Review

MicroRNA-139, an Emerging Gate-Keeper in Various Types of Cancer

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Abstract: Mounting data show that MIR139 is commonly silenced in solid cancer and hematological malignancies. MIR139 acts as a critical tumor suppressor by tuning the cellular response to different types of stress, including DNA damage, and by repressing oncogenic signaling pathways. Recently, novel insights into the mechanism of MIR139 silencing in tumor cells have been described. These include epigenetic silencing, inhibition of POL-II transcriptional activity on gene regulatory elements, enhanced expression of competing RNAs and post-transcriptional regulation by the microprocessor complex. Some of these MIR139-silencing mechanisms have been demonstrated in different types of cancer, suggesting that these are more general oncogenic events. Reactivation of MIR139 expression in tumor cells causes inhibition of tumor cell expansion and induction of cell death by the repression of oncogenic mRNA targets. In this review, we discuss the different aspects of MIR139 as a tumor suppressor gene and give an overview on different transcriptional mechanisms regulating MIR139 in oncogenic stress and across different types of cancer. The novel insights into the expression regulation and the tumor-suppressing activities of MIR139 may pave the way to new treatment options for cancer.

Keywords: MIR139; cancer; tumor suppressor; transcriptional regulation; microRNAs

1. Introduction

MiRNAs are small non-coding RNAs (19–22 nt) and post-transcriptionally regulate the expression of target mRNAs involved in cell proliferation and differentiation, stress responses and the prevention of oncogenesis [1–3]. Almost all primary miRNA transcripts (pri-miRNAs) are transcribed by RNA Polymerase II and commonly contain a 5′ cap and, in most cases, a poly-A tail [4] (for reviews, see [5–8]). The pri-miRNAs form a hairpin structure and are cleaved by the RNase III enzyme DROSHA that is bound to RNA binding protein DiGeorge syndrome chromosome region 8 (DGCR8) into a premature miRNA (pre-miRNA) [9–11]. The pre-miRNA is transported to the cytoplasm by Exportin-5 (XPO5), where the hairpin is cleaved by the RNase III enzyme DICER and stabilized by trans-activation-responsive RNA binding protein (TRBP) [12–16]. Only one of the two miRNA strands, either miRNA-5p or miRNA-3p, is then loaded by the RNA-induced silencing complex (RISC) loading complex (RLC) into RISC [17–21], which consists of Argonaute 2 (AGO2), DICER, TRBP, proteins of the Glycine-Tryptophan protein of 182 kDa (GW182) family, such as trinucleotide repeat-containing gene 6A–6C (TNRC6A–TNRC6C), and the carbon catabolite repressor 4-negative on TATA (CCR4-NOT) complex [22–28]. Nucleotides 2–7 at the 5′ end of the miRNA, the seed region, are critical for target binding specificity on the 3′ UTR of target transcripts [7,23,29]. The activities of miRNAs are highly cell-type- and cellular-state-dependent [30,31]. There is strong evidence for miRNA functions in stress responses [3]. MIR139 is an example of a stress-responsive gene. Silencing of MIR139 is critical for the oncogenic transformation of cells. The role for mir-139 in the diagnosis and prognosis of cancer is described in the following reviews [32,33]. Here, we discuss the
recent findings regarding the transcriptional and post-transcriptional regulation of MIR139 in cellular stress conditions. Furthermore, we discuss some of the major oncogenic targets that are regulated by miR-139.

2. Genomic Localization and Host Gene PDE2A

MIR139, encoding miR-139-5p and miR-139-3p, is a well-conserved miRNA located on human chromosome 11q13.4 in intron-1 of the Phosphodiesterase 2A (PDE2A) gene. PDE2A is an essential cAMP-cGMP hydrolizing enzyme and is a signal transducer in different cellular processes [34–36]. Genomic deletion of Pde2a in mice (B6; 129P2-Pde2A< tm1Dgen>/H; EM: 02366) is embryonically lethal and mutant mice die in utero at embryonic day (E) 15.5 [37]. In addition, despite multiple attempts of our research team, mice with a genomic deletion of the putative Pde2a promoter could not be generated, indicating that Pde2a is essential for survival [38]. In agreement, other investigators have found that Pde2a KO embryos display lethal defects in fetal liver development and hematopoiesis [39]. Livers from Pde2a KO embryos (E14.5) displayed an increased level of cleaved Caspase-3, expressed decreased levels of anti-apoptotic protein BCL2 and contained Annexin-V-positive apoptotic cells compared to heterozygous and wild-type (WT) littermates [39]. In addition, in Pde2a-deficient fetal livers, the development of myeloid and erythroid lineages is impaired [39]. However, the Pde2a deficiency does not affect the colony-forming capacity of myeloid progenitors, indicating that PDE2A is dispensable for the expansion and maturation of hematopoietic progenitors.

Despite a significant correlation between the expression of PDE2A and MIR139 in lung cancer cell lines [40], we and other investigators have shown that miR-139-5p and/or miR-139-3p expression is not correlated to PDE2A expression levels in leukemia [38], gastric [41] and colorectal cancer cells [42]. We have recently shown that MIR139 expression is strongly silenced in MLL-AF9 AML, whereas the expression of Pde2a was not affected [38]. These data indicate that post-transcriptional mechanisms other than splicing and subsequent processing of pri-miR-139 by the microprocessor complex play a role in the stability and processing of miR-139-5p and miR-139-3p. In agreement, a transcriptional start site (TSS) of MIR139 was established on pri-miR-139 by rapid amplification of cDNA ends (5′-RACE) in gastric SGC-7901 cells, which is 2327 base pairs upstream of the pre-miR-139 (Figure 1A) [41]. Together, these data indicate that MIR139 is regulated, at least in part, independently of PDE2A. The different mechanisms involved in transcriptional and post-transcriptional MIR139 regulation are discussed below. An overview of the different in vitro and in vivo models used to study MIR139 in cancer can be found in Table 1.

Table 1. Overview of experimental models used for functional MIR139 investigation in the various types of cancer.

| Experimental Model | Type of Cancer, Cell Types | References |
|--------------------|---------------------------|------------|
| MIR139 KO mice    | Bone marrow, T-cells and colon | [38,43,44] |
| Ercc1 KO mice     | Bone marrow, Fanconi anemia | [45]       |
| Mouse 32D cells   | AML                        | [45]       |
| Mouse MLL-AF9 leukemia and human AML cell lines MOLM-13, THP-1, MV4-11, HL-60, HEL and U937, Kasumi-1, SKNO-1 | MLL-AF9 AML, AML | [38,46] |
| Human AML and CML, AML cell lines NB4, HP-1, KG-1a, OCI-AML3, U937, HL-60 Human T-ALL cell lines HPB-ALL, TALL-1, KOPFK1, Jurkat, CCRF-CEM, Molt16 | Diverse types of leukemia | [47–51] |
| Colon cancer cell lines HT29, SW480, SW620, KM12, SW116, HCT116, HCT-8, HCT-116, LoVo, Caeo2, DLD1, LS180, NCM460, Houlipic and Human colon cancer in NOD/SCID mice | Colon cancer | [42,52–61] |
| Human lung cancer cells, H460, IC11L13, NSCLC cell lines A549, H1299, H1975, HCC827, H1650, H460, SK-MES-1 and SPC-A-1, PM2.5-treated mice | Lung cancer | [40,60–65] |
| Diabetes mouse model, Streptozotocin-injected Kunming mice | Blood cells, liver | [66] |
| Patient-derived glioma stem-like cells, Human glioma cell lines LN229, A172, SHG44, T98G, U87 and U251, BALB/c nude mice | Glioma | [67–69] |
| Primary Human Ovarian cancer, cell lines A2780, SKOV3, OVCAR3 and OYG0 | Ovarian cancer | [70–72] |
| SCC-7901, MKN-45 and AGS | Gastric cancer | [41] |
| SW1990, BxPC-3, PANC-1 and AsPC-1 | Pancreatic cancer | [73] |
| HepG2, PLC/PRF/5, MHCC97L and SM. Human HCC cell lines (SK-Hep-3B, HepG2, HCC-LM3) and MHCC97-HMC-7721 | Liver cancer | [74,75] |
| Cell lines RC-4B/C (CRL-1901) and GH3 (CCL-82.1) | Pituitary adenomas | [76] |
| Cell line SNU46 | Laryngeal squamous cell carcinoma | [77] |
| Human cell lines K1, IHH-4, BCPAP and TCP1 | Papillary thyroid carcinoma | [78] |
Figure 1. Overview of the transcriptional regulation of MIR139. (A) Schematic representation of the PDE2A locus (chr11: 72,605,000–72,644,500) with the promoter (P), transcriptional start site of MIR139 (TSS), the first two exons of PDE2A (E1 and E2), enhancer regions (in blue) and MIR139 (red box). The transcription of PDE2A is indicated by the black arrow. The enhancer regions are critical for MIR139 transcription (red arrows). (B) Schematic overview of the model in which, under cellular stress conditions, p53 binds to the PDE2A promoter and stimulates transcription (red arrow) and processing of pri-miR-139.

3. MIR139 Is Induced by p53-Mediated Cellular Stress Response

The level of miR-139-3p, but not miR-139-5p, is elevated in hematopoietic stem and progenitor cells (HSPCs) of Fanconi anemia patients and in HSPCs of nucleotide excision repair gene Ercc1-deficient mice [45]. Elevated miR-139 levels in these cells are a direct result of interstrand DNA crosslinks (ICLs) and cause apoptosis [45]. In agreement, treatment of normal HSPCs with ICL-inducing agent Mitomycin C induces miR-139-3p expression. This effect is counteracted by increased miR-199 expression in these cells [45]. Blocking of miR-139-3p with antagomirs rescues HSPC expansion in colony assays, demonstrating the relevance of miR-139-3p for ICL-mediated bone marrow failure. The expression of miR-139-3p is undetectable in Fanconi AML cells, suggesting that MIR139 silencing is an oncogenic driver event that allows for the acceptance of high oncogenic stress levels in the affected cells, which ultimately leads to the transformation of pre-leukemic Fanconi myeloid progenitor cells towards AML [45]. We showed that p53 is responsible for ICL-induced bone marrow failure and that loss of p53 drives leukemogenesis in this model [45]. The loss of p53 coincided with the loss of miR-139 expression in Ercc1-deficient leukemia cells. This result suggests that MIR139 expression is regulated by the tumor suppressor p53.

A well-conserved p53-responsive element (p53RE) is mapped at the −28,747 bp position downstream of MIR139 (Figure 1B), which was experimentally confirmed by ChIP experiments with human lung carcinoma cells after p53 induction [52]. Treatment of lung cancer cell lines with Inauhzin-C, a p53-activating compound, induces MIR139 expression only in p53-positive cells, but not in p53 KO cells [52]. In the human colon cell line HT29-tsp53 expressing a temperature-sensitive variant of murine p53 (V135A), miR-139-5p
and miR-139-3p were both rapidly upregulated at the permissive temperature, as well as the expression of PDE2A [53,54]. P53 binds to the promoter of PDE2A (Figure 1B), which may explain the correlation of miR-139 levels with the increased expression of the PDE2A gene. A different study of colorectal cancer presents evidence for differential transcriptional regulation of pri-miR-139 transcripts independent of PDE2A [79]. However, it is likely that one of the mechanisms by which p53 regulates MIR139 expression is via the induction of PDE2A expression. PDE2A is already expressed in the absence of p53, which suggests that p53 may play a role in the processing of intronic pri-miR-139 that occurs after splicing of PDE2A premature mRNA (Figure 1B). The tumor suppressor p53 has been shown to enhance miRNA biogenesis by association with DEAD-Box Helicase-5 (DDX5) in cellular stress responses [80]. Mechanisms other than p53-mediated transcription are involved in the regulation of MIR139 expression, which will be discussed in the next section.

4. MIR139 Expression Is Repressed in Various Types of Cancer

4.1. The Expression of MIR139 Is Frequently Silenced in AML

Acute myeloid leukemia (AML) is a complex disorder of the bone marrow (BM) that results from the aberrant clonal expansion of myeloid progenitors that have acquired genomic aberrations and mutations, which provide a growth advantage and a block of differentiation [81]. In addition, miRNAs are aberrantly expressed in all subtypes of AML [82–84]. We [38,45] and other investigators [46–51] have found that MIR139 is a tumor suppressor gene that is frequently silenced in leukemia, including Fanconi anemia-related leukemia, caused by interstrand crosslink (ICL)-induced DNA damage [45], Breakpoint Cluster Region Protein-Abelson Murine Leukemia Viral Oncogene Homolog 1 (BCR-ABL)-mediated leukemogenesis [49], AML [46,47] and T-cell acute lymphoblastic leukemia [51]. We found that miR-139 expression levels are low in normal HSPCs and induced by DNA damage [45]. We showed that miR-139-3p is not expressed in clinical AML samples. In agreement, analysis of deep sequencing data of AML samples from the Cancer Genome Atlas (TCGA) further indicated that miR-139-3p is not expressed or is expressed at low levels in AML [45]. In addition, miR-139-5p is undetectable in most AML cases, except for a low expression level in AML samples characterized by a M2 FAB classification and t(8;21), in samples with inv-(16) and some cases with various abnormalities (our unpublished data). Furthermore, miR-139-5p is downregulated in different subtypes of AML and in AML cell lines, compared to differentiated myeloid cells, which further supports a role of miR-139-5p as a tumor suppressor [46]. Krowiorz et al. show that miR-139-5p is downregulated in FLT-3 mutants, in NPM1/FLT3 double mutants and in CN AML compared to the average expression of all AML samples tested in the TCGA cohort [47]. In this comparison, miR-139 expression in the t-(9;11) cases was very similar to other subtypes of AML. However, we presented strong evidence that MIR139 is downregulated in AML expressing the MLL-AF9 oncogene compared to normal HSPCs. Together, these data indicate that the tumor suppressor gene MIR139 is commonly silenced in AML.

4.2. The Effect of MIR139 KO on Development and Oncogenesis

To investigate the functions of MIR139 in oncogenesis, we have generated Mir139 knockout (KO) mice [38,43]. We found that C57BL/6 Mir139 KO mice were born at Mendelian ratios, developed normally and had expected HSPC counts and mature hematopoietic cell types in peripheral blood and BM [38,43]. Notably, the expression of Pde2a was not affected in the HSPCs of Mir139 KO mice [38]. A panel of 22 Mir139 KO and 18 Mir139 WT mice were monitored for the development of leukemia and other types of cancer for 2 years. Only one Mir139 KO mouse developed acute leukemia at the age of 89 weeks, suggesting that additional oncogenic driver events are needed for oncogenesis (unpublished data). Clinical data show that acute myeloid leukemia (AML) patients with the lowest miR-139 levels have a poor prognosis [46]. In agreement, we found that Mir139 KO HSPCs gave rise to more and larger colonies when transformed with the MLL-AF9 oncogene in colony-forming unit assays, showing that miR-139-depleted leukemia cells have a growth
Whether MIR139 silencing is a critical early driver of leukemogenesis still needs further investigation.

Mir139 KO mice were also used for the investigation of MIR139 tumor suppressor functions in different types of cancer. For instance, other investigators have found that Mir139 KO mice are highly susceptible to the development of dextran sulfate salt (DSS)-induced colitis and colon cancer [44]. The investigators found that miR-139-5p expression is lost in colorectal cancer tissue over time. The proliferation rate of Mir139 KO tumor cells was enhanced, confirming the growth advantage of Mir139 KO tumor cells. Furthermore, Zhou et al. showed increased expression levels of anti-apoptotic genes Bcl-Xl and Bcl-2 in Mir139 KO cells compared to Mir139 WT tumor cells in colitis-associated colorectal cancer [44]. They found that the expression of Mir139 dampens the expression of phosphorylated MAPK, NF-κB and STAT3, all factors that drive inflammation and colitis-associated oncogenesis [44]. These data demonstrate that MIR139 inactivation is an oncogenic driver event that results in prolonged intracellular stress-induced signaling and the survival of cells.

4.3. MIR139 Is Silenced by POLR2M Downstream of PRC2 in AML

Polycomb group (PcG) proteins have been implicated in the silencing of tumor suppressor genes [85–87]. Mounting evidence shows that MIR139 is silenced by the Polycomb repressive complex-2 (PRC2) in various types of cancer [38,70,73,74]. PRC2 consists of the methyltransferase Enhancer of Zeste Homolog-1/2 (EZH1/2), Embryonic Ectoderm Development (EED), Suppressor of Zeste 12 Homolog (SUZ12) and Retinoblastoma-binding protein-4 (RBBP4) [88,89]. EZH1/2 hypermethylates K27 on Histone-H3 (H3K27), which marks silenced genes [90]. Deregulation of PRC2 contributes to AML pathogenesis [91–93]. We have recently identified POLR2M as a novel downstream mediator of PRC2-induced transcriptional repression of MIR139 by interaction with the TSS and enhancer regions of MIR139 (Figure 2A) [38]. POLR2M (also known as GDOWN1) pauses POL-II-mediated transcription by binding to the POL-II complex [94,95]. Promoter-proximal pausing of POL-II at TSSs has been correlated with H3K27me3 and PcG-silenced genes [96,97]. We have shown that depletion of POLR2M results in the expression of MIR139 and induction of apoptosis of human and mouse MLL-AF9 AML cells [38]. The repressive activity of POLR2M can be reversed by interaction with the multi-subunit protein complex Mediator, which results in the high induction of transcription [95]. Mediator is a transcriptional co-regulator that consists of approximately 30 subunits, including MED4, MED6, MED7, MED8, MED10, MED11, MED14, MED 17, MED21 and MED22, which are essential for Mediator function [98]. Various Mediator subunits are mutated, aberrantly expressed or deregulated in human cancer including leukemia [99,100]. For example, MED12 mutations are found in up to 9% of chronic lymphocytic leukemia (CLL) cases and contribute to the pathogenesis by activating NOTCH signaling [101,102]. CDK8 transiently associates with Mediator and controls its activity [98]. The Mediator complex provides communication between active enhancers and promoters by forming a molecular bridge within actively transcribed genes and interacts with transcription factors, POL-II and elongation factors [103–107]. In addition, Mediator binds to acetylated Histones [108]. For instance, H4K16 acetylation inhibits the interaction of MED5 and MED17 to chromatin [108,109]. Moreover, H3K27 acetylation correlates with high levels of Mediator complex subunits at regular and super enhancers with high POL-II occupancy [79,110,111]. Proteomics studies in yeast revealed that 17 subunits of the Mediator complex are dynamically phosphorylated by an unidentified kinase in response to stress and regulate the expression of stress-induced genes [112] (for review, see [98]). Vice versa, there is evidence that the phosphorylation of transcription factor ELK in response to ERK activation fine-tunes the interaction with Mediator and thereby transcriptional activity [113]. However, how Mediator interacts with other transcription factors to facilitate the transcription of MIR139 remains elusive.
Figure 2. Overview of MIR139 molecular silencing mechanisms. (A) Model of MIR139-silencing mechanism in AML. PRC2 is recruited to the promoter region of PDE2A downstream of MLL-AF9. The host gene PDE2A is expressed at normal levels (black arrow). However, under these conditions, POLR2M is recruited to the enhancer regions and to the TSS of MIR139 (red arrows), which results in transcriptional silencing of MIR139 (red cross). (B) Additional silencing mechanisms of MIR139. Mutant KRAS recruits TCF4-β-CATENIN to the TSS of MIR139, thereby inhibiting transcription. Activated NOTCH1 signaling results in HES1 binding close to the promoter of PDE2A, which causes downregulation of MIR139 expression. NOTCH1 is a validated target of miR-139 (red inhibitor arrow), thereby creating a feed-forward loop. (C) P21 is a central player in the regulation of pri-miR-139 processing. Activation of P21 stimulates the processing of tumor suppressor pri-miRNAs, including pri-miR-139. However, when P21 is repressed by the oncogene MYC (red inhibitor arrow), this results in further stimulation of the microprocessor that is bound by NPM1 and DHX9 to preferentially process oncogenic miRNAs. KRAS-induced MYC transcription activates KMAT expression, which stabilizes NPM1-DHX9 complex, thereby contributing to the enhanced processing of oncogenic miRNAs.

4.4. Oncogene Mediated MIR139 Silencing

Multiple well-known oncogenes silence the expression of MIR139 in cancer. For instance, NOTCH1 signaling suppresses MIR139 expression via the transcriptional repressor
HES1, which binds to the E-box site at position +644 bp in the \textit{PDE2A} gene in glioma cells (Figure 2B) [67]. In this study, the authors show that miR-139 modulates stemness by inhibiting Wnt/\(\beta\)-catenin signaling, which is a hallmark of cancer [67]. As NOTCH1 is a direct target of \textit{miR-139} (discussed below), this creates a feedback mechanism that fine-tunes NOTCH1 signaling (Figure 2B).

In colorectal cancer, \textit{MIR139} is strongly downregulated in KRAS mutant cells compared to KRASWT cells [55]. In this study, the investigators found that the expression of \textit{MIR139} is controlled by two TCF4 sites flanking the TSS of \textit{MIR139} (Figure 2B). TCF4 binds to \(\beta\)-catenin and transcriptionally silences target genes. Furthermore, the investigators found that, in KRAS mutant cells, the \textit{MIR139} expression is suppressed in a WNT3A-activated \(\beta\)-catenin-TCF4 complex-dependent manner [55]. The expression of \textit{MIR139} is inhibited in KRASWT-overexpressing lung tumor cells in a very different way [62]. KRAS overexpression induces the expression of the long non-coding RNA KRAS-Induced-Metastasis-Associated-Transcript 1 (\textit{KMAT1}) by activation of MYC-mediated transcription. \textit{KMAT1} induces the processing of oncogenic miRNAs, including \textit{miR-17}, \textit{miR-18} and \textit{miR-27}, through stabilization of the RNA-binding proteins DExH-Box Helicase 9 (DHX9) and Nucleophosmin-1 (NPM1). NPM1 binds to DHX9, which is part of the microprocessor complex, in a RNA-dependent manner and is involved in the selection of pri-miRNAs for processing [62]. On the other hand, MYC silences CDKN1A (P21), which is a component of the microprocessor complex, by interaction with DROSHA in specific conditions. The authors show that pri-miRNA transcripts of tumor-suppressing miRNAs, including \textit{pri-miR-139}, are not processed when P21 is transcriptionally silenced by MYC [62]. When P21 is overexpressed, it antagonizes the stimulating effects of DHX9 and NPM1 on the biogenesis of oncogenic miRNAs, whereas the expression of a subset of tumor-suppressing miRNAs, including \textit{pri-miR-139}, is enhanced. P21 interacts directly with the microprocessor complex and with a subset of pri-miRNAs. In addition, the authors showed that the levels of \textit{pre-miR-139} and \textit{miR-139} were both dependent on P21 expression, whereas the expression of \textit{pri-miR-139} was not [62]. This indicates that P21 is involved in the selective processing of \textit{pri-miR-139} by the microprocessor complex (Figure 2C). The abovementioned \textit{MIR139} regulatory genes, including KRAS, MYC, NOTCH1 and NPM1, are frequently mutated in leukemia. However, whether the above-described aberrant \textit{MIR139} mechanisms play a direct role in leukemogenesis is unknown and needs further investigation.

4.5. Post-Transcriptional Regulation of MIR139

\textit{Mir139} expression is regulated by a post-transcriptional mechanism. The first indication for the post-transcriptional regulation of \textit{pre-miR-139} was found in colorectal cancer samples from patients in which \textit{miR-139} was detected at reduced levels, whereas the levels of \textit{pre-miR-139} were similar to the expression in normal tissue [79]. These data suggest that DICER or specific RNA-binding proteins, which interact with \textit{pre-miR-139} and regulate further processing, are deregulated in colorectal cancer. In addition, our data in MLL-AF9 leukemia, where \textit{Pde2a} is normally expressed and spliced but \textit{miR-139} levels are strongly decreased, can only be explained by reduced \textit{pre-miR-139} stability and/or processing. The following mechanisms may explain this phenomenon. In MLL-AF9 leukemia, P21 is silenced by Inhibitor of DNA binding 1 (ID1), which is critical for MLL-AF9 leukemogenesis [56,114]. According to the role for P21 in the selection of \textit{pre-miR-139} for further processing as described above, the downregulation of P21 in MLL-AF9 AML may largely explain the low mature \textit{miR-139} levels, but this still needs proper validation.

We found that the enhancer regions in intron-1 of \textit{Pde2a} and upstream of \textit{Mir139} are critical for normal \textit{Mir139} expression levels [38]. Thus, our results indicate that other still unknown mechanisms interact with the enhancer regions and are involved in \textit{Mir139} expression regulation. DROSHA and DGCR8, associated with transcriptional regulators, are thought to be recruited co-transcriptionally and process pri-miRNAs during transcription [115]. Recent data present evidence that super enhancers boost the transcription and
DROSHA/DGCR8-mediated processing of a subset of cell-specific miRNAs [116]. Whether these interactions exist at the enhancers of MIR139 is currently under investigation.

Downregulation of mir-139 activities in tumors may be due to the overexpression of competing target RNAs, the so-called sponge activity. For instance, LINCO00324 overexpression acts as a miR-139 sponge, thereby releasing Insulin-like Growth Factor-1 Receptor (IGF1R) from miR-139 regulation and increasing the IGF1R protein expression in non-small-cell lung cancer [63]. In addition, the 3′-UTR of LNCRNA PCAT6 competes with the 3′-UTR of BRD4 transcripts for miR-139 binding and downregulates miR-139 expression when overexpressed in pituitary adenomas [76]. The levels of mir-139 may also be downregulated by circular RNAs with miR-139 sponge activities. To date, only a few circular RNAs have been reported in the regulation of MIR139. Strikingly, the circular RNAs that are described to have sponge activity against miR-139 contain only one binding site for either miR-139-5p or miR-139-3p. To be able to compete with other mRNAs containing sites for miR-139 in their 3′-UTR, the expression of functional circular RNAs should be at least higher than the target mRNA. For instance, Circ-0038718 consists of exons 2 and 3 derived from the gene encoding the Interleukin-4 Receptor (IL4R) and is highly overexpressed in hepatocellular carcinoma [75]. Circ-0038718 contains one miR-139-3p binding site and interacts with AGO2-loaded miR-139-3p, thereby competing for oncogenic miR-139-3p mRNA targets. Furthermore, CircKIF4A acts as a sponge for miR-139-3p in glioma, thereby activating oncogenic WNT3A signaling [68]. In addition, Circ-000218 controls miR-139-3p levels in a very similar way in laryngeal and colorectal cancer [57,77]. CircBACH2 is a circular RNA that is expressed at elevated levels in papillary thyroid carcinoma and downregulates the expression of miR-139-5p [78]. How the interaction of AGO2-loaded miR-139 with circular RNA causes degradation of the miRNA is unknown. However, mechanisms by which miRNA-target miRNAs degrade miRNAs have been described [117]. Furthermore, how the increased expression of non-coding RNA or circular RNA, containing only one interaction site, competes with all other miR-139 targets in such a way that it efficiently represses the activity of miR-139 on other target mRNAs is not well understood and suggests a specific RNA-mediated miRNA degradation pathway. An overview of miR-139 regulators is given in Table 2.

| Regulator of MIR139 | Activator/Repressor | Type of Cells | miR-139 Targets | References |
|---------------------|---------------------|---------------|----------------|------------|
| PDE2A (host gene)   | Activator           | Lung cancer cell lines | EIF4G2, BTG3 | [40]       |
| Epigenetic          | Repressor           | AML           | EIF4G2, HPGD, PTPRT | [38,70,73,74] |
| PRC2                | Repressor           | AML           | EIF4G2, HPGD, PTPRT | [38]       |
| POLR2M              | Repressor           | HSPCs Fanconi anemia | ELAVL1, PDE4D, P53 targets | [45,52]  |
| PS3                 | Activator           | Colon cancer  | EIF4G2, HPGD, PTPRT | [38,70,73,74] |
| PS3                 | Activator           | Colon cancer  | EIF4G2, HPGD, PTPRT | [38]       |
| NOTCH1/HES1         | Repressor           | Glioma        | EIF4G2, HPGD, PTPRT | [38,70,73,74] |
| TCF4                | Repressor           | Colorectal cancer | EIF4G2, HPGD, PTPRT | [38]       |
| KRAS/MYC/P21        | Repressor           | Lung cancer   | EIF4G2, HPGD, PTPRT | [38]       |
| LINC00324           | Repressors          | Non-small-cell lung cancer | IGF1R, BRD4 | [63,76]    |
| PCAT6               | Repressors          | Pituitary adenomas | IGF1R, BRD4 | [63,76]    |
| Circ-0038718        | Repressors          | Hepatocellular carcinoma | IGF1R, BRD4 | [63,76]    |
| CircKIF4A           | Repressors          | Glioma        | IGF1R, BRD4 | [63,76]    |
| Circ-000218         | Repressors          | Laryngeal/Colorectal cancer | IGF1R, BRD4 | [63,76]    |
| CircBACH2           | Repressors          | Papillary thyroid carcinoma | IGF1R, BRD4 | [63,76]    |
| SNHG3               | Repressors          | Ovarian cancer | IGF1R, BRD4 | [63,76]    |

Table 2. Overview of Activators and Repressors of MIR139 Expression.
5. MIR139 Targets Involved in Oncogenesis

Overexpression of MIR139 in Kasumi-1 and SKNO-1 cells, both AML cell lines with t(8;21), and mRNA expression profiling revealed EIF4G2 as one of the most downregulated transcripts [46]. According to Targetscan, the database that lists predicted miRNA targets [118], EIF4G2 has one well-conserved 8-mer site for miR-139-5p in the 3′-UTR. This miR-139-mediated silencing of EIF4G2 was confirmed on the protein level in Kasumi-1 cells [46]. ShRNA-mediated silencing, at least in part, phenocopied the effects of miR-139 expression on the viability and proliferation of Kasumi-1 cells [46]. EIF4G2 mRNA lacking miR-139 binding sites in the 3′-UTR rescued the anti-proliferative and apoptotic effects of miR-139 overexpression in Kasumi cells. We recently confirmed Eif4g2 as a critical target of miR-139 in mouse MLL-AF9 AML [38], suggesting that Eif4g2 is a more common miR-139 target in leukemia. In addition, EIF4G2 has been recently identified as a miR-139 target in other types of cancer, including glioblastoma and colorectal cancer [119,120]. EIF4G2 is important for protein synthesis [121]. Accordingly, MIR139 overexpression resulted in reduced overall protein expression, which may explain the inhibitory effects of miR-139 expression on tumor cell proliferation and survival [46].

There is mounting evidence that miR-139-5p targets NOTCH1 in different cell types, thereby preventing aberrant NOTCH1 signaling and oncogenic transformation. According to Targetscan, NOTCH1 contains one broadly conserved site for miR-139-5p in the 3′-UTR. This explains that, in cancers with silenced MIR139 expression, the expression of NOTCH1 is increased. Forced expression of miR-139-5p causes the downregulation of NOTCH1 via direct binding to the 3′-UTR in colorectal cancer and inhibits the migration and invasion of tumor cells [58,59]. Increased levels of RP11-59H7.3, a long non-coding RNA that is aberrantly expressed and correlates with poor prognosis of colorectal cancer, compete with NOTCH1 for miR-139 binding, thereby enhancing NOTCH1 oncogenic functions [60]. Another tumor-suppressing activity of miR-139-5p via NOTCH1 repression in colorectal cancer is the prevention of CD44+/CD133+–associated multidrug resistance [61]. In ovarian cancer, overexpression of the IncRNA SNHG3 competes for miR-139-5p binding, thereby increasing NOTCH1 levels [71]. The authors showed that reduced miR-139-5p expression enhanced the proliferation and migration of ovarian cancer cells. In addition, downregulation of Notch-1 expression and reduced blood glucose levels were observed as a result of oxidative-stress-induced miR-139 expression in the liver cells of diabetic mice [66]. Furthermore, reduced miR-139 levels as a consequence of chronic fine particulate matter (PM 2.5)-induced cellular damage in the lung cause Notch-1 upregulation and Epithelial–Mesenchymal Transition (EMT) in mice [64]. Vey similar tumor-suppressing activities of miR-139 on NOTCH1 levels, tumor cell growth, EMT and metastasis have been described in a mouse model for glioma [69]. NOTCH1 signaling is frequently deregulated in various types of leukemia [122–124]. Whether MIR139 plays a major role in NOTCH1 signaling during leukemia development remains to be investigated.

Other miR-139 targets that are described in leukemia and some other types of cancer are BTG3 [46], the RNA-binding protein ELAVL1 [45,65,72], Tetraspanin-3 (TSPAN3), MAX Network Transcriptional Repressor (MNT) [48], 15-Hydroxyprostaglandin Dehydrogenase (HPGD) and Protein Tyrosine phosphatase Receptor Type-T (PTPRT) [38]. Although knockout and knockdown studies show the relevance of these downregulated targets for miR-139-mediated functions as a tumor suppressor, more in-depth studies are needed for the understanding of their oncogenic role in leukemia.

6. Conclusions

Mounting data show that the targeting of miRNAs and their controlled pathways may be a successful approach for anti-cancer treatment [82,125,126]. It becomes increasingly evident that MIR139 is a critical tumor suppressor gene in different types of cancer and that the deregulation of MIR139 transcription, processing or targeting activity inhibits its tumor-suppressive activities. Although the mechanism of MIR139 silencing in various
types of cancer is not fully unraveled, targeting MIR139 to reactivate its expression is a promising avenue for novel targeted therapies.

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