

Review Article

MicroRNAs Regulate Key Effector Pathways of Senescence

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MicroRNAs (miRNAs) are small (approximately 22 nt) noncoding endogenous RNA molecules that regulate gene expression and protein coding by base pairing with the 3' untranslated region (UTR) of target mRNAs. miRNA expression is associated with cancer pathogenesis because miRNAs are intimately linked to cancer development. Senescence blocks cell proliferation, representing an important barrier that cells must bypass to reach malignancy. Importantly, certain miRNAs have been shown to have an important role during cellular senescence, which is also involved in human tumorigenesis. Therefore, therapeutic induction of senescence by drugs or miRNA-based therapies is a potential method to treat cancer by inducing a persistent growth arrest in tumors.

1. Introduction

miRNAs are small noncoding RNAs (approximately 22 nt) that regulate gene expression by interfering with protein translational machinery and/or inducing degradation of target mRNAs [1]. Hundreds of microRNA (miRNA) genes have been found in animals, plants, and viruses [2–4] making them one of the largest gene families.

Recent studies revealed the key roles of miRNAs in diverse regulatory pathways including development timing control, hematopoietic cell differentiation, apoptosis, cell proliferation, and organ development [2]. miRNAs and their targets constitute remarkably complex regulatory networks because a single miRNA can bind to and regulate many different mRNA targets, and conversely, several different miRNAs can bind to and cooperatively control a single mRNA target [5]. In general, miRNAs repress protein expression at the posttranscriptional level through base pairing with the 3'-UTR leading to reduced translation, or in some cases, degradation. However, some miRNAs have been shown to bind to the open reading frame or to the 5'-UTR of the target mRNAs. In some cases, miRNAs have been shown to activate rather than inhibit gene expression [6–8].

miRNAs are involved in many aspects of cell biology including physiological modulation and pathological disruption of basic pathways. In this regard, miRNAs are key mediators in cancer where they regulate many aspects of tumorigenesis and tumor progression from the initiating steps to metastasis formation and chemosensitivity [9, 10]. Therefore, miRNA expression may be deregulated in cancer because abnormal miRNA activity may lead to tumorigenesis. It has been shown that human tumors exhibit distinctive miRNA expression signatures [11]. miRNA expression is tissue specific, and certain cancer histotypes can be classified based on miRNA expression profiles [12]. Some miRNAs have been found to be upregulated or downregulated in cancer. An overexpressed miRNA that downregulates a tumor suppressor gene is defined as an oncomir, and a downregulated miRNA that normally downregulates the expression of an oncogene is defined as a tumor suppressor miR (TS-miR). However, some miRNAs may function as oncogenes in some cell types and as tumor suppressors in other cell types [13]. Aberrant miRNA expression in cancer due to chromosomal abnormalities, polymorphism, and/or epigenetic changes has a direct impact on miRNA biogenesis. In this study, we reviewed the potential impact of miRNAs in senescence and cancer. We suggest that the biological

function of miRNAs is extensively studied in the near future to identify their potential clinical applications.

2. MicroRNA Biogenesis

miRNA biogenesis has been studied by many scientists. A schematic overview of miRNA biogenesis is shown in Figure 1. Most of the miRNA genes exist in clusters in the genome and are polycistronically expressed from their own promoter. Other miRNA genes are found in intronic regions and are transcribed as a part of annotated genes. The transcription of most miRNA genes is mediated by RNA polymerase II (Pol II), producing long primary miRNAs (pri-miRNAs) that are capped at the 5' end and polyadenylated at the 3' end. These pri-miRNAs contain a stem of approximately 33 base pairs, a terminal loop, and flanking ssRNA segments [14]. However, a small group of miRNAs associated with Alu repeats can be transcribed by Pol III [15]. Two steps of ribonuclease processing reactions are required to generate mature miRNAs. The first step occurs in the nucleus and involves the release of a 70 nt intermediate hairpin structure (pre-miRNA) from the RNA duplex in the pri-miRNA by the RNase III-type protein, Droscha [16]. Moreover, Droscha-mediated pri-miRNA processing requires the cofactor, DiGeorge syndrome critical region gene 8 (DGCR8). Together with DGCR8, Droscha forms a large complex known as the microprocessor complex, which is approximately 650 kDa in humans [17, 18]. Specifically, DGCR8 interacts with pri-miRNAs through the ssRNA segments and the stem (approximately 33 bp), and DGCR8 assists Droscha to cleave the substrate (approximately 11 bp) from the ssRNA/dsRNA junction [19, 20]. The resulting pre-miRNA is transported out of the nucleus and into the cytoplasm by Exportin-5 and its cofactor, Ran-GTP [21].

Apart from the canonical miRNA pathway, an alternative nuclear pathway for miRNA biogenesis has been recently described in invertebrates [22, 23] and mammals [24]. This noncanonical pathway involves short introns with hairpin potential, which are termed mirtrons. Mirtrons bypass are processed by the microprocessor. Therefore, they are processed by splicing and debranching. Debranched mirtrons access the canonical miRNA pathway during nuclear export. The debranched mirtrons are cleaved by Dicer and incorporated into silencing complexes [22, 23].

The miRNA maturation process in the cytoplasm is carried out by Dicer, which is a highly conserved RNase III-type endoribonuclease present in almost all eukaryotic organisms. PremiRNAs are cleaved near the terminal loop by Dicer-releasing miRNA duplexes (approximately 22 nt) [25]. Human Dicer interacts with proteins, such as TAR RNA binding protein (TRBP; also known as TARBP2) [26, 27]. However, current studies have suggested that they are not required for miRNA processing but that they contribute to the formation of the RNA-induced silencing complex (RISC) [28]. Following Dicer cleavage, the 22-nt RNA duplex binds to Argonaute (Ago) proteins to generate the effector complex, RISC. One strand of the 22-nt RNA duplex remains in the Ago complex as a mature miRNA (the guide strand or miRNA), and the other strand (the passenger strand

or miRNA*) is degraded [25]. Next, the miRNA guides RISC to specifically recognize and repress target mRNAs. In most cases, miRNAs repress protein expression through base pairing with the 3'-UTRs of the target mRNA [28]. Perfect complementarity, which is rare in animal miRNA/mRNA base pairing, allows Ago-catalyzed cleavage of the mRNA strand. In contrast, central mismatches exclude cleavage and promote repression of mRNA translation.

The specificity of miRNA targeting is defined by Watson-Crick complementarities between positions 2 to 8 from the 5'-miRNA (also known as the seed) with the 3'-UTR of the target mRNAs. When miRNAs and their target mRNA sequence have perfect complementarities, RISC induces mRNA degradation. When an imperfect miRNA/mRNA target pairing occurs, protein translation is blocked. Regardless which of these two events occurs, the net result is a decrease in the amount of proteins encoded by the mRNA targets.

3. miRNAs Involved in Senescence

Cellular senescence was originally described in primary cells as a process that limits the replicative potential of human diploid fibroblasts in culture. This type of senescence is called replicative senescence. Senescence is an important block to cell cycle progression during the aging of cells in culture and is a fundamental barrier that cells must bypass during carcinogenesis. Senescent cells are characterized by the expression of β -galactosidase, overexpression of plasminogen activator protein 1 (PAI-1), and altered cell morphology characterized by a giant cell size, increased cytoplasmic granularity, and a single large nucleus [29].

Cellular senescence is a process that is triggered by several types of stresses as follows: telomeric erosion resulting from repeated cell division (replicative senescence); DNA damage; oxidative stress resulting from mitochondrial deterioration; overexpression of oncogenes; loss of tumor suppressors such as PTEN and VHL (oncogene-induced senescence; OIS) [29, 30]. OIS was first observed when an oncogenic form of Ras (e.g., Ras^{G12V}), which is a cytoplasmic transducer of mitogenic signals, was expressed in normal human fibroblasts [31]. Other members of the Ras signaling pathway, such as v-raf-1 murine leukemia viral oncogene homolog 1 (RAF), mitogen-activated protein kinase kinase 1 (MEK), v-mos Moloney murine sarcoma viral oncogene homolog (MOS), and v-raf murine sarcoma viral oncogene homolog B1 (BRAF), in addition to pro-proliferative nuclear proteins, such as the E2F transcription factor, can also induce a senescence response upon overexpression [32]. Moreover, OIS can be caused by the loss of the tumor suppressors that function upstream of oncogenes, such as phosphatase and tensin homolog (PTEN), von Hippel-Lindau tumor suppressor (VHL), and neurofibromin 1 (NF1), resulting in an increase of oncogenic signaling that leads to senescence [30]. In general terms, OIS has similar characteristics to replicative senescence including the presence of β -galactosidase-positive cells, induction of cell cycle inhibitory proteins, and phenotypic morphology of giant cells.

The major pathways that regulate cellular senescence are the p53/p21^{Cip1} and p16^{INK4A}-pRB tumor suppressor

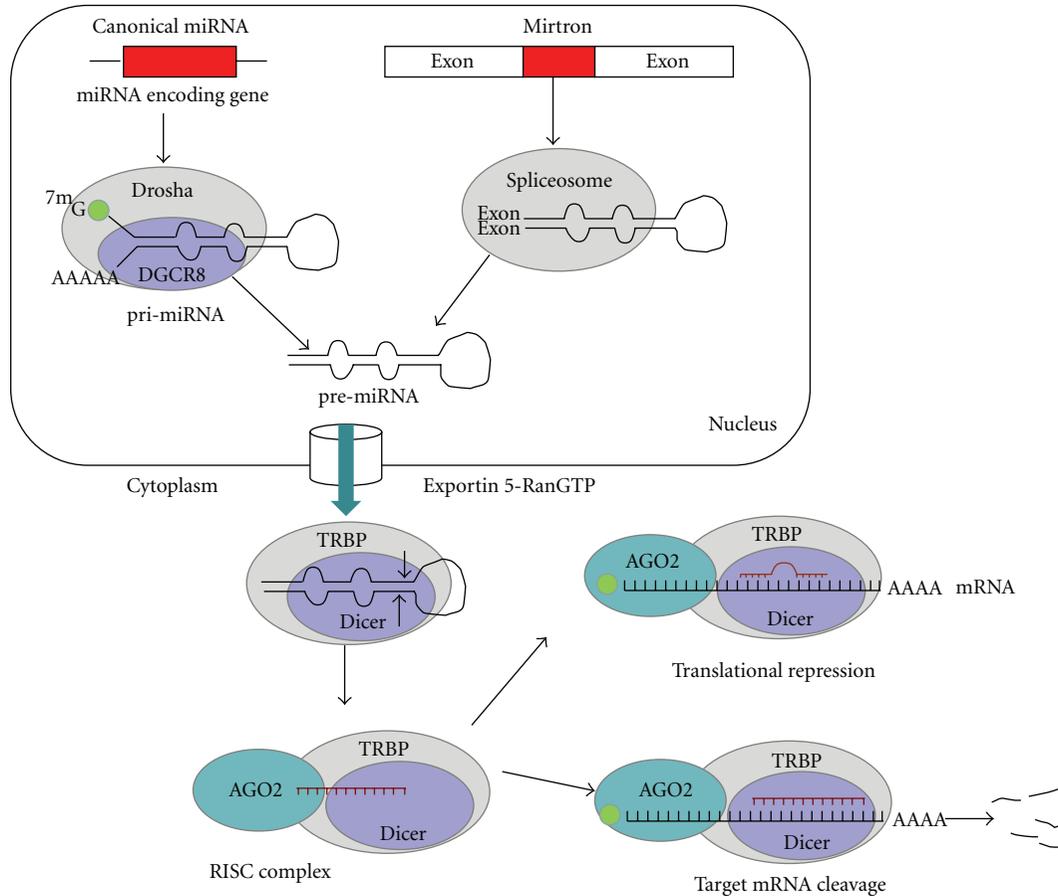


FIGURE 1: miRNA biogenesis. In the nucleus, canonical miRNAs are processed by the endoribonuclease, Drosha, in partnership with DGCR8. In contrast, mirtrons are processed by the spliceosome. The pre-miRNA is then exported from the nucleus into the cytoplasm by Exportin-5, and it is processed into a mature miRNA by Dicer. After RISC incorporation, mature miRNAs inhibit translation or promote degradation of their target mRNA transcripts depending on the degree of complementarity between the 3'-UTR of the target mRNA and the seed region of the miRNA.

pathways. p53 provokes growth arrest, in part by inducing the expression of p21^{Cip1}, which is a cyclin-dependent kinase (CDK) inhibitor that suppresses the phosphorylation and, hence, the inactivation of pRB [32, 33]. In addition, senescence signals that engage the p16^{INK4A}-pRB pathway generally do so by inducing the expression of p16^{INK4A}, which is another CDK inhibitor that prevents pRB phosphorylation and inactivation [32]. In this regard, the loss of tumor suppressors that function downstream of oncogenes, such as p53, impair senescence and allow progression to malignant stages providing a link between tumor suppression and the induction of senescence by p16^{INK4A}, p19^{ARF}, and p53 [30]. In general, oncogenes that elicit a senescence response often converge on the activation of p53 and/or pRB. However, RAF-induced senescence independent of both p53 and pRB has been reported in human cells [34].

Importantly, several groups have shown that benign tumors contain senescent cells and that these cells fully disappear in the corresponding malignant areas of the patients. Senescent cells are found in premalignant lesions in mice and humans, and they are absent in their corresponding malignant stages, which suggests a role for senescence as a

barrier to tumor progression [35, 36]. In addition, senescent cells are relatively rare in young organisms, but their number increases with age. Consistent with a role in aging, senescent cells accumulate with age in many rodent, primate, and human tissues [37, 38]. Moreover, they are found at sites of age-related pathology including degenerative disorders, such as osteoarthritis and atherosclerosis [37], in addition to hyperproliferative lesions, such as benign prostatic hyperplasia [39].

Several miRNAs have been reported to be differentially expressed in senescent cells when compared to primary cells, providing a role for miRNAs in senescence (Figure 2, Table 1). Recently, it has been reported that miR-34a overexpression during senescence can be p53 dependent and p53 independent [40–44]. p53 activates transcription of a set of genes, which induces cell cycle arrest, senescence, or apoptosis. Moreover, p53 also regulates the expression of miR-34a because genes in the family of miR-34 genes contain p53-binding sites in their promoters, which are conserved among humans and rodents. In turn, miR-34a increases the activity of p53 by means of reducing expression of sirtuin 1 (SIRT1), which interacts with p53 and deacetylates the Lys382 residue

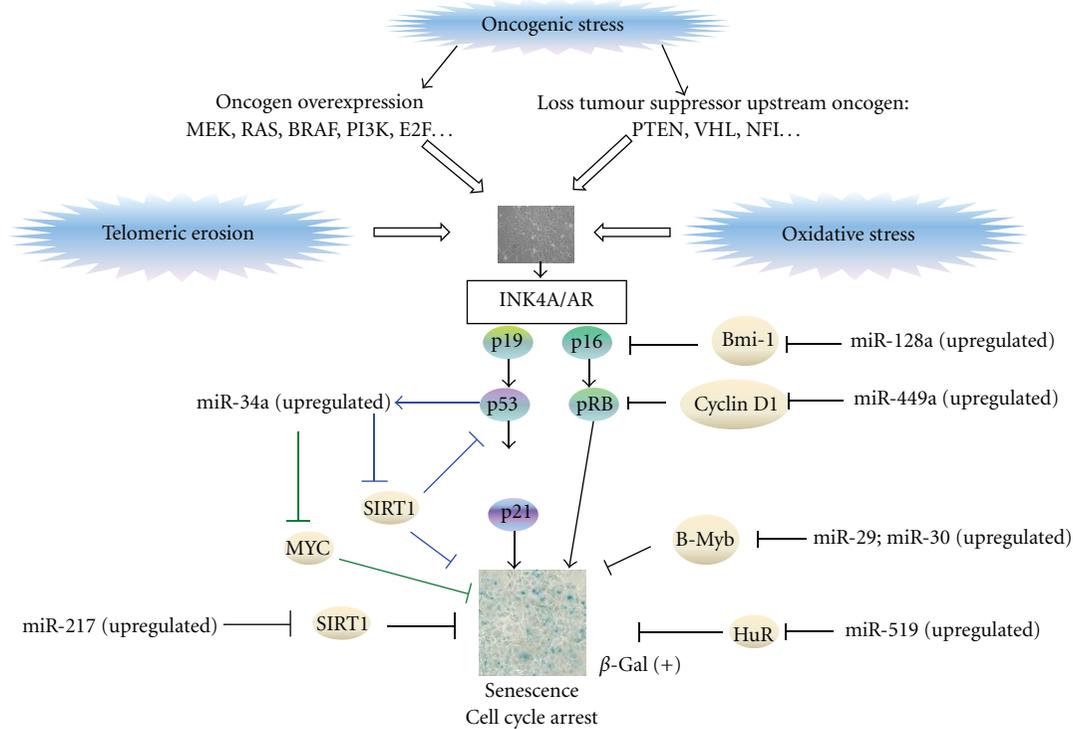


FIGURE 2: Role of miRNAs in senescence. Cellular senescence is triggered by several factors including telomeric erosion, oncogenic stress, oxidative stress, and miRNA modulation. The following miRNAs are key regulatory miRNAs modulating senescence: miR-128a, miR-449a, miR-29, miR-30, miR-519, miR-217, and miR-34a.

of p53 in a NAD⁺-dependent manner, thereby decreasing p53-mediated transcriptional activation and reducing the expression levels of downstream proteins, such as p21^{Cip1}. Therefore, overexpression of miR-34a decreases SIRT1 expression, allowing an increase in p53 acetylation and p53 activity and thus mediating the senescence response [43, 45]. On the other hand, several studies have shown that miR-34a causes senescence in a p53-independent manner. miR-34a induces senescence and suppression of cell proliferation through downregulation of the E2F pathway in human colon cancer cells p53 (+/+) leading to the upregulation of the p53/p21^{Cip1} pathway, but also in human colon cancer cells p53 (-/-) [42]. In addition, another study has reported a strong upregulation of miR-34a during B-RAF-induced senescence independent of p53. In this case, miR-34a is transcriptionally upregulated by ELK1, which is a member of the ETS oncogene family and has previously been implicated in cellular senescence. Moreover, miR-34a is upregulated after activation of the B-RAF oncogene. Finally, miR-34a provokes senescence through repression of v-myc myelocytomatosis viral oncogene homolog (Myc) [44]. Importantly, miR-34a, which is a tumor suppressor in the miR-34 family, is downregulated in pancreatic cancer cells, neuroblastomas, colon cancer cells, and lung cancer cells [40–42, 46].

The expression levels of miR-29 and miR-30 increase during cellular senescence in a Rb-dependent manner. Moreover, these microRNAs directly repress v-myc myeloblastosis viral oncogene homolog (avian)-like 2 (B-Myb) by binding

TABLE 1: Novel miRNAs involved in senescence.

miRNA	miRNA function	Reference
hsa-miR-29/30	Oncomir/Tumour suppressor	[47–51]
hsa-miR-34a	Tumour suppressor	[40–44]
hsa-miR-519	Tumour suppressor	[52]
hsa-miR-449a	Tumour suppressor	[53, 54]
hsa-miR-128a	Tumour suppressor	[55–57]
hsa-miR-217	Tumour suppressor	[58, 59]
hsa-miR-372/373	Oncomir	[60–63]
hsa-miR-17-5p	Oncomir	[60, 64–69]
hsa-miR-130b	Oncomir	[60, 70]
hsa-miR-15b/25/141	Oncomir	[71–74]
mmu-miR-20a	Tumour suppressor	[75]
mmu-miR-290	Tumour suppressor	[76]

to its 3'-UTR acting in conjunction with Rb-E2F complexes at the B-Myb promoter to mediate repression of B-Myb expression during Rb activation resulting in senescence [47]. miR-29 is downregulated in mantle cell lymphomas [48], and the overexpression of miR-29 is suppressed during tumorigenicity in lung cancer cells [49]. Moreover, miR-29 is upregulated in indolent human B-cell chronic lymphocytic leukemia (B-CLL) when compared to aggressive B-CLL and normal CD19+ B-cells, suggesting that miR-29 can function as an oncogene and contribute to the pathogenesis

of indolent CLL. In contrast, miR-29 is downregulated in aggressive CLL when compared to indolent CLL, and miR-29 may function as a tumor suppressor in CLL by targeting T-cell leukemia/lymphoma 1 (TCL-1) [50]. In addition, miR-30 directly represses LIN28 (a lin-28 homolog of *C. elegans*) in embryonic stem cells and cancer cells. Importantly, LIN28 functions as an oncogene promoting malignant transformation and tumor progression [51]. Another miRNA involved in senescence is miR-449a. miR-449a induces senescence by suppressing Rb phosphorylation by directly repressing the upstream regulatory factors of Rb, such as cyclin D1 (CCND1) [53], histone deacetylase 1 (HDAC1) [53], cyclin-dependent kinase 6 (CDK6), and cell division cycle 25 homolog A (CDC25A) [54]. A recent study has shown that miR-449a is downregulated in prostate cancer, indicating that this miRNA regulates cell growth and viability, in part by repressing the expression of HDAC-1 [53].

The functional role of miR-128a in senescence is also evident. miR-128a directly targets the Bmi-1 oncogene (polycomb ring finger oncogene; BMI1), increasing p16^{INK4A} expression and reactive oxygen species (ROS), which promote cellular senescence in medulloblastoma cell lines [55]. Recently, it has been reported that this tumor suppressive miRNA (miR-128a) is downregulated in medulloblastomas [55], glioblastomas [56], and acute myeloid leukemia [57], suggesting that this miRNA has an important role in these types of cancer.

miR-217, which is expressed in endothelial cells during aging, promotes premature senescence by inhibiting SIRT1 expression, thus increasing forkhead box O1 (FoxO1) expression and endothelial nitric oxide synthase (eNOS) acetylation [58]. In addition, miR-217 has been reported to be a novel tumor suppressive miRNA in pancreatic ductal adenocarcinoma due to decreases in tumor cell growth both *in vitro* and *in vivo* by targeting K-Ras [59].

miR-290 also acts as a physiological effector of senescence in murine cells including mouse embryonic fibroblasts (MEFs) [76], and miR-20a induces senescence in MEFs through the direct downregulation of the transcriptional regulator leukemia/lymphoma-related factor (LRF), leading to an induction of p19^{ARF} [75]. In addition, miR-519 is another miRNA that induces senescence in cancer cell lines. miR-519 elicits these actions by repressing HuR expression [52]. On the other hand, there are miRNAs that are downregulated during senescence, such as miR-15b, miR-24, miR-25, and miR-141, which directly target mitogen-activated protein kinase kinase (MKK4) [71].

Importantly, the escape from OIS is a requirement for transformation into tumor cells. Therefore, high-throughput genomic and miRNA screens have been performed to identify novel mediators of OIS in human mammary epithelial cells (HMECs), which contain OHT-inducible Ras^{G12V} [60]. Borgdorff and colleagues showed that 28 miRNAs prevented senescence upon Ras^{G12V} induction. These miRNAs are as follows: miR-17-5p, miR-20a-b, miR-93, miR-106a-b, miR-130b, miR-302a-d, miR-372, miR-373, miR-512-3p, miR-515-3p, miR-519c-e, miR-520a-g, miR-526b*, and miR-146a-b. These miRNAs bypass Ras^{G12V}-induced senescence by directly targeting the 3'-UTR of p21^{Cip1}. Moreover,

miR-372, miR-373, miR-302, and miR-520 can also bypass Ras^{G12V}-induced senescence through the downregulation of LATS2 in addition to p21^{Cip1} [60–63]. miR-372 and miR-373 also prevent Ras-induced senescence in human fibroblasts [61], suggesting that the immortalization mechanism of these miRNAs is universal. Importantly, these identified proliferative miRNAs have been demonstrated to be associated with cancer development. For example, miR-17-5p is overexpressed in pancreatic cancer [64], squamous cell carcinoma [65], breast cancer [66], hepatocellular cancer [67], renal cell carcinoma [68], and thyroid cancer [69], suggesting a potential oncogenic role of miR-17-5p. Furthermore, miR-130b promotes gastric cancer by downregulating the tumor suppressor, runt-related transcription factor 3 (RUNX3) [70]. In addition, miR-372 and miR-373 have been found to be upregulated in testicular germ cell tumors [61]. Finally, miR-302 is expressed specifically in embryonic stem cells and embryonic carcinoma cells [77, 78], suggesting a possible role of this miRNA in cancer stem cell biology.

4. Senescence Induction Based upon miRNA Modulation as a Therapeutic Approach

It is well known that the overexpression of several oncogenes (e.g., Ras^{G12V}) or tumor suppressor genes (e.g., ribosomal protein S6 kinase, 90 kDa, polypeptide 6; RSK4) [79] induces senescence. However, cancer cells can be induced to a senescent state with conventional anticancer treatments such as Doxorubicin [80, 81]. The use of senescence as a novel modality of cancer therapy has been considered in clinical trials with promising results [81].

Senescence may promote carcinogenesis in surrounding tissues [82] by secreting interleukins, chemokines, growth factors, and proteases, which stimulate malignant phenotypes in neighboring cells. In this regard, miR-146a and miR-146b have been demonstrated to negatively regulate the senescence-associated secretion of IL-6 and IL-8 by directly targeting IRAK1 and reducing NF- κ B activity [83]. Therefore, these miRNAs may be promising tools to restore the protective potential against development of the senescence-associated secretory phenotype (SASP).

The rationale for using miRNAs as novel anticancer molecules is based on the following two major findings: (1) miRNA expression is deregulated in cancer when compared with normal tissues; (2) the cancer phenotype can be changed by targeting miRNA expression [13].

The therapeutic application of miRNAs involves two major strategies. For oncogenic miRNAs (oncomirs), which promote proliferation when overexpressed, the major therapeutic strategy is directed toward reducing oncomir expression. These therapies include anti-miRNA oligonucleotides, microRNA sponges, miRNA masking, and small molecule inhibitors. For TS-miRs, the therapeutic strategy is directed toward restoring the levels of TS-miRs by exogenous expression (Figure 3).

4.1. Anti-miRNA Oligonucleotides. The base pair interaction between miRNAs and mRNAs is essential for the function of

[101]. In addition, let-7 expression is downregulated in other cancer types such as hepatocellular carcinoma, melanoma, and nasopharyngeal carcinoma. Let-7 acts by suppressing protein expression of several genes such as high mobility group AT-hook 2 (HMGA2), Myc, CCND1, and BCL2-like 1 (BCL-XL) [102–106]. Functional studies using cultured lung cancer cells and mouse models of lung cancer have shown that administration of let-7 mimics blocks the proliferation of cancer cells and reduces the growth of lung tumors, respectively [107–109]. Moreover, in hepatocellular carcinoma cells, the transfection of a let-7 family member, let-7g mimics, inhibits cell proliferation by downregulating the oncogene, c-Myc, and upregulating the tumor suppressor gene, p16^{INK4A} [110]. miRNA replacement is also demonstrated by miR-34a [111], which is underexpressed in multiple cancer types. miR-34a, a key effector of the p53 signaling pathway, induces apoptosis, G2 arrest, and senescence in cancer cell lines by repressing the expression of direct targets, such as cyclin-dependent kinase 4 (CDK4), cyclin-dependent kinase 6 (CDK6), CCND1, SIRT1, cyclin E2 (CCNE2), E2F transcription factor 3 (E2F3), neuroblastoma-derived Myc (MYCN), and B-cell CLL/lymphoma 2 (BCL2) [42, 46, 112–114].

One of the major problems for the use of miRNAs as therapeutic molecules relates to the tissue-specific delivery and cellular uptake of sufficient amounts of synthetic oligonucleotides to achieve sustained target inhibition [115]. Consequently, strategies have been developed to deliver miRNA-based therapeutics, including viral and nonviral vector systems. Viral vector-systems have high gene transfer efficiency but have limitations due to their lack of tumor-targeting capability and to residual viral elements that can be immunogenic, cytopathic, or recombinogenic. However, adenovirus-associated vectors (AAVs) do not integrate into the genome and are efficiently eliminated with minimal toxicity as shown in Phase I and Phase II clinical trials [13]. Furthermore, systemic administration of mir-26a using an AAV in an animal model of hepatocellular carcinoma results in apoptosis induction and significant protection from disease progression without toxicity [116]. On the other hand, nonviral vector systems include cationic liposome-mediated, nanoparticle-mediated, and polymer-mediated gene transfer systems for *in vivo* human therapy [117–119].

5. Conclusions

miRNAs have an important role in tumor development, progression, chemosensitivity, and cellular senescence. A better understanding of the function of miRNAs is required for the development of novel therapies, such as restoring TS-miRs and targeting oncomirs with anti-miRNA technology.

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