

## Review Article

# Genetic Networks Lead and Follow Tumor Development: MicroRNA Regulation of Cell Cycle and Apoptosis in the p53 Pathways

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During the past ten years, microRNAs (miRNAs) have been shown to play a more significant role in the formation and progression of cancer diseases than previously thought. With an increase in reports about the dysregulation of miRNAs in diverse tumor types, it becomes more obvious that classic tumor-suppressive molecules enter deep into the world of miRNAs. Recently, it has been demonstrated that a typical tumor suppressor p53, known as the guardian of the genome, regulates some kinds of miRNAs to contribute to tumor suppression by the induction of cell-cycle arrest and apoptosis. Meanwhile, miRNAs directly/indirectly control the expression level and activity of p53 to fine-tune its functions or to render p53 inactive, indicating that the interplay between p53 and miRNA is overly complicated. The findings, along with current studies, will underline the continuing importance of understanding this interlocking control system for future therapeutic strategies in cancer treatment and prevention.

## 1. Introduction

Cancer is commonly an age-related disease triggered by the accumulation of genomic mutations that lead to the dysregulation of tumor-suppressive genes and/or protooncogenes. For example, the functions of *TP53* (tumor-suppressive gene) and *c-MYC* (oncogene) have been extensively investigated, and their critical roles in complexly regulating tumorigenesis, including cell-cycle progression/arrest, apoptosis, senescence, and energy metabolism, have been uncovered [1–4]. Specifically, the significance of tumor suppressor p53 has been suggested by the fact that DNA mutation or loss of *TP53* is observed in many types (over 50%) of human tumors and by the possibility that the dysfunctions affect the p53 signaling network in over 80% of tumors [5, 6]. As a transcriptional activator, the p53 protein induces various kinds of tumor-suppressive genes, such as *p21* ( $G_1/S$ -arrest), *I4-3-3 $\sigma$*  ( $G_2/M$ -arrest), and *PUMA* (apoptosis) [7–10]. p53 has also been reported to negatively regulate specific proteins: for instance, the p53-mediated repression of the cell-cycle regulators, such

as cyclin-dependent kinase 4 (CDK4) and cyclin E2, may lead to cell-cycle arrest [10, 11]. These prove the pivotal roles of p53 as a cellular gatekeeper.

Recently, it has been realized that small noncoding RNAs known as microRNAs (miRNAs) contribute to many human diseases, including cancers; that a general downregulation of miRNAs is observed in cancers as compared with normal tissues; and that miRNA expression profiles can be used to classify poorly differentiated tumors [12]. In addition, some kinds of miRNAs are shown to be connected to a well-studied tumor-suppressive or oncogenic network [13]. It remains to be investigated how miRNAs are regulated by transcription factors, but it is suggested that p53 enters the miRNA world to control the expression patterns of some miRNAs and promote cell-cycle arrest and apoptosis through the miRNA effector pathway. *miR-34a* is one of the representative miRNAs under the direct control of p53, and this upregulation induces cell-cycle arrest and apoptosis [14–18]. Moreover, there are many studies about miRNA effects on cell proliferation and survival in cancers, with attention

given to the interplay between p53 and the miRNA network. In this review, we will focus on the regulation of the cancer cell cycle and apoptosis by miRNA linked with the p53 axis. We will also summarize the key miRNAs concerned with the cell cycle and apoptosis in cancers.

## 2. miRNA Discovery, Biogenesis, and Mechanism

The first miRNAs discovered were *lin-4* and *let-7*, both of which are the key regulators in the pathway controlling the timing of postembryonic development in *Caenorhabditis elegans* [19–21]. After this discovery, miRNAs have been identified in diverse organisms, such as worms, flies, mice, humans, and plants. Several miRNAs are conserved among different species, indicating that these miRNAs might have important functions and modulate gene expression. Currently, in humans, over 2,000 microRNAs have been identified or predicted based on the miRBase database (<http://www.mirbase.org/>). Computational analyses suggest that about 5,300 genes contain miRNA target sites: ~30% of human genes might be subject to the translational regulation of miRNAs [22, 23].

miRNAs are initially transcribed by RNA polymerase II/III into primary transcripts (pri-miRNAs) [24, 25], which are processed by the complex of RNase III enzyme, Drosha, and its partner DGCR8 [26]. The pri-miRNAs are converted into ~65 nucleotides (nt) of a stem-loop precursor (pre-miRNA) [27]. These pre-miRNAs are transported to cytoplasm by Exportin-5/Ran-GTP and processed by another RNase III, Dicer, to generate a double-strand RNA of about 19–25 nt in length [28–30]. One strand of miRNA gives rise to the mature miRNA, which is incorporated into the RNA-induced silencing complex (RISC). The miRNAs guide the RISC complex to the 3'-untranslated region (3'-UTR) of the target mRNAs, leading to the translational repression or destabilization of the mRNA [31, 32]. In animal systems, the recognition of target mRNA usually requires the "seed" sequence, which is 2–8 nt from the 5'-end of the miRNA [22, 33]. Unlike with plant systems, because of this imperfect complementarity, there are extensive base-pairings to the sequence of mRNAs, and this makes it more complicated to predict miRNA targets and study miRNA biology. Recently, it has been shown that animal miRNAs can induce the degradation of target mRNAs (mRNA degradation and decay) besides translational repression: inhibition of translation elongation; cotranslational protein degradation; competition for the cap structure; and inhibition of ribosomal subunit joining [34–37]. However, the exact order and impact of these events still need to be investigated further.

## 3. p53 Transactivation Function in a Relationship with Tumorigenesis

Based on numerous studies at both structural and functional levels, p53 is known as a key player in genome stability and tumor suppression. In an unstressed condition, the expression level of p53 is kept low by the activity of an E3

ubiquitin ligase, mouse double minute 2 (MDM2) [38–40]. Under stressed conditions, p53 is activated in response to diverse intrinsic and extrinsic signals, such as DNA damage, oncogene activation, and hypoxia. As a sequence-specific transcription factor, the activated p53 acts directly on cancer-associated pathways to suppress tumor progression by modulating cell-cycle arrest, senescence, apoptosis, angiogenesis, or invasion and metastasis [41–43]. There are also demonstrations showing that p53 is involved in the regulation of DNA repair, oxidative stress, energy metabolism, and differentiation [44–48]. The approach of genome-wide analyses has identified many p53-binding sites and p53-regulated genes which are related to tumorigenesis and various stress signals [49, 50]. Recent works have highlighted that p53 directly induces some specific miRNAs which function as tumor suppressors through a novel transcriptional mechanism. Now, although unknown aspects of the mechanism still need to be investigated, the cooperative contribution of p53 and miRNAs has been shown to be more important for tumor formation and development.

## 4. miRNA Network with p53: Cell Cycle and Apoptosis

**4.1. miR-34 Family.** In 2007, several groups reported that the *miR-34* family members are direct p53 targets and that their expression level is strongly upregulated by genotoxic stress in a p53-dependent manner, inducing cell-cycle arrest and apoptosis [14–16, 51, 52]. In mammals, the *miR-34* family is composed of *miR-34a*, *miR-34b*, and *miR-34c*, which are encoded by two different genes in the *miR-34a* and *miR-34-b/c* loci. With the overexpression of the *miR-34* family in certain kinds of cell lines, microarray analyses unveiled hundreds of putative candidate target genes of *miR-34s* [15, 16, 18]. Actually, ectopic expression of *miR-34s* promotes cell-cycle arrest in the G<sub>1</sub> phase, senescence, and apoptosis by directly repressing CDK4, CDK6, cyclin E2, E2F3, MYC, and B-cell CLL/lymphoma 2 (BCL-2) [53]. Note that the triggering event of cell-cycle arrest or apoptosis by *miR-34s* depends on the cell type and context, and the expression level of *miR-34s* would affect the decision to proceed [15, 17, 54]. As seen in the decreased expression of *miR-34s* in several types of malignant cancers, the *miR-34* family powerfully prevents tumorigenesis in general.

In addition to the *miR-34* family, p53 is also engaged in the direct regulation of the transcriptional expression of additional miRNAs, such as *miR-107*, *miR-143/145*, *miR-192/194/215*, *miR-200c/141*, the *let-7* family, and the *miR-17-92* cluster (Figure 1 and Table 1).

**4.2. miR-107.** *miR-107* is encoded within an intron of pantothenate kinase 1 (*PANK1*), and *miR-107* and its host gene are directly activated by p53 under hypoxia condition or with the treatment of DNA damage agents [55, 56]. Hypoxia induces angiogenesis, which is essential for solid tumors to grow in severe environments. *miR-107* inhibits hypoxia signaling and antiangiogenesis by repressing the expression of hypoxia inducible factor-1 $\beta$  (HIF-1 $\beta$ ), which interacts with HIF-1 $\alpha$  to form the HIF-1 transcription factor complex [55].

TABLE 1: Key microRNAs regulated by p53.

miRNA	Genomic location	Cancer type	Target	Phenotype	References
<i>miR-34s</i>	1p36 and 11q23	Colon cancer, neuroblastoma, pancreatic cancer, CLL, NSCLC, OSCC, breast cancer, bladder cancer, kidney cancer, melanoma	CDK4, CDK6, cyclin E2, E2F3, MYC BCL-2	Cell-cycle arrest apoptosis	[14–16, 18, 51, 53, 54]
<i>miR-107</i>	10q23	Colon cancer, breast cancer	CDK6, P130	Cell-cycle arrest	[55–57]
<i>miR-145</i>	5q23	Colon cancer, breast cancer, MDS, prostate cancer	MYC, E2F3, cyclin D2, CDK4, CDK6	Cell-cycle arrest	[58–61]
<i>miR-192/215</i>	1q41 and 11q13	Colon cancer, lung cancer, multiple myeloma, renal cancer	CDC7, MAD2L1	Cell-cycle arrest	[66–69]
<i>miR-200c</i>	12p13	Breast cancer, ovarian cancer	FAP-1	Apoptosis	[71, 81]
<i>let-7</i>	Multiple locations (11 copies)	Lung cancer, colon cancer, ovarian cancer, breast cancer, lymphoma	CDK6, CDC25A, cyclin D, CDC34, MYC, E2F1, E2F3	Cell-cycle arrest	[61, 83–90]
<i>miR-15a/16-1</i>	13q14	B-CLL, pituitary adenomas, gastric cancer, NSCLC, prostate cancer, ovarian cancer, pancreatic cancer	CDK1, CDK2, CDK6, cyclin D1, D3, E1 BCL-2	Cell-cycle arrest apoptosis	[98–112]

CLL: chronic lymphocytic leukemia; NSCLC: non-small cell lung cancer; OSCC: oral squamous cell carcinoma; MDS: myelodysplastic syndromes; B-CLL: B-cell chronic lymphocytic leukemia.

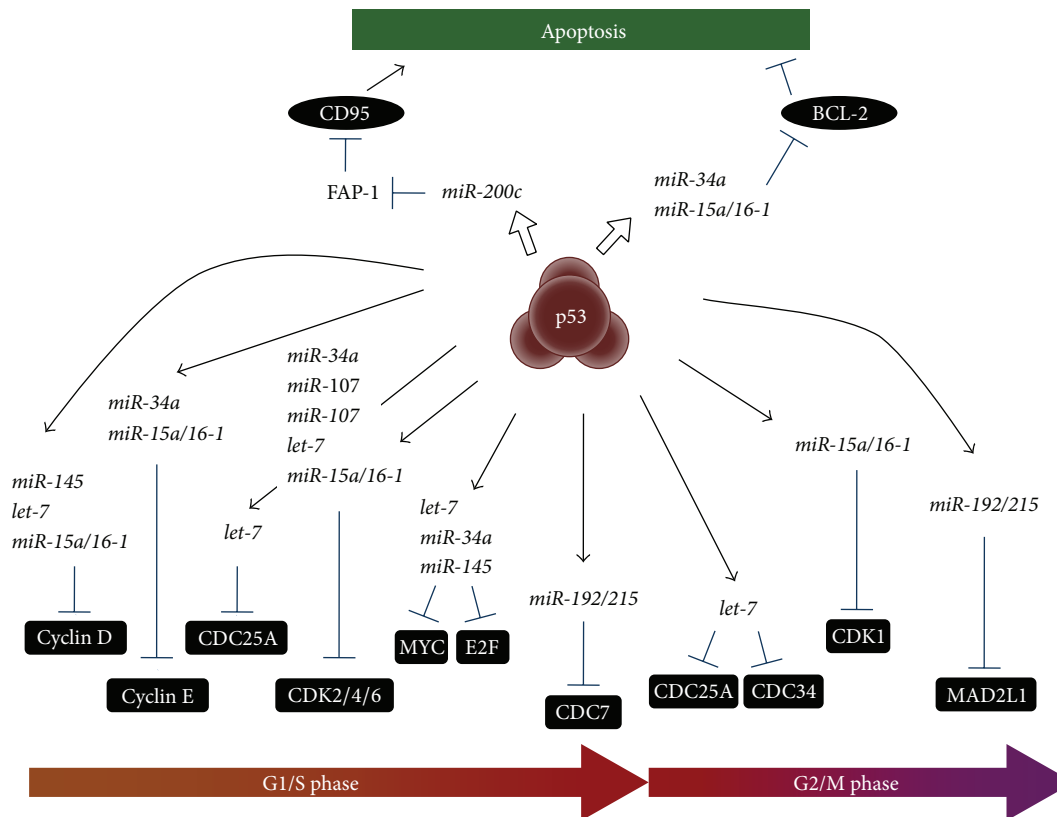


FIGURE 1: p53-induced miRNAs control cell cycle and cell survival. p53 directly induces many kinds of miRNAs, which repress cell-cycle regulators and/or antiapoptotic proteins and contribute to cell-cycle arrest and apoptosis. The miRNAs regulating apoptosis are shown in the top part of this figure, and the miRNAs regulating the cell cycle are at the bottom.

Furthermore, *miR-107* promotes cell-cycle arrest in the G<sub>1</sub>/S phase via targeting the cell-cycle activator CDK6 and the antimitogenic p130 [56]. Nevertheless, *miR-107* has another aspect for directly targeting *DICER1* mRNA and the high level of *miR-107* might affect the production and function of p53-induced miRNAs [57].

**4.3. *miR-145*.** It has been reported that the expression of *miR-145* is frequently decreased in colon tumors, breast and prostate cancers and that the chromosomal region (chromosome 5 [5q32-33] within a 4.09 kb region) is deleted in myelodysplastic syndrome, suggesting *miR-145* acts as a tumor suppressor [58–61]. The expression of *miR-145* is transcriptionally induced by p53, and *miR-145* downregulates c-MYC, E2F3, cyclin D2, CDK4, and CDK6 and leads to G<sub>1</sub> cell-cycle arrest [62, 63].

Recently, it has been found that *miR-145* contains several CpG sites in its promoter region and that the expression of *miR-145* is affected by epigenetic events such as DNA methylation [60]. The CpG regions are located adjacent to p53 response element upstream of *miR-145*, and DNA hypermethylation inhibits p53 from binding to *miR-145*. In addition to this miRNA, it has been reported that *miR-34a*, *miR-124a*, and *miR-127* are downregulated by DNA methylation [64].

**4.4. *miR-192/215*.** *miR-192* and *miR-215* share a similar seed sequence and are composed of two clusters: the *miR-215/miR-194-1* cluster on chromosome 1 (1q41) and the *miR-192/miR-194-2* cluster on chromosome 11 (11q13.1) [65]. *miR-192* and *miR-215* are downregulated in colon cancers, lung cancers, multiple myeloma, and renal cancers [66–69]. Some studies have suggested that these miRNAs are also under the control of p53 and can induce p21 expression and cell-cycle arrest in a partially p53-dependent manner [66, 70]. Gene expression analyses indicated that *miR-192* and *miR-215* target a number of transcripts that regulate DNA synthesis and the G<sub>1</sub> and G<sub>2</sub> cell-cycle checkpoints, such as CDC7 and MAD2L1 [70]. Therefore, *miR-192/215* functions as a tumor suppressor contributing to the G<sub>1</sub> and G<sub>2</sub>/M cell-cycle arrest.

**4.5. *miR-200c*.** It is well known that p53 acts as an important regulator in modulating epithelial-mesenchymal transition (EMT) that is implicated in tumor progression, metastasis, and the correlation of poor patient prognosis [71, 72]. The p53-induced *miR-200c* represses EMT by targeting the E-cadherin transcriptional repressors ZEB1 and ZEB2, Krüppel-like factor 4 (KLF4), and the polycomb repressor BMI1, all of which are involved in the maintenance of stemness [73–80]. Moreover, *miR-200c* contributes to the induction of apoptosis in cancer cells via the apoptosis-inducing receptor CD95 by targeting the apoptosis-inhibitor FAS-associated phosphatase 1 (FAP-1) [81].

**4.6. *let-7a* and *let-7b*.** *let-7* is known to be important for the regulation of development and is evolutionally conserved across bilaterian phylogeny [82]. In humans, some *let-7* gene clusters are located in fragile regions involved in cancers [61]. In lung cancers, it has been reported that the downregulated

expression of *let-7* members is correlated with poor prognosis [83, 84]. Recent works suggested that *let-7a* and *let-7b* expression is dependent on p53 in response to genotoxic stress and *let-7* miRNAs target CDK6, CDC25A, cyclin D, CDC34, and MYC [85–89]. On the other hand, *let-7a-d* and *let-7i* are direct targets of E2F1 and E2F3 during the G<sub>1</sub>/S transition and are repressed in E2F1/3-null cells [90]. The *let-7* family plays multiple roles in the regulation of the cell cycle and goes a long way toward suppressing tumor progression.

**4.7. *miR-17-92 Cluster*.** The *miR-17-92* cluster consists of *miR-17-5p*, *miR-17-3p*, *miR-18a*, *miR-19a*, *miR-20a*, *miR-19b*, and *miR-92-1*. Some of these are known to be oncogenic, as suggested in the research showing that the cluster is upregulated in human B-cell lymphoma and amplified in malignant lymphoma [91, 92].

Different from the miRNAs mentioned above, *miR-17-92* miRNAs are more or less repressed transcriptionally by p53 under hypoxia, which leads to the p53-mediated apoptosis [93]. The p53-binding site overlaps with the TATA box of the *miR-17-92* promoter region, and p53 prevents the TATA-binding protein (TBP) transcription factor from binding to the site during hypoxic conditions. Moreover, *miR-17-92* is transcriptionally regulated by c-Myc [94]. Although c-Myc is repressed by p53 activation under some stress conditions, the repression of *miR-17-92* is not dependent on c-MYC but on p53 under hypoxia [93, 95].

Note that some members of *miR-17-92* are likely to function as tumor suppressors in different cancers. For example, in breast cancer, *miR-17-5p* represses the expression of the nuclear receptor coactivator amplified in breast cancer 1 (*AIB1*) that enhances the transcription activity of E2F1 to promote the cell proliferation of breast cancer cells [96]. A recent study showed that *miR-17-3p* reduces tumor growth by targeting MDM2 in glioblastoma cells [97].

**4.8. *miR-15a/miR-16-1*.** *miR-15a* and *miR-16-1* were identified to be deleted and/or downregulated in approximately 68% of B-cell chronic lymphocytic leukemia (B-CLL) [98], as is the case in pituitary adenomas [99], gastric cancer cells [100], prostate cancer [101–104], non-small cell lung cancer [105, 106], ovarian cancer [107], and pancreatic cancer [108], which indicates their important functions for tumor formation. The miRNAs are encoded by an intron of a long noncoding RNA gene, deleted in lymphocytic leukemia 2 (*DLEU2*), and *DLEU2* (*miR-15a/miR-16-1*) was shown to be transactivated by p53 [109]. In addition, p53 regulates the expression level of precursor and mature *miR-15a* and *miR-16-1* as well as *miR-143* and *miR-145* [110]. It has been reported that *miR-15a/miR-16-1* negatively regulates the antiapoptotic protein BCL-2 and the cell-cycle regulators, such as CDK1, CDK2, and CDK6, and cyclins D1, D3, and E1 [102, 110–112].

## 5. miRNAs Regulating Negative Regulators of p53

It has been shown that MDM2 negatively controls the stability and transcription activity of p53, which attenuates the tumor-suppressive functions of p53 [40]. Actually, overexpression



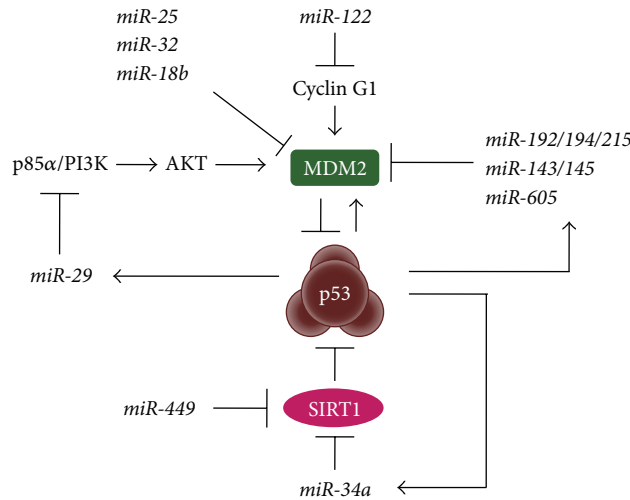


FIGURE 2: Indirect p53 regulation with miRNAs. p53 controls its stability and activity with the p53-inducible miRNAs that directly or indirectly target the negative regulators (MDM2 and SIRT1). *miR-25*, *miR-32*, *miR-18b*, and *miR-449* are not direct targets of p53 but repress the negative regulators and lead to p53 activation.

of MDM2 is often found in many types of human cancers, such as soft tissue sarcomas, brain tumors, and head and neck squamous cell carcinomas [113, 114]. On the flip side, p53 inhibits MDM2 expression using several miRNAs and establishes the regulatory circuit between p53 and MDM2 (Figure 2). For instance, *miR-192/194/215*, *miR-143/145*, and *miR-605*, which are the transcriptional targets of p53, directly inhibit MDM2 expression [68, 114, 115]. *miR-29* family members are also p53-inducible miRNAs and indirectly control the MDM2 level by targeting p85 $\alpha$ , a regulatory subunit of PI3 kinase (PI3K), in the PI3K/AKT/MDM2 axis [116, 117]. Furthermore, the *miR-29* family directly suppresses cell division cycle 42 (CDC42) and PPM1D phosphatase, both of which negatively regulate p53 [116, 117]. While a liver-specific *miR-122* is not a transcriptional target of p53, the miRNA increases p53 activity through the downregulation of cyclin G1, which inhibits the recruitment of phosphatase 2A (PP2A) to dephosphorylate MDM2 and causes the decrease of MDM2 activity [118, 119]. Recent studies indicated that tumor-suppressive miRNAs, *miR-25*, *miR-32*, and *miR-18b* are also not transcriptionally regulated by p53 but affect the p53 pathway by targeting *MDM2* mRNA directly [120, 121].

Besides MDM2, a NAD-dependent deacetylase, silent information regulator 1 (SIRT1), increases the level of deacetylated p53 and negatively regulates the p53 activity [122, 123]. SIRT1 is targeted by the p53-inducible *miR-34a* and joins the positive feedback loop connecting the miRNA, SIRT1, and p53 (Figure 2) [124]. Additionally, *miR-499* participates in this regulatory circuit as the miRNA possesses a very similar seed sequence of *miR-34* members [125–127]. *miR-449* is upregulated by E2F1, not by p53, and *miR-34* and *miR-449* bring in an asymmetric network to balance the functions between p53 and E2F1.

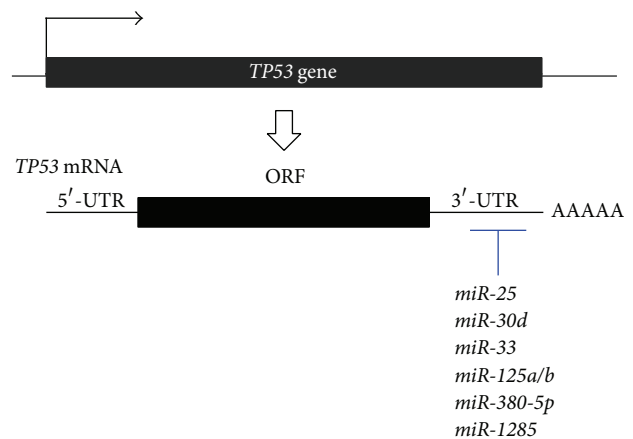


FIGURE 3: Direct p53 regulation by miRNAs. miRNAs directly interact with *TP53* mRNA by binding to sites in the 3'-UTR. This interaction inhibits the translation of mRNA, resulting in the repression of p53 activity. ORF: open reading frame.

## 6. miRNAs Directly Targeting *TP53* mRNA

As is the case in the control of negative regulators of p53 via miRNAs, p53 itself is repressed by several miRNAs through direct interaction with the 3'-UTR of *TP53* mRNA (Figure 3).

*miR-125b* is a first-identified p53-repressive miRNA and blocks the p53 expression level to suppress apoptosis in human neuroblastoma and lung fibroblast cells; in contrast, the knockdown of *miR-125b* leads to the opposite results [128]. Plus, *miR-125a*, an isoform of *miR-125*, was suggested to inhibit the translation of *TP53* by binding to a region of the 3'-UTR [129]. The high expression of *miR-125b* is associated with poor prognosis in patients with colorectal cancer [130].

Some studies have shown that *miR-125b* represses factors in the p53 network, including apoptosis regulators like *PUMA*, insulin-like growth factor-binding protein 3 (*IGFBP3*), and *BCL2*-antagonist/killer 1 (*BAK1*) and cell-cycle regulators like *cyclin C*, *CDC25C*, and cyclin-dependent kinase inhibitor 2C (*CDKN2C*) [131]. These suggest that *miR-125b* modulates and buffers the p53 pathway.

Subsequently, *miR-504* was reported to directly repress the p53 protein level and reduce the p53-mediated apoptosis and cell-cycle arrest in response to stress, and its overexpression promotes the tumorigenicity of colon cancer cells *in vivo* [132]. Additionally, *miR-380-5p*, *miR-33*, and *miR-1285* can downregulate the p53 protein expression by directly binding to the two sites in the 3'-UTR of *TP53*, resulting in the reduction of apoptosis and cell-cycle arrest [133–135]. Indeed, *miR-380-5p* is highly expressed in neuroblastomas with neuroblastoma-derived v-myc myelocytomatosis viral-related oncogene (*MYCN*) amplification, and the high expression level correlates with poor diagnosis [133]. More recently, *miR-30d* and *miR-25* also directly interacted with the 3'-UTR of *TP53* to decrease the p53 level. So then, these miRNAs affect apoptotic cell death, cell-cycle arrest, and cellular senescence in some cell lines, such as multiple myelomas, colon cancer, and lung cancer cells [136–138]. When taken together, the miRNAs targeting *TP53* would hinder p53 from exerting its tumor-suppressive functions (senescence, apoptosis, cell-cycle arrest, etc.) under stressed conditions.

## 7. Concluding Remarks

For more than a decade, small noncoding RNAs have become increasingly central to the study of tumor biology. The accumulating evidence of cancer-associated miRNAs reveals the missing link between classic tumor-suppressive networks and complex oncogenic pathways. In a stress situation, p53 directly induces various protein-coding genes such as *p21* and *PUMA* to contribute to cell-cycle arrest and apoptosis and, furthermore, utilizes tumor-suppressive miRNAs, such as *miR-34s*, *miR-107*, and *miR-145* (Figure 1 and Table 1). Some of the p53-inducible miRNAs target p53-negative regulators (*MDM2* and *SIRT1*), which creates a positive feedback loop to reinforce p53 stability and activity (Figure 2). However, as expected, miRNAs are not always on p53's side: p53-repressive miRNAs (*miR-125s*, *miR-504*, *miR-380-5p*, etc.) reduce the p53 expression level by binding to a region of the 3'-UTR of *TP53* mRNA and result in the inhibition of cell-cycle arrest and apoptosis (Figure 3). There will be more than one way to arrest the cell-cycle and/or induce apoptosis, and the balance between miRNAs and tumor suppressors might be crucial in deciding which strategy to adapt.

For future diagnostic and therapeutic advances, more extensive studies will be needed to find hidden messages in the tumor-suppressive networks of miRNA. The regulatory mechanism of the p53-miRNA circuit has been excellently shown, but the upstream regulators of almost all miRNAs are unknown at this time. What is more, regardless of computational prediction, the downstream targets of miRNA are hard to identify exactly because of the imperfect complementarity

and the possibility that miRNAs can bind to not only the 3'-UTR but also the 5'-UTR and coding regions.

In recent years, the competitive endogenous RNA (ceRNA) hypothesis has suggested that noncoding pseudogenes and long noncoding RNAs act as miRNA sponges, which is likely to counteract the effect of miRNAs on the target mRNA transcripts [139]. Therefore, we need to move deeper inside the world of noncoding RNAs in order to prevent and treat diverse cancers.

Besides the miRNAs described in this paper, there are many miRNAs related to cell-cycle regulation and apoptosis [140–142]. However, it is unclear how these miRNAs act additively/synergistically on tumor suppression. Even the longest journey to understand the role of miRNA begins with a single experiment. The next ten years will be more exciting in the quest to see cancer conquered.

## Conflict of Interests

The authors declare no competing financial interests.

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