

REVIEW

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Dysregulation of MicroRNAs in cancer

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Abstract

MicroRNAs (miRNAs) are involved in multiple biological activities as well as disease progression including cancer. Interestingly, miRNAs could act as either tumor suppressors or oncogenes depending on the functions of their targets. Using high-throughput profiling, dysregulation of miRNAs has been widely observed in different stages of cancer, and there is mounting evidence demonstrating several misguided mechanisms that cause miRNA dysregulation. In this review, we summarize the key functions of miRNAs in cancer, especially those affecting tumor metastasis and drug resistance. Moreover, the mechanisms leading to dysregulation of miRNAs, including genomic abnormalities, DNA/histone modifications, transcriptional regulation, abnormal biogenesis, and interaction between miRNAs, are also discussed.

Keywords: Cancer progression, miRNA biogenesis, miRNA dysregulation

Review

Introduction

MicroRNAs (miRNAs) are small noncoding RNAs which enhance the cleavage or translational repression of specific mRNA with recognition site(s) in the 3'-untranslated region (3'UTR). The biogenesis of miRNA is controlled by two RNase-dependent processing steps that converts a long primary transcript into a mature ~20 nt miRNA. The mature miRNA are released and then loaded onto the miRNA-induced silencing complex (miRISC), which acts as a guiding strand to recognize specific mRNA targets. Since the discovery of miRNAs, several large-scale studies have compared the profiles of miRNA expression patterns between corresponding non-tumor and tumor tissues [1,2]. Dysregulation of miRNAs has been documented in different types of human cancers [1,2]. As miRNA expression is tissue-specific, the expression profile of miRNAs has been proposed as a marker to identify tumor origin [1]. Several studies have also suggested that the expression of miRNAs may even be a more reliable and better prognostic indicator than proteins or mRNAs under certain conditions [1,3,4]. For example, a five-miRNA signature profile could predict the cancer relapse and survival in NSCLC patients [3]. In addition, the expression of 25

miRNAs could classify tissues as normal pancreas, chronic pancreatitis, or pancreatic adenocarcinoma [5]. Currently, numerous cancer-specific miRNAs have been functionally identified, and the mechanisms underlying miRNA regulation are becoming more complete.

Emerging roles of miRNAs in cancer

Let-7 is the most studied miRNA both in development and cancer. The human let-7 family comprises 12 closely related members of miRNA (let-7-a-1, a-2, a-3, b, c, d, e, f-1, f-2, g, i and miR-98). Johnson *et al.* reported that let-7 is downregulated in lung cancer and is associated with elevated RAS expression [6]. They further showed that let-7 is complementary to multiple sites in the 3'UTR of the human RAS genes, allowing let-7 to suppress the expression of K-RAS and N-RAS. The tumor suppressive roles of let-7 are further strengthened by its antagonistic roles toward the expression of multiple oncogenes including RAS, MYC, and other cell cycle regulators in a variety of human cancer tissues [6-8]. For example, let-7 directly targets other proto-oncogenes such as CDK6, cyclin D, CCND2, and CDC25A and represses cell proliferation by promoting the G1 to S transition [7]. In addition, high mobility group A2 (HMGA2), an oncogene frequently mutated in multiple types of cancers, is also hindered by let-7 [9]. There are seven let-7 binding sites in the 3'UTR of HMGA2 mRNA. Disrupting the interaction between let-7 and these binding sites reduces let-7-mediated HMGA2

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downregulation and consequently enhances anchorage-independent growth of cancer cells [9,10]. Recent studies also suggest that let-7 regulates metastasis-associated genes such as *MYH9* and C-C chemokine receptor type 7 (*CCR7*) to facilitate invasion ability of cancer cells [11,12].

MiRNAs derived from miR-17-92 cluster, which contains seven homologous miRNAs, including miR-17-3p, miR-17-5p, miR-18a, miR-20a, miR-19a, miR-19b-1, and miR-92a-1, have been identified as oncogenic miRNAs. These miRNAs target multiple genes involved in proapoptotic pathways, reflecting their oncogenic activities [13,14]. The oncogenic roles of miR-17-92 cluster were reported by He *et al.* in which expression of this cluster accelerated c-Myc-induced lymphoma development and resulted in an advanced tumor in Eu-Myc transgenic mouse model of human B cell lymphoma [14]. The direct targets of miR-17-92 cluster have been identified to include Bim, PTEN, and p21 [13,15]. However, several controversial studies indicated that miR-17-92 possesses tumor suppressor activities. For instance, miR-17-92 cluster inhibits E2F1 to abolish Myc-induced cell proliferation, and miR-17-5p represses proliferation of breast cancer cells through targeting AIB1 [16,17].

MiR-21 has been shown to be overexpressed in a wide variety of cancers, including malignant human glioblastoma tumor tissues [18]. Knockdown of miR-21 induced activation of caspases and resulted in apoptosis in glioblastoma cells [19]. In addition, Papagiannakopoulos *et al.* indicated that knockdown of miR-21 activates the p53 pathway, mediates the induction of TGF- β signaling, and eventually suppresses cell growth, increases apoptosis, and induces cell cycle arrest in glioblastoma cells [20]. Downregulation of miR-21 also repressed cell growth in breast cancer cells by directly regulating PDCD4 tumor suppressor [21]. Moreover, Yao *et al.* reported a proliferation-promoting function of miR-21 in which knockdown of miR-21 suppressed proliferation of HeLa cells [22]. These studies suggest that miR-21 enables cells to gain their growth advantages.

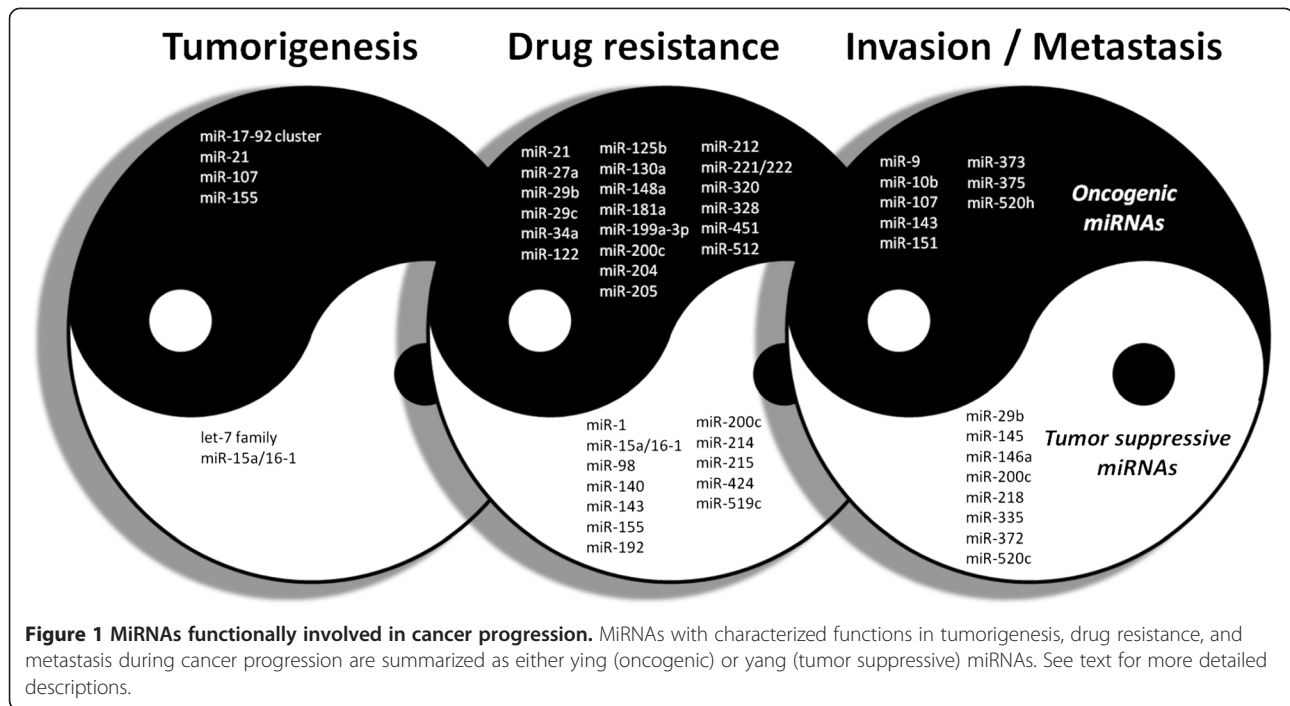
The roles of miRNAs in tumor metastasis

In addition to their abilities to mediate cell growth, miRNAs also affect tumor metastasis when the target genes are related to metastatic phenotypes of cancer cells (Figure 1) [23,24]. MiR-10b is the most studied miRNA with metastasis-promoting effect [25] and is directly regulated by Twist1, an oncoprotein facilitating epithelial-mesenchymal transition (EMT). Expression of miR-10b is markedly elevated and maintains the invasiveness of metastatic human breast cancer cells. Overexpression of miR-10b in non-metastatic breast cancer cells results in enhanced invasiveness and distant metastasis. MiR-10b targets *HOXD10* mRNA and enhances the

expression of RhoC, a prometastatic gene suppressed by *HOXD10* [25]. In addition, Tavazoie *et al.* demonstrated that *SOX4* and cadherin C could be downregulated by miR-335, leading to a reduction of the metastatic ability of breast cancer cells [26]. EMT and stemness have been shown to be closely related [27]. For instance, a recently study demonstrated that miR200c is upregulated by p53, and this in turn inhibits both EMT and stemness through *ZEB1* and *BMII*, respectively [28]. MiR-335 also acts as metastasis suppressor in neuroblastoma and gastric cancer [29,30]. CD44, an adhesion molecule that represses tumor metastasis, is suppressed by miR-373 and miR-520c [31]. Moreover, miR-373 has been identified as an oncomir in testicular germ cell tumor [32]. MiR-218 is an intronic miRNA coexpressed with its host gene, *Slit*, which encodes the ligand of Robo1, and downregulation of *Slit* reduces miR-218 expression, leading to increased Robo1 expression. As *Slit* interacts with Robo1 to facilitate metastasis, this pathway provides a negative feedback loop in gastric cancer [33]. Using a metastasis selection model of mouse colorectal cancer, Ding *et al.* identified a set of genes, including *APOBEC3G*, *CD133*, *LIPC*, and *S100P*, which play key roles in enhancing liver metastasis of colorectal cancer [34]. One of these genes, *APOBEC3G*, was further identified to downregulate miR-29b and subsequently restores the expression of MMP2, leading to enhanced invasion *in vitro* and metastasis *in vivo* [34].

Functions of miRNAs in drug resistance

In addition to the studies showing that miRNAs are associated with tumorigenesis and metastasis, several miRNAs have also been found to affect the drug resistance of cancer cells (Figure 1). MiR-519c was first found to increase drug sensitivity of colon cancer cells by regulating ABCG2 [35] and was later shown to suppress the expression of HIF-1 α which consequently attenuates tumor angiogenesis [36]. Paradoxically, Su *et al.* showed that E1A downregulates the expression of miR-520h, induces protein phosphatase PP2A/C upregulation, suppresses IKK/NF- κ B pathway, and eventually, mitigates Twist expression in breast cancer [37]. Recently, Yu *et al.* further demonstrated an oncogenic effect of miR-520h via repression of PP2A/C. Interestingly, the expression of miR-520h is inhibited by resveratrol, leading to NF- κ B-mediated reduction of Forkhead box protein C2 (FOXO2) [38]. These studies indicate that miR-520 family could act as tumor suppressor or oncogenes depending on their downstream signaling. MiR-15a and miR-16-1 have been documented as tumor suppressor in chronic lymphocytic leukemia (CLL) [39]. They are clustered on human chromosome 13q14, which is frequently deleted or downregulated in CLL and some solid tumors. Because the 3'UTR region of antiapoptotic



BCL2 mRNA contains a potential binding site for these miRNAs, a deficiency in miR-15a and miR-16-1 enhances the expression of *BCL2*, blocking the cleavage of pro-caspase 9 and poly-ADP-ribose polymerase (PARP) required to activate the intrinsic apoptosis pathway. Further studies revealed that expression of miR-15b and miR-16 negatively regulate the Bcl-2 protein level, leading to sensitization of gastric cancer cells to anticancer drugs [40]. Another miRNA, miR-451, has been found to be downregulated in the doxorubicin-resistant breast cancer cells. While expression of miR-451 sensitized breast cancer cells to doxorubicin treatment through regulating Mdr1/P-glycoprotein [41], Zhu *et al.* identified a controversial role of miR-451 in protecting cancer cells from anticancer drugs [42]. Functional inhibition of miR-21 has been shown to dramatically reduce the topotecan-resistance of breast cancer cells [43]. The tumor suppressor function of miR-29 has also been identified in human cholangiocarcinoma [44]. Mott *et al.* observed an inverse correlation between Mcl-1 protein and miR-29b expression. They further demonstrated the ability of miR-29 to inhibit expression of Mcl-1 protein and sensitize cancer cells to TRAIL cytotoxicity through targeting a putative target site in the 3'UTR of *Mcl-1* mRNA. Later, Garzon *et al.* found that ectopic expression of miR-29b downregulates the expression of DNA methyltransferases DNMT1, DNMT3A, and DNMT3B in AML cell, resulting in increased global DNA hypomethylation and restoring the expression of tumor suppressor genes such as the CDK inhibitor p15^{INK4b} and oestrogen receptor, ESR1 [45]. In

nasopharyngeal carcinoma, miR-29c also suppresses the metastasis by downregulating collagen and laminin 1 [46].

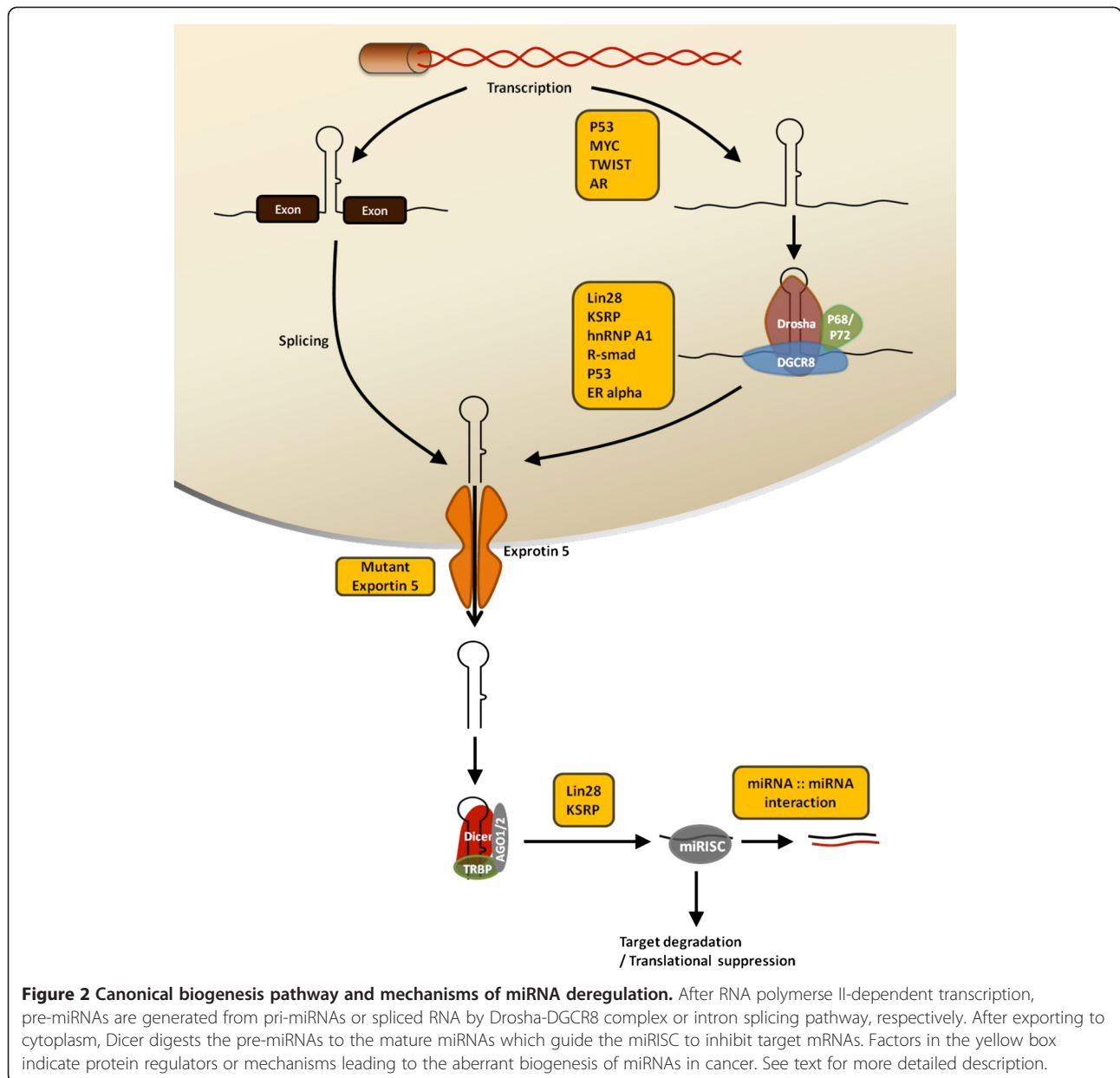
Mechanisms of dysregulation of miRNAs in cancer

Genomic abnormalities

Like protein-coding genes, more than half of miRNA genes in human cancers are located in chromosomal regions that frequently exhibit amplification, deletion, or translocation (Figure 2) [47]. A fundamental example of this region is 13q14 of the chromosome where *miR-15* and *miR-16* are located and frequently deleted in B cell chronic lymphocytic leukemias (B-CLL), resulting in the loss or downregulated expression of *miR-15* and *miR-16* [39,48]. In addition, using a high-throughput method, Zhang *et al.* demonstrated that deletion of *miR-17-92* cluster exists in melanomas, ovarian, and breast cancers [49]. The oncogenic miR-155 was found to be upregulated along with its host gene, *BIC*, in Burkitt's lymphoma patients [50]. These studies provide an important connection between the expression of miRNAs and genomic deletion/amplification in cancer.

CpG methylation and histone modification

Transcriptional silencing of tumor suppressor genes by CpG island promoter hypermethylation is a common hallmark of cancer. Similar phenomenon has been identified in miRNA regulation in which Saito *et al.* showed that a subset of miRNAs is upregulated by treatment of inhibitors specific for DNA methylation (5-aza-2'-deoxycytidine) or histone deacetylase (4-phenylbutyric acid) in cancer cells [51]. One of these miRNAs, miR-127, is downregulated in



human cancers. MiR-127 is embedded in a CpG island and dramatically upregulated through its own promoter, suggesting that DNA methylation or histone modification at this promoter region hinders the expression of miR-127 in cancer cells. The downstream target of miR-127, Bcl-6, is also consistently repressed after the treatments [51]. Lujambio *et al.* later identified another miRNA that is transcriptionally repressed in cancer cells by CpG island hypermethylation [52]. They investigated the profile of miRNA expression in cells lacking DNA methyltransferases and found that miRNA-124a is downregulated by CpG island hypermethylation. This epigenetic silencing subsequently activates CDK6 and induces Rb phosphorylation

[52]. One of the let-7 genes, Let-7a-3, is also located within the CpG islands. Lu *et al.* found that let-7a-3 gene is hypermethylated in ovarian cancer and hypermethylated let-7a-3 is associated with downregulation of IGFII expression and poor prognosis in ovarian cancer patients, suggesting that let-7 expression may target IGF-II [53]. Recently, Mazar *et al.* identified several miRNAs regulated epigenetically in melanoma. MiR-375 is one of these miRNAs with hypomethylation in melanocytes, keratinocytes, and normal skin. In contrast, tissues of melanoma exhibits hypermethylated miR-375 [54]. Overexpression of miR-375 alters the cell morphology and attenuates proliferation and invasion of melanoma cells, indicating a tumor suppressive function of

miR-375 [54]. These studies explain the mechanisms of DNA/histone methylation-regulated miRNAs in human cancers.

Transcriptional regulation

MiRNA expression is also regulated by transcription factors (Figure 2). p53 is a fundamental tumor suppressor which transcriptionally regulates hundreds of protein-coding genes. In 2007, three studies that published at the same time uncovered the subsets of miRNA regulated by p53 [55-57]. They analyzed the profiles of p53-dependent miRNA expression and found that a family of these miRNAs, miR-34a-c, was consistently upregulated by p53, which directly recognizes the promoters and activates the transcription of these miRNAs. These miRNAs function as powerful effectors to control p53-mediated cell cycle arrest and apoptosis [55-57]. As mentioned above, Chang *et al.* identified another tumor suppressor miRNA, miR-200c, that is also controlled by p53. Through binding to the miR-200c promoter, p53 induces miR-200c expression and consequently attenuates EMT and reduces stem-cell-like population in breast cancer by targeting ZEB1 and BMI1, respectively (Figure 3) [28]. Two other transcription factors, Myc and E2F1, were found to affect the expression of oncogenic miR-17-92 cluster [58,59]. These studies demonstrated that c-Myc induces expression of a miRNA cluster on human chromosome 13 by binding to this locus. E2F1, a Myc-regulated transcription factor that induces cell cycle progression, is suppressed by the miR-17-92 cluster and its paralog, miR-106b-25 [58-60]. As E2F1 and Myc upregulates miR-17-92, the suppressive effect on these transcription factors forms a negative feedback loop [58].

Abnormal maturation pathways

After generation of primary miRNAs, a two-step RNase-dependent maturation pathway is required to produce mature miRNAs (Figure 2). First, primary miRNAs (pri-miRNA) are processed by Drosha-containing complex to stem-loop pre-miRNAs, which are then further processed by the second RNase, Dicer, to short, double-strand duplexes. Eventually, one of the functional strands in the resulting duplexes is preserved, forming a

functional complex with the RISC proteins, and acts as guiding strands for specific recognition. Currently, several RNA-binding proteins have been found to affect this canonical pathway with some that are involved in the regulation of cancer progression.

Lin-28 is the most studied RNA-binding protein being capable of regulating let-7 biogenesis. Overexpression of Lin-28 has been shown as an unfavorable prognostic marker in human cancers [61]. Lin-28 modulates the structural alternation of pre-let-7g to inhibit Dicer-dependent processing [62]. Another mechanism underlying let-7-mediated Dicer processing step also has been uncovered in which the terminal uridylyltransferase 4 (TUT4) is recruited by Lin-28 to promote uridylation of pre-let-7, and thus destabilizing pre-let-7 and blocking Dicer-dependent maturation [63]. Lin-28B, a homolog of Lin-28 (also called Lin-28A), also modulates let-7 maturation in a TUT4-independent pathway [64]. Both mechanisms result in the downregulation of mature let-7, leading to cancer progression.

The KH-type splicing regulatory protein (KSRP) was identified to enhance both Drosha- and Dicer-mediated miRNA processing through interaction with specific sequences in the loop region of a subset of pri-miRNAs [65]. Knockdown of KSRP represses the expression of specific mature miRNAs, such as let-7a and miR-206, and consequently affects cell proliferation and differentiation. Regulation at the pri-miRNA to pre-miRNA processing step is also affected by hnRNP A1, a nucleocytoplasmic shuttling heterogeneous nuclear ribonucleoprotein. HnRNP A1 facilitates pri-miR-18a for conversion into pre-miR-18a [66] and recognizes the highly-conserved loop region of miR-18a, resulting in a structural rearrangement of this hairpin to generate a more favorable cleavage site for Drosha [67]. Furthermore, upon binding to hnRNP A1, pri-let-7a-1 is unable to be processed by KSRP because the conserved binding site of hnRNP A1 for pri-let-7a overlaps with that of KSRP [68].

The two DEAD-box RNA helicases, p68 (DDX5) and p72 (DDX17), are components of the Drosha microprocessor complex [69]. Recently, protein factors associating with the Drosha-p68 or Drosha-p72 have been identified as key regulators controlling miRNA biogenesis. The

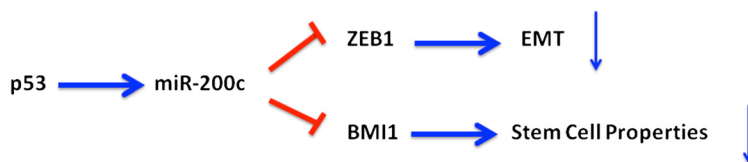


Figure 3 The roles of p53-regulated miR-200c in EMT and stem-cell-like properties. p53 directly binds to the miR-200c promoter and activates its expression. The elevated miR-200c hinders EMT via ZEB1 and reduces cell populations with stem-cell-like properties by BMI1. These pathways prevent the formation of metastatic cancer cells.

transforming growth factor- β (TGF- β) family and its signal transducers, Smads, play important roles during cancer progression. TGF- β and one of its family members, the bone morphogenetic protein 4 (BMP4), was found to induce the expression of mature miR-21 through an R-smad-dependent pathway [70]. This effect was further identified to be posttranscriptional, as they upregulate pre- and mature miR-21 without affecting pri-miR-21 [70]. R-smad interacts and stabilizes Drosha-p68 complex on the pri-miR-21 hairpin, thus promoting the maturation of miR-21. In addition to its function as a transcription factor, p53 was also identified to modulate miRNA biogenesis directly by binding to Drosha-p68 complex [71]. A subset of miRNAs, such as miR-143 and miR-16, are induced posttranscriptionally under DNA damage condition, whereas this effect could not be observed in p53-null HCT116 cells [71]. Another report indicated that estrogen receptor- α (ER α) also interacts with Drosha-p72 complex, leading to a reduced affinity of Drosha complex to a subset of miRNA in the presence of estradiol [72]. Recently, Kawai *et al.* demonstrated that breast cancer 1 (BRCA1), a human tumor suppressor gene, regulates miRNA biogenesis by recognizing pri-miRNA and binding to the Drosha microprocessor and Smads/p53, which enhances processing of a subset of miRNAs [73]. As the above-mentioned protein factors are critical determinants during cancer progression, it would be interesting to investigate the detailed mechanisms mediating miRNA biogenesis in the context of cancer.

miRNA-miRNA interaction

After processing, mature miRNAs are produced as functional strands, loaded onto miRISC, and targeted to specific 3'UTRs, thereafter. In addition to the binding between miRNA and 3'UTR of its target mRNA, Chen *et al.* recently identified a direct interaction between two individual miRNAs, miR-107 and let-7 (Figure 2). This study provides the first evidence that two different miRNAs could interact directly with each other through sequence match [74]. Using a mutation system, Chen *et al.* further identified the essential role of an internal loop within the miR-107::let-7 duplex, which provides important clues for further investigation on the underlying mechanism [74]. MiR-107 mitigates the tumor suppressive effects of let-7, and thus facilitating cancer progression. As endogenous let-7 is capable of suppressing the expression of multiple oncogenes including Ras and Hmga2, inhibition of let-7 allows cancer cells becoming aggressive. During the progression of cancer, overexpressed miR-107 targets and destabilizes let-7, enabling oncoproteins to escape from let-7-mediated suppression. Another study simultaneously published by Tang *et al.* also provides functional evidence of miRNA-miRNA

interaction between miR-709 and pri-miR-15a/16-1 [75]. This newly discovered regulation sheds light on our current knowledge in the posttranscriptional control of miRNA. Considering the interaction and the multifaceted roles of a given miRNA may have, the regulation network of miRNA becomes more complex than we originally thought.

Conclusion

MiRNAs have been known to function in most physiological processes in humans. As dysregulated expression of specific miRNAs is a common phenomenon observed in human cancers, unraveling the underlying mechanisms misguided at each step of miRNA biogenesis is crucial to our knowledge on how these miRNAs are altered. Accumulating evidence in both transcriptional and posttranscriptional regulation have enabled us to understand the novel functions of classical transcription factors, and more interestingly, RNA binding proteins, in controlling cancer-specific miRNAs. Because miRNAs play key roles in human cancer, identifying the underlying pathways will provide a more complete understanding of their functions and regulations during cancer progression and may have clinical applications in the future.

Competing interests

The authors have no conflicts of interest to declare.

Authors' contributions

P-SC, J-LS, and M-CH equally conceived and prepared this review. All of the authors read and approved the final manuscript.

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