. Genet.* **1999**, 23, 474–478. [CrossRef] [PubMed]

249. Witt, O.; Deubzer, H.E.; Milde, T.; Oehme, I. Hdac family: What are the cancer relevant targets? *Cancer Lett.* **2009**, 277, 8–21. [CrossRef] [PubMed]

250. Noonan, E.J.; Place, R.F.; Pookot, D.; Basak, S.; Whitson, J.M.; Hirata, H.; Giardina, C.; Dahiya, R. miR-449a targets HDAC-1 and induces growth arrest in prostate cancer. *Oncogene* **2009**, 28, 1714–1724. [CrossRef] [PubMed]

251. Noonan, E.J.; Place, R.F.; Pookot, D.; Basak, S.; Whitson, J.M.; Hirata, H.; Giardina, C.; Dahiya, R. miR-449a targets HDAC-1 and induces growth arrest in prostate cancer. *Oncogene* **2009**, 28, 1714–1724. [CrossRef] [PubMed]
251. Noh, J.H.; Chang, Y.G.; Kim, M.G.; Jung, K.H.; Kim, J.K.; Bae, H.J.; Eun, J.W.; Shen, Q.; Kim, S.J.; Kwon, S.H.; et al. miR-145 functions as a tumor suppressor by directly targeting histone deacetylase 2 in liver cancer. *Cancer Lett.* 2013, 335, 455–462. [CrossRef] [PubMed]

252. Sandhu, S.K.; Volinia, S.; Costinean, S.; Galasso, M.; Neinast, R.; Santhanam, R.; Parthun, M.R.; Perrotti, D.; Marcucci, G.; Garzon, R.; et al. miR-155 targets histone deacetylase 4 (HDAC4) and impairs transcriptional activity of B-cell lymphoma 6 (BCL6) in the Eu-miR-155 transgenic mouse model. *Proc. Natl. Acad. Sci. USA* 2012, 109, 20047–20052. [CrossRef] [PubMed]

253. Canzio, D.; Larson, A.; Narlikar, G.J. Mechanisms of functional promiscuity by HP1 proteins. *Trends Cell Biol.* 2014, 24, 377–386. [CrossRef] [PubMed]

254. Dialynas, G.K.; Vitalini, M.W.; Wallrath, L.L. Linking heterochromatin protein 1 (HP1) to cancer progression. *Mutat. Res.* 2008, 647, 13–20. [CrossRef] [PubMed]

255. Liu, M.; Huang, F.; Zhang, D.; Ju, J.; Wu, X.B.; Wang, Y.; Wu, Y.; Nie, M.; Li, Z.; Ma, C.; et al. Heterochromatin protein HP1γ promotes colorectal cancer progression and is regulated by miR-30a. *Cancer Res.* 2015, 75, 4593–4604. [CrossRef] [PubMed]

256. Zhang, H.; Yan, T.; Liu, Z.; Wang, J.; Lu, Y.; Li, D.; Liang, W. MicroRNA-137 is negatively associated with clinical outcome and regulates tumor development through EZH2 in cervical cancer. *J. Cell Biochem.* 2018, 119, 938–947. [CrossRef] [PubMed]

257. Takata, A.; Otsuka, M.; Yoshikawa, T.; Kishikawa, T.; Hikiba, Y.; Obi, S.; Goto, T.; Kang, Y.J.; Maeda, S.; Yoshida, H.; et al. MicroRNA-140 acts as a liver tumor suppressor by controlling NF-κB activity by directly targeting DNA methyltransferase 1 (DNMT1) expression. *Hepatology* 2013, 57, 162–170. [CrossRef] [PubMed]

258. Song, B.; Wang, Y.; Xi, Y.; Kudo, K.; Bruheim, S.; Botchkina, G.I.; Gavin, E.; Wan, Y.; Formentini, A.; Kornmann, M.; et al. Mechanism of chemoresistance mediated by miR-140 in human osteosarcoma and colon cancer cells. *Oncogene* 2009, 28, 4065–4074. [CrossRef] [PubMed]

259. Ng, E.K.; Tsang, W.P.; Ng, S.S.; Jin, H.C.; Yu, J.; Li, J.J.; Rocken, C.; Ebert, M.P.; Kwok, T.T.; Sung, J.J. MicroRNA-143 targets DNA methyltransferases 3a in colorectal cancer. *Br. J. Cancer* 2009, 101, 699–706. [CrossRef] [PubMed]

260. Matsui, M.; Chu, Y.; Zhang, H.; Gagnon, K.T.; Shaikh, S.; Kuchimanchi, S.; Manoharan, M.; Corey, D.R.; Janowski, B.A. Promoter RNA links transcriptional regulation of inflammatory pathway genes. *Nucleic Acids Res.* 2013, 41, 10086–10109. [CrossRef] [PubMed]

261. Zhu, A.; Xia, J.; Zuo, J.; Jin, S.; Hou, H.; Yao, L.; Huang, H.; Han, Z. MicroRNA-148a is silenced by hypermethylation and interacts with DNA methyltransferase 1 in gastric cancer. *Med. Oncol.* 2012, 29, 2701–2709. [CrossRef] [PubMed]

262. Zhang, Z.; Tang, H.; Wang, Z.; Zhang, B.; Liu, W.; Hu, H.; Xiao, L.; Liu, X.; Wang, R.; Li, X.; et al. miR-185 targets the DNA methyltransferases 1 and regulates global DNA methylation in human glioma. *Mol. Cancer* 2011, 10, 124. [CrossRef] [PubMed]

263. Shimono, Y.; Zabala, M.; Cho, R.W.; Lobo, N.; Dalerba, P.; Qian, D.; Diehn, M.; Liu, H.; Panula, S.P.; Chiao, E.; et al. Downregulation of miRNA-200c links breast cancer stem cells with normal stem cells. *Cell* 2009, 138, 592–603. [CrossRef] [PubMed]

264. Bae, H.J.; Jung, K.H.; Eun, J.W.; Shen, Q.; Kim, H.S.; Park, S.J.; Shin, W.C.; Yang, H.D.; Park, W.S.; Lee, J.Y.; et al. MicroRNA-221 governs tumor suppressor hdac6 to potentiate malignant progression of liver cancer. *J. Hepatol.* 2015, 63, 408–419. [CrossRef] [PubMed]

265. Hwang, H.W.; Wentzel, E.A.; Mendell, J.T. A hexanucleotide element directs microRNA nuclear import. *Science* 2007, 315, 97–100. [CrossRef] [PubMed]

266. Kim, D.H.; Villeneuve, L.M.; Morris, K.V.; Rossi, J.J. Argonaute-1 directs siRNA-mediated transcriptional gene silencing in human cells. *Nat. Struct. Mol. Biol.* 2006, 13, 793–797. [CrossRef] [PubMed]

267. Janowski, B.A.; Huffman, K.E.; Schwartz, J.C.; Ram, R.; Nordsell, R.; Shames, D.S.; Minna, J.D.; Corey, D.R. Involvement of AGO1 and AGO2 in mammalian transcriptional silencing. *Nat. Struct. Mol. Biol.* 2006, 13, 787–792. [CrossRef] [PubMed]

268. Huang, V.; Zheng, J.; Qi, Z.; Wang, J.; Place, R.F.; Yu, J.; Li, H.; Li, L.C. Ago1 interacts with RNA polymerase ii and binds to the promoters of actively transcribed genes in human cancer cells. *PLoS Genet.* 2013, 9, e1003821. [CrossRef] [PubMed]

269. Tan, Y.; Zhang, B.; Wu, T.; Skogerbo, G.; Zhu, X.; Guo, X.; He, S.; Chen, R. Transcriptional inhibition of Hoxd4 expression by miRNA-10a in human breast cancer cells. *BMC Mol. Biol.* 2009, 10, 12. [CrossRef] [PubMed]
270. Majid, S.; Dar, A.A.; Saini, S.; Yamamura, S.; Hirata, H.; Tanaka, Y.; Deng, G.; Dahiya, R. MicroRNA-205-directed transcriptional activation of tumor suppressor genes in prostate cancer. *Cancer* 2010, 116, 5637–5649. [CrossRef] [PubMed]

271. Zardo, G.; Ciolfi, A.; Vian, L.; Starnes, L.M.; Billi, M.; Racinicici, S.; Maresca, C.; Fazi, F.; Travaglini, L.; Noguera, N.; et al. Polymers and microRNA-223 regulate human granulopoiesis by transcriptional control of target gene expression. *Blood* 2012, 119, 4034–4046. [CrossRef] [PubMed]

272. Kim, D.H.; Saetrom, P.; Snove, O., Jr.; Rossi, J.J. MicroRNA-directed transcriptional gene silencing in mammalian cells. *Proc. Natl. Acad. Sci. USA* 2008, 105, 16230–16235. [CrossRef] [PubMed]

273. Place, R.F.; Li, L.C.; Pookot, D.; Noonan, E.J.; Dahiya, R. MicroRNA-373 induces expression of genes with complementary promoter sequences. *Proc. Natl. Acad. Sci. USA* 2008, 105, 1608–1613. [CrossRef] [PubMed]

274. Younger, S.T.; Corey, D.R. Transcriptional gene silencing in mammalian cells by miRNA mimics that target gene promoters. *Nucleic Acids Res.* 2011, 39, 5682–5691. [CrossRef] [PubMed]

275. Liu, M.; Roth, A.; Yu, M.; Morris, R.; Bersani, F.; Rivera, M.N.; Lu, J.; Shioda, T.; Vasudevan, S.; Ramaswamy, S.; et al. The IGFL intronic mir-483 selectively enhances transcription from IGFL2 fetal promoters and enhances tumorigenesis. *Genes Dev.* 2013, 27, 2543–2548. [CrossRef] [PubMed]

276. Huang, V.; Place, R.F.; Portnoy, V.; Wang, J.; Qi, Z.; Jia, Z.; Yu, A.; Shuman, M.; Yu, J.; Li, L.C. Upregulation of Cyclin B1 by miRNA and its implications in cancer. *Nucleic Acids Res.* 2012, 40, 1695–1707. [CrossRef] [PubMed]

277. Morris, K.V.; Chan, S.W.; Jacobsen, S.E.; Looney, D.J. Small interfering RNA-induced transcriptional gene silencing in human cells. *Science* 2004, 305, 1289–1292. [CrossRef] [PubMed]

278. Weinberg, M.S.; Villeneuve, L.M.; Elsani, A.; Amarzguioui, M.; Aagaard, L.; Chen, Z.X.; Riggs, A.D.; Rossi, J.J.; Morris, K.V. The antisense strand of small interfering RNAs directs histone methylation and transcriptional gene silencing in human cells. *RNA* 2006, 12, 256–262. [CrossRef] [PubMed]

279. White, R.J. Rna polymerase III transcription and cancer. *Oncogene* 2004, 23, 3208–3216. [CrossRef] [PubMed]

280. Osborne, C.K.; Yochmowitz, M.G.; Knight, W.A., 3rd; McGuire, W.L. The value of estrogen and progesterone receptors in the treatment of breast cancer. *Cancer* 1980, 46, 2884–2888. [CrossRef]

281. Starnes, L.M.; Sorrentino, A.; Pelosi, E.; Ballarino, M.; Morsilli, O.; Biffoni, M.; Santoro, S.; Felli, N.; Castelli, G.; et al. NFI-A directs the fate of hematopoietic progenitors to the erythroid or granulocytic lineage and controls β-globin and G-CSF receptor expression. *Blood* 2009, 114, 1753–1763. [CrossRef] [PubMed]

282. Janowski, B.A.; Younger, S.T.; Hardy, D.B.; Ram, R.; Huffman, K.E.; Corey, D.R. Activating gene expression in mammalian cells with promoter-targeted duplex RNAs. *Nat. Chem. Biol.* 2007, 3, 166–173. [CrossRef] [PubMed]

283. Bjornsson, H.T.; Brown, L.J.; Fallin, M.D.; Rongione, M.A.; Bibikova, M.; Wickham, E.; Fan, J.B.; Feinberg, A.P. Epigenetic specificity of loss of imprinting of the IGF2 gene in wilms tumors. *J. Natl. Cancer Inst.* 2007, 99, 1270–1273. [CrossRef] [PubMed]

284. Jiang, Y.; Qin, Z.; Hu, Z.; Guan, X.; Wang, Y.; He, Y.; Xue, J.; Liu, X.; Chen, J.; Dai, J.; et al. Genetic variation in a hsa-let-7 binding site in RAD52 is associated with breast cancer susceptibility. *Carcinogenesis* 2013, 34, 689–693. [CrossRef] [PubMed]

285. Esteller, M.; Pandolfi, P.P. The epitranscriptome of noncoding RNAs in cancer. *Cancer Discov.* 2017, 7, 359–368. [CrossRef] [PubMed]

286. Jacob, R.; Zander, S.; Gutschner, T. The dark side of the epitranscriptome: Chemical modifications in long non-coding RNAs. *Int. J. Mol. Sci.* 2017, 18, 2387. [CrossRef] [PubMed]

287. Alarcon, C.R.; Lee, H.; Goodarzi, H.; Halberg, N.; Tavazoie, S.F. N6-methyladenosine marks primary microRNAs for processing. *Nature* 2015, 519, 482–485. [CrossRef] [PubMed]

288. Wang, Y.; Xu, X.; Yu, S.; Jeong, K.J.; Zhou, Z.; Han, L.; Tsang, Y.H.; Li, J.; Chen, H.; Mangala, L.S.; et al. Systematic characterization of A-to-I RNA editing hotspots in microRNAs across human cancers. *Genome Res.* 2017, 27, 1112–1125. [CrossRef] [PubMed]

289. Monnier, P.; Martinet, C.; Pontis, J.; Stancheva, I.; Ait-Si-Ali, S.; Dandolo, L. H19 IncRNA controls gene expression of the imprinted gene network by recruiting MBD1. *Proc. Natl. Acad. Sci. USA* 2013, 110, 20693–20698. [CrossRef] [PubMed]

290. Kallen, A.N.; Zhou, X.B.; Xu, J.; Qiao, C.; Ma, J.; Yan, L.; Lu, L.; Liu, C.; Yi, J.S.; Zhang, H.; et al. The imprinted H19 IncRNA antagonizes let-7 microRNAs. *Mol. Cell* 2013, 52, 101–112. [CrossRef] [PubMed]
291. Chiyomaru, T.; Fukuhara, S.; Saini, S.; Majid, S.; Deng, G.; Shahryari, V.; Chang, I.; Tanaka, Y.; Enokida, H.; Nakagawa, M.; et al. Long non-coding rna hotair is targeted and regulated by miR-141 in human cancer cells. *J. Biol. Chem.* 2014, 289, 12550–12565. [CrossRef] [PubMed]

292. Cai, H.; Yao, J.; An, Y.; Chen, X.; Chen, W.; Wu, D.; Luo, B.; Yang, Y.; Jiang, Y.; Sun, D.; et al. LncRNA HOTAIR acts a competing endogenous RNA to control the expression of Notch3 via sponging miR-613 in pancreatic cancer. *Oncotarget* 2017, 8, 32905–32917. [CrossRef] [PubMed]

293. Tsai, M.C.; Manor, O.; Wan, Y.; Mosammaparast, N.; Wang, J.K.; Lan, F.; Shi, Y.; Segal, E.; Chang, H.Y. Long noncoding RNA as modular scaffold of histone modification complexes. *Science* 2010, 329, 689–693. [CrossRef] [PubMed]